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Vitamin C: Is it Relevant or Obsolete in the Modern Era?

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Abstract

Purpose In this review, we discuss the historic background of vitamin C, vitamin C's physiology, its dietary sources, and how deficiency can manifest. We also discuss modern studies investigating the role of Vitamin C in immunity, in cardiovascular disease, and in chronic conditions.

Summary In the body, vitamin C acts as an essential cofactor in several enzymatic reactions including, but not limited to, neurotransmitter synthesis, hormone amidation, collagen synthesis, hypoxic transcription factor modification, and epigenetic modifications. Scurvy, caused by severe vitamin C deficiency, is an infamous disease recorded in historical documents, with patients presenting with joint ache, bleeding gums, depression, and hysteria. Since humans are unable to naturally synthesize ascorbic acid, they must rely on dietary sources such as fruits and vegetables in order to maintain their vitamin C levels and avoid such manifestations. Maintaining stable vitamin C levels remains increasingly important in the modern era, particularly for the vulnerable pediatric patient with chronic conditions or critical illness. Regulating vitamin C levels could decrease morbidity and mortality in the chronic and critically ill pediatric population. Moving forward, there is a need for more head-to-head trials pertaining to vitamin C's role in improving immunity, modifying cardiovascular risk, and altering cancer prognosis.

Keywords Vitamin C · Scurvy · Nutritional deficiency

Historic Perspective on Vitamin C

Vitamin C is an important water-soluble vitamin; a deficiency of vitamin C causes scurvy. Scurvy, a term originating from the Latin word "scorbutus," French "scorbut," and German "skorbut," is a condition thought to have historically affected millions [1]. Though recognized due to its effect on sailors, scurvy also affected many individuals in the Great Potato Famine in Ireland as well as several large armies in Europe returning from months of intercontinental voyage or warfare [2]. Those afflicted by scurvy described lethargy, gum rotting, joint ache, and death. Furthermore, those with scurvy have experienced depression, hysteria, and other psychological issues. Historian Stephen Bown described the cure to scurvy as a "vital factor determining the destiny of nations" [3]. James Lind, a Scottish physician in the eighteenth century is credited with initiating the search for a cure to scurvy. In a first of its kind research study, a controlled trial, he evaluated six different treatments, including sulfuric acid, for 12 different sailors with scurvy, of which oranges and lemons were the only effective treatments for scurvy [4]. While Lind was able to elucidate that fresh fruits and vegetables cured scurvy, he was not able to identify the specific agent responsible for the cure. In 1928, Hungarian scientist Albert Gyorgyi isolated a reducing agent from the adrenal glands that he named hexuronic acid; later, it was revealed to be the same as vitamin C [5].

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Physiology of Vitamin C

Lifecycle of Vitamin C

Vitamin C (ascorbic acid) acts primarily by donating electrons to other molecules, and hence predominantly acting

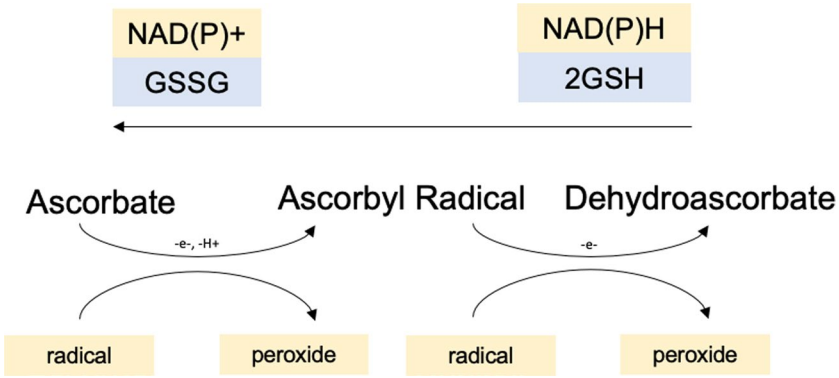

Fig. 1 Vitamin C Redox States

as a reducing agent. Although frequently referred to as an antioxidant, it is also able to reduce metals such as iron and copper to generate various reactive oxidant species. When ascorbate loses an electron, the first product is the ascorbyl radical which, unlike other radical species, can last seconds to minutes depending on the presence of oxygen or other electron acceptors. When another electron is lost, a more stable dehydroascorbic acid (DHA) is formed, which has an affinity for glucose transporters (GLUTs) and can be transported by them. DHA also has a half-life in the range of minutes due to hydrolytic ring rupture. Once the ring has ruptured, neither DHA, the ascorbyl radical nor ascorbate can be remade (Fig. 1) [2, 6, 7].

Vitamin C Transport

Sodium-dependent vitamin C Transporter (SVCT) 1 and 2 transport vitamin C throughout the body. SVCT1 is found in the intestines, renal tubules, skin, lungs, and liver. SVCT1 knockout mice were found to lose significant amounts of vitamin C via the urine compared to wild type mice. However, SVCT1 knockout mice were found to still absorb vitamin C and a structural analog in the intestine, suggesting that there are other transporters facilitating intestinal absorption of vitamin C as well [8]. SVCT2 is widely distributed; SVCT2 knockout mice were found to die within a few minutes of birth with fetal tissue expressing low vitamin C concentrations in all tissues [9].

