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REVIEW ARTICLE

Pharmacist Attention on the Significance of Vitamin C

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ABSTRACT

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin found in many multivitamin supplements and single-entity nutritional supplements. The body stores approximately 1.5 g of ascorbic acid; the highest levels are found in the brain, pituitary and adrenal glands, leukocytes, and eye tissues. The bioavailability of vitamin C in foods is approximately 70% to 90%; Described the RDA (Recommended daily allowances) of vitamin C. It has many vital uses in therapy of diseases like common cold, cancer, asthma. It lowers the blood pressure, it has an antihistamine effect. It is used in cataracts and Preeclampsia. The excessive intake or the over supplementation of ascorbic acid cause toxicity including diarrhoea, nausea, and abdominal cramps. The pharmacist should aware about the ADR's of vitamin C and should council the patients about recommended doses. Deficiency of vitamin c cause scury disease. The pharmacist should aware about the RDA of vitamin C .the RDA varies from normal people to smokers and pregnancy women. The pharmacist should suggest to patients to take the fruits and vegetables which are high sources of vitamin C. This present study has attempted to review the significance of vitamin C for the humans and the attention for pharmacist about the dispensing, prescribing and counselling of vitamin C to the patients.

KEYWORDS

Vitamin C, RDA, Benefits of Vitamin C, Pharmacist Counselling

INTRODUCTION

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin found in many multivitamin supplements and single-entity nutritional supplements. Vitamin C has an important role in the formation of collagen, carnitine, amino acids, and hormones; is an essential component in the healing of wounds and burns; and aids in the absorption of iron[1,2]. Moreover, vitamin C is classified as an antioxidant, and many clinical studies report that megadoses (500 to 1000 mg/day) of ascorbic acid may prevent, or shorten the duration of, the common cold[1,2].

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Vitamin C is a six-carbon lactone which is synthesized from glucose by many animals. Vitamin C is synthesized in the liver in some mammals and in the kidney in birds and reptiles. However, several species—including humans, non-human primates, guinea pigs, Indian fruit bats, and Nepalese red-vented bulbuls—are unable to synthesize vitamin C. When there is insufficient vitamin C in the diet, humans suffer from the potentially lethal deficiency disease scurvy[3].

Vitamin C plays significant functions in the human body, though its function at the cellular level is not very clear. Vitamin C is needed for collagen synthesis, the protein that serves so many connective functions in the body. Among the body's collagen-containing materials and

structures are the framework of bone, gums and binding materials in skin muscle or scar tissue. Production of certain hormones and of neurotransmitters and the metabolism of some amino acids and vitamins require vitamin C.

This vitamin also helps the liver in the detoxification of toxic substances in the system, and the blood in fighting infections. Ascorbic acid is important in the proper function of the immune system. As an antioxidant, it reacts with compounds like histamines and peroxides to reduce inflammatory symptoms. Its antioxidant property is associated with the reduction of cancer incidences[4,5].

Metabolism of Vitamin C

Ascorbic acid is a white crystalline sugar that naturally occur in chemical forms of L-xylo-ascorbic acid and D-xylo-ascorbate. L-xylo-ascorbate is without vitamin activity. It is reversibly oxidized to L-dehydroascorbic acid on exposure to copper, heat or mildly alkaline conditions. Both L- ascorbic acid and L-dehydroascorbic acid are physiologically active forms of vitamin C. Further oxidation of L-dehydroascorbic acid to 2,3-diketo-L- gulonic acid and oxalate is irreversible (Thurnham, 2000). The sulphation of ascorbate to ascorbate-2- sulphate is a minor pathway with at present, no known clear biological significance for man. It is unlikely neither to have antiscorbutic properties nor to act as an important sulphating agent in vivo (Bates, 1981).

The principal pathway of oxidation and turnover of ascorbic acid is believed to involve the removal of two electrons in succession and to yield first the ascorbate free radical (AFR) and then dehydroascorbate. Two molecules of AFR may react together to form one molecule of ascorbate and one of dehydroascorbate. Alternatively, AFR may be reduced by a microsomal NADH-dependant enzyme, mono-dehydro-L-ascorbate oxidoreductase to ascorbate (Bates, 1981).

Ascorbic acid acts as a reducing agent by being an electron donor to 8 human enzymes, including those enzymes that assist in synthesizing collagen, carnitine, norepinephrine, peptide hormone, and tyrosine metabolism[6]. There are a few examples of how vitamin C may provide protection benefits by acting as an antioxidant. By decreasing low-density lipoprotein (LDL) oxidation, vitamin C interferes with LDL's structural modification, which leads to atherogenesis in vitro; unfortunately, in vivo effects are not as consistent[6].

