Vitamin C

FOR OPTIMAL THERAPEUTIC BENEFIT

ARTICLE BY
LISA COSTA-BIR

Vitamin C, well known for its immune support action, forms a major part of most Australian diets, leading to presumptions that clients are meeting nutritional requirements. While this essential vitamin has a plethora of other health benefits, more Australians may be deficient than we realise with the re-emergence of scurvy in modern day populations.

Vitamin C (also known ascorbic acid, AA) is a hydrophilic molecule that is vital for optimal functioning. Humans cannot synthesise vitamin C endogenously as they do not make the enzyme L-gulono-1,4 lactone oxidase which is essential for the biosynthesis of vitamin C.[1] Instead, dietary vitamin C must be obtained to ensure daily adequate intake.

> **In Australia, the recommended dietary intake (RDI) of vitamin C is 45 mg/day for adults with an upper limit of 1000 mg/day.**[2]

Measurement of vitamin C

- Intake and storage of vitamin C may be measured by both plasma and leucocyte levels.
- Leucocytes hold 50-100-fold higher vitamin C versus plasma.
- Plasma is reflective of recent intake and does not reflect tissue and body stores reliably when compared to leucocyte ascorbic acid.[3]

The reference interval for vitamin C used by the Royal College of Pathologists of Australasia is generally between:

- Plasma: 30-80 µmol/L
- Leucocytes: 1.1-3.0 µmol/10^9 [4]

KEY HIGHLIGHTS:

- Vitamin C is an essential nutrient and must be consumed in the diet.
- Vitamin C deficiency is on the rise and should not be overlooked.
- Vitamin C absorption takes place in the small intestine. Intestinal dysfunction may impede absorption.
- Smaller, frequent doses of vitamin C enhance bioavailability.
- Vitamin C is involved in processes throughout the body, including the immune system, collagen production, adrenal health, and iron absorption.
- Pairing vitamin C supplementation with bioflavonoids or glutathione can enhance the therapeutic action of both.

Vitamin C deficiency – a rarity?

It is generally assumed that vitamin C deficiency is rare, however, research suggests otherwise highlighting a rising incidence in Australia.

A 2023 retrospective study examining serum vitamin C status in 13,000 individuals tested in a public hospital in NSW, observed vitamin C insufficiency in 29.9% and deficiency in 24.5% of individuals.[5] Several studies looking at serum vitamin C levels found sub-optimal levels in the following cohorts:

- 50% of individuals with diabetic foot ulcers visiting Westmead Hospital, Sydney.[6]
- 50% of a cohort of patients in a mental health setting in South Australian had vitamin C levels lower than 26 µmol/L.[7]
- 30% of individuals with periodontal disease consulting a periodontal clinic in Sydney.[8]

The rising incidence of vitamin C insufficiency may be due to several factors including dietary changes (e.g. inadequate consumption of fruit and vegetables), increased chronic illness causing malabsorption, and/or increased requirements.[9]

Modern agricultural practices are considered to be a contributing factor to reduced vitamin C sufficiency, with research suggesting a 15-30% decrease in vitamin C content in a variety fruits and vegetables over the last 50 years due to nutrient depletion as a result of poor soil quality due to over farming.[10]

Table 1. Food sources of vitamin C[11]

FOOD SOURCE	VITAMIN C CONTENT
Cantaloupe melon (¼ medium)	60 mg
Papaya (1 cup cubed)	85 mg
Orange (1 medium)	70 mg
Watermelon (1 cup)	15 mg
Cooked cabbage, red (½ cup)	25 mg
Broccoli (½ cup cooked)	60 mg
Kiwi fruit (1 medium)	75 mg
Capsicum (½ cup)	65 mg

Figure 1. Suggested screening questions to assess for vitamin C insufficiency.[12]

