Chapter

Vitamin C Dosage in Health and Disease

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Abstract

The dosage of any compound determines its efficacy in therapy and/or prevention of any disease. Such is also true about vitamin C. Unlike most other vitamins, L-ascorbic acid seldom leads to toxicity or an overdose. It is well-tolerated at extremely high dosages with little or no side effect. Vitamin C at different doses can act as either an antioxidant or a pro-oxidant. Either way, it is therapeutic in several conditions. In this chapter, we consider the appropriate doses used under normal conditions, for the maintenance of healthy state. The recommended daily allowances of vitamin C vary from country to country, and different organizations have varying values. Therefore, we look at some of the factors responsible for these variations and those that determine the efficacy of ascorbic acid at different doses. We also explore the different dosages used in several randomized controlled clinical trials for either treatment or prevention of certain disease conditions. The high dose used in disease conditions is to first replenish the depleted stores before improving the health status of the patients.

Keywords: disease, dosage, recommended daily allowance, high-dose, health, low-dose, vitamin C

1. Introduction

There are two forms of vitamin C, the *L*-ascorbic acid and dehydroascorbic acid. Unlike most animals and plants, humans cannot synthesize this ubiquitous vitamin due to the defective gene encoding for *L*-gulonolactone oxidase, the catalyst for the final step of vitamin C synthesis [1]. Vitamin C is widely known for its role in prevention of scurvy, the Latin name for "scorbutus" [2], as well as the origin of the word "ascorbic" [3]. Scurvy is a clinical manifestation of vitamin C deficiency.

Vitamin C serves as a water-soluble vitamin in addition to several other functions, owing to its ability to donate electrons, and gets reduced to the ascorbic acid radical in the process [4, 5]. It serves as a co-factor to about 8 enzymes involved in hormonal synthesis, wound healing, or collagen synthesis as well as immune boosting [5].

2. Vitamin C dosage in health

The dosage of vitamin C needed for maintenance of normal health is called the recommended daily allowance (RDA). Australia's National Health and Medical Research Council [6] defines it as the "average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals in a particular life stage and gender group." This value is highly variable, depending on the region, country, or organization concerned [7]. For example, the RDA is 90 mg/day for men and 75 mg/day for women in the US and Canada; 40–45 mg/day in the UK, India, and Australia; and 110 mg/day in France, Germany, and other European countries [7]. As reviewed by Carr and Lykkesfeldt [7], there are various reasons for these discrepancies ranging from optimization of health (up to 200 mg/day), boosting the immune system, and replacing the daily turnover to prevention of scurvy (45 mg/day).

2.1 Factors affecting the dosage of vitamin C in health

A number of factors determine the choice of vitamin C dosage. These include age, gender, pregnancy, lactation, and body mass index. Another very important determinant of the vitamin C RDA is the amount that will sufficiently provide an antioxidant protection [8].

2.1.1 Smoking status and obesity

Smokers and obese people often need higher RDA (at least 35 mg/day more than that needed by non-smokers and average weight individuals) to maintain an optimal health [5, 7]. This is due to the low plasma concentrations of vitamin C usually seen among these groups of people. For example, a study by Langlois et al. [9] revealed that 29.2% of smokers compared to 9% of non-smokers and 17% of obese and 14% of overweight individuals compared to the 5.5% of the general US population that do not take vitamin C supplement had deficient levels (>28 Umol/L).

The prevalence of vitamin C deficiency can be as high as 15% in the general population [10], but it doubled among smokers [11]. Oxidative stress and increased vitamin C turnover associated with smoking are responsible for the low vitamin C status among smokers [12, 13], but supplementation had been shown to counter such effects [14, 15].

Several studies in a review by Carr and Lykkesfeldt [7] linked a low vitamin C status with higher BMI. This is because the response to vitamin C is smaller among those with higher body weights [16]. The plasma vitamin C concentration as well as the RDA depend on the body weight of the individual largely [17].

2.1.2 Age and gender

The RDA in the US and Canada among infants is 40–50 mg/day but falls rapidly to only about 15 mg/day at age 2–3 years before rising to about 75 mg/day in males and 65 mg/day in females after puberty and reaching its normal value in adults [5]. The reason behind the high RDA in neonates and infants is probably due to the numerous developmental processes they pass through. These processes might be associated with oxidative stress, requiring some antioxidant boost. Most of the vitamin C comes from the breast milk of the mother and other highly supplemented vitamin C-rich food items [8].

Lower vitamin C plasma levels have also been reported among the elderly in several studies [18–20], thereby increasing the RDA to a higher value in that age group. The lower doses required in women are attributed to their lower body mass compared to men [21]. The same reason applies to the difference in RDA between adults and children [7].

