

# Vitamin C Deficiency (or Scurvy): Pathophysiology and Clinical Manifestations According to Age Groups

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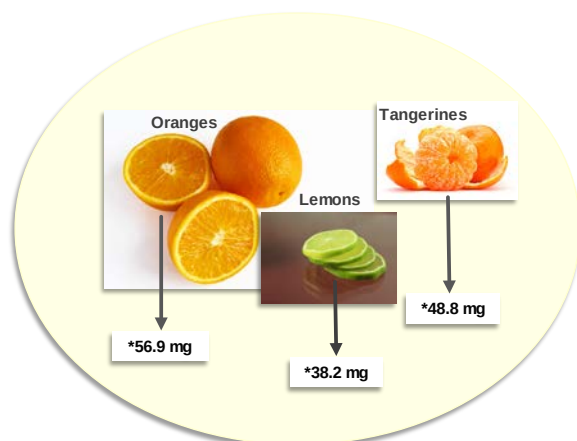
**Abstract** Pathophysiology may be defined as a hybrid fundamental science, focusing on changes in the body's major functions during diseases, such as scurvy and other nutritional deficiencies. Mostly, it allows to understand the biological modifications triggering the illness-related manifestations. Thus, the aim of this study is to critically review the pathophysiological and clinical alterations of this metabolic disorder under various age groups (i.e., children, adults, and the elderly). Other vulnerable populations are revised too, for instance, individuals with malnutrition and (or) alcoholism, and diabetes mellitus. Nevertheless, the present work does not discuss in detail the mandatory vitamin C supplementation in scurvy.

**Keywords:** adults, ascorbic acid, children, diabetes mellitus, metabolism, pathophysiology, signs

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## 1. Introduction

Vitamin C functions as both an organic acid and a reducing agent and displays strong reactivity, involving important reactions in living beings [1]. The inability to synthesize vitamin C implies humans need exogenous sources of this essential micronutrient daily, and its plasma concentration correlates with the vitamin short-term intake (Figure 1) [2-4]. In principle, individuals do not store water-soluble vitamins, such as vitamin C, in large quantities throughout the body, before excreting them through urine (cobalamin is a water-soluble vitamin (B<sub>12</sub>) too, but the organism (liver) has reserves for 3-5 years) [2-6].



**Figure 1.** Widespread citrus fruits are rich sources of vitamin C (\*100 g fresh weight), among other important bioactive compounds [7].

The bioactive form of vitamin C is further identified as L-ascorbic acid or ascorbate (ASC); the other enantiomer, D-ascorbic acid, is not bioactive and has less affinity for vitamin C transporter proteins (see below) [8].

ASC is the reduced form of the vitamin and dehydroascorbic acid (or dehydroascorbate or yet DHA) is the oxidized form (in the human body, the reduced form of ASC is the most abundant and is recognized as an essential micronutrient) [9]. As touched upon above, in the role of an electron donor, or a reducing agent, ASC accounts for all the known physiological effects of the vitamin [10].

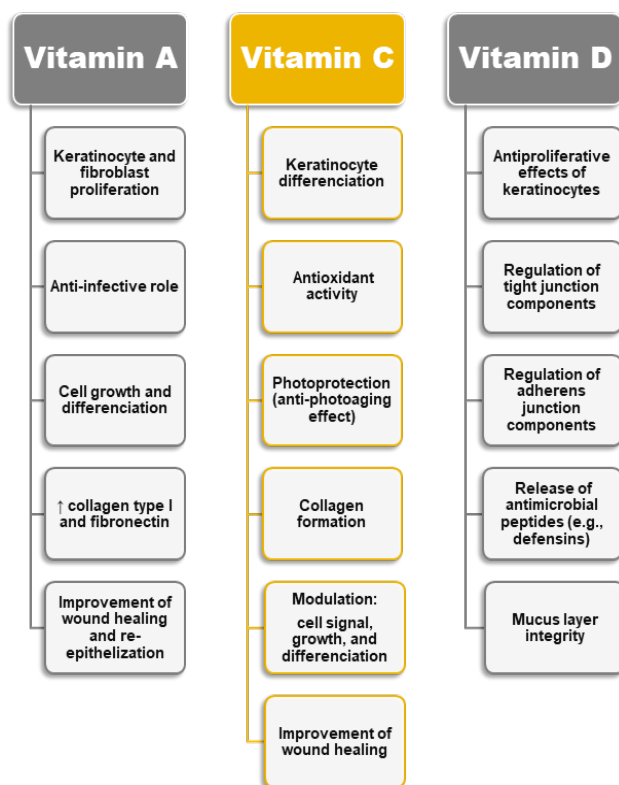
Vitamin C does not have well-described receptors in humans neither on the cell membrane, nor inside the cellular nucleus (as do the fat-soluble vitamins A and D) [11]. To exert biological effects, vitamin C must be transferred into cells by two different membrane transport families: (i) the sodium-dependent vitamin C transporter (or SVCT) protein isoforms (i.e., variants of a functional protein), SVCT1 (intestinal, renal, and liver epithelial cells) and SVCT2 (ubiquitous, but, most of all, in metabolically active tissues such as brain, heart, and retina), and (ii) the glucose transporters (or GLUTs), i.e., the glucose transporter isoform 1 or GLUT1 (ubiquitous, but, chiefly, in endothelial cells, osteoblasts, muscle cells, and retina), GLUT2 (small intestine,  $\beta$ -cells, liver, and brain), GLUT3 (neurons and cerebral cortex), the insulin-stimulated GLUT4 (heart, muscle, and adipose tissue), and GLUT8 (small intestine) [8,9] [12-19].