Table 2. Vitamin C deficiency signs and symptoms

SYMPTOMS ASSOCIATED WITH VITAMIN C DEFICIENCY	MECHANISM OF ACTION
Mood changes: depression, hypochondriasis, irritability	• Vitamin C may produce mood-elevating effects in patients with subclinical depression.[13] • Vitamin C modulates neurotransmitter synthesis and release in the brain.[14] – This includes acting as a co-factor for dopamine beta-hydroxylase in the conversion of dopamine to noradrenaline.[14]
Lethargy	• Vitamin C is required for the synthesis of carnitine.[15] • Decreased synthesis of carnitine results in low energy due to the decreased oxidation of fatty acids in muscles and other tissues.[14] • Vitamin C is required for the synthesis of norepinephrine and epinephrine. • Decreased synthesis of neurotransmitters, e.g., norepinephrine and epinephrine can result in fatigue.
Anaemia	• Vitamin C facilitates iron absorption via the reduction of ferric ions into ferrous ions.[16]
Perifollicular hyperkeratosis **Coiled hairs** **Swollen, bleeding gums** **Poor wound healing**	• Vitamin C functions as a cofactor for proline and lysine hydroxylases, needed to stabilise collagen, enabling cross-linking and assisting with procollagen transcription into collagen.[17] • Inadequate collagen production leads to dermal disruption and atrophy, reduced collagen fibres and their fragmentation. This results in weak skin and blood vessels, gingival bleeding, easy bruising, and slow wound healing.[17]

Absorption of vitamin C

Plasma and tissue concentrations of vitamin C are mediated by gastrointestinal absorption. Absorption takes place primarily in the distal ileum,[18] followed by renal reabsorption and excretion via the urine.[19] Subsequently it is unsurprising that individuals with irritable bowel disease commonly exhibit insufficient serum vitamin C levels.[20,21]

Bioavailability

- Vitamin C bioavailability declines rapidly as the dose increases.
- Small frequent doses appear more efficacious than large doses. Low dose of 200-400 mg results in 100% absorption, however if 500 mg is exceeded, bioavailability reduces, decreasing to approximately 30% when 1000 mg is consumed orally in one bout. This is due to maximal saturation of the intestinal transporter SVCTI.[22]
- Because vitamin C is water soluble, almost all the absorbed dose is excreted in urine within 24 hours.[23] It is therefore important to be aware of a person's daily vitamin C intake and ensure they are replenishing levels daily.

Table 3. Functions of vitamin C in the body[24]

BODY TISSUE	FUNCTION OF VITAMIN C
Brain	• Dopamine conversion to noradrenaline
GIT	• Non-heme iron absorption • Bile acid formation via cholesterol hydroxylation
Endocrine	• Corticosteroids, aldosterone, and adrenal hormone synthesis
Immune	• Leukocyte function
Metabolic	• Tyrosine degradation • Maintenance of iron and copper in reduced form • Folate metabolism • Carnitine synthesis
Connective Tissue	• Collagen formation
Genetic	• Epigenetic regulation

VITAMIN C: CLINICAL APPLICATION

Immunity

When it comes to immunity, vitamin C improves chemotaxis, stimulates interferon production, supports lymphocyte proliferation, modulates regulatory T-cells, and can assist with the production of host defence peptides, highlighting its importance for both innate and adaptive immunity.[25]

In individuals with low levels of vitamin C, 250 mg/day of vitamin C (from kiwi fruit) resulted in a 20% increase in neutrophil migration capacity.[26] Supplemental vitamin C at 1 g/day taken for 90 days throughout the winter months is associated with reduced duration of colds in those that are deficient.[27]

Iron absorption

Iron absorption is shown to be improved with vitamin C via the reduction of ferric to ferrous iron. Despite this, human clinical trials have not convincingly shown the superiority of co-supplementing with iron and vitamin C compared to iron alone for the management of anaemia.[28,29] This may be because an ascorbic acid-to-iron molar ratio of 2:1 is necessary to increase iron bioavailability[30] and many studies do not adopt these ratios. Additionally, large doses of vitamin C may become oxidative in the presence of large doses of iron, subsequently impeding absorption.[31]