In-vitro studies suggest that DHA, the product of ascorbate oxidation, can be transported by GLUTs. Structurally, DHA can reversibly form a hemiketal structure that resembles glucose. Once transported, DHA can be reduced back to ascorbate; this process is often known as ascorbate recycling. In-vitro cell models suggest that DHA conversion to ascorbate could be the primary pathway for ascorbate accumulation. However, our understanding of DHA and GLUTs in vivo is limited. Considering SVCT2 knockout mice who are dependent on placental vitamin C transport die at birth, it is more likely that DHA transport via GLUT transporters is a salvage pathway rather than a primary pathway for transport; however, mice and humans may also have different pathways for vitamin C absorption [2].

Vitamin C Absorption, Storage, Tissue Distribution, and Excretion

Vitamin C absorption primarily occurs in the distal ileum, reaching maximum levels 2–3 h after ingestion. The average vitamin C level among healthy adults is between 40 and 65 micromolar [10]. Most vitamin C absorption occurs via ascorbate transporters; there may be, however, some passive diffusion at low pH levels in the upper GI tract since vitamin C is not ionized at low pH levels. Vitamin C is most frequently transported via SVCT1, although DHA may also be transported by GLUT2 in specific regions such as the neurons, then reduced to ascorbate. Since vitamin C is water-soluble, it is then distributed throughout the extracellular space. Tissues accumulate vitamin C, likely with the help of SVCT2. The brain, liver, and skeletal muscle accumulate a majority of the body's vitamin C. Since vitamin C is water soluble, it cannot be easily stored in the body. On average, adults have 1.2–2 g of vitamin C in the body provided that they consume adequate amounts of vitamin C. Vitamin C in the adult body has a half life of 10–20 days; thus, regular supplementation is crucial [11, 12]. There is minimal pediatric data on half-life of vitamin C storage; our general assumption is that pediatric stores last the same duration.

Red blood cells (RBCs) get vitamin C through the dehydroascorbic acid pathway. Progenitor erythroid cells have SVCT2 transporters that are lost during maturation; therefore circulating RBCs do not have any known vitamin C transporters. RBCs obtain ascorbate via transport of small amounts of DHA on glucose transporters, after which DHA is immediately reduced via glutaredoxin or via glutathione [2].

Thus far, the mechanism of efflux of vitamin C is unknown. Although, radioactive studies show that most of the vitamin C is eliminated by the kidney, less than 1% is excreted via feces. Since SVCT1 knockout mice had high levels of vitamin C in the urine, it is possible that this transporter plays a role in reabsorption at the brush border of the proximal tubule.

Additionally, there may be minimal passive diffusion in the setting of low urine pH [10]. Other products that are excreted with vitamin C include DHA and oxalic acid. Previous studies demonstrate that 40% of adult subjects who were given 2000 mg/day of vitamin C had over a 10% increase in oxalate excretion, thus increasing their risk of kidney stone formation. In individuals at risk for nephrolithiasis, limiting additional vitamin C supplementation is appropriate [13].

Physiologic Roles of Vitamin C

Vitamin C acts as an electron donor for 15 mammalian enzymes. In the nervous system, it is essential to dopamine beta-hydroxylase activity. This enzyme is found in neurosecretory vesicles and adrenal chromaffin granules and is essential to norepinephrine synthesis. Vitamin C also plays a role in enzymatic reactions involving peptidylglycine alpha-amidating monooxygenase, which is needed to amidate many peptide hormones, including hypothalamic and gastrointestinal hormones such as calcitonin, oxytocin, cholecystokinin, and gastrin-releasing peptide.

Vitamin C also catalyzes post-translational modifications of collagen to produce structurally normal collagen by acting as a cofactor in enzymatic reactions involving prolyl and lysyl hydroxylation. Historic accounts of vitamin C deficiency frequently note poor wound healing, gum bleeds and teeth loosening, as collagen provides structural strength to connective tissue. Specifically, vitamin C maintains iron in the reduced ferrous (Fe^{2+}) state that is needed for enzyme activity [4]. The initially produced pre-collagen is made in the endoplasmic reticulum of the cell and consists of amino acid proline repeats. Vitamin C is essential in converting proline into 3- or 4- hydroxyproline and in converting lysine to hydroxylysine. This hydroxylation is needed to form stable triple-helix structures of collagen that will then be transported into the Golgi apparatus and ultimately secreted via secretory granules. Without hydroxylation, procollagen secretion decreases and degradation is expedited. Independent of hydroxylation, vitamin C may also independently stimulate collagen synthesis [14, 15].