SVCT1 and SVCT2 assure active transport at the expense of the sodium electrochemical gradient across the cell membrane in an ATP-dependent manner [16,19]. In this transport, ASC is coupled to sodium and transported

directly by SVCTs; the excess intracellular sodium being actively exported in exchange for extracellular potassium through a sodium-potassium ATPase [16,19].

DHA, the oxidized form of ASC, competes with glucose for its uptake into cells via GLUT1 and GLUT3, followed by immediate DHA intracellular reduction to vitamin C [19,20]. GLUTs determine the cellular uptake of vitamin C via a facilitated diffusion in an energy-independent manner [19,21]. This transport requires the extracellular oxidation of ASC to DHA, which is imported by GLUTs and reduced back to ASC in the cell, thereby maintaining the concentration gradient of DHA [19].

Once in the intracellular environment (cytoplasm), the main activity of ASC-dependent dioxygenases is the hydroxylation of prolines in proteins involved in the formation of extracellular matrix (chiefly collagen synthesis) and the regulation of the metabolism and hypoxia responses, whereas in the nucleus, ASC is important for oxidative demethylation of 5-methylcytosine in deoxyribonucleic acid and removal of methyl groups from histone lysines [22]. Other significant effects include antioxidant activity (also a potential anti-cataract activity); iron transfer from transferrin to ferritin; reduction of iron and copper in hydroxylation reactions; conversion of folic acid into L-methylfolate (the active form of vitamin B<sub>9</sub>); enzymatic amidation of neuropeptides; inhibition of low-density lipoprotein (LDL) oxidation; immune process (various aspects); possible anticancer effects [23-25]. Similar to retinoic acid (the active form of vitamin A) and to 1,25-dihydroxycholecalciferol (the active form of vitamin D), vitamin C helps to maintain tissue health, especially by upholding the very complex tissue histophysiology (Figure 2) [26-37].



**Figure 2.** Examples of vitamin actions maintaining tissue integrity [26-37]. ↑: increased. The dynamic combination of these actions clearly strengthens the defense of epithelial barriers.

## 2. Laboratory Definition of Scurvy

Nowadays, laboratory tests for vitamin C have become routine and accessible to everyone, almost everywhere. Several authors consider vitamin C deficiency when its plasma concentration is below 0.2 mg/dL (11 μmol/L); symptoms then may occur [2,3] [38-43]. It is usually calculated from plasma and leucocyte vitamin C (the latter keeping vitamin C concentrations several times higher than plasma vitamin C, and probably being a better reflection of long-term dietary intakes of the vitamin, but somewhat tedious) [38,40,42,44]. However, according to other authors, there is not a definitive low plasma vitamin C concentration at which scurvy occurs [10]. In daily medical practice, it is common to encounter asymptomatic scurvy patients who have subclinical vitamin C deficiency, with significantly lower laboratory values than previously mentioned [3]. In reality, the threshold of vitamin C deficiency at which symptoms arise has not yet been defined. Perhaps it is partly because of the multifaceted causality of this disease, involving other factors (e.g., 10% of the general population, 30% of cigarette smokers, and 60% of acutely hospitalized patients), in whom it could contribute to fatigue and mood disturbance, immune system dysfunction, impaired wound healing, intricate regional pain syndrome, and complications at the cardiovascular level [45].

