

## Review Article

## OPEN ACCESS

# What if it is just vitamin C deficiency? The role of vitamin C deficiency in musculoskeletal pain. Mechanisms, clinical implications, and therapeutic approaches

Wissem Soumia HADDAD<sup>1</sup>, Kamel REMITA<sup>2</sup>, Faten OMAR<sup>3</sup>

1. Consultant, physical medicine and rehabilitation clinic, Batna 05000, Algeria

2. Consultant, Rheumatology Clinic, Skikda 21000, Algeria

3. Specialist, Rheumatology Clinic, Doha, Qatar

### ABSTRACT

Subclinical vitamin C deficiency, while less apparent than scurvy, is increasingly recognized as a contributing factor to idiopathic musculoskeletal pain, yet it remains underdiagnosed in clinical settings. This review consolidates mechanistic and clinical evidence that links vitamin C insufficiency to dysfunction in joints, bones, and muscles, advocating for its integration into pain management protocols. A comprehensive literature analysis of peer-reviewed studies was conducted, focusing on the roles of vitamin C in collagen biosynthesis, antioxidant defense, and immunomodulation. Clinical trials, observational studies, and mechanistic research were evaluated to clarify associations with musculoskeletal symptoms and therapeutic outcomes. Vitamin C deficiency disrupts collagen stability, increases oxidative stress, and triggers pro-inflammatory cytokine cascades, leading to nonspecific myalgia, arthralgia, and delayed recovery. High-risk populations, including smokers, the elderly, bariatric surgery patients, and socioeconomically disadvantaged groups, are disproportionately affected. Repletion trials indicate that vitamin C supplementation can reduce pain and improve functional outcomes, supporting its therapeutic use. Clinicians should routinely screen for vitamin C deficiency in patients presenting with unexplained musculoskeletal pain, particularly among at-risk groups. Evidence-based supplementation, dietary modifications, and interdisciplinary collaboration are essential to address this reversible contributor to chronic pain. The prevalence of vitamin C deficiency remains a significant public health concern, with estimates suggesting that approximately 7% of the U.S. population is affected, based on NHANES data from 2003 to 2006 and 2017–2018. In India, the prevalence is notably higher, with 74% of adults in North India and 46% in South India exhibiting deficiency, with men showing a higher prevalence than women. Further research is necessary to establish causality and optimize dosing regimens to mitigate the burden of vitamin C deficiency on musculoskeletal health.

### ARTICLE HISTORY

Received 11 May 2025

Accepted 17 May 2025

### KEYWORDS

Vitamin C deficiency;  
musculoskeletal pain; collagen  
synthesis; oxidative stress;  
subclinical deficiency

### CORRESPONDING AUTHOR

Kamel REMITA  
kremita2001@yahoo.fr

## 1. INTRODUCTION

Vitamin C (ascorbic acid) is an essential micronutrient with pleiotropic roles in human physiology, including collagen biosynthesis, antioxidant activity, and immune regulation (1). As

a cofactor for prolyl and lysyl hydroxylases, it ensures the post-translational hydroxylation of collagen, a process critical for the structural integrity of connective tissues in joints, bones, and

muscles (2, 3). Historically associated with scurvy, a disease marked by haemorrhagic joints, impaired wound healing, and lethargy. Vitamin C deficiency is now recognized to manifest insidiously as subclinical insufficiency, particularly in vulnerable populations such as smokers, older adults, and individuals with chronic inflammatory or malabsorptive conditions (4,5).

The prevalence of vitamin C deficiency in the U.S. is approximately 7%, based on NHANES data from 2003 to 2006 and 2017–2018. (1) In India, vitamin C deficiency was observed in 74% of adults in North India and 46% in South India, with men showing higher prevalence than women. (6) Despite advancements in nutritional science, mild-to-moderate vitamin C deficiency is frequently overlooked in the differential diagnosis of chronic musculoskeletal pain. While scurvy's classic signs are rare, suboptimal vitamin C levels impair collagen crosslinking, exacerbate oxidative tissue damage, and perpetuate inflammatory cascades, culminating in nonspecific pain syndromes that mimic rheumatologic or degenerative disorders (6,7). This gap in clinical recognition deprives patients of low-risk, cost-effective interventions and underscores the need for heightened vigilance. This review aims to: elucidate the biochemical mechanisms by which vitamin C deficiency destabilizes musculoskeletal integrity, including collagen defects, mitochondrial oxidative stress, and cytokine dysregulation; evaluate clinical evidence associating insufficiency with pain phenotypes such as arthralgia, myofascial discomfort, and delayed post-injury recovery; propose evidence-based strategies for screening, supplementation, and dietary optimization in multidisciplinary pain management.

By integrating mechanistic insights with clinical data, this work seeks to bridge the gap between bench research and bedside practice, reducing the burden of undiagnosed deficiency in chronic pain populations.

## 2. BIOCHEMICAL MECHANISMS AND PHYSIOLOGICAL FUNCTIONS OF VITAMIN C

Vitamin C is a key element in many functions, including:

### Collagen Synthesis Impairment

Vitamin C (ascorbic acid) plays a crucial biochemical role in the post-translational modification of collagen, serving as a required cofactor for the enzymes prolyl hydroxylase and lysyl hydroxylase. These enzymes catalyse the hydroxylation of proline and lysine residues in collagen precursors—an essential step for the stabilization of the collagen triple helix and the formation of cross-links between collagen fibrils, which are necessary for the tensile strength and structural integrity of connective tissues. (2,3)

In vitamin C deficiency, the lack of proline and lysine hydroxylation leads to the production of unstable and under-

hydroxylated collagen molecules. This defective collagen disrupts the extracellular matrix and compromises the function of tissues that rely on collagen for structure and support, particularly the musculoskeletal system, including joints, tendons, cartilage, and bone. (4)

Clinically, this presents as musculoskeletal pain, joint swelling, and impaired wound healing, often seen in the condition scurvy, the severe manifestation of prolonged vitamin C deficiency. In children, it can result in subperiosteal haemorrhages and pseudo-paralysis due to pain, while in adults, joint effusion and muscle weakness are common. (5)

The deficiency also compromises bone health by impairing the formation of type I collagen, which constitutes the organic matrix of bone. This leads to a weakened bone structure, reduced mineralization, and an increased risk of osteopenia and fractures. Studies have shown a correlation between low serum vitamin C levels and decreased bone mineral density, suggesting that vitamin C plays a protective role against bone loss (6,7).

