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Mini Review

Vitamin C deficiency: a review

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Introduction

Described in seafarers in the 18th century, Vitamin C deficiency is the cause of the clinical syndrome that became known as 'The Scurvy' [1]. Observations that dietary supplementation with citrus fruits effected a rapid cure led to organized preventative measures, and helped to establish the importance of a balanced diet in maintaining health. Vitamin C is an essential nutrient also known as Ascorbic acid, isolated in 1923, and chemically produced in 1933. This was the first example of a vitamin being developed and then used as a therapeutic pharmacological preparation [2].

The importance of recognizing Scurvy has, in modern times, perhaps been overshadowed by numerous claims for largely unproven benefits of vitamin C supplementation, suggested as a panacea in treating everything from the common cold to cardiovascular diseases and cancer [3]. Classical scurvy is rare in otherwise healthy young adults in the west, but in less affluent societies the condition may be related to mal-nutrition, particularly in areas troubled by conflict and famine.

The diagnosis of scurvy may be easily overlooked by physicians. However, a case presenting with full blown and typical characteristic clinical manifestations is readily recognizable and prompt diagnosis permits inexpensive and highly effective treatment [4-5].

Epidemiology

There is a common misconception that scurvy is a disease of a bygone era. However, insufficient levels of vitamin C may be more prevalent in the population than is generally acknowledged. A large UK community-based study reported that 1.2 % of adults were found to have insufficient vitamin C levels. Another study from Scotland reported nearly 20% with insufficient levels. However, the clinical implications of these findings are not fully understood [6–9].

Dietary Recommendations, Absorption and Pharmacokinetics

Recommended daily allowance (RDA) for vitamin C in the UK is 40mg for adults [10]. Additional requirements are important in particular sub-populations e.g., in pregnancy 50-60 mg daily. In the USA, Canada and some European states, smokers are also advised to take an additional supplement due to increased utilization of vitamin C [11].

Between 70-90% of vitamin C is absorbed based on a daily intake of 180 mg, and oral supplements are absorbed similarly [12]. Passive diffusion occurs across the buccal mucosa [13], but most absorption occurs in the Jejunum, at the surface of the villi, using an active sodium dependent Vitamin C transporters (SVCTs) [14,15]. SVCT1 is also present in the renal tubules and promotes active resorption of ascorbic acid into the renal capillary bed from the proximal convoluted tubules. Vitamin C is a water-soluble, and is excreted by the kidneys proportional to plasma concentration of metabolites, specifically dehydroascorbic acid; 2,3-diketogulonic acid and oxalic acid [16]. Vitamin C is rarely toxic as excretion is increased as plasma concentrations rise. Minor gastro-intestinal effects such as diarrhea have been reported with very high oral doses of up to 4g/day [17]. In most healthy individuals overzealous consumption poses no serious threat. Uncommonly, certain patient populations maybe at risk of toxicity e.g. those with renal disease, caused by effects of oxalate accumulation. Reports describe hypouricemia causing increased susceptibility to hemolysis [18], and vitamin C toxicity was suggested as a contributing factor in a fatal outcome associated with Glucose – 6- phosphate dehydrogenase deficiency [17].

The biochemical role of vitamin C is mediated by its active form L-Ascorbic Acid, essential in the formation and repair of collagen [19]. *In-vitro* studies have confirmed the importance of ascorbic acid in the synthesis of Type 1, III and IV collagens. Type IV collagen is a key component required for the structural integrity of blood vessel walls and the cutaneous basement membrane. Collagen is the major structural element in nails, cartilage, bones, teeth and hair [20,21]. Lack of Vitamin C has also been demonstrated to increase DNA hypermethylation further impairing collagen synthesis, leading to poor wound healing, along with predisposition to soft tissue infections with potentially lethal complications [22] (Table 1).

Vitamin C Deficiency

Unlike other species, in humans there is no system for *in-vivo* synthesis of vitamin C and thus this necessitates adequate and regular dietary intake. This is readily achieved by eating a balanced diet containing fruits and vegetables. Animal sources contain low levels of vitamin C whilst many plant sources are rich. It should be noted that prolonged food storage and boiling of vegetables rapidly denatures ascorbic acid. Normal serum concentration of Vitamin C ranges between 0.6-2 mg/dl. A deficiency state may develop following dietary absence of vitamin C intake in just 2 weeks, as ascorbic acid is water soluble with no specific binding protein nor any specific storage mechanism [25,27].

In any patient identified with a deficiency state, it is crucial to consider and assess for other states of depletion, alongside a careful review and consideration of causes, potential underlying conditions, as well as dealing with effects of the deficiency. Table 2 provides a practical classification and an approach which may guide a detailed assessment and understanding of the causes of vitamin C deficiency.