## 3. Pathophysiology and Clinical Manifestations of Scurvy in Various Age Groups

As previously stated, relying solely on laboratory tests may not lead to a proper scurvy diagnosis. In addition, food record is considered the golden standard method for evaluating meals, especially the regular consumption of sources high in vitamin C, such as fruits and vegetables [46]. Crucial for confirming the disease diagnosis are clinical signs, symptoms, and radiographic data (see farther below). Nonetheless, it is imperative to first define the age groups because of the ongoing, connected controversy surrounding it.

Children are individuals from 0 to 17 years old [47-49]. Adults are people from 18 to 59 years old (but in Scotland, the age of adulthood is 16 years or over) [50-52]. According to most authors, elderly are humans 60 years old or more (although few authors, including the World Health Organization, consider this age group from 65 years on) [53-57]. The oldest old are defined as individuals aged 85 or older [58,59].

There are subdivisions for each age segment and the reader is kindly requested to review these aspects in the aforementioned literature.

### 3.1. Scurvy in Children

This nutritional deficiency is rare in children of developed countries today, but warnings on its importance as a neglected clinical entity are frequent in the medical literature, particularly in infants of developing communities [60-69]. The lack of knowledge of this disease by health

professionals leads to misdiagnoses of bleeding, osteoarticular, and muscular conditions [60-69]. As an example, in a study of 106 scurvy cases in children (mean age of 44.65 months), 74 misdiagnoses (69%) were identified [61].

In reality, the accurate diagnosis of a particular nutritional deficiency may be complex and made amidst (or consider) the possibility of the coexistence of states of multiple deficiencies; hence the current rationale to classify the nutrients into those that cause specific clinical signs (type I nutrients) and those responsible for growth failure (type II nutrients), in the broader context of human malnutrition, as detailed in Tables 1 and 2 [70-73].

**Table 1. Type I Nutrients\***

|                                                                                                                                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Micronutrients:                                                                                                                                                                                               |
| (i) Microminerals (daily needs $\leq$ 100 mg):                                                                                                                                                                |
| Copper (Cu), fluorine (F), iodine (I), iron (Fe), manganese (Mn), selenium (Se)                                                                                                                               |
| (ii) Macrominerals (daily needs $\geq$ 100 mg):                                                                                                                                                               |
| Calcium (Ca)                                                                                                                                                                                                  |
| (iii) Water-soluble vitamins:                                                                                                                                                                                 |
| Cobalamin (B <sub>12</sub> ), folate (B <sub>9</sub> ), nicotinic acid (B <sub>3</sub> ), pyridoxine (B <sub>6</sub> ), riboflavin (B <sub>2</sub> ), thiamine (B <sub>1</sub> ), vitamin C (L-ascorbic acid) |
| (iv) Fat-soluble vitamins:                                                                                                                                                                                    |
| A (retinol), D (calcitriol or 1,25-dihydroxycholecalciferol), E ( $\alpha$ -tocopherol), K (phyloquinone in plant-based foods; menaquinones in fermented and animal-based foods [74])                         |

\*: adapted from [70,71].  $\leq$ : less than or equal to.  $\geq$ : greater than or equal to. Significant responses to essential micronutrient deficiencies include sustained growth in the early stages, specific signs of nutritional deficiencies, depletion of body stores, and reduction of nutrient-dependent metabolic functions; non-anorexic patients, diagnosis by biochemical tests, and anthropometric abnormalities only in late deficiencies [71].

**Table 2. Type II Nutrients\***

|                                                                              |
|------------------------------------------------------------------------------|
| Micronutrients:                                                              |
| (i) Microminerals (daily needs $\leq$ 100 mg):                               |
| Zinc (Zn)                                                                    |
| (ii) Macrominerals (daily needs $\geq$ 100 mg):                              |
| Magnesium (Mg), phosphorus (P), potassium (K), sodium (Na)                   |
| Macronutrients such as proteins (4 kcal/g) and constituents:                 |
| Carbon skeletons of essential amino acids, sulfur (S), nitrogen (N)          |
| Other molecules:                                                             |
| Energy substrates (carbohydrates, 4 kcal/g; lipids, 9 kcal/g), oxygen, water |

\*: adapted from [70,71].  $\leq$ : less than or equal to.  $\geq$ : greater than or equal to. Type II nutrients are components of all tissues in rather fixed amounts, and a lack of these nutrients causes an immediate cessation of growth and an inability to maintain the balance of the other type II nutrients [72]. Signs of deficiency are nonspecific because they can be attributable to the lack of any type II nutrient [72]. Biochemical abnormalities are absent and diagnosis is made by anthropometric abnormalities [71].