Vitamin C is also involved in hydroxylation of proline in hypoxia-inducible factor-1 alpha (HIF-1a), a transcription factor involved in oxygen sensing in multicellular animals. Of note, the alpha subunit of the enzyme is oxygen-regulated while the beta subunit is constitutively expressed. When oxygen tension is normal, HIF-1a is hydroxylated at specific proline and asparagine residues and the hydroxylated version of the factor is targeted for proteasome degradation. HIF-1a is negatively regulated by factor inhibiting HIF (FIH), an asparaginyl hydroxylase that also requires ascorbate. In-vitro studies show that FIH is necessary for electron donation and hydroxylation of asparagine and aspartate residues on HIF-1a [2, 16, 17].

Ascorbic acid is also required for tyrosine catabolism, particularly as a cofactor in the step involving the p-hydroxyphenyl-pyruvic hydroxylase [18]. Lysine, methionine, and multiple hydroxylases are required for carnitine biosynthesis and fatty acid transport. In-vitro studies have revealed that the hydroxylases require a reductant, of which ascorbic acid is the most optimal [2]. In DNA methylation and histone modification, vitamin C acts at the catalytic domain of ten-eleven translocation (TET) proteins which are involved in locus-specific DNA methylation reversal and Jumonji C-domain-containing histone demethylases (JHDM) [19]. Ascorbic acid is also able to increase iron levels by providing electrons to transmembrane enzymes of the cytochrome b_{561} class. As a result, non-heme iron in the gut is reduced and can be taken up across the duodenal enterocyte by ferrous-iron transporters [20]. Other roles of ascorbic acid include reduction of reactive oxygen species, thereby acting as scavengers during mitochondrial oxidative metabolism [19]. Enzymatic cofactor roles of vitamin C have been further summarized in Table 1.

Sources of Vitamin C

In contrast to all plants and most animals, humans cannot synthesize ascorbic acid. In humans, the gulonolactone oxidase gene that is involved in the ascorbic acid synthesis pathways has been mutated such that it is no longer functional [2, 10, 21]. As a result, humans are entirely dependent to obtain vitamin C from their diet. Vitamin C in the diet primarily comes from fruits and vegetables (Table 2). Since liver and fish eggs are the most vitamin C-heavy contributions from animals and these food sources are less commonly consumed, animal sources do not contribute much to dietary vitamin C. Among fruits that are common in the western diet, guava, kiwi, and strawberry are good sources of vitamin C. Citrus fruits contain a lower but sufficient amount of vitamin C [10, 22–24]. Boiling vegetables decreases the vitamin C content in vegetables since high pH and high temperature environments cause decomposition of vitamin C. Meanwhile, frying vegetables does not cause a similar amount of vitamin C leaching. Steaming can relatively preserve vitamin C levels compared to boiling. To minimize instability, the ideal storage of vitamin C involves rapid thermal inactivation followed by rapid cooling. In children, breast milk provides an adequate source of ascorbic acid for newborns and infants.

Vitamin C Deficiency and its Manifestations

Defining optimal vitamin C status has been a challenge amongst the scientific community. The Recommended Dietary Allowance (RDA) for vitamin C has most recently been

Table 1 Physiologic Functions of Vitamin C

Enzyme	Enzyme Function
Dopamine B-hydroxylase	Norepinephrine Synthesis
Peptidyl-glycine a-amidating monooxygenase	Peptide Hormone Amidation
Collagen Prolyl 4-hydroxylase Collagen Prolyl 3-hydroxylase Pro-collagen lysine 2-oxoglutarate 5-dioxygenase	Collagen Synthesis and Maturation
Prolyl Hydroxylase Domain-Containing Proteins Factor Inhibiting HIF	HIF-1a Hydroxylation and Regulation
4-Hydroxyphenylpyruvate Dioxygenase	Tyrosine Metabolism
Jumonji-C domain Histone Demethylase Lysine Demethylases	Histone Demethylation
Alkylated DNA Repair Protein AlkB Homologs Fat-Mass and Obesity Associated Protein	DNA/RNA Demethylation
Myc-induced Nuclear Antigen 53 Nucleolar Protein 66	Ribosome Hydroxylation
Ten-Eleven Translocases (TETs)	Cytosine Demethylation
Trimethyllysine hydroxylase Gamma-Butyrobetaine hydroxylase	Carnitine Synthesis

Table 2 Dietary Sources of Vitamin C

Sources of Vitamin C
Kakadu Plum[a]
Camu-camu[a]
Bilimbi[a]
Acerola
Star Fruit
Sea Buckthorn
Guava
Cashew Apple
Emblic
Rose Hip
Sauerkraut
Black Currant
Red Pepper[b]
Kale[b]
Chive[b]
Coriander[b]
Broccoli[b]
Kiwi[b]
Parsley[b]
Strawberry[b]
Orange[b]
Lemon[b]
Potato[c]