2.1.3 Pregnancy and lactation

The RDA in the US and Canada for pregnant mothers is usually doubled (up to 85 mg/day) and is tripled during lactation [5, 22]. This is probably due to the high turnover of vitamin C, increasing the need for vitamin C by the developing fetus and suckling infants and hemodilution in pregnancy [23]. In fact, complications associated with pregnancy are significantly reduced by vitamin C intake [24]. That is why the RDA is higher in these groups of people.

2.1.4 Body pool of Vitamin C

Kallner *et al*. [25] had estimated the total body pool of vitamin C to be 2 mg/100 g body weight (excluding the amount in cells and tissues). Under normal, non-smoking conditions, the daily turnover is expected to be replaced continuously by dietary intake. Hence, as the daily metabolic loss (2.9%) and urinary loss (25%) increases [7], the RDA also increases to maintain the total body pool. This is the basis for setting the RDA for vitamin C by some important organizations like the World Health Organization.

Doses of vitamin C ≥ 250 mg/day can increase the body pool to the plasma level (40-60 μmol) necessary to maintain optimal health [26]. With adequate dietary intake, vitamin C supplementation above 400 mg/day often reach a saturated level in which the sodium-dependent vitamin C transporter can no longer permit entry of more vitamin C into the plasma [26]. This leads to increased renal excretion. Therefore, the optimal dose needed to saturate the plasma and blood corpuscles apart from the erythrocytes is 200–400 mg/day [26]. A review by the Nobel Prize winner Linus Pauling [27] had much earlier suggested 250–4000 mg/day as the daily intake of vitamin C to make allowance for saturation and restoration of depleted stores.

3. Vitamin dosage in disease conditions

Several disease conditions worsen vitamin C deficiency especially among hospitalized patients [28–30]. Critically ill patients required higher doses (at least 2–3 g/day) of vitamin C supplementation to restore their normal plasma levels [31, 32]. Much higher doses improved outcome in burn patients administered infusions at 60 mg/kg/hour within the first day of admission [33]. Higher doses of vitamin C administration could be lifesaving in patients with severe illnesses such as sepsis as reviewed by [34].

The **Table 1** below summarizes the different doses of vitamin C in some controlled trials. Most of the earlier trials used an average dose of 500 mg/day, but the recent trials are now utilizing much higher doses.

S/N	Type of study	Sample of participants	Sample size	Dosage used/ day	Outcome of trial
1	Double-blind randomized clinical trial (over 6.3 years)	Patients with age-related macular degeneration and vision loss	3640 patients from 11 centers	500 mg	Significant odds reduction compared to placebo [35].
2	Prospective cohort study (over 15 years)	Post-menopausal diabetic women	1923	>300 mg	Significant increase in CVD disease mortality [36]
3	Randomized double-blind placebo-controlled trial (8 years follow-up)	Male physicians ≥50 years old in the US with cancer	Prostate cancer: 1008. Total cancer: 1943	500 mg	No significant effect on incidence of total cancer or prostate cancer [37]
4	Randomized double-blind placebo-controlled trial (8 years follow-up)	Male physicians ≥50 years old in the US with CV disease	1245 men with CV events	500 mg	No significant effect on CV event and mortality [38]
5	Randomized double-blind placebo-controlled trial (9.4 years follow-up)	Female health professionals ≥40 years old in the US	8171	500 mg	No significant overall benefit in occurrence of CV event was recorded but slight decrease in stroke incidence in those on combined vitamins C and E [39].
6	RCCT (18 months follow-up)	Patients on first line HAART regimen	200 on vitamin C; 200 on placebo	70 mg	No significant benefit in both primary and secondary outcomes (e.g., CD4 count, body weight, quality of life, etc.) was reported [40].
7	RCCT (45 days follow-up)	Diabetic patients with high BP	42 on vitamin C; 42 on placebo	1000 mg (4 × 250 mg)	Significant improvement in both systolic and diastolic BP was noted [41]
8	RCCT (8 weeks follow-up)	Depressed patients on citalopram	21 on vitamin C; 22 on placebo	1000 mg	No significant benefits in mood [42]

AREDS: Age-Related Eye Disease Study Research Group; BP: blood pressure; CV: cardiovascular; CVD: cardiovascular disease; HAART: highly active antiretroviral therapy; RCCT: randomized double-blind controlled clinical trial; US: United States of America.

Table 1.
Outcomes of vitamin C supplementation at different doses in some studies.

4. Vitamin C dosages in some disease conditions

4.1 Type 2 diabetes (T2D)

Patients with type 2 diabetes received chewable vitamin C tablets (1000 mg/day) for 45 days in a randomized controlled trial [41]. At the end of the study, there was a remarkable reduction of both systolic and diastolic blood pressures among the vitamin C group compared to the placebo group. The mechanism behind is not clearly elucidated. However, other parameters such as hip and waist circumferences, body weights, and BMI were relatively the same compared to the placebo group.