In a well-documented series of 28 cases of pediatric scurvy (mean age of 29 months), there was the following frequency of signs: limping or inability to walk (96%), lower limb tenderness (86%), bleeding gums (36%), fever (18%), and petechial hemorrhage (3.6%) [75].

It should be emphasized that bleeding gum is a significant and historical sign of scurvy, resulting from impaired collagen formation (indispensable support of periodontal tissue) and vascular fragility [76,77].

Additionally, every case of the above cited series displayed abnormal radiographic findings consistent with

scurvy (see the discussion below), and two cases had epiphyseal detachment [75]. In each instance, clinical improvement occurred within the first week after vitamin C administration [75].

The conventional radiographic findings of scurvy are recognizable but nonspecific (on magnetic resonance imaging (MRI), they are less well-characterized as pointed out ahead) [78]. They help to diagnose childhood, but not adult scurvy, and localize in the metaphysis of long bones (e.g., femur, tibia) [79].

More precisely, a metaphysis situates between an epiphysis (forming the bone growth plate) and a diaphysis, yet decomposing into two different regions, the primary and secondary spongiosa [80]. This latter metaphyseal region is the most affected during scurvy [81].

These are regions of active bone formation and, for this reason, with profuse vascularization, acting as a calcium depot [81,82]. Vitamin C seems to modulate the maturation of osteoblasts (bone-forming cells) and osteoclasts (large multinucleated cells taking part in bone resorption) [12,81,83,84]. Of interest, a pioneer study showed that vitamin C activates osteoblastogenesis and inhibits osteoclastogenesis via Wnt/ $\beta$ -catenin/ATF4 signaling pathways in ovariectomized Wistar rats—an osteoprotective effect of vitamin C [85].

As mentioned above, radiographic alterations localize in the metaphysis of all long bones, being more prominent in the lower limb, particularly at the knees, and comprising an increased density of periostitis (or inflammation of the periosteum) and epiphyseal shell with a central lucency (or Wimberger sign of scurvy); a clear metaphyseal band named Trummerfeld zone (or zone of rarefaction); a marked white line corresponding to thickened zone of calcification (or white line of Frankel); irregular margins (or Pelkan spurs); diffuse osteopenia (i.e., a low bone density less important than osteoporosis) [78,79,86-89].

The MRI and radiographic results are concordant, i.e., multifocal, symmetric bone-marrow changes in the metaphysis of long bones [86].

Remarkably, the first radiographic alteration may be a fracture or a subperiosteal hemorrhage, both manifestations of late or severe disease [78].

### 3.2. Scurvy in Adults

In adults, a latency period precedes before scurvy manifests, and the initial symptoms are lassitude, weakness, and irritability, vague, dull aching pains in the muscles or joints of the legs and feet, myalgia; shortness of breath may occur and the skin becomes dry and rough [90]. The weight loss is an important sign, especially in a multiproblem patient, i.e., with marasmus and severe wasting, alcoholism, drug addiction, AIDS (acquired immune deficiency syndrome), several opportunistic infections, who also developed dermatological manifestations of scurvy [90-93].

The most common cutaneous findings are follicular hyperkeratosis, perifollicular hemorrhages, ecchymoses (or small spots of discoloration in the skin or mucosa, arising from extravasation of blood), xerosis (or dry skin without scaling), leg edema, poor wound healing (Figure 2), and bent or coiled body hairs [94-96]. Of importance, perifollicular hemorrhage with corkscrew hair deformity,

resultant of follicular hyperkeratosis, is pathognomonic of scurvy [94,97,98].

As stated earlier, insufficient vitamin C results in faulty collagen synthesis, which increases vascular fragility, bleeding tendency, and related clinical signs [27,65]. As the clinical manifestations worsen, fever, hemarthrosis, subperiosteal bleeding, vasomotor instability, and fatality may ensue [40].