Table 1: Non-Collagen related functions of Ascorbic Acid

Non-collagen related functions of Ascorbic Acid	
Synthesis of Neuro-transmitters	• Synthesis of nor-epinephrine from dopamine by acting as a co-enzyme for dopamine beta-hydroxylase [19]
Bile acid and cholesterol homeostasis	• Synthesis of bile acids from cholesterol. • Potentiating the action of cholecystokinin Theoretical possibility of gall stone formation and hypercholesterolemia in deficient states [23,24]
Iron absorption	• Augments the absorption of iron by inhibiting Hepcidin • Reduction of ferric to ferrous iron • Stimulate transferrin iron uptake via an intra-cellular reductive mechanism [25,26]

Table 2: Etiology of Vitamin C deficiency.

Etiology of Vitamin C Deficiency	
Social and Economic factors associated with poor dietary intake of Vitamin C	• Children fed exclusively on cow's milk • Children in situations of dietary neglect • Poverty, famine, and conflict zones • 'Food Deserts'; Cheap foods, low in nutritional value are easily available (Incidence 10-17%) [28] • Substance abuse including alcohol and narcotic abuse, often associated with poor nutrition [29]
Gastrointestinal conditions, often caused by reduced absorption	• Inflammatory bowel disease involving small bowel • Short bowel syndrome [30–33] • Severe IBS on restrictive diets
Systemic illnesses and reduced utilization	• Type 1 Diabetics • Vitamin C uptake is enhanced by insulin and suppressed by high blood sugar levels [34] • Chronic Kidney Disease and hemodialysis. At risk of deficiency, but also toxicity leading to oxalate injury [16,18]
Miscellaneous causes, due to multiple factors, and common in the wider society	• Smokers. Increased consumption of vitamin C [11] • Elderly populations and 'Tea and Toast' diet • Psychiatric illnesses and dementia [35,36] • Neglect among the elderly and infirm • Eating disorders [37-39]

Clinical Manifestations

Clinical features of Vitamin C deficiency typically begin to develop within weeks of dietary deprivation with irritability, weight loss and anorexia. This is followed by marked gingival swelling, peri-follicular skin hemorrhages, corkscrew hairs, loss of teeth and hyperkeratosis. Other manifestations are linked to small vessel wall fragility with mucocutaneous petechial rashes, nailbed splinter hemorrhages, retinal vitreous and optic nerve hemorrhages and extensive sub-cutaneous ecchymoses. Bones may become brittle and characteristic so called sternal scorbutic rosary may develop in children. Hemarthroses and subperiosteal hemorrhage typically result in excruciating bone and joint pains. Hair loss is common as is dependent 'woody oedema' secondary to capillary leak, due to the vessel wall being unable to withstand hydrostatic pressure. Untreated, scurvy is a severely debilitating condition and potentially fatal [4,12,27].

Diagnosis

A detailed history and thorough examination provide vital information, but it is the recognition characteristic pattern of features which should prompt the physician to consider scurvy, which remains a clinical diagnosis. A focused and nutrition centric history may provide valuable insights into a potential deficiency state. Epidemiologically, deficiency of Vitamin C occurs when the plasma concentration of Ascorbic Acid is below 0.3 mg/dl. Serum values do not necessarily reflect the intra-cellular concentration of ascorbic acid, although measurement of leukocyte concentration of ascorbic acid is seldom required [27].

Vitamin C is a negative acute phase reactant and many laboratories advise caution in the interpretation of results in the context of an acute illness, when inflammatory markers may be elevated [40,41]. Samples must be transported immediately (within 15-60 minutes) to the laboratory, shielded from light and then the plasma is centrifuged before being sent to a reference laboratory by same day courier [42]. Accordingly, results should always be interpreted with caution and it is the clinical picture which is paramount for diagnosis.

Treatment

Therapy for scurvy is remarkably simple using supplemental Vitamin C at 500-1000 mg daily doses in adults and 300 mg for children. An alternate regimen suggested is 1-2 gm daily for the first 3 days followed by 500 mg per day for a week and 100 mg per day thereafter for 3 months. Importantly, other concomitant vitamin deficiencies are frequently encountered and must be considered. Clinicians should ensure that all efforts are made to identify and correct the factors that may have contributed. Dietetic and community nutritionist follow up are strongly recommended. General symptoms improve rapidly, and bleeding often resolves in days. Hair and skin changes take months to recover. Dentition, bone and joint involvement may need surgical correction, and a bleed into the vitreous may require vitrectomy [27]. Finally, and depending on the social situation of a patient and potential concerns around neglect, it may be appropriate to trigger safeguarding procedures, especially if children are identified at potential risk.

Conclusion

Vitamin C deficiency is more prevalent than is generally acknowledged. While socio-economic factors associated with poor nutrition are the most common cause for symptomatic disease worldwide, organic disease may be an important contributing factor and is increasingly recognized. In addition, the prevalence of scurvy in urban areas with lower socio-economic status where cheap, low nutritious diet, combined with a propensity for substance abuse, is on the rise. Simply put, the demographic is changing and although rare, physicians must be aware and be able to diagnose scurvy promptly, permitting immediate and highly effective treatment, along with measures to protect individuals from deficiency states in the future. The health implications of low vitamin C levels, without the manifestations of scurvy, needs further investigation.

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