Although no overall benefit of vitamin C was noted on glucose level and HbA1c and insulin concentrations in a systematic review and a meta-analysis of RCTs [43], the blood glucose levels were significantly reduced among diabetic patients on vitamin C supplementation for a longer duration (>30 days). Nevertheless, the dosage was not considered in the analysis hence the need to interpret the results carefully. However, this shows that the duration of supplementation and not necessarily the dosage may determine the impact of vitamin C on type-2 diabetes.

4.2 Cardiovascular diseases (CVDs)

Vitamin C supplementation generally has no association to CVD risks, especially among people with normal plasma levels, except among those with deficient vitamin C levels who have increased risks [5]. However, supplementation among diabetic women of postmenopausal age demonstrated a conflicting increased CVD risk [36]. The possible reason given for this phenomenon is the imbalance caused by the supplemented vitamin C at high dosages, upsetting the antioxidant-pro-oxidant balance [44]. However, this is also debatable as it is common knowledge that CVD risk increases with increasing age, and postmenopausal women even have higher risk than men.

In a randomized-controlled double-blind placebo-controlled factorial trial involving 14,641 male physicians aged ≥50 years in the United States [38], about 1245 of them had at least one cardiovascular event in the space of 8 years follow-up. Vitamin C at a dose of 500 mg/day failed to reduce the risk of such CV events and mortality (**Table 1**). However, earlier trials showed the ability of vitamin C at much higher doses (6–7 g/day for 2–3 days) to restore endothelial function in hypertensive patients [45] and in those with coronary artery disease or hyperglycemia-induced endothelial dysfunction [46, 47]. Even in normal individuals without CVDs, arterial wall stiffness and platelet aggregation were ameliorated by ingestion of vitamin C at 2 g/day via a yet to be elucidated mechanism [48].

It is therefore important to consider recent trials that will settle this controversy behind vitamin C supplementation among patients with CVD at both lower and higher dosages. As a water-soluble antioxidant, vitamin C may play a role in the bioavailability of nitric oxide (NO) by activating the endothelial NO synthase, thereby reducing nitrosative stress as well as restoring the endothelial integrity, which is the underlying mechanism behind conditions such as CVDs.

4.3 Depression

Some patients with depressive disorders on citalopram were involved in a clinical trial with vitamin C (1000 mg/day) and placebo for 8 weeks [42]. The result showed no significant benefit in the mood of the patients. In contrast, supplementation with a higher dosage (3000 mg/day) in earlier studies demonstrated significant improvement in mood (reduced Beck's depression scores) and sexual activity [49], as well as decreased blood pressure and subjective stress response to social stress test [50]. Therefore, it is not out of place to postulate that the dosage of vitamin C is crucial to its effect in depressive disorders.

4.4 Cancer

Vitamin C at a dose of 500 mg/day showed no beneficial effect after 8 years of supplementation among 1943 male patients with several cancers, including 1008 patients with prostate cancer in a randomized controlled trial [37]. More recently, vitamin C at 500 mg/day caused some epigenetic changes in patients suffering from myeloid leukemia [51]. This implies the ability of vitamin C to augment the efficacy of cancer chemotherapy even at such a low dose. The study also demonstrated restoration of the depleted plasma concentration of vitamin C in the supplemented group compared to the placebo group.

In an experimental study, high-dose vitamin C showed great efficacy in inhibiting proliferation and inducing apoptosis of various cell lines of breast cancer, and in combination with anti-cancer agents, the vitamin C administration showed an added advantage [52]. This was probably due to the ability of vitamin C to augment the cellular catalase level and boost the cells defense response against oxidative damage [52]. Interestingly, the normal breast epithelial cells were spared from these effects. These effects are due to the epigenetic modulatory role that vitamin C plays in cancer and other disease conditions [53]. However, the effect of high-dose vitamin C on cancer is highly controversial as many trials fail to show any anti-cancer effect of high-dose vitamin C supplementation in a review by Nowak [54].

4.5 Neurodegenerative diseases

Vitamin C intake has proven effective against neuro-degeneration at different doses in several studies, as reviewed by Harrison [55]. Nevertheless, this is also controversial as shown in a case-control study involving patients with Parkinson's disease [56]. In a countywide study involving 3000 participants over a 7.2-year follow-up period, a positive correlation was observed between high intake of vitamin C and cognition even though dosages above 500 mg/day did not give any added benefit [57, 58]. Again, a cohort study over the same period of 7 years, involving elderly people (61–87 years) on different combinations of vitamins (including vitamin C) and minerals, showed no significant correlation with cognition [59]. However, baseline cognitive assessment was not done as such might have shown a positive correlation.