### 3.3. Scurvy in the Elderly and Other At-risk Groups

In industrialized countries, people most at-risk for developing scurvy are single, elderly men who, through chronic alcoholism, limited budget, or mental incapacity, have an inadequate diet [27,99]. Physicians should consider scurvy in vulnerable elderly patients who display a purpuric rash and edema, as these individuals may respond well to vitamin C treatment [100].

In the present-day world, other high-risk groups for scurvy encompass individuals susceptible to malnutrition, such as those with psychiatric illness, eating disorders, limited food access in homeless situations, and malabsorptive states (e.g., gastric bypass, celiac disease, and hemodialysis) [101,102].

Inflammatory bowel diseases are chronic inflammatory conditions of the gastrointestinal tract comprising two main clinical entities: Crohn's disease and ulcerative colitis [103]. In such patients, the avoidance of fruits and vegetables can be so strict that they may develop symptoms of scurvy [103]. In fact, there are several case reports of patients with Crohn's disease developing scurvy [104-106]. As a result, patients with Crohn's disease should be screened for vitamin C deficiency and receive prophylactic vitamin C supplements everyday [106].

There is a marked decrease in vitamin C levels in women using oral contraceptives (OCs) compared to control subjects [107]. Using OCs, i.e., those containing estrogens, correlates with lower levels of vitamin C, owing to the increased rate of the catabolism of the vitamin [108,109]. The inherent lack of vitamin C reserves in the body, a poor diet in this essential micronutrient, and the use of hormonal contraceptive, can end up provoking scurvy [108,109].

At present, there is very limited information on vitamin C deficiency in the oldest old population.

### 3.4. Scurvy in Patients with Diabetes Mellitus in the 21st Century?

There are several lines of evidence suggesting a greater need for vitamin C supplementation in diabetes mellitus (DM). Essentially, plasma concentrations of this vitamin are lowered in diabetic patients compared to healthy subjects [110]. There is a renal leak of the vitamin in DM whose clinical relevance depends on the (still undetermined) magnitude of this phenomenon [111]. Furthermore, carnitine is an essential cofactor in fatty acid (FA) metabolism (i.e., in the transport of long-chain FA from the cytoplasm into the mitochondrial matrix for the  $\beta$ -oxidation), being found in higher amounts in animal and fish proteins when compared to vegetal sources [12,112,113]. Diminished carnitine levels resultant from

vitamin C deficiency may lead to defective transport of long-chain FA into the mitochondria and more triglyceride (TG) synthesis [114]. Indeed, diabetic dyslipidemia is the most common disorder of lipoprotein metabolism in patients with DM, being characterized by the atherogenic triad of increased TG, decreased high-density lipoprotein cholesterol (HDL-C), and small, dense LDL particles [115]. According to a systematic review and dose-response meta-analysis, vitamin C supplementation significantly improved lipid profile via decreases in TG and total cholesterol, but failed to affect small, dense LDL and HDL-C in DM populations [116]. Also, a 12-month single blind multicenter randomized control trial even concluded that vitamin C with metformin (a first-line antidiabetic drug, i.e., an antihyperglycemic and insulin-sensitizing biguanide derivative) is more effective in reducing risks for DM long-term complications, compared to acetylsalicylic acid and metformin [117,118].

Taken together, these data point to the necessity of a more careful monitoring of the nutritional status in DM patients, i.e., of the alterations of carbohydrates (primary concern of the disease), lipids (e.g., glucose is the major precursor of 3-glycerol phosphate for triglyceride synthesis in white adipose tissue in the fed state), and vitamin C metabolism, so that to diagnose and promptly treat the atherogenic diabetic dyslipidemia and prevent vitamin C deficiency (or scurvy) [119,120].

## 4. Concluding Remarks

Humans are at the highest level of the phylogenetic scale. In such complex organisms, researchers must consider diverse molecules and their interactions, rather than focusing on a single aspect. It is impressive how an organic function may be intricate enough to be accomplished by different molecules, such as the reinforcement of epithelial barriers by vitamins A, C, and D (Figure 2). ASC is in fact a versatile vitamin and a reactive compound, interacting with many other substances and, in doing so, promoting health to humans.

Advances in medicine have largely contributed to longer human lifespans. However, it is still necessary to better understand the prevalence of chronic diseases (e.g., nutritional deficiencies such as scurvy) as well as their features in certain populations of older adults, in particular in the oldest old population.

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## Conflict of Interest

The author declares no conflict of interest.

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