Additionally, cartilage degradation occurs due to impaired synthesis of type II collagen and proteoglycans, key components of articular cartilage. This can contribute to degenerative joint conditions and may exacerbate osteoarthritic changes. (8)

### Oxidative Stress and Tissue Damage

Vitamin C functions as a powerful antioxidant, playing a central role in neutralizing reactive oxygen species (ROS) and maintaining redox homeostasis in various tissues. It scavenges free radicals such as superoxide anion ( $O_2^-$ ), hydroxyl radical ( $OH\cdot$ ), and hydrogen peroxide ( $H_2O_2$ ), thereby preventing oxidative damage to lipids, proteins, and DNA. (9,10)

In skeletal muscle and joint tissues, where metabolic activity and mechanical stress are high, ROS are generated as byproducts of mitochondrial respiration and inflammatory responses. Under normal physiological conditions, vitamin C and other antioxidants counteract ROS production to prevent cellular damage. However, in the case of vitamin C deficiency, this balance is disrupted, leading to oxidative stress—a condition characterized by excessive accumulation of ROS. (11)

Oxidative stress contributes to muscle fatigue by damaging mitochondrial membranes and impairing energy metabolism. It has been shown to reduce contractile efficiency and increase muscle soreness following physical activity. (12) Furthermore, ROS can activate signaling pathways that upregulate pro-inflammatory cytokines, contributing to chronic inflammation and tissue degradation. (13)

In joint tissues, oxidative stress plays a pivotal role in the pathogenesis of osteoarthritis and other degenerative joint diseases. ROS-mediated damage to chondrocytes, synovial fluid, and articular cartilage accelerates the breakdown of extracellular matrix components such as collagen and proteoglycans. (14)

Vitamin C, through its antioxidative and anti-inflammatory actions, can mitigate these effects, and its deficiency may therefore exacerbate joint degeneration and inflammation. (15)

Additionally, vitamin C contributes to regeneration and repair by protecting against oxidative modifications of cellular components and enhancing immune response, further highlighting its importance in maintaining musculoskeletal health. (16)

### Immune dysregulation and inflammation

Vitamin C exerts significant immunomodulatory effects that influence both the innate and adaptive immune systems. One of its key roles is in the regulation of cytokine production, including the modulation of pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), which play critical roles in inflammatory processes and pain pathways. (17,18) Under conditions of oxidative stress or infection, immune cells (such as macrophages and neutrophils) produce elevated levels of these cytokines, contributing to systemic inflammation. Vitamin C inhibits excessive production of TNF- $\alpha$  and IL-6 by reducing NF- $\kappa$ B activation, a transcription factor that promotes the expression of numerous inflammatory genes. (19) By maintaining redox balance and modulating signaling cascades, vitamin C helps to limit the magnitude and duration of inflammatory responses. (20)

When vitamin C levels are deficient, the immune system becomes dysregulated, leading to persistent low-grade inflammation. This chronic inflammatory state contributes to pain sensitization by stimulating nociceptors and lowering the threshold for pain perception. Pro-inflammatory cytokines like IL-6 have been shown to directly sensitize peripheral nerve endings and increase central nervous system excitability, leading to hyperalgesia and chronic musculoskeletal pain. (21,22) Moreover, IL-6 and TNF- $\alpha$  contribute to the catabolic degradation of musculoskeletal tissues by promoting matrix metalloproteinase (MMP) activity and suppressing anabolic repair pathways in cartilage and muscle. This further propagates tissue damage and reinforces the inflammatory-pain cycle. (23)

Therefore, adequate vitamin C intake is critical not only for supporting immune defense but also for modulating inflammation and reducing pain-related sensitivity, particularly in conditions associated with chronic musculoskeletal pain and fatigue syndromes.

### Other Functions

Vitamin C supports numerous physiological systems beyond its antioxidative action. It enhances non-heme iron absorption by reducing ferric to ferrous iron, thereby improving iron bioavailability. (24,25) It helps maintain healthy lipid profiles by lowering LDL cholesterol and triglycerides. (24,26) Within the endocrine system, vitamin C plays roles in catecholamine synthesis in the adrenal glands, thyroid hormone production, and

enhancing insulin secretion from pancreatic  $\beta$ -cells. (27,28) It is essential for collagen formation, serving as a cofactor in hydroxylation reactions and stimulating fibroblast activity. (24) In the nervous system, it acts as a neuromodulator, influencing multiple neurotransmitter pathways, including dopaminergic, cholinergic, and glutamatergic systems. (24) Vitamin C also contributes to skin depigmentation by inhibiting melanin synthesis and protecting against UV-induced damage. (24,26) and supports energy metabolism via its role in carnitine biosynthesis, crucial for mitochondrial fatty acid transport. (27)

## 3. MAIN DIETARY SOURCES AND FACTORS AFFECTING VITAMIN C AVAILABILITY AND BIOAVAILABILITY

Vitamin C is predominantly obtained from dietary sources such as fruits, including citrus (oranges, lemons, grapefruits), berries (strawberries, raspberries, blackberries), and tropical fruits (mango, pineapple, papaya, guava, kiwi), and vegetables such as green vegetables (asparagus, peas, avocado), leafy greens (kale, Swiss chard, dandelion), cruciferous vegetables (broccoli, Brussels sprouts), and bell peppers. (29) It is also present in various herbs, including parsley, thyme, cilantro, alfalfa, fenugreek, kelp, and burdock. (29) Several factors reduce vitamin C content and stability in foods. These include exposure to light and air, which accelerates oxidation via polyphenol oxidase and ascorbate oxidase activity (30), high temperatures during cooking that degrade vitamin C, especially in the presence of oxygen and ferric ions (Fe<sup>3+</sup>) (31), and storage conditions, processing, wilting, and pH, which promote oxidation via hydrogen peroxidase. (28) Soil quality and harvesting conditions also affect plant-based synthesis of ascorbic acid. (28)

Vitamin C bioavailability is regulated by intestinal absorption, tissue transport, and renal reabsorption (32,33). The human body absorbs up to 200 mg efficiently, after which absorption becomes fractional, and excess is excreted in urine. (34) Several dietary and physiological factors impact this process. Glucose and cellulose can impair absorption by competing or inhibiting vitamin C uptake (35,36), whereas polyphenols enhance its bioavailability by up to 35% (37,38), and vitamin E helps preserve ascorbate levels in vivo. (39) Lifestyle factors such as smoking (40), physical inactivity, and obesity (41) reduce plasma vitamin C concentrations. Age, stress, and chronic illnesses (e.g., malabsorption, iron overload, haemodialysis, and psychiatric conditions) also impair availability. (42) Dietary habits, including eating disorders, restrictive diets, or limited intake of fresh produce, contribute to deficiency (41), while food allergies may restrict vitamin C-rich food intake (42). Genetic polymorphisms affecting sodium-dependent vitamin C transporters (SVCTs) also

play a significant role in determining tissue and plasma levels of vitamin C. (43)

#### 4. RISK FACTORS AND VULNERABLE POPULATIONS

Although overt scurvy is rare, subclinical deficiency remains prevalent among specific populations. Risk factors span socioeconomic, dietary, behavioural, and medical domains, necessitating a high index of suspicion in at-risk individuals. (Table 1).