In mice, vitamin C administration at 250 mg/kg was shown to protect the brain of mice against reserpine-induced motor [60] and cognitive [61] impairments after 4 weeks of administration. In addition, vitamin C preserved, to some extent, the level of dopamine in the mouse brain exposed to auto-oxidation by reserpine [62]. Converted into human equivalent dose, 40.5 mg/kg was obtained [63]. Whether this dosage can be translated in human research or not, the bottom line is that vitamin C showed great potential in halting the progression of some of these neurodegenerative diseases.

4.6 Viral diseases including COVID-19

Biancatelli et al. [64] had reported the efficacy of vitamin C at different dosages against several viral diseases in their review. For example, 50 mg/kg of intravenous vitamin C were given to about 41 herpes zoster patients on days 1, 3, and 5 in a double-blind randomized controlled trial [65]. There was a marked reduction in the pain scale scores of those patients compared to the placebo group. In a similar randomized controlled trial, involving 87 patients who received a much higher dose (5 g/day on days 1, 3, and 5), lower pain scale scores and post herpetic neuralgia were recorded [66]. In a review by Hemila [67], trials that utilized high doses (6–8 g/day) of vitamin C were associated with significant reduction in duration and severity of common cold and pneumonia compared to those that used lower doses (3–4 g/day).

In COVID-19, high-dose vitamin C infusion (50 mg/kg 6 hourly for 4–7 days) could act as a pro-oxidant to the over-reactive, hyper-excited immune cells participating in the cytokine storm but as an antioxidant to the normal lung parenchymal cells as well as some of the innate cells, thereby protecting them [68]. This therapy is often combined with a glucocorticoid to prevent treatment-induced inflammation. High-dose vitamin C infusion showed significant improvement in the primary outcomes with reduced mortality and better prognosis among patients with sepsis and adult respiratory distress syndrome [69]. In a similar but multicenter, prospective randomized, placebo-controlled trial involving 308 patients with COVID-19, high-dose vitamin C infusion (24 g/day for 7 days) was initiated and expected to improve pulmonary functions and other parameters and reduce mortality [70]. Therefore, extremely high doses of vitamin C should be considered in severe disease conditions.

4.7 Other disease conditions

A randomized factorial clinical trial from 11 centers in the US involving 3640 patients with age-related macular degeneration (AMD) and vision loss due to cataract was carried out over a follow-up period of 6.3 years [35]. The participants received antioxidants including vitamin C at a dose of 500 mg/day. The results showed no significant effect of the antioxidants on both development and progression of the diseases. However, there was no adverse effect recorded. In addition, the doses used were lower as compared to other trials. For example, an inverse relationship was found between the risk of cataract development and vitamin C intake [71, 72], with a decrease in odds at dosages greater than 102 mg/day [73].

In rare cases, some studies used very high doses of vitamin C. For example, in a prospective cohort study among 71 patients with confirmed acute and chronic allergic diseases [74], 7.5 g of vitamin C infusion (2–3 times per week) was given to the participants over a mean period of 3.2 weeks (acute) or 11.9 weeks (chronic). At the end of the treatment, there was a significant reduction in both allergy-specific and non-specific symptoms. The use of such very high doses of vitamin C was due to its well-known wide safety margin—continuous usage of vitamin C because of oxidative stress and the need to restore the already depleted pool in the patients. A review by Carr and McCall [75] revealed that high doses of vitamin C had also been used in the management of acute and chronic pain syndromes such as cancer and post-herpetic neuralgia with positive outcomes.

5. Discussion and conclusion

Most interventional studies involving vitamin C supplementation show no benefit irrespective of the dosage, but deficient plasma levels are associated with adverse clinical outcomes [5]. This entails that vitamin C supplementation may only produce a significant effect when there is a deficiency. As demonstrated by Granger and Eck [5], a peak plasma concentration (plateau) is reached in a deficient individual who is taking vitamin C up to 200–400 mg/day [26].

Due to the wide safety margin of vitamin C and the rapid urinary clearance above the saturation level, most countries and organizations have set the upper level of intake to be 1000–2000 mg/day [6, 8], beyond which the risk of adverse side effects such as gastrointestinal disturbances is increased. Despite the wide margin of safety, doses above 500 mg/day might increase the likelihood of urinary stones in patients prone to urolithiasis [76].

It is important to note that most of the interventional studies considered here were not on vitamin C supplementation alone but on a combination of several vitamins especially vitamins C and E. However, the two vitamins can interact in a synergistic manner [77, 78] to potentiate their effects [79] at different dosages. In addition, some of the estimated doses of vitamin C were from self-reported dietary questionnaires, which might not be accurate.

Sequeira [80] has reported high doses (≥500 mg/kg) of vitamin C, in a review, to cause increase para-cellular transport of drugs, nutrients, and substances not readily absorbed by the intestines probably via some poorly understood mechanisms. However, a possible mechanism could be alteration in the architecture of the tight junctions and the constituted proteins. This could enhance the para-cellular transport of some molecules of interest.