[a] Best Natural Sources of vitamin C

[b] Best Commonly Available Sources of vitamin C

[c] Given availability and frequency of consumption, potatoes contribute significantly to vitamin C intake

defined as 90 mg/day for men and 75 mg/day for women [25]. The pediatric RDA is 15–45 mg for children up to 13 years and 65–75 mg for children of age 14–18 years [25, 26]. Vitamin C intake and storage can be measured through both plasma and leukocyte levels. There is still significant debate regarding which levels to measure. While plasma ascorbate levels are easier to measure, require a small amount of plasma, and reflect recent vitamin C intake, plasma ascorbate levels may not reflect accurate body stores of ascorbic acid as measured by leukocyte ascorbate levels [27]. Clinical manifestations of scurvy, a prolonged and severe form of vitamin C deficiency, are seen among those with plasma vitamin C concentrations below 0.2 mg/dL or 11.4 umol/L (reference range: 23–114 umol/L). These patients commonly present with the following: collagen abnormalities that manifest as loss of teeth due to modified dentine production; vessel wall damage and bleeding that manifest through petechiae; ecchymoses and perifollicular hemorrhage; and skin and bone abnormalities due to abnormal keratin production, inability of osteoblasts to produce the osteoid seam, and alterations in the transcriptional profile of the bone [26, 28]. Skeletal findings among patients with low vitamin C levels include increased bone pain, skeletal fragility, and bone fractures [28, 29]. In infants, periostitis leads to pseudo paralysis. Radiographic findings of scurvy include the Frankel sign (dense line at the end of metaphyses from increased width at the zone of provisional calcification), Wimberger ring sign (circular calcification at the epiphyseal center of ossification), scorbutic rosary (costochondral junction expansion), and Pelkin spurs (metaphyseal spurs) and fractures [30]. Since vitamin C is essential to neurotransmitter production and cortical neurons are highly susceptible to oxidative stress, many individuals with scurvy also present with psychological

symptoms including depression and cognitive impairment as well as pseudoparalysis [27, 31]. Additionally, since vitamin C hydroxylation is required for carnitine production, one of the first manifestations that patients with vitamin C deficiency recognize is low energy and muscle ache in the setting of not being able to transport long chain fatty acids into the mitochondrial matrix [26].

While frequently associated with historical accounts, vitamin C deficiency is a modern concern as well, even in resource-rich nations. In fact, there are several reports of scurvy being either misdiagnosed or delayed in diagnosis in modern literature. Often, there are clues available in the diet history including lack in consumption of fresh fruits and vegetables in their diets [32]. Additionally, individuals who smoke cigarettes and those with chronic hyperglycemia in the setting of diabetes or high stress conditions, such as sepsis, tend to present with symptoms of vitamin C deficiency [33]. Others who are commonly affected by deficiency include those who have recently received stem cell transplantation, patients with anorexia nervosa, and patients with chronic conditions who require long-term tube feeds [34–37].

Even among children, scurvy affects certain subsets of the population. Particularly at-risk populations include: critically ill children; asthmatics; children with intestinal failure and short bowel syndrome; autism spectrum disorder; global developmental delays and genetic syndromes associated with feeding difficulties; those requiring enteral/parenteral nutrition; and those with iron overload from repeat transfusions (i.e. sickle cell or thalassemia patients, and those with a history of chemotherapy) [38]. Critically ill children are particularly at risk of vitamin C deficiency. A recent prospective single-center observational study of children with congenital heart disease demonstrated decreases in vitamin C levels postoperatively following cardiopulmonary bypass [39]. In a 2022 study comparing vitamin C levels within 24 hours of admission in a group of Pediatric Intensive Care Unit (PICU) patients to vitamin C levels among pediatric patients in an outpatient procedure room, 18% of PICU patients displayed vitamin C deficiency compared to 0% in the noncritical group [40]. In a 2024 study of critically ill children who were evaluated for sepsis, vitamin C levels and severity of Sequential Organ Failure Assessment (SOFA) score were inversely correlated [41]. Children with severe asthma and airway obstruction have also been found to have vitamin C deficiency [42]. A recent case–control study of children with transfusion dependent B- thalassemia demonstrated significantly lower plasma vitamin C levels in participants with transfusion-dependent thalassemia compared to the control group. Higher serum ferritin levels inversely correlated with vitamin C levels in accordance with the hypothesis that vitamin C is destroyed through oxidation by ferric iron. Supplementation of vitamin C in participants with low vitamin C resulted in decreased malondialdehyde (MDA) oxidant levels, further enforcing the antioxidant role of vitamin C [43]. Children with these risk factors should be considered for periodic screening [38].

Vitamin C Supplementation

Per the National Institutes of Health (NIH), the recommended daily allowance of vitamin C is 90 mg in adult men and 75 mg in adult women. In pregnant women, the recommended amount is 85 mg per day. In breastfeeding women, the recommended daily intake is 120 mg. For male teens, the recommended daily intake of vitamin C is 75 mg and for female teens, the recommended intake is 65 mg per day. Children 9–13 years of age should receive 45 mg of vitamin C daily, those 4–8 years should receive 25 mg and from 1–3 years of age should receive 15 mg of vitamin C daily. Infants below 6 months should consume 40 mg of vitamin C daily while those between 7 and 12 months should receive 50 mg daily. Individuals who smoke should increase their total daily recommended amount by 35 mg[25].