**Table 1.** Vitamin C deficiency risk factors.

|                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Social isolation and dietary habits:</b> often called a "tea and toast" diet, particularly common among older individuals and institutionalized patients, |
| <b>Limited access to fruits and vegetables</b>                                                                                                               |
| <b>Smoking:</b> due to increased oxidative stress.                                                                                                           |
| <b>Alcohol use disorder:</b> more than 80 g/d of ethanol may experience increased renal excretion of vitamin C and poor dietary habits.                      |
| <b>Bariatric surgery:</b> due to reduced absorption capacity.                                                                                                |
| <b>Type 1 diabetes:</b> increased vitamin C requirements,                                                                                                    |
| <b>Malabsorptive disorders:</b> such as inflammatory bowel disease, celiac disease, and cystic fibrosis                                                      |
| <b>Restrictive or low carbohydrate diets:</b> reduced vitamin C intake.                                                                                      |
| <b>Food allergies:</b> can limit dietary diversity                                                                                                           |
| <b>Iron-overload conditions:</b> renal losses                                                                                                                |
| <b>Eating disorders:</b> inadequate vitamin C intake.                                                                                                        |
| <b>Developmental disabilities and mental illness:</b> inadequate vitamin C consumption.                                                                      |
| <b>Infant feeding practices:</b> Cow's milk instead of breast milk or fortified formula                                                                      |
| <b>Haemodialysis:</b> increased renal losses of vitamin C, potentially leading to its deficiency.                                                            |

#### Socioeconomic Disadvantage and Dietary Insufficiency

Limited access to fresh produce due to poverty, homelessness, or food insecurity remains a leading cause of vitamin C deficiency. Populations dependent on institutional diets or highly processed foods—such as the elderly or incarcerated individuals—are particularly vulnerable. (44) The “tea and toast” dietary pattern,

characterized by high carbohydrate and low micronutrient intake, exemplifies such inadequate nutrition.

#### Smoking and Alcohol Use

Smoking increases oxidative stress and accelerates vitamin C depletion. Smokers require approximately 35 mg/day more vitamin C than non-smokers to maintain physiological levels. (45) Chronic alcohol use further impairs dietary intake and vitamin C absorption while increasing renal excretion, compounding the risk of deficiency. (46)

#### Bariatric Surgery and Malabsorptive Disorders

Bariatric procedures, particularly those with a malabsorptive component (e.g., Roux-en-Y gastric bypass), are associated with significant risk for micronutrient deficiencies. Postoperative alterations in gastrointestinal anatomy reduce the absorption of water-soluble vitamins, including vitamin C. (47) A study by Gasmi et al. reported a 34.6% prevalence of vitamin C deficiency among patients within one year of surgery. (48) Similarly, gastrointestinal diseases such as inflammatory bowel disease (IBD), celiac disease, and cystic fibrosis impair absorption and elevate nutritional requirements. (49)

#### Restrictive Eating Behaviours and Developmental Disorders

Eating disorders such as anorexia nervosa and orthorexia can result in prolonged avoidance of fruits and vegetables, leading to micronutrient deficiencies including ascorbate deficiency. Additionally, individuals with autism spectrum disorder or intellectual disabilities may exhibit selective eating patterns, further increasing risk. (50)

#### Infant Feeding Practices and Pregnancy

Infants fed unfortified cow's milk in place of breast milk or formula are at risk for scurvy, as cow's milk lacks adequate vitamin C. (51) During pregnancy and lactation, metabolic demands increase, and without sufficient dietary intake, maternal deficiency may compromise both maternal and foetal health. (52)

#### Chronic Illness and Haemodialysis

Chronic diseases such as diabetes, chronic kidney disease (CKD), and hemochromatosis alter vitamin C metabolism or increase its clearance. Haemodialysis, in particular, accelerates the loss of water-soluble vitamins, requiring supplementation to prevent deficiency-related complications. (52)

#### 5. MUSCULOSKELETAL MANIFESTATIONS

Vitamin C deficiency, though often underdiagnosed, can lead to a wide range of systemic and musculoskeletal symptoms. Both overt and subclinical deficiencies have been observed across

diverse populations, particularly those with dietary inadequacies or underlying medical conditions.

Musculoskeletal symptoms are among the most prominent features of vitamin C deficiency. It is estimated that approximately 80% of affected individuals experience musculoskeletal pain or dysfunction, especially in paediatric populations. (53) These manifestations often mimic rheumatologic or orthopaedic disorders, leading to diagnostic delays.

### Bone Pain and Osteopenia

Besides its critical role for bone matrix development and mineralization, deficiency impairs osteoblast differentiation and collagen formation, resulting in osteopenia and increased fracture risk, particularly in the spine and lower extremities. (18,47,54)

### Joint Involvement

Vitamin C deficiency leads to vascular fragility within joint tissues, promoting hemarthrosis, joint effusion, and arthralgia. Large joints such as the knees and elbows are commonly involved, with some cases mimicking juvenile idiopathic arthritis or septic arthritis. (5,55)

### Myopathy, fatigue, and Muscle Pain

Muscle symptoms arise due to decreased carnitine synthesis, which compromises mitochondrial fatty acid oxidation. Patients often report proximal muscle weakness, fatigue, and myalgias. In severe cases, histological studies show muscle fibre atrophy and interstitial haemorrhage. (56,57)

### Subperiosteal Haemorrhages

Capillary fragility and impaired connective tissue integrity result in subperiosteal haemorrhages, especially in children. These are commonly found along the femur and tibia and may present with intense localized pain and swelling. Radiographic signs include periosteal elevation and calcified hematomas. (58,59)

**Overlap with Chronic Pain Syndromes:** Some case series have suggested that vitamin C supplementation may reduce pain in conditions such as fibromyalgia and osteoarthritis, indicating a broader role in musculoskeletal health. (60)

### Historical and Paediatric Considerations

Scurvy, the classic manifestation of prolonged vitamin C deficiency, develops within 4–12 weeks of inadequate intake. Initial symptoms include fatigue, malaise, and anorexia, followed by mucocutaneous signs such as gingival bleeding, perifollicular haemorrhages, ecchymoses, and impaired wound healing. (61) Musculoskeletal findings, including myalgias and joint swelling, are especially prominent in children, with refusal to ambulate and limping often being early signs. (53,62) Pathognomonic signs include corkscrew hairs and "scorbutic rosary," tender

costochondral junctions. Advanced disease may result in pseudo-paralysis, ocular haemorrhages, anasarca, seizures, and multiorgan failure if untreated. (62–64)

## 6. DIAGNOSTIC CHALLENGES AND KEY RECOMMENDATIONS TO AVOID MISDIAGNOSIS

Musculoskeletal manifestations are nonspecific and often lead to misdiagnoses such as malignancy, osteomyelitis, or autoimmune arthritis. A careful dietary history, along with biochemical testing (e.g., serum ascorbate levels  $<11.4 \mu\text{mol/L}$ ), is essential for diagnosis. (60) (Figure 1). Oral supplementation with 500–1000 mg/day of vitamin C usually results in rapid symptomatic improvement within 72 hours, with complete resolution over weeks. (65,1)