In conclusion, vitamin C dosage recommended in health is dependent on a number of factors such as age, gender, body built, smoking status, pregnancy and lactation, and so on. In disease conditions, the dosage is determined by the type and severity of the disease based on the need to replenish the depleted or deficient levels. In general, taking vitamin C supplement doses higher than the recommended doses is highly encouraged due to the continuous metabolic turnover.

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References

[1] Nishikimi M, Yagi K. Molecular basis for the deficiency in humans of gulonolactone oxidase, a key enzyme for ascorbic acid biosynthesis. The American Journal of Clinical Nutrition. 1991;**54** (Suppl. 6):1203S-1208S

[2] Bartholomew M. James Lind's treatise of the scurvy (1753). Postgraduate Medical Journal. 2002;**78**(925):695-696

[3] Grzybowski A, Pietrzak K. Albert Szent-Gyorgyi (1893-1986): The scientist who discovered vitamin C. Clinics in Dermatology. 2013;**31**(3):327-331

[4] Padayatty SJ, Levine M. Vitamin C: The known and the unknown and goldilocks. Oral Diseases. 2016;**22**(6):463-493

[5] Granger M, Eck P. Dietary vitamin C in human health. Advances in Food and Nutrition Research. 2018;**83**:281-310. DOI: 10.1016/bs.afnr.2017.11.006

[6] National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand: Executive Summary. Canberra: Department of Health and Ageing; 2006. Available from: https://www.nhmrc.gov.au/sites/default/files/images/nutrient-refererence-dietary-intakes.pdf

[7] Carr AC, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: A review of RDA criteria and underlying health perspectives. Critical Reviews in Food Science and Nutrition. 2021;**61**(5):742-755. DOI: 10.1080/10408398.2020.1744513

[8] Institute of Medicine Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for vitamin C, vitamin E, Selenium, and Carotenoids. Washington: National Academies Press; 2000. p. 529

[9] Langlois K, Cooper M, Colapinto CK. Vitamin C status of Canadian adults: Findings from the 2012/2013 Canadian health measures survey. Health Reports. 2016;**27**(5):3-10

[10] Lindblad M, Tveden-Nyborg P, Lykkesfeldt L. Regulation of vitamin C homeostasis during deficiency. Nutrients. 2013;**5**(8):2860-2879

[11] Pfeiffer CM, Sternberg MR, Schleicher RL, Rybak ME. Dietary supplement use and smoking are important correlates of biomarkers of water-soluble vitamin status after adjusting for sociodemographic and lifestyle variables in a representative sample of U.S. adults. The Journal of Nutrition. 2013;**143**:957S-965S

[12] Lykkesfeldt J, Viscovich M, Poulsen HE. Ascorbic acid recycling in human erythrocytes is induced by smoking in vivo. Free Radical Biology & Medicine. 2003;**35**(11):1439-1447

[13] Lykkesfeldt J, Viscovich M, Poulsen HE. Plasma malondialdehyde is induced by smoking: A study with balanced antioxidant profiles. The British Journal of Nutrition. 2004;**92**(2):203-206

[14] Moller P, Viscovich M, Lykkesfeldt J, Loft S, Jensen A, Poulsen HE. Vitamin C supplementation decreases oxidative DNA damage in mononuclear blood cells of smokers. European Journal of Nutrition. 2004;**43**(5):267-274

[15] Lykkesfeldt J, Christen S, Wallock LM, Chang HH, Jacob RA, Ames BN. Ascorbate is depleted by smoking and repleted by moderate

supplementation: A study in male smokers and nonsmokers with matched dietary antioxidant intakes. The American Journal of Clinical Nutrition. 2000;**71**(2):530-536

[16] Carr AC, Pullar JM, Bozonet SM, Vissers MC. Marginal ascorbate status (hypovitaminosis C) results in an attenuated response to vitamin C supplementation. Nutrients. 2016;**8**(6):341

[17] Block G, Mangels AR, Patterson BH, Levander OA, Norkus EP, Taylor PR. Body weight and prior depletion affect ascorbate levels attained on identical vitamin C intake: A controlled-diet study. Journal of the American College of Nutrition. 1999;**18**(6):628-637

[18] Birlouez-Aragon I, Delcourt C, Tessier F, Papoz L. Associations of age, smoking habits and diabetes with plasma vitamin C of elderly of the POLA study. International Journal for Vitamin and Nutrition Research. 2001;**71**(1):53-59

[19] Faure H, Preziosi P, Roussel AM, Bertrais S, Galan P, Hercberg S, et al. Factors influencing blood concentration of retinol, alpha-tocopherol, vitamin C, and beta-carotene in the French participants of the SU.VI.MAX trial. European Journal of Clinical Nutrition. 2006;**60**(6):706-717