There is no good consensus on vitamin C dosing in the setting of significant vitamin C deficiency. The dosing suggestions below are based on our center's standard of practice formulated after thoughtful considerations. For vitamin C supplementation in the setting of deficiency in high risk infants, we propose that neonates (birth to 28 days) may receive 50 mg of vitamin C orally daily or intravenously (IV) as indicated. Premature infants may receive 25 mg of vitamin C orally daily or IV. Beyond the neonatal/infantile status, patients under 10 kg are advised to receive 125 mg vitamin C orally daily or 75 mg IV vitamin C daily. Those between 10 and 39.9 kg may receive 250 mg vitamin C BID orally or 250 mg IV daily. Individuals above 40 kg should receive 500 mg vitamin C orally twice daily or 500 mg IV vitamin C daily. We recommend that all doses be adjusted based on follow up levels and that levels be rechecked 2–4 weeks after starting supplementation. IV vitamin C can interfere with bedside glucose estimation by finger stick secondary to its oxidative mechanism and thereby falsely elevating sugar reading. Extremely low vitamin C levels may have very poor prognostic implications and we recommend due attention, intervention and follow up of the lab result.

There has been significant debate regarding the negative consequences of excess vitamin C intake; particularly, there are mixed results regarding the association between high vitamin C levels and kidney stone development since one of the metabolites of vitamin C is oxalate [44, 45].

Implications of Vitamin C in the Modern Era

Vitamin C and Immunity

There is some data supporting vitamin C decreasing both the severity and duration of cold symptoms. Specifically,

vitamin C destroys the imidazole ring of histamine, acting as an antihistamine and enhancing the body's immune response. Studies have shown that after 2 weeks of vitamin C at 2 g/day, in vivo plasma histamine levels decrease by 40% [46]. There are no current clinical recommendations supporting the possibility of vitamin C significantly decreasing the risk of respiratory infections in a well-nourished general population, although there is some data supporting this role in athletes/military people or subjects with a low plasma vitamin C [47]. In those with high risk of infection, including people with obesity, diabetes, and the elderly, vitamin C can modulate inflammation with positive effects on immune response. Furthermore, in patients hospitalized with COVID-19, there continue to be ongoing trials pertaining to the role of IV vitamin C therapy in improving their condition [48]. More head-to-head studies are required in these settings and vitamin C supplementation does not negate the need for specific treatments for individual disease states mentioned above.

Vitamin C in Cardiovascular Disease

In a prospective population-based study in Norfolk, United Kingdom, increasing plasma ascorbic acid concentration was independently associated with decreased overall mortality, as well as risk of cardiovascular and ischemic heart disease [49]. NHANES data from the United States showed that for a 0.5 mg/dL rise in plasma vitamin C, the prevalence of coronary artery disease and stroke decreased by 11% [50]. While there is some consensus on increased levels of vitamin C being associated with decreased mortality, there continues to be debate regarding the role of vitamin C supplementation. Mechanistically, vitamin C may decrease cardiovascular disease risk by preventing endothelial dysfunction. Its actions are multifold: it scavenges reactive oxygen species, prevents leukocyte adhesion to endothelial cells in the setting of oxidized LDLs, and increases flow-dependent vasodilation in patients with CAD and in smokers [10, 51, 52]. Major clinical trials such as the Physicians Health Study II which evaluated the role of 500 mg/day of ascorbic acid in healthy males showed no effect on major cardiovascular events after 8 years of supplementation [53]. However, other studies investigating specific markers of cardiovascular health such as arterial stiffness, endothelial dysfunction, and blood pressure showed improvements in endothelial function and reduced systolic and diastolic blood pressure in participants who received vitamin C supplementation [54, 55].

Vitamin C and Chronic Conditions

In patients (median age: 17.5 years) with unique conditions such as chronic graft versus host disease (cGVHD) with mucous membrane involvement who were found to be vitamin C deficient and who did not respond to cGVHD treatment, 2000 mg of daily vitamin C by mouth improved mucositis and consequently their ability to eat [34]. In cancer patients, increased vitamin C intake has been associated with lower occurrence of several GI cancers, including pharyngeal, oral cavity, esophageal, and stomach cancers. Particularly, its antioxidant properties may limit molecular damage that would traditionally promote carcinogenesis. Vitamin C is present at high concentrations in gastric juice, protecting the gastric mucosa from reactive oxygen species. Helicobacter pylori infection (H. pylori) has been associated with gastric adenocarcinoma. H. pylori can significantly reduce or even eradicate vitamin C levels in gastric juice. In-vitro studies indicate that vitamin C can induce cell growth inhibition and cell cycle arrest in gastric cancer cells affected by H. pylori [56].