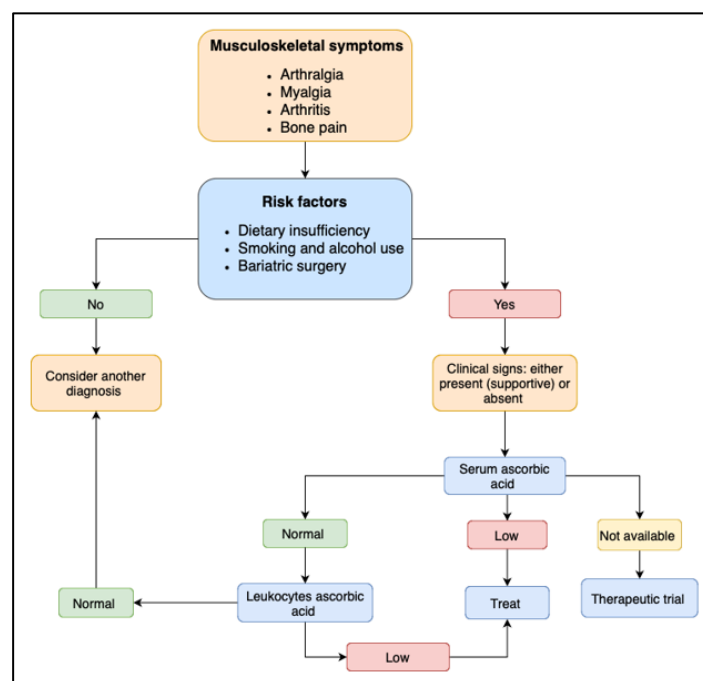


Figure 1. Vitamin C diagnostic and therapeutic algorithm.

**Suspect Vitamin C Deficiency in High-Risk Populations:** patients with **poor dietary habits** (e.g., limited fruits/vegetables, "tea and toast" diets in elderly/institutionalized individuals); **Smokers**, **chronic alcohol users** ( $>80 \text{ g/day}$  ethanol), and those with **malabsorptive conditions** (e.g., IBD, celiac disease, post-bariatric surgery); **Paediatric patients** fed unfortified cow's milk or with developmental disabilities affecting dietary diversity. (18,55).

**Recognize Red Flag Symptoms:** **Unexplained bone pain** (especially weight-bearing bones) or arthralgia or unresponsive to anti-inflammatory therapy. **Proximal muscle**

**weakness** or **pseudo-paralysis** (children refusing to walk/limp without trauma). **Poor wound healing** or **gingival bleeding** alongside musculoskeletal complaints. (58,59)

**Identify Pathognomonic Clinical Signs:** **corkscrew hairs** (coiled hair shafts) or **swan neck hairs** (multiple bending points); **scorbutic rosary** (sharp, tender costochondral swellings) vs. rachitic rosary (rounded, non-tender in rickets). **perifollicular haemorrhages** (lower extremities) or **subperiosteal hematomas** (painful limb swelling). (57,66)

**Leverage Imaging Clues:** **X-ray:** Look for **Fraenkel's line** (metaphyseal sclerosis), **Trümmerfeld zone** (lucent band), or **periosteal elevation** (subperiosteal haemorrhage). **MRI:** bone marrow oedema or periosteal fluid in the absence of trauma/infection. (67,68)

**Rule Out Mimickers:** **inflammatory arthritis** (e.g., RA, JIA): Check CRP/ESR (typically normal in scurvy); **osteomyelitis:** Look for fever, leucocytosis, or focal bone destruction on imaging. **metabolic bone disease** (e.g., rickets/osteomalacia): Differentiate via serum calcium, phosphate, and vitamin D levels. (69,70)

**Confirm with Laboratory Testing:** **serum ascorbic acid**  $<11.4 \mu\text{mol/L}$  (gold standard); consider a **therapeutic trial:** rapid symptom improvement (1–2 weeks) with vitamin C supplementation (1–2 g/day) supports diagnosis. (64,65)

**Avoid Common Pitfalls:** **overreliance on age stereotypes:** Scurvy is not exclusive to historical/developing-world contexts; **misinterpreting imaging:** Subperiosteal hematomas may mimic trauma or malignancy; correlate with dietary history, **ignoring psychosocial factors:** Screen for food insecurity, eating disorders, or caregiver neglect in paediatric/geriatric cases. (71,66).

## 7. THERAPEUTIC STRATEGIES

### Vitamin C Therapy for Musculoskeletal Symptoms

Vitamin C supplementation represents a targeted therapeutic strategy for mitigating musculoskeletal pain and dysfunction, particularly in individuals with confirmed or suspected deficiency. (Figure 2) Given its dual role in collagen synthesis and antioxidant defense, vitamin C is critical for maintaining the structural integrity of connective tissues (e.g., cartilage, tendons, and bone matrix) and mitigating oxidative stress-induced inflammation. Clinical studies suggest that repletion of vitamin C in deficient individuals can lead to measurable improvements in pain scores and functional outcomes. For instance, trials in patients with osteoarthritis or chronic myalgia have demonstrated reductions in joint stiffness and muscle tenderness following daily supplementation with 500–1000 mg of ascorbic acid, doses sufficient to saturate plasma levels and restore tissue reserves (72,73). Clinical evidence supports the rapid resolution of musculoskeletal symptoms following vitamin C repletion, with significant improvements observed in pain,

mobility, and fatigue within days to weeks of initiating supplementation (58).

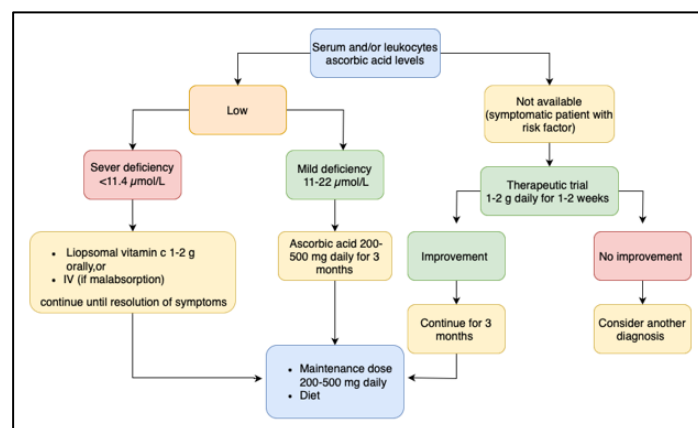


Figure 2. Vitamin C treatment modalities algorithm.