[20] Ravindran RD, Vashist P, Gupta SK, Young IS, Maraini G, Camparini M, et al. Prevalence and risk factors for vitamin C deficiency in North and South India: A two Centre population based study in people aged 60 years and over. PLoS One. 2011;**6**(12):e28588

[21] Jungert A, Neuhauser-Berthold M. The lower vitamin C plasma concentrations in elderly men compared with elderly women can partly be attributed to a volumetric dilution effect due to differences in fat-free mass. The British Journal of Nutrition. 2015;**113**(5):859-864

[22] Monsen ER. Dietary reference intakes for the antioxidant nutrients: Vitamin C, vitamin E, selenium, and carotenoids. Journal of the American Dietetic Association. 2000;**100**:637-640

[23] Juhl B, Lauszus FF, Lykkesfeldt J. Is diabetes associated with lower vitamin C status in pregnant women? A prospective study. International Journal for Vitamin and Nutrition Research. 2017;**86**(3-4):184-189

[24] Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy. Cochrane Database of Systematic Reviews. 2015;**2015**(9):CD004072. DOI: 10.1002/14651858.CD004072

[25] Kallner A, Hartmann D, Hornig D. Steady-state turnover and body pool of ascorbic acid in man. The American Journal of Clinical Nutrition. 1979;**32**:530-539. DOI: 10.1093/ajcn/32.3.530

[26] Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. Proceedings of the National Academic Science USA. 2001;**98**(17):9842-9846. DOI: 10.1073/pnas.171318198

[27] Pauling A. Are recommended daily allowances for vitamin C adequate? Proceedings of the National Academic Science USA. 1974;**71**(11):4442-4446

[28] Gan R, Eintracht S, Hoffer LJ. Vitamin C deficiency in a university teaching hospital. Journal of the American College of Nutrition. 2008;**27**(3):428-433

[29] Evans-Olders R, Eintracht S, Hoffer LJ. Metabolic origin of hypovitaminosis C in acutely hospitalized patients. Nutrition. 2009;**26**(11-12):1070-1074

[30] Wang Y, Liu XJ, Robitaille L, Eintracht S, Macnamara E, Hoffer LJ. Effects of vitamin C and vitamin D administration on mood and distress in acutely hospitalized patients. The American Journal of Clinical Nutrition. 2013;**98**(3):705-711

[31] Long CL, Maull KI, Krishnan RS, Laws HL, Geiger JW, Borghesi L, et al. Ascorbic acid dynamics in the seriously ill and injured. The Journal of Surgical Research. 2003;**109**(2):144-448. DOI: 10.1016/s0022-4804(02)00083-5

[32] de Grooth HJ, Manubulu-Choo WP, Zandvliet AS, Spoelstra-de Man AME, Girbes AR, Swart EL, et al. Vitamin C pharmacokinetics in critically ill patients: A randomized trial of four IV regimens. Chest. 2018;**153**(6):1368-1377. DOI: 10.1016/j.chest.2018.02.025

[33] Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: A randomized, prospective study. Archieves of Surgery Chicago Ill. 1960;**2000**(135):326-331

[34] Gordon DS, Rudinsky AJ, Guillaumin J, Parker VJ, Creighton KJ. Vitamin C in health and disease: A companion animal focus. Topics in Companion Animal Medicine. 2020;**39**:100432. DOI: 10.1016/j.tcam.2020.100432

[35] Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Achieves in Ophthalmology. 2001;**119**(10):1439-1452

[36] Lee D-H, Folsom AR, Harnack L, Halliwell B, Jacobs DR. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? The American Journal of Clinical Nutrition. 2004;**80**(5):1194-1200

[37] Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: The Physicians' Health Study II randomized controlled trial. Journal of the American Medical Association. 2009;**301**(1):52-62. DOI: 10.1001/jama.2008.862

[38] Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. Journal of the American Medical Association. 2008;**300**(18):2123-2133. DOI: 10.1001/jama.2008.600

[39] Cook NR, Albert CM, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, et al. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant Cardiovascular Study. Archives of Internal Medicine. 2007;**167**(15):1610-1618. DOI: 10.1001/archinte.167.15.1610

[40] Guwatudde D, Wang M, Ezeamama AE, Bagenda D, Kyeyune R, Wamani H, et al. The effect of standard dose multivitamin supplementation on disease progression in HIV-infected adults initiating HAART: A randomized double blind placebo-controlled trial in Uganda. BMC Infectious

Diseases. 2015;**15**:348. DOI: 10.1186/s12879-015-1082-x

[41] Shateri Z, Ali Keshavarz S, Hosseini S, Chamari M, Hosseini M, Nasli E. Effect of Vitamin C supplementation on blood pressure level in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled trial. Biosciences, Biotechnology Research Asia. 2016;**13**(1):279-286