Adrenal health/stress management

The central nervous system contains large concentrations of vitamin C where it assists with stress adaptation via its role in adrenal hormone synthesis. Exposure to stress has been shown to influence the metabolism of vitamin C, whereby human adrenal glands secrete vitamin C in response to adrenocorticotropin hormone (ACTH),[32] however, supplementation with vitamin C appears to blunt cortisol secretion triggered by ACTH.[33] Interestingly, high-dose sustained-release vitamin C (1000 mg/t.i.d.) for 14 days has been shown to attenuate anxiety and blood pressure in response to acute psychological stress when compared to placebo.[34]

Collagen formation

Vitamin C supports wound healing by promoting the proliferation of dermal fibroblasts as well as the biosynthesis of connective tissue such as collagen. Additionally, vitamin C facilitates tensile strength to newly formed collagen allowing it to stretch, thus preventing the tearing of tissue.[35]

RESEARCH HIGHLIGHT:

- In individuals with diabetic foot ulcers, vitamin C (as ascorbic acid) (500 mg/day for 8 weeks) was shown to increase wound healing compared to controls. The vitamin C group recorded no amputations compared to 5 amputations seen in the control group.[36]
- A 2021 single blind RCT observed that 600 mg/day of vitamin C taken for 2 weeks sped up wound healing associated with dental extraction, with reduced socket depth observed in the vitamin C group compared to the controls.[37]

PERFECT PAIRINGS

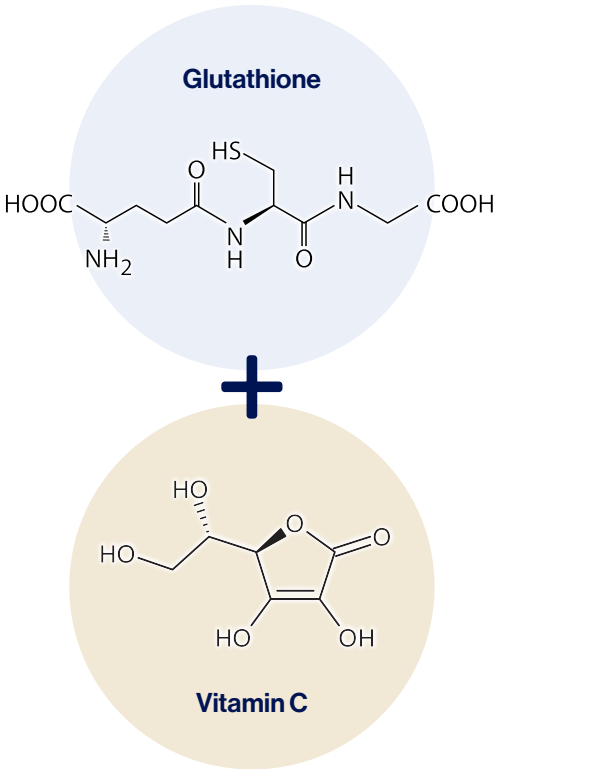
Bioflavonoids

The benefits of vitamin C are enhanced when used in combination with bioflavonoids compared to the use of vitamin C alone.[38]

Glutathione regeneration: prescribing vitamin C and glutathione together

As powerful antioxidants, both vitamin C and glutathione play an important role in cellular antioxidant defence systems. Both antioxidants appear to augment each other, assisting with the transformation from their reduced forms and the recycling of one another.[39] Supplementation with vitamin C has been shown to increase plasma glutathione levels, enhancing antioxidant activity. Deficiency of either vitamin C or glutathione appears to impede the action of the other.[39]

Figure 2. The combination of glutathione and vitamin C and their combined, additive effect[32]



SAFETY CONSIDERATIONS:

- Vitamin C is generally well tolerated when used at low doses.[40]
- Vitamin C 5–10 g/day orally may produce transient osmotic diarrhea.[41]
- There is conflicting data regarding increased risk of oxalate containing kidney stones with use of vitamin C, however at low doses this is unlikely to occur.[42]

SUMMARY

Vitamin C is an essential nutrient with immune supportive roles. Vitamin C plays a pivotal role in the production of neurotransmitters, collagen production, as well as being a cofactor in various enzymes responsible for energy production.