Vitamin C Pharmacokinetics

The body stores approximately 1.5 g of ascorbic acid; the highest levels are found in the brain, pituitary and adrenal glands, leukocytes, and eye tissues. The pharmacokinetics of vitamin C is dependent upon its route of administration. It is available orally, both in foods and as an oral supplement, as well as by intramuscular, subcutaneous, and intravenous injection.

The bioavailability of vitamin C in foods is approximately 70% to 90%; the range is due to the degradation that occurs secondary to cooking or the interaction with preservatives such as sodium bicarbonate. Higher plasma concentrations are possible with the intravenous routes due to the lack of tolerability of oral vitamin C at higher doses.

Additionally, in doses more than 1 g/day or in patients with gastrointestinal disease, absorption decreases to less than 50%. Ascorbic acid is reversibly oxidized to dehydroascorbic acid or excreted in the urine, either after being metabolized to inactive metabolites or unchanged with higher intake[7].

The RDA for vitamin C differs among gender, age, and smoking status, as noted in Table 1. In regard to gender, studies have found that the serum ascorbate level is higher in women of the same population, which may be in part because of the larger body and muscle mass of men as well as hormonal or metabolic differences among men and women. Therefore, adult men require a higher dietary intake of vitamin C versus adult women[8].

The RDA for infants is determined by the AI(Adequate intake), defined as the average

vitamin C intake of infants fed primarily with breast milk from the age of 0 to 6 months and the average intake of vitamin C from breast milk and solid foods for infants 7 to 12 months. For children and adolescents, the RDA is estimated by relative body weight. Evaluative studies were completed to determine if there should be a difference in the RDA for adults aged 19 to 30 years, 31 to 50 years, and older than 51 years.

Table 1: Recommended Daily Allowances of Vitamin C

Recommended Daily Allowances of Vitamin C			
Group	RDA(Recommended dietary allowances)		
Adult men	90 mg/day		
Adult women	75 mg/day		
Pregnant women	80-85 mg/day		
Lactating women	115-120 mg/day		
Smoker	Addotional 35 mg/day		
Adolescents, male 14-18 years	75 mg/day		
Adolescents, female 14-18 years	65 mg/day		
Children	1-3 years	4-8 years	9-13 years
	15 mg/day	25 mg/day	45 mg/day
Infants	0-6 months : 40 mg/day	7-12 months : 70 mg/day	

Because the absorption or metabolism of ascorbic acid did not change in these various age groups, the RDA recommendations are the same for adults older than 18 years; RDAs are adjusted based on gender, smoking status, and pregnancy, however. Hemodilution and active transport to the fetus decreases the plasma vitamin C level during pregnancy and, therefore, the RDA is higher at this time. Additionally, if a woman continues to abuse drugs or smoke cigarettes during pregnancy, she should be advised to further increase her vitamin C intake.

Similarly, any adult who smokes has a higher RDA, because smokers have a higher vitamin C turnover in their plasma, possibly because of substances found in the cigarette that cause increased oxidative stress. Although the RDA has not been adjusted for people who are exposed to second hand smoke, because of the exposures to the dangerous substances in cigarettes that second hand smokers experience, it is recommended that they fully meet the RDA[8].

Uses of Vitamin C

Cancer

Inverse relationships between dietary vitamin C and certain cancers, as well as lower levels of vitamin C in patients with cancer, have been noted in case control studies. Considering vitamin C's antioxidant properties, it has also been studied prospectively to evaluate its effectiveness. Most studies have found that there is little evidence to support that the incidence of cancer is decreased with additional vitamin C supplementation at modest doses.

Additionally, research has been conducted to see the effect of both oral and intravenous vitamin C on cancer mortality. One study concluded that oral vitamin C did not show a difference in patients when compared with placebo; however, newer data suggest that because intravenous vitamin C can produce higher plasma levels than oral vitamin C due to saturation issues, it is possible that dosage form may play a role. Patients need to discuss vitamin C supplementation, especially at higher doses, with their oncologists, due to potential interactions with chemotherapy and radiation[8,9].