These benefits are attributed to enhanced collagen crosslinking, which stabilizes articular cartilage and reduces mechanical stress on joints, as well as the quenching of reactive oxygen species (ROS) that perpetuate nociceptive signaling and tissue degradation. (5) Populations at heightened risk of deficiency, such as smokers, the elderly, and those with malabsorption syndromes, may derive particular benefit from tailored supplementation, as suboptimal vitamin C status exacerbates musculoskeletal fragility and delays recovery from injury. (57)

In haemodialysis patients, serum vitamin C should be monitored at least twice a year due to increased losses during dialysis (74,75). Co-administration with iron may enhance non-heme iron absorption and alleviate anaemia-related fatigue contributing to musculoskeletal pain (76), though caution is advised in individuals with iron-overload conditions like hemochromatosis (77). Combined supplementation with collagen peptides or omega-3 fatty acids may further support anti-inflammatory and tissue-repair mechanisms (78). While generally safe, prolonged high-dose intake ( $>2000 \text{ mg/day}$ ) is not recommended due to risks such as gastrointestinal upset and oxalate nephropathy in susceptible individuals (79).

### How to Optimize Vitamin C Supplementation for Musculoskeletal Pain?

Selecting the optimal form of vitamin C for managing musculoskeletal symptoms depends on bioavailability, tolerability, clinical context, (Table 2,3) and patient-specific factors. Below is an evidence-based analysis of available formulations to guide therapeutic decisions. (Table 4)

Table 2. Vitamin C supplementation key factors.

| Key Factors                | Details                                                                                                                         |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Condition Severity:        | Mild deficiency: ascorbic acid or mineral ascorbates.<br><br>Chronic pain/inflammation: liposomal or IV vitamin C.              |
| Tolerability               | Buffered forms (mineral ascorbates) for GI sensitivity.                                                                         |
| Dosing Frequency           | Liposomal or sustained-release formulas for steady plasma levels.                                                               |
| Collagen Synthesis         | All forms are equally effective if plasma levels are saturated (≥200 mg/day)                                                    |
| Antioxidant/Immune Support | Liposomal or IV vitamin C may offer superior ROS quenching in high oxidative stress (e.g., post-surgery, chronic inflammation). |
| Chronic Pain               | Trials favour liposomal or IV forms for reducing myalgia and joint pain.                                                        |
| Upper Limit                | 2000 mg/day for most adults to avoid GI side effects.                                                                           |
| Contraindications          | Hemochromatosis (vitamin C enhances iron absorption).<br><br>Kidney disease (risk of oxalate stones with high doses).           |

Table 3. Vitamin C forms and characteristics.

| Form                                      | Best For                                                   | Pros                                               | Cons                                    | Dose Range                |
|-------------------------------------------|------------------------------------------------------------|----------------------------------------------------|-----------------------------------------|---------------------------|
| Liposomal C                               | -High-dose therapy<br>-Chronic illness,<br>-Immune support | -Near-IV absorption<br>-No GI upset                | -Expensive<br>-Quality varies           | 1,000–6,000+ mg/day       |
| IV Vitamin C (Sodium Ascorbate)           | -Severe deficiency,<br>-Cancer support<br>-Infections      | -Direct bloodstream delivery,<br>-Ultra-high doses | Requires clinic/doctor                  | 10,000–100,000 mg/session |
| Ester-C (Calcium Ascorbate + Metabolites) | -Sensitive stomachs<br>-Daily maintenance                  | Gentle, long-lasting in cells                      | -Contains calcium<br>-Mid-range cost    | 500–3,000 mg/day          |
| Sodium Ascorbate (Buffered)               | -High-dose oral/IV<br>-Immune support                      | -Non-acidic<br>-Good absorption                    | -High doses may still cause diarrhoea   | 1,000–10,000 mg/day       |
| Ascorbic Acid (Pure)                      | -Budget-friendly<br>-General use                           | -Cheap<br>-widely available                        | -GI distress at high doses              | 500–2,000 mg/day          |
| Vitamin C + Bioflavonoids                 | -Antioxidant synergy<br>-Skin/collagen support             | -Enhanced uptake<br>-Anti-inflammatory             | -Mildly better than plain ascorbic acid | 500–2,000 mg/day          |
| Mineral Ascorbates (Mg/Zn/Ca)             | -Long-term use<br>-Mineral deficiency                      | -Gentle<br>-Provides minerals                      | -Lower potency per gram                 | 500–2,000 mg/day          |

Ascorbic Acid (Pure Vitamin C)

Ascorbic acid, the most studied and cost-effective form, achieves plasma saturation at doses of 200–400 mg/day, with excess excreted renally. Higher doses (≥1000 mg) split throughout the day improve absorption efficiency (80). It is rapidly absorbed in the small intestine via sodium-dependent transporters (SVCT1) and effectively corrects deficiency while supporting collagen synthesis. However, its acidic nature may cause gastrointestinal irritation (e.g., nausea, diarrhoea) at high doses and exacerbate

symptoms in acid-sensitive individuals, such as those with gastroesophageal reflux disease (GERD) (81).

Table 4. Vitamin C adverse effects and their management.

| Risk Factor         | Potential Issue                                                                                | At-Risk Groups                                                                  | Prevention/Solution                                                        |
|---------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Kidney Stones       | High-dose vitamin C (>2,000 mg/day) may increase oxalate excretion, raising kidney stone risk. | People with a history of oxalate stones, kidney disease.                        | Limit doses to ≤1,000 mg/day; hydrate well; monitor urine oxalate.         |
| GI Distress         | Diarrhoea, nausea, cramps (due to osmotic effect at high doses).                               | Those with sensitive stomachs, IBS, or taking >3,000 mg/day.                    | Use buffered forms (sodium/calcium ascorbate) or liposomal C; split doses. |
| Iron Overload       | Vitamin C enhances non-heme iron absorption, which may be harmful in iron overload disorders.  | Hemochromatosis patients, frequent blood transfusions.                          | Avoid high-dose vitamin C; monitor serum iron levels.                      |
| Drug Interactions   | May interfere with certain medications (e.g., chemotherapy, statins, anticoagulants).          | Cancer patients (especially on platinum drugs), warfarin users.                 | Consult a doctor before combining with medications.                        |
| Pro-Oxidant Effects | Very high doses (>10,000 mg in one dose) may act as a pro-oxidant in some cases.               | People with high oxidative stress (e.g., advanced cancer, metabolic disorders). | Avoid mega-doses unless under medical supervision.                         |
| Hypoglycaemia Risk  | Vitamin C may lower blood sugar slightly (enhances insulin sensitivity).                       | Diabetics on glucose-lowering meds.                                             | Monitor blood sugar; adjust meds if needed.                                |
| Dental Erosion      | Chewable/vitamin C tablets may erode enamel due to acidity.                                    | People with enamel damage or acid sensitivity.                                  | Use non-acidic forms (ester-C, sodium ascorbate); rinse mouth after.       |
| False Lab Tests     | Mega-doses can skew blood glucose, stool occult blood, or LDH tests.                           | Patients undergoing medical testing.                                            | Stop high-dose vitamin C 48–72 hrs before lab work.                        |

Mineral Ascorbates (Buffered Forms)