[42] Sahraian A, Ghanizadeh A, Kazemeini F. Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo-controlled clinical trial. Trials. 2015;**16**:94. DOI: 10.1186/s13063-015-0609-1

[43] Ashor AW, Werner AD, Lara J, Willis ND, Mathers JC, Siervo M. Effects of vitamin C supplementation on glycaemic control: A systematic review and meta-analysis of randomised controlled trials. European Journal of Clinical Nutrition. 2017;**71**(12):1371-1380. DOI: 10.1038/ejcn.2017.24

[44] Eastwood MA. Interaction of dietary antioxidants in vivo: How fruit and vegetables prevent disease? QJM. 1999;**92**:527-530

[45] Solzbach U, Hornig B, Jeserich M, Just H. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. Circulation. 1997;**96**(5):1513-1519. DOI: 10.1161/01.CIR.96.5.1513

[46] Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF Jr, Vita JA. Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation. 1996;**93**(6):1107-1113. DOI: 10.1161/01.CIR.93.6. 1107

[47] Beckman JA, Goldfine AB, Gordon MB, Creager MA. Ascorbate restores endothelium-dependent vasodilation impaired by acute hyperglycemia in humans. Circulation. 2001;**103**(12):1618-1623. DOI: 10.1161/01.CIR.103.12. 1618

[48] Wilkinson IB, Megson IL, MacCallum H, Sogo N, Cockcroft JR, Webb DJ. Oral vitamin C reduces arterial stiffness and platelet aggregation in humans. Journal of Cardiovascular Pharmacology. 1999;**34**(5):690-693. DOI: 10.1097/ 00005344-199911000-00010

[49] Brody S. High-dose ascorbic acid increases intercourse frequency and improves mood: A randomized controlled clinical trial. Biological Psychiatry. 2002;**52**(4):371-374. DOI: 10.1016/s0006-3223(02)01329-x

[50] Brody S, Preut R, Schommer K, Schürmeyer TH. A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress. Psychopharmacology (Berlin). 2002;**159**(3):319-324. DOI: 10.1007/s00213-001-0929-6

[51] Gillberg L, Ørskov AD, Nasif A, Ohtani H, Madaj Z, Hansen JW, et al. Oral vitamin C supplementation to patients with myeloid cancer on azacitidine treatment: Normalization of plasma vitamin C induces epigenetic changes. Clinical Epigenetics. 2019;**11**(1):143. DOI: 10.1186/s13148-019-0739-5

[52] Lee SJ, Jeong J, Lee IH, Lee J, Jung JH, Park HY, et al. Effect of high-dose vitamin C combined with anti-cancer treatment on breast cancer cells. Anticancer Research. 2019;**39**:751-758. DOI: 10.21873/anticanres.13172

[53] Camarena V, Wang G. The epigenetic role of vitamin C in health and disease. Cellular and Molecular Life Sciences. 2016;**73**(8):1645-1658. DOI: 10.1007/s00018-016-2145-x

[54] Nowak D. Vitamin C in human health and disease. Nutrients. 2021;**13**:1595-1597. DOI: 10.3390/nu13051595

[55] Harrison FE. A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. Journal of Alzheimer's Disease. 2012;**29**(4):711-726. DOI: 10.3233/JAD-2012-111853

[56] Miyake Y, Fukushima W, Tanaka K, Sasaki S, Kiyohara C, Tsuboi Y, et al. Dietary intake of antioxidant vitamins and risk of Parkinson's disease: A case-control study in Japan. European Journal of Neurology. 2011;**18**(1):106-113. DOI: 10.1111/j.1468-1331.2010.03088.x

[57] Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: The Cache County Study. Archives of Neurology. 2004;**61**:82-88

[58] Wengreen HJ, Munger RG, Corcoran CD, Zandi P, Hayden KM, Fotuhi M, et al. Antioxidant intake and cognitive function of elderly men and women: The Cache County Study. The Journal of Nutrition, Health & Aging. 2007;**11**:230-237

[59] Yaffe K, Clemons TE, McBee WL, Lindblad AS. Impact of antioxidants, zinc, and copper on cognition in the elderly: A randomized, controlled trial. Neurologija. 2004;**63**:1705-1707

[60] Danboyi T, Jimoh A, Alhassan AW, Hassan-Danboyi E, Sadiq M, Solomon NE, et al. Co-administration of vitamins C and E is protective against reserpine-induced motor impairment in mice. Annals of Basic Medical Science. 2021;**2**(2):106-110. DOI: org/10.51658/ABMS.202122.3

[61] Danboyi T, Jimoh A, Alhassan AW, Hassan-Danboyi E. Protective effect of co-administration of vitamins C and E on reserpine-induced cognitive impairment in mice. Nigeria Journal of Science Research. 2019a;**18**(3):261-268