Sub-optimal levels of vitamin C appear to be relatively common and should be screened for and corrected to assist with optimal client health.

References

1. Carità AC, et al. Vitamin C: One compound, several uses. Advances for delivery, efficiency, and stability. Nanomedicine. 2020 Feb;24:102117.
2. Eat For Health.gov.au, Vitamin C (Internet). Available from:https://www.eatforhealth.gov.au/nutrient-reference-values/nutrients/vitamin-c
3. Plevin D & Galletly C. The neuropsychiatric effects of vitamin C deficiency: a systematic review. BMC Psychiatry. 2020 Jun 18;20(1):315.
4. Vitamin C RCPA Pathology Manual (Internet). Available from: https://www.rcpa.edu.au/Manuals/RCPA-Manual/Pathology-Tests/V/Vitamin-C#:~:text=Reference%20Interval%3A,(may%20vary%20by%20laboratory).
5. Bhattacharyya P, et al. Serum vitamin C status of people in New South Wales: retrospective analysis of findings at a public referral hospital. Med J Aust. 2023 Nov 20;219(10):475-481.
6. Gunton JE, Girgis CM, Lau T, Vicaretti M, Begg L, Flood V. Vitamin C improves healing of foot ulcers: a randomised, double-blind, placebo-controlled trial. Br J Nutr. 2021 Nov 28;126(10):1451-1458. doi: 10.1017/S0007114520003815. Epub 2020 Sep 28. PMID: 32981536.
7. Plevin D & Galletly C. The neuropsychiatric effects of vitamin C deficiency: a systematic review. BMC Psychiatry. 2020 Jun 18;20(1):315
8. Munday MR et al. A Pilot Study Examining Vitamin C Levels in Periodontal Patients. Nutrients. 2020 Jul 28;12(8):2255
9. Carr AC & Rowe S. Factors Affecting Vitamin C Status and Prevalence of Deficiency: A Global Health Perspective. Nutrients. 2020 Jul 1;12(7):1963.
10. Bhardwaj RL, et al. An Alarming Decline in the Nutritional Quality of Foods: The Biggest Challenge for Future Generations' Health. Foods. 2024 Mar 14;13(6):877
11. Lee E, et al. Vitamin C and glutathione supplementation: a review of their additive effects on exercise performance. Phys Act Nutr. 2023 Sep;27(3):36-43.
12. Gunton JE, Bechara N. Vitamin C insufficiency in Australia: underrated and overlooked? Med J Aust. 2023 Nov 20;219(10):463-464
13. Yosaee S, et al. The effect of vitamin C supplementation on mood status in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Gen Hosp Psychiatry. 2021 Jul-Aug;71:36-42.
14. Plevin D & Galletly C. The neuropsychiatric effects of vitamin C deficiency: a systematic review. BMC Psychiatry. 2020 Jun 18;20(1):315.
15. Doseděl M et al. On Behalf Of The Oemonom. Vitamin C-Sources, Physiological Role, Kinetics, Deficiency, Use, Toxicity, and Determination. Nutrients. 2021 Feb 13;13(2):615.
16. Loganathan V, et al. Treatment efficacy of vitamin C or ascorbate given as co-intervention with iron for anemia - A systematic review and meta-analysis of experimental studies. Clin Nutr ESPEN. 2023 Oct;57:459-468.
17. Maxfield L, et al. Vitamin C Deficiency. [Updated 2023 Nov 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493187/
18. Doseděl M, et al. On Behalf Of The Oemonom. Vitamin C-Sources, Physiological Role, Kinetics, Deficiency, Use, Toxicity, and Determination. Nutrients. 2021 Feb 13;13(2):615.
19. Padayatty SJ, et al. Human adrenal glands secrete vitamin C in response to adrenocorticotrophic hormone. Am J Clin Nutr. 2007 Jul;86(1):145-9.
20. Gordon BL, et al. Prevalence and factors associated with vitamin C deficiency in inflammatory bowel disease. World J Gastroenterol. 2022 Sep 7;28(33):4834-4845.