Examples include sodium ascorbate, calcium ascorbate, and magnesium ascorbate. These buffered forms exhibit bioavailability comparable to ascorbic acid, but are gentler on the stomach due to their neutral pH. Sodium ascorbate is particularly unsuitable for individuals with hypertension or kidney issues. (82) Advantages include better tolerability in patients with gastritis and the provision of trace minerals (e.g., calcium, magnesium) that support bone health. A limitation is the sodium content in sodium ascorbate (≈131 mg per 1000 mg ascorbate), which may require monitoring in sodium-restricted diets. (83)

Liposomal Vitamin C

Liposomal vitamin C is encapsulated in phospholipid vesicles to enhance absorption. It bypasses SVCT1 transporters, potentially increasing cellular uptake, with some studies reporting 1.5–2x higher plasma levels compared to oral ascorbic acid. (84, 85) This form minimizes gastrointestinal distress and is suitable for high-dose therapy (3000–6000 mg/day) in chronic conditions like inflammatory arthritis. However, it is costlier than standard forms, and long-term safety data remain limited. (86)

Ester-C® (Calcium Ascorbate + Metabolites)

Ester-C® combines calcium ascorbate with vitamin C metabolites (e.g., dehydroascorbate, threonate). While its neutral pH improves tolerability, evidence for enhanced tissue retention in leukocytes is mixed (41). It is often preferred for joint health due to its calcium content, which may synergize with collagen stabilization. (87)

## Intravenous (IV) Vitamin C

Reserved for severe deficiency, critical illness, or malabsorption, IV vitamin C achieves supraphysiological plasma concentrations (up to 25 mM vs. 70  $\mu$ M with oral dosing). (86) It bypasses gastrointestinal absorption limits and is used in chronic pain syndromes, cancer support, and sepsis. (88) However, it requires medical supervision due to risks of oxalate nephropathy at high doses. (87)

## Natural vs. Synthetic Vitamin C

Natural sources (e.g., acerola cherry, camu camu) and synthetic ascorbic acid are chemically identical, with no significant difference in bioavailability or therapeutic efficacy. (89) Natural sources often include flavonoids (e.g., quercetin), which may enhance antioxidant synergy. (9)

## 8. SAFETY CONSIDERATIONS

**Upper Limit:** 2000 mg/day for most adults to avoid gastrointestinal side effects.

**Contraindications:** *Hemochromatosis:* Vitamin C enhances iron absorption, risking iron overload (87) ; *Kidney disease:* High doses may increase oxalate stone risk (90).

**Clinical Evidence Summary :** **collagen Synthesis:** All forms are equally effective when plasma levels are saturated ( $\geq 200$  mg/day) (90) ; **antioxidant/Immune Support:** Liposomal or IV vitamin C may offer superior ROS quenching in high oxidative stress (e.g., post-surgery, chronic inflammation) (91); **chronic Pain:** Trials favour liposomal or IV forms for reducing myalgia and joint pain (72).

## 9. CONCLUSION

Vitamin C deficiency, historically synonymous with scurvy, remains a clinically relevant yet underrecognized contributor to musculoskeletal pain in modern practice. This review elucidates the biochemical and clinical pathways through which suboptimal vitamin C levels impair collagen synthesis, exacerbate oxidative stress, and perpetuate inflammatory cascades, culminating in joint, bone, and muscle dysfunction. Clinically, deficiency manifests as nonspecific arthralgia, myalgia, osteopenia, and delayed recovery, often mimicking rheumatologic or degenerative disorders. High-risk populations, including smokers, the elderly, bariatric surgery patients, and socioeconomically disadvantaged groups, are disproportionately affected due to increased metabolic demands, malabsorption, or inadequate dietary intake. Despite the growing recognition of vitamin C's role in musculoskeletal health, significant research gaps remain. Evidence is still limited regarding the optimal supplementation dose for specific subgroups, such as the elderly or those recovering from surgery, which is crucial for tailoring

effective treatment protocols. Addressing these gaps through further research will enhance our understanding and management of vitamin C deficiency in clinical practice.

**Competing interests:** The authors declare that they have no competing interest.

## REFERENCES

1. Léger D. Scurvy: reemergence of nutritional deficiencies. *Can Fam Physician*. 2008;54(10):1403-6.
2. 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):1135S-40S. doi:10.1093/ajcn/54.6.1135S.
3. Kivirikko KI, Myllylä R. Post-translational processing of procollagens. *Ann N Y Acad Sci*. 1982;401:187-201. doi:10.1111/j.1749-6632.1982.tb45742.x.
4. Pullar JM, Carr AC, Vissers MC. The roles of vitamin C in skin health. *Nutrients*. 2017;9(8):866. doi:10.3390/nu9080866.
5. Weinstein M, Babyn P, Zlotkin S. An orange a day keeps the doctor away: scurvy in the year 2000. *Pediatrics*. 2001;108(3). doi:10.1542/peds.108.3.e55.
6. Sahni S, Hannan MT, Gagnon D, Blumberg J, Cupples LA, Kiel DP, Tucker KL. High vitamin C intake is associated with lower 4-year bone loss in elderly men. *J Nutr*. 2008;138(10):1931-8. doi:10.1093/jn/138.10.1931.
7. Gaggini M, Gorini G, Vassalle C. Vitamin C and cardiovascular risk. *Nutrients*. 2020;12(6):1904. doi:10.3390/nu12061904.
8. Kwan Tat S, Lajeunesse D, Pelletier JP, Martel-Pelletier J. Targeting interleukin-1 for treating osteoarthritis: a critical review of clinical studies. *Arthritis Res Ther*. 2010;12(3). doi:10.1186/ar2983.
9. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr*. 1999;69(6):1086-107. doi:10.1093/ajcn/69.6.1086.
10. Duarte TL, Lunec J. Review: When is an antioxidant not an antioxidant? A review of novel actions and reactions of vitamin C. *Free Radic Res*. 2005;39(7):671-86. doi:10.1080/10715760500104025.
11. Valko M, Leibfriz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol*. 2007;39(1):44-84. doi:10.1016/j.biocel.2006.07.001.
12. Powers SK, Duarte J, Kavazis AN, Talbert EE. Reactive oxygen species are signalling molecules for skeletal muscle adaptation. *Exp Physiol*. 2010;95(1):1-9. doi:10.1113/expphysiol.2009.050526.
13. Packer L, Weber SU, Rimbach G. Molecular aspects of  $\alpha$ -tocotrienol antioxidant action and cell signalling. *J Nutr*. 2001;131(2):369S-73S. doi:10.1093/jn/131.2.369S.
14. Lepetos P, Papavassiliou AG. ROS/oxidative stress signaling in osteoarthritis. *Biochim Biophys Acta*. 2016;1862(4):576-91. doi:10.1016/j.bbdis.2016.01.003.
15. Henrotin Y, Kurz B, Aigner T. Oxygen and reactive oxygen species in cartilage degradation: friends or foes? *Osteoarthritis Cartilage*. 2005;13(8):643-54. doi:10.1016/j.joca.2005.04.002.
16. Jacob RA. The Integrated Antioxidant System. *Nutr Res*. 1995;15(5):755-66. doi:10.1016/0271-5317(95)00022-I.
17. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab*. 2006;50(2):85-94. doi:10.1159/000090495.
18. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*.