[62] Danboyi T, Jimoh A, Alhassan AW, Hassan-Danboyi E. Protective effect of co-administration of vitamins C and E on reserpine-induced oxidative stress in mice. Journal of Association African Physiological Science. 2019b;**7**(1):30-37

[63] Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. Journal of Basic Clinical Pharmacy. 2016;**7**(2):27-31. DOI: 10.4103/0976-0105.177703

[64] Biancatelli RMLC, Berrill M, Marik PE. The antiviral properties of vitamin C. Expert Review of Anti-Infective Therapy. 2020;**18**(2):99-101. DOI: 10.1080/14787210.2020.1706483

[65] Chen JY, Chang CY, Feng PH, Chu CC, So EC, Hu ML. Plasma vitamin C is lower in postherpetic neuralgia patients and administration of vitamin C reduces spontaneous pain but not brush-evoked pain. The Clinical Journal of Pain. 2009;**25**(7):562-569. DOI: 10.1097/AJP.0b013e318193cf32

[66] Kim MS, Kim DJ, Na CH, Shin BS. A study of intravenous administration of vitamin C in the treatment of acute herpetic pain and postherpetic neuralgia. Annals of Dermatology. 2016;**28**(6):677-683. DOI: 10.5021/ad.2016.28.6.677

[67] Hemila H. Vitamin C and infections. Nutrients. 2017;**9**:339-366. DOI: 10.3390/nu9040339

[68] Erol A. High-dose intravenous vitamin treatment for COVID-19 (a mechanistic approach). (n.d.). 7 pages. Unpublished article

[69] Fowler AA 3rd, Truwit JD, Hite RD, Morris PE, DeWilde C, Priday A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI Randomized Clinical Trial. JAMA. 2019;**322**(13):1261-1270. DOI: 10.1001/jama.2019.11825. Erratum in: Journal of the American Medical Association. 2020; 323(4): 379

[70] Liu F, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: Study protocol for a multicentre randomised controlled trial. BMJ Open. 2020;**10**(7):e039519. DOI: 10.1136/bmjopen-2020-039519

[71] Vishwanathan R, Johnson EJ. In: Erdman JW, Macdonald IA, Zeisel SH, editors. Present Knowledge in Nutrition. 10th ed. Wiley Blackwell: Ames; 2012. pp. 942-946

[72] Wei L, Liang G, Cai C, Jin L. Association of vitamin C with the risk of age-related cataract: A meta-analysis. Acta Ophthalmologica. 2016;**94**:e170-e176. DOI: 10.1111/aos.12688

[73] Combs GF Jr, McClung JP. The Vitamins: Fundamental Aspects in Nutrition and Health. 5th ed. London: Academic Press; 2017. p. 278

[74] Vollbracht C, Raithel M, Krick B, Kraft K, Hagel AF. Intravenous vitamin C in the treatment of allergies: An interim subgroup analysis of a long-term observational study. The Journal of International Medical Research. 2018;**46**(9):3640-3655. DOI: 10.1177/0300060518777044

[75] Carr AC, McCall C. The role of vitamin C in the treatment of pain: New insights. Journal of Translational Medicine. 2017;**15**:77-90. DOI: 10.1186/s12967-017-1179-7

[76] Urivetzky M, Kessaris D, Smith AD. Ascorbic acid overdosing: A risk factor for calcium oxalate nephrolithiasis. The Journal of Urology. 1992;**147**:1215-1218

[77] Bursac-Metrovic M, Milovanovic DR, Mitic R, Jovanovic D, Sovrlic M, Vasiljevic P, et al. Effects of L-ascorbic acid and alpha-tocopherol on biochemical parameters of swimming-induced oxidative stress in serum of guinea pigs. African Journal of Traditional, Complementary, and Alternative Medicines. 2016;**13**(4):29-33

[78] Maggini S, Maldonado P, Cardim P, Fernandez Newball C, Sota Latino ER. Vitamins C, D and zinc: Synergistic roles in immune function and infections. Vitamins and Minerals. 2017;**6**(3):167-176. DOI: 10.4172/2376-1318.1000167

[79] Faria RR, Abílio VC, Grassl C, Chinen CC, Negrão LT, de Castro JP, et al. Beneficial effects of vitamin C and vitamin E on reserpine-induced oral dyskinesia in rats: Critical role of striatal catalase activity. Neuropharmacology. 2005;**48**(7):993-1001. DOI: 10.1016/j.neuropharm.2005.01.014

[80] Sequeira IR. Higher doses of ascorbic acid may have the potential to promote nutrient delivery via intestinal paracellular absorption. World Journal of Gastroenterology. 2021;**27**(40):6750-6756. DOI: 10.3748/wjg.v27.i40.6750