21. Dunleavy KA, et al. Vitamin C Deficiency in Inflammatory Bowel Disease: The Forgotten Micronutrient. Crohns Colitis 360. 2021 Feb 23;3(1):otab009.
22. Cerullo G, et al. The Long History of Vitamin C: From Prevention of the Common Cold to Potential Aid in the Treatment of COVID-19. Front Immunol. 2020 Oct 28;11:574029.
23. Padayatty SJ & Levine M. Vitamin C: the known and the unknown and Goldilocks. Oral Dis. 2016 Sep;22(6):463-93.
24. Plevin D & Galletly C. The neuropsychiatric effects of vitamin C deficiency: a systematic review. BMC Psychiatry. 2020 Jun 18;20(1):315.
25. Carr AC, Maggini S. Vitamin C and Immune Function. Nutrients. 2017 Nov 3;9(11):1211
26. Bozonet SM, et al. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich SunGold kiwifruit. Nutrients (2015) 7:2574–88.
27. Yingcharoenthana, S. et al. A split-mouth randomized clinical trial to evaluate the effect of local and systemic administration of vitamin C on extraction wound healing. J. Oral Sci. 2021, 63, 198–200
28. Loganathan V, et al. Treatment efficacy of vitamin C or ascorbate given as co-intervention with iron for anemia - A systematic review and meta-analysis of experimental studies. Clin Nutr ESPEN. 2023 Oct;57:459-468.
29. Low, M. et al. Daily iron supplementation for improving anaemia, iron status and health in menstruating women. Cochrane Database of Systematic Reviews 2016, Issue 4, No:CD009747
30. Hurrell R. How to ensure adequate iron absorption from iron-fortified food. Nutr. Rev. 2002;60:S7–S15.
31. Crawford C, et al. Select Dietary Supplement Ingredients for Preserving and Protecting the Immune System in Healthy Individuals: A Systematic Review. Nutrients. 2022 Nov 1;14(21):4604.
32. Padayatty SJ & Levine M. Vitamin C: the known and the unknown and Goldilocks. Oral Dis. 2016 Sep;22(6):463-93.
33. Moritz, B., et al. The role of vitamin C in stress-related disorders. J Nutr Biochem. 2020 Nov;85:108459
34. Brody S, et al. A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress. Psychopharmacology (Berl). 2002 Jan;159(3):319-24
35. Bechara N, et al. A Systematic Review on the Role of Vitamin C in Tissue Healing. Antioxidants (Basel). 2022 Aug 19;11(8):1605.
36. Gunton, J.E. et al. Vitamin C improves healing of foot ulcers: A randomised, double-blind, placebo-controlled trial. Br. J. Nutr. 2021, 126, 1451–1458
37. Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two Faces of Vitamin C-Antioxidative and Pro-Oxidative Agent. Nutrients. 2020 May 21;12(5):1501.
38. Murray, M. 81 - Flavonoids — Quercetin, Citrus Flavonoids, and Hydroxyethylrutosides (Pg 613-619.e2) in Pizzorno, J. & Murray, M. (2020) Textbook of Natural Medicine (5th Ed.) Churchill-Livingstone
39. Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA. 1999 Apr 21;281(15):1415-23
40. Olczak-Pruc M, et al. Vitamin C Supplementation for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. Nutrients. 2022 Oct 10;14(19):4217.
41. Doseděl M, et al. On Behalf of The Oemonom. Vitamin C-Sources, Physiological Role, Kinetics, Deficiency, Use, Toxicity, and Determination. Nutrients. 2021 Feb 13;13(2):615
42. Chmiel JA, Stuivenberg GA, Al KF, Akouris PP, Razvi H, Burton JP, Bjazevic J. Vitamins as regulators of calcium-containing kidney stones - new perspectives on the role of the gut microbiome. Nat Rev Urol. 2023 Oct;20(10):615-637.