- 2017;9(11):1211. doi:10.3390/nu9111211.
19. Molina N, Morandi AC, Bolin AP, Otton R. Comparative effect of antioxidant vitamins C and E on NF- $\kappa$ B activation in skeletal muscle of diabetic rats. *J Nutr Biochem*. 2014;25(4):386-92. doi:10.1016/j.jnutbio.2013.12.004.
20. Hemilä H. Vitamin C and infections. *Nutrients*. 2017;9(4):339. doi:10.3390/nu9040339.
21. Berta T, Qadri YJ, Ji RR. Targeting IL-17 and TNF- $\alpha$  for pain control: Mechanisms and clinical significance. *Neurotherapeutics*. 2017;14(3):637-47. doi:10.1007/s13311-017-0541-5.
22. Schaible HG. Nociceptive neurons detect cytokines in arthritis. *Arthritis Res Ther*. 2014;16(5):470. doi:10.1186/s13075-014-0470-1.
23. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol*. 2011;7(1):33-42. doi:10.1038/nrrheum.2010.196.
24. Xu ZS, Yeo WS, Saptoro A. A comprehensive review and recent advances of vitamin C: Overview, functions, sources, applications, market survey and processes. *Process Saf Environ Prot*. 2024;206:108-29. doi:10.1016/j.cherd.2024.04.048.
25. Deng J, Ramelli L, Li PY, Eshaghpour A, Li A, Schuenemann GA, Crowther MA. Efficacy of vitamin C with Fe supplementation in iron deficiency anemia patients: a systematic review and meta-analysis. *Blood Vessels*. 2024;100023. doi:10.1016/j.bvth.2024.100023.
26. McRae MP. Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides: a meta-analysis of 13 randomized controlled trials. *J Chiropr Med*. 2008;7(2):48-58. doi:10.1016/j.jcme.2008.01.002.
27. Rebouche CJ. Renal handling of carnitine in experimental vitamin C deficiency. *Metabolism*. 1995;44(12):1639-43. doi:10.1016/0026-0495(95)90087-x.
28. Magwaza LS, Mditshwa A, Tesfay SZ, Opara UL. An overview of preharvest factors affecting vitamin C content of citrus fruit. *Scientia Horticulturae*. 2017;216:12-21. doi:10.1016/j.scienta.2016.12.021.
29. Balch PA. Prescription for nutritional healing: a practical A-to-Z reference to drug-free remedies using vitamins, minerals, herbs & food supplements. London: Penguin; 2011.
30. Djaledje LK, Napitupulu M, Nuryanti S. Analysis of vitamin C in Kecombrang (Etlingera elatior). *Jurnal Akademika Kimia*. 2019;8(4):214-7. doi:10.22487/j24775185.2019.v8.i4.pp214-217.
31. Oxygen availability in model solutions and purées during heat treatment and the impact on vitamin C degradation. *LWT - Food Sci Technol*. 2017;85:493-9. doi:10.1016/j.lwt.2016.09.033.
32. Levine M, Padayatty SJ, Espey MG. Vitamin C: A concentration-function approach yields pharmacology and therapeutic discoveries. *Adv Nutr*. 2011;2(2):78-88. doi:10.3945/an.110.000109.
33. McColl KEL. Effect of proton pump inhibitors on vitamins and iron. *Am J Gastroenterol*. 2009;104 Suppl 2. doi:10.1038/ajg.2009.45.
34. Higdon J. Vitamin C. Linus Pauling Institute. Available from: <https://lpi.oregonstate.edu/mic/vitamins/vitamin-C>.
35. Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of vitamin C. *Nutrients*. 2019;11(10):2412. doi:10.3390/nu11102412.
36. Palafox-Carlos H, Ayala-Zavala JF, González-Aguilar GA. The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants. *J Food Sci*. 2011;76(1):6-15.
37. Kolniak-Ostek J, Oszmiański J, Wojdyło A. Effect of l-ascorbic acid addition on quality, polyphenolic compounds and antioxidant capacity of cloudy apple juices. *Eur Food Res Technol*. 2013;236(5):777-98. doi:10.1007/s00217-013-1931-z.
38. Vinson JA, Bose P. Comparative bioavailability to humans of ascorbic acid alone or in a citrus extract. *Am J Clin Nutr*. 1988;48(3):601-4. doi:10.1093/ajcn/48.3.601.
39. Tanaka K, Hashimoto T, Tokumaru S, Iguchi H, Kojo S. Interactions between vitamin C and vitamin E are observed in tissues of inherently scorbutic rats. *J Nutr*. 1997;127(10):2060-4. doi:10.1093/jn/127.10.2060.
40. Drewnowski A, Rock CL, Henderson SA, Shore AB, Fischler C, Galan P, Preziosi P, Herberg S. Serum  $\beta$ -carotene and vitamin C as biomarkers of vegetable and fruit intakes in a community-based sample of French adults. *Am J Clin Nutr*. 1997;65(6):1796-802.
41. Schleicher RL, Carroll MD, Ford ES, Lacher DA. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003-2004 National Health and Nutrition Examination Survey (NHANES). *Am J Clin Nutr*. 2009;90(5):1252-63. doi:10.3945/ajcn.2008.27016.
42. Maxfield L, Crane JS, Daley SF. Vitamin C deficiency (scurvy). *Natl Libr Med*. 2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK493187/>.
43. Michels AJ, Hagen TM, Frei B. Human genetic variation influences vitamin C homeostasis by altering vitamin C transport and antioxidant enzyme function. *Annu Rev Nutr*. 2013;33:45-70. doi:10.1146/annurev-nutr-071812-161246.
44. Smith A, Di Primio G, Humphrey-Murto S. Scurvy in the developed world. *CMAJ*. 2011;183(11).
45. Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academies Press; 2000.
46. Finkelstein FO, Juergensen P, Shah HH. Vitamin C in dialysis patients: a forgotten but essential micronutrient. *Semin Dial*. 2001;14(3):146-50.
47. Gasmi A, Björklund G, Mujawdiya PK, et al. Micronutrients deficiencies in patients after bariatric surgery. *Eur J Nutr*. 2022;61:55-67.
48. Kaushal M, Sanyal A, Kumar M. Nutritional aspects of inflammatory bowel disease. *JPEN J Parenter Enteral Nutr*. 2011;35(5):563-73.
49. Norris ML, Spettigue W, Hammond NG, et al. Micronutrient deficiencies in adolescents with eating disorders. *J Adolesc Health*. 2012;50(4):431-3.
50. Leung AK, Sauve RS. Scurvy in children. *J Pediatr Health Care*. 2005;19(2):90-4.
51. Brown EM, Boyle CA. Nutritional considerations in dialysis patients. *Kidney Int Suppl*. 2006;(103).
52. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of bariatric surgery patients. *Obesity (Silver Spring)*. 2013;21(Suppl 1).
53. Gnoni M, Beas R, Grewal R, Diaz-Pardave C, Osterbur J. Scurvy: an often-misdiagnosed condition in the modern days? *Folia Med (Plovdiv)*. 2022;64(3):543-6.
54. Sahni S, Hannan MT, Gagnon D, et al. Protective effect of vitamin C on bone mass in postmenopausal women. *J Nutr*. 2009;139(4):647-54.
55. Popovich D, McAlhany A, Adewumi A, Barnes MM. Scurvy: Forgotten but not gone. *J Pediatr Health Care*. 2009;23(6):405-15.
56. Johnston CS, Barkyoumb GM, Schumacher SS. Vitamin C supplementation slightly improves physical activity levels and reduces cold incidence in men with marginal vitamin C status: a randomized controlled trial. *J Nutr*. 2014;144(9):1426-32.
57. Hirschmann JV, Raugi GJ. Adult scurvy. *J Am Acad Dermatol*. 1999;41(6):895-910.
58. Fain O. Musculoskeletal manifestations of scurvy. *Joint Bone Spine*. 2005;72(2):124-8.
59. Al-Dabagh A, Nguyen M, Wang A, Hussain S. A case of scurvy presenting with subperiosteal hemorrhage. *Clin Pract Cases Emerg Med*. 2019;3(2):130-3.
60. Mosdøl A, Vist GE, Havelsrud K. Effect of vitamin C on common cold: Randomized controlled trials. *Am J Epidemiol*. 2001;153(9):879-88.
61. Miraj F, Abdullah A. Scurvy: Forgotten diagnosis, but still exists. *Int J Surg Case Rep*. 2020;68:263-6.
62. Larralde M, Martinez F, Boggio P, et al. Scurvy in a 10-month-old boy. *Int J Dermatol*. 2007;46(2):194-8.
63. Desai VD, Khan M, Joshi A. Scurvy extinct? Think again! *Int J Clin Pediatr Dent*.