Clinical trials have mixed results regarding the benefit of vitamin C supplementation in cancer prevention and reduction. While in the 1970s, physicians used high dose ascorbate for cancer treatment, two large double-blind randomized controlled trials did not note any benefit from ascorbate [57–59]. Furthermore, in patients undergoing cancer treatment, there has been significant debate regarding whether antioxidants like vitamin C scavenge the reactive oxygen species that are needed for certain chemotherapeutic activity. Alternatively, there is a question of whether antioxidants can decrease the toxicity of chemotherapeutics, thus allowing patients to undergo longer treatment with higher chemotherapy doses [60]. Newer studies investigate the role of high-dose IV ascorbate as a synergistic cytotoxic agent alongside chemotherapy agents that, together, kill cancer cells. Specifically, mice in preclinical models of pancreatic cancer that were treated with a combination of gemcitabine and ascorbate had consistent inhibition of growth compared to mice who were only treated with gemcitabine. This preclinical model suggests a potentially significant role for ascorbate treatment as an adjunct treatment for cancers with high failure rates with conventional therapies [61].

Conclusion

Vitamin C is a water-soluble vitamin that plays a crucial role as an enzyme cofactor, reducing agent, and antioxidant. Humans must pay close attention to dietary intake of vitamin C as low vitamin C levels can manifest with bleeding, bone fractures, and neuropsychiatric manifestations. Particularly, physicians should have a high index of suspicion for low vitamin C levels in high-risk children. When assessing the pediatric patient, rather than looking solely for clinical signs of deficiencies, their chronic disease state should be considered. While more studies need to be completed on the pediatric patient to define normative

distribution data and optimal dosing practices, we call to question the morbidity and mortality for those children with vitamin and mineral compromise. Moving forward, more head-to-head studies must be performed to better reveal the role of vitamin C in boosting immunity and improving cardiovascular disease and cancer management.

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Author contributions SR- wrote the main manuscript, as well as tables and figures and worked on revisions.
SY- helped with manuscript, reviewing and editing.
AR- Reviewing and editing.
SB- Reviewing and editing.
KR- Conceptualizing the manuscript, working on the outlines, reviewing, editing and revising.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Carpenter KJ. The discovery of vitamin C. Ann Nutr Metab. 2012;61(3):259–64. https://doi.org/10.1159/000343121.
2. Padayatty SJ, Levine M. INVITED MEDICAL REVIEW Vitamin C: the known and the unknown and Goldilocks. Oral Dis. 2016;22:463–93. https://doi.org/10.1111/odi.12446.
3. Price C, The Age of Scurvy, Distillations Magazine: Unexpected Stories from Science's Past.
4. Schlueter AK, Johnston CS, "Vitamin C: Overview and Update, https://doi.org/10.1177/1533210110392951.
5. Schlueter AK, Johnston CS. Vitamin C: Overview and Update. J Evid Based Complementary Altern Med. 2011;16(1):49–57. https://doi.org/10.1177/1533210110392951.
6. Corpe CP, Eck P, Wang J, Al-Hasani H, Levine M. Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. J Biol Chem. 2013;288(13):9092–101. https://doi.org/10.1074/jbc.M112.436790.