- 2009;2(3):39-42.
64. Levavasseur M, Desbois AC, Fain O. Severe scurvy: An underestimated disease. *Eur J Clin Nutr.* 2015;69(9):1076-7.
65. Stephen R, Utecht T. Scurvy identified in the emergency department: A case report. *J Emerg Med.* 2001;21(3):235-7.
66. Ratanachu-Ek S, et al. Scurvy in pediatric patients. *J Med Assoc Thai.* 2003;86(Suppl 3).
67. Agarwal A, et al. Skeletal manifestations of pediatric scurvy. *Pediatr Radiol.* 2015;45(12):1841-9.
68. Levin TL, et al. Radiographic features of scurvy in a child with cerebral palsy. *Pediatr Radiol.* 2019;49(11):1575-8.
69. Weinstein M, et al. Scurvy: A case report. *J Am Acad Dermatol.* 2001;45(6).
70. Chakhtoura M, et al. Nutritional deficiencies post-bariatric surgery. *Obes Surg.* 2018;28(7):2075-82.
71. Sthoeger ZM, Sthoeger D. Scurvy in a patient with depression: A case report. *Isr Med Assoc J.* 2014;16(6):392-3.
72. Chiu PR, Hu YC, Huang TC, et al. Vitamin C protects chondrocytes against monosodium iodoacetate-induced osteoarthritis by multiple pathways. *Int J Mol Sci.* 2019;20(15):3759. doi:10.3390/ijms20153759.
73. de Oliveira GV, Alves CA, de Sousa JFR, et al. Vitamin C supplementation reduces exercise-induced muscle damage in soccer players: a randomized controlled trial. *Nutrients.* 2021;13(8):2603. doi:10.3390/nu13082603.
74. Olmedo JM, Yiannias JA, Windgassen EB, Gornet MK. Scurvy: a disease almost forgotten. *Int J Dermatol.* 2006;45(8):909-13.
75. Gasmi A, Nasreen A, Menzel A, et al. Prevalence of micronutrient deficiencies in patients undergoing bariatric surgery: A systematic review. *Nutrients.* 2022;14(15):3265. doi:10.3390/nu14153265.
76. Cano NJM, Fouque D, Roth H, et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: A 2-year multicenter, prospective, randomized study. *Nutrients.* 2021;13(9):3058. doi:10.3390/nu13093058.
77. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Natl Acad Sci USA.* 1996;93(8):3704-9. doi:10.1073/pnas.93.8.3704.
78. Cook JD, Monsen ER. Vitamin C, the common cold, and iron absorption. *Am J Clin Nutr.* 1977;30(2):235-41. doi:10.1093/ajcn/30.2.235.
79. Barton JC, Acton RT, Rivers CA, et al. Hemochromatosis risk genotypes and vitamin C status: findings from the HEIRS Study. *Blood Cells Mol Dis.* 2013;51(2):69-73. doi:10.1016/j.bcmd.2013.03.003.
80. Clark KL, Sebastianelli W, Flechsenhar KR, et al. 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain. *Curr Med Res Opin.* 2008;24(5):1485-96. doi:10.1185/030079908x291967.
81. Massey LK, Liebman M, Kynast-Gales SA. Ascorbate increases human oxaluria and kidney stone risk. *J Nutr.* 2005;135(7):1673-7. doi:10.1093/jn/135.7.1673.
82. Padayatty SJ, Levine M. Vitamin C: the known and the unknown and Goldilocks. *Oral Dis.* 2016;22(6):463-93.
83. Carr AC, Vissers MCM. Synthetic or food-derived vitamin C—are they equally bioavailable? *Nutrients.* 2013;5(11):4284-304.
84. Davis JL, Paris HL, Beals JW, et al. Liposomal-encapsulated ascorbic acid: influence on vitamin C bioavailability. *Nutr Metab Insights.* 2016;9:25-30.
85. Hickey S, Roberts HJ, Miller NJ. Pharmacokinetics of oral vitamin C. *J Nutr Environ Med.* 2008;17(3):169-77.
86. Gruenewald J, Graubaum HJ, Busch R, et al. Safety and tolerance of Ester-C®. *Adv Ther.* 2006;23(1):171-8.
87. Carr AC, Rosengrave PC, Bayer S, et al. Hypovitaminosis C in critically ill patients. *Crit Care.* 2017;21(1):300.
88. Mikirova N, Casciari J, Rogers A, et al. High-dose IV vitamin C in cancer patients. *J Transl Med.* 2012;10:189.
89. Johnston CS, Luo B. Absorption of vitamin C sources. *J Am Diet Assoc.* 1994;94(7):779-81.
90. DePhillipo NN, Aman ZS, Kennedy MI, et al. Vitamin C supplementation post-injury. *Orthop J Sports Med.* 2018;6(10):2325967118804544.
91. May JM, Harrison FE. Vitamin C in vascular endothelium. *Antioxid Redox Signal.* 2013;19(17):2068-83.