7. Buettner GR. The pecking order of free radicals and antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. Arch Biochem Biophys. 1993;300(2):535–43. https://doi.org/10.1006/abbi.1993.1074.
8. Corpe CP, et al. Vitamin C transporter Slc23a1 links renal reabsorption, vitamin C tissue accumulation, and perinatal survival in mice. J Clin Invest. 2010;120(4):1069–83. https://doi.org/10.1172/JCI39191.
9. Sotiriou S, et al. Ascorbic-acid transporter Slc23a1 is essential for vitamin C transport into the brain and for perinatal survival. Nat Med. 2002;8(5):514–7. https://doi.org/10.1038/0502-514.
10. Doseděl M, et al. Vitamin C-Sources, Physiological Role, Kinetics, Deficiency, Use, Toxicity, and Determination. Nutrients, 2021;13:2. https://doi.org/10.3390/nu13020615.
11. Naidu KA. Vitamin C in human health and disease is still a mystery? An overview. Nutr J. 2003;2:7. https://doi.org/10.1186/1475-2891-2-7.
12. Hellman L, Burns JJ. Metabolism of L-ascorbic acid-1-C14 in man. J Biol Chem. 1958;230(2):923–30.
13. Massey LK, Liebman M, Kynast-Gales SA. Ascorbate increases human oxaluria and kidney stone risk. J Nutr. 2005;135(7):1673–7. https://doi.org/10.1093/jn/135.7.1673.
14. Prockop DJ, Kivirikko KI. Collagens: molecular biology, diseases, and potentials for therapy. Annu Rev Biochem. 1995;64:403–34. https://doi.org/10.1146/annurev.bi.64.070195.002155.
15. Peterkofsky B. Ascorbate requirement for hydroxylation and secretion of procollagen: relationship to inhibition of collagen synthesis in scurvy. Am J Clin Nutr. 1991;54(6 Suppl):1135S-1140S. https://doi.org/10.1093/ajcn/54.6.1135s.
16. Yang M, et al. Asparagine and aspartate hydroxylation of the cytoskeletal ankyrin family is catalyzed by factor-inhibiting hypoxia-inducible factor. J Biol Chem. 2011;286(9):7648–60. https://doi.org/10.1074/jbc.M110.193540.
17. Yang M, et al. Factor-inhibiting hypoxia-inducible factor (FIH) catalyses the post-translational hydroxylation of histidinyl residues within ankyrin repeat domains. FEBS J. 2011;278(7):1086–97. https://doi.org/10.1111/j.1742-4658.2011.08022.x.
18. Robinson R, Warburton FG. Tyrosine Metabolism in Human Scurvy. Nature. 1966;212(5070):1605–1605. https://doi.org/10.1038/2121605a0.
19. Pavlovic V, Ciric M, Petkovic M, Golubovic M, Vitamin C and epigenetics: A short physiological overview, Open Med, 2023;18:1. https://doi.org/10.1515/med-2023-0688.
20. Lane D, Bae D-H, Merlot A, Sahni S, Richardson D. Duodenal Cytochrome b (DCYTB) in Iron Metabolism: An Update on Function and Regulation. Nutrients. 2015;7(4):2274–96. https://doi.org/10.3390/nu7042274.
21. Linster CL, Van Schaftingen E. Vitamin C. Biosynthesis, recycling and degradation in mammals. FEBS J. 2007;274(1):1–22. https://doi.org/10.1111/j.1742-4658.2006.05607.x.
22. Prakash A, Baskaran R. Acerola, an untapped functional superfruit: a review on latest frontiers. J Food Sci Technol. 2018;55(9):3373–84. https://doi.org/10.1007/s13197-018-3309-5.
23. Arihanan VN, Kalirajan K, Devi VN, Prasad P. An exotic fruit which forms the new natural source for Vitamin-C, Rasayan J Chem. 2012;5:3 356–359.
24. Williams DJ, et al. Organic acids in Kakadu plum (Terminalia ferdinandiana): The good (ellagic), the bad (oxalic) and the uncertain (ascorbic). Food Res Int. 2016;89(Pt 1):237–44. https://doi.org/10.1016/j.foodres.2016.08.004.
25. Vitamin D. Fact Sheet for Health Professionals, National Institutes of Health. Office of dietary supplements. 2019. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/Updated.
26. Trapani S, Rubino C, Indolfi G, Lionetti P, A narrative review on pediatric scurvy: The Last Twenty Years.," Nutrients, 2022;14:3. https://doi.org/10.3390/nu14030684.

27. Plevin D, Galletly C, The neuropsychiatric effects of vitamin C deficiency: a systematic review.," BMC Psychiatry, 2020;20 315. https://doi.org/10.1186/s12888-020-02730-w.
28. Thaler R, et al. Vitamin C epigenetically controls osteogenesis and bone mineralization., Nat Commun, 2022;13:1 5883. https://doi.org/10.1038/s41467-022-32915-8.
29. Chalouhi C, et al. Scurvy: A New Old Cause of Skeletal Pain in Young Children. Front Pediatr. 2020;8:8. https://doi.org/10.3389/fped.2020.00008.
30. Popovich D, McAlhany A, Adewumi AO, Barnes MM. Scurvy: forgotten but definitely not gone. J Pediatr Health Care. 2009;23(6):405–15. https://doi.org/10.1016/j.pedhc.2008.10.008.
31. Paul AJ, Pseudoparalysis secondary to Vitamin C deficiency: A Rare Presentation in a Toddler.," JBJS Case Connect, 2023;13:4. https://doi.org/10.2106/JBJS.CC.23.00313.
32. Thomas JM, Burtson KM, Scurvy: A Case Report and Literature Review., *Cureus*, 2021;13:4 e14312. https://doi.org/10.7759/cureus.14312.
33. Wei W, Kim Y, Boudreau N. Association of smoking with serum and dietary levels of antioxidants in adults: NHANES III, 1988–1994. Am J Public Health. 2001;91(2):258–64. https://doi.org/10.2105/ajph.91.2.258.
34. Kletzel M, Powers K, Hayes M. Scurvy: A new problem for patients with chronic GVHD involving mucous membranes; An easy problem to resolve. Pediatr Transplant. 2014;18(5):524–6. https://doi.org/10.1111/petr.12285.
35. Nannya Y, Shinohara A, Ichikawa M, Kurokawa M. Serial profile of vitamins and trace elements during the acute phase of allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2014;20(3):430–4. https://doi.org/10.1016/j.bbmt.2013.12.554.
36. Rasheed M, et al. Reduced plasma ascorbic acid levels in recipients of myeloablative conditioning and hematopoietic cell transplantation. Eur J Haematol. 2019;103(4):329–34. https://doi.org/10.1111/ejh.13287.
37. Huijskens MJAJ, Wodzig WKWH, Walczak M, Germeraad WTV, Bos GMJ. Ascorbic acid serum levels are reduced in patients with hematological malignancies. Results Immunol. 2016;6:8–10. https://doi.org/10.1016/j.rinim.2016.01.001.
38. Golriz F, Donnelly LF, Devaraj S, Krishnamurthy R. Modern American scurvy — experience with vitamin C deficiency at a large children's hospital. Pediatr Radiol. 2017;47(2):214–20. https://doi.org/10.1007/s00247-016-3726-4.
39. Al-Subu AM, et al. Risk of Hypovitaminosis and Vitamin C Deficiency in Pediatric Patients Undergoing Cardiopulmonary Bypass. Pediatr Cardiol. 2023;44(7):1487–94. https://doi.org/10.1007/s00246-023-03243-5.
40. Fathi A, Downey C, Rabiee Gohar A, Vitamin C Deficiency in Critically Ill Children: Prospective Observational Cohort Study., Pediatr Crit Care Med, 2022;23:5 395–398. https://doi.org/10.1097/PCC.0000000000002914.
41. McWhinney B, et al. Serum Levels of Vitamin C and Thiamin in Children With Suspected Sepsis: A Prospective Observational Cohort Study. Pediatr Crit Care Med. 2024;25(2):171–6.
42. Siripornpanich S, Chongviriyaphan N, Manuyakorn W, Matangkasombut P. Zinc and vitamin C deficiencies associate with poor pulmonary function in children with persistent asthma. Asian Pac J Allergy Immunol. 2022;40(2):103–10. https://doi.org/10.12932/AP-100620-0878.
43. Bhat KV, et al. Vitamin C Deficiency and Oxidant Levels in Children with Transfusion-Dependent B-Thalassemia. Indian Pediatr. 2021;58(7):631–4.
44. Chmiel JA, et al. Vitamins as regulators of calcium-containing kidney stones - new perspectives on the role of the gut microbiome. Nat Rev Urol. 2023;20(10):615–37. https://doi.org/10.1038/s41585-023-00768-5.
45. Fontana F, et al. Oxalate Nephropathy Caused by Excessive Vitamin C Administration in 2 Patients With COVID-19. Kidney Int Rep. 2020;5(10):1815–22. https://doi.org/10.1016/j.ekir.2020.07.008.
46. Johnston CS, Retrum KR, Srilakshmi JC. Antihistamine effects and complications of supplemental vitamin C. J Am Diet Assoc. 1992;92(8):988–9.
47. Peters EM, Goetzsche JM, Grobbelaar B, Noakes TD. Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners. Am J Clin Nutr. 1993;57(2):170–4. https://doi.org/10.1093/ajcn/57.2.170.
48. Hemilä H, Chalker E. Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. J Intensive Care. 2020;8:15. https://doi.org/10.1186/s40560-020-0432-y.
49. Khaw KT, et al. Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. European Prospective Investigation into Cancer and Nutrition. Lancet. 2001;357(9257):657–63. https://doi.org/10.1016/s0140-6736(00)04128-3.
50. Simon JA, Hudes ES, Browner WS. Serum Ascorbic Acid and Cardiovascular Disease Prevalence in U.S. Adults. Epidemiology. 1998;9(3):316–21.
51. Gokce N, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation. 1999;99(25):3234–40. https://doi.org/10.1161/01.cir.99.25.3234.
52. Motoyama T, et al. Endothelium-dependent vasodilation in the brachial artery is impaired in smokers: effect of vitamin C. Am J Physiol. 1997;273(4):H1644–50. https://doi.org/10.1152/ajpheart.1997.273.4.H1644.
53. Sesso HD, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2008;300(18):2123–33. https://doi.org/10.1001/jama.2008.600.
54. Juraschek SP, Guallar E, Appel LJ, Miller ER. Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2012;95(5):1079–88. https://doi.org/10.3945/ajcn.111.027995.
55. Ashor AW, Lara J, Mathers JC, Siervo M. Effect of vitamin C on endothelial function in health and disease: a systematic review and meta-analysis of randomised controlled trials. Atherosclerosis. 2014;235(1):9–20. https://doi.org/10.1016/j.atherosclerosis.2014.04.004.
56. Zhang Z-W, Abdullahi M, Farthing MJG. Effect of physiological concentrations of vitamin C on gastric cancer cells and Helicobacter pylori. Gut. 2002;50(2):165–9. https://doi.org/10.1136/gut.50.2.165.
57. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. N Engl J Med. 1985;312(3):137–41. https://doi.org/10.1056/NEJM198501173120301.
58. Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. Br J Cancer. 2001;84(11):1544–50. https://doi.org/10.1054/bjoc.2001.1814.
59. Du J, Cullen JJ, Buettner GR, Ascorbic acid: Chemistry, biology and the treatment of cancer, Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 2012;1826:2 443–457. https://doi.org/10.1016/J.BBCAN.2012.06.003.
60. Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. Cancer Treat Rev. 2007;33(5):407–18. https://doi.org/10.1016/j.ctrv.2007.01.005.

61. Espey MG, et al. Pharmacologic ascorbate synergizes with gemcitabine in preclinical models of pancreatic cancer. Free Radic Biol Med. 2011;50(11):1610–9. https://doi.org/10.1016/j.freeradbiomed.2011.03.007.