Cataracts

An 8-year, multicenter prospective study was conducted in 1980 evaluating the relationship between vitamins C and E, carotene, and riboflavin and cataract extraction. This study included 50,828 registered female nurses aged 45 to 67 years. The conclusion in regard to vitamin C was that supplementation with vitamin C for at least 10 years may decrease the risk of severe cataracts requiring extraction. There is a high concentration of vitamin C found in the ocular tissues, suggesting a

connection between the oxidative destruction to the eye and the use of vitamin C[10].

Even though the aforementioned study did show a benefit, however, there is no strong recommendation about the use of vitamin C supplementation in preventing extractions due to cataracts[8].

Cardiovascular

The use of vitamin C supplementation (and/or vitamin E) at 500 mg daily to decrease cardiovascular events in 14,641 male physicians 50 years or older was evaluated in the Physician's Health Study II Randomized Control Trial (PHS II). The study found no statistically significant difference between the study and placebo groups in preventing cardiovascular or adverse events. PHS II authors concluded that although this study did not show beneficial effects of vitamin C on cardiovascular events, consideration should be made to study vitamin C at varying doses among other populations[11].

Preeclampsia

Antioxidants such as vitamin C inhibit perioxidation reactions so cellular integrity is maintained during pregnancy, and there is evidence that shows women who have preeclampsia have lower levels of vitamin C. In one study that gave vitamin C to 283 women at risk of preeclampsia, a 17% versus 8% decrease in preeclampsia was noted. In another study of 109 women, no difference was noted. Finally, a multicenter study of 1877 women, the Australian Collaborative Trial of Supplements, evaluated the effect of the supplementation of vitamin C 1000 mg (and vitamin E 400 IU) in women pregnant with their first child. Of note, the dietary intake was higher than the RDA in most of the women enrolled in the study. The authors concluded that daily supplementation did not decrease the risk of preeclampsia[12].

Ascorbic Acid and Wound Healing

Ascorbic acid plays a critical role in wound repair and healing/regeneration process as it stimulates collagen synthesis. Adequate supplies of ascorbic acid are necessary for normal healing process especially for post-operative patients. It has been suggested that there will be rapid utilization of ascorbic acid for the synthesis of collagen at the site of wound/ burns during post-operative period[14]. Hence, administration of 500 mg to 1.0 g/day of ascorbic acid are recommended to accelerate the healing process[13].

Ascorbic Acid and Common Cold

The most widely known health beneficial effect of ascorbic acid is for the prevention or relief of common cold. Pauling[15] suggested that ingestion of 1–2 g of ascorbic acid effectively prevents/ ameliorate common cold.

Ascorbic Acid has also been helpful for relief of back pain and pain from inflamed vertebral discs. Antioxidants such as vitamin C and vitamin E are an important part of the body's defence against muscle damage from exercise. Strenuous exercise increases the body's production of free radicals, which in turn can cause muscle damage, which manifest as swollen or painful muscles. While exercise increases the body’s natural defence against free radicals, athletes who are doing intense training may benefit from the addition of antioxidant supplements to their diets (Dekkers *et al.*, 1996).

Vitamin C acting as an antioxidant is helpful in the treatment of asthma (Ruskin, 1947). In asthma, vitamin C may relieve the bronchospasm caused by noxious stimuli or when this tight-chest feeling is experienced during exercise (Meric *et al.*, 1991). Large doses (1-2 g/d) of vitamin C have been found to reduce asthma symptoms significantly (Hatch *et al.*, 1995).

Vitamin C is a natural laxative and may help with constipation problem. Bioflavenoids, taken with vitamin C (1200 mg each) has been shown to help relieve hot flashes associated with menopause (Smith, 1964).

Indications of Vitamin C

Considering that vitamin C is a nutraceutical and that these agents do not always have strong scientific data to support various indications, there are only 2 FDA-approved indications for vitamin C: the treatment of scurvy and

Table 2: Indications of Vitamin C

Indication	Adult dose	Other dosing
Treatment of scurvy	100-250 mg PO, SC, IM, 1-2 times daily	Children: 100-300mg/day PO, SC, IM, or IV in divided doses. Infant: 50-100mg/day PO, SC, IM, or IV in divided doses.
Prevention of vitamin C deficiency in TPN	100 mg IV in TPN	N/A
Idiopathic methemoglobinemia	300-600 mg/day PO in divided doses	N/A
Adjunct to deferoxamine therapy in treatment of chronic iron toxicity	100-200 mg/day PO daily, 1-2 hours after deferoxamine infusion starts	N/A
Urinary acidification	4-12 g/day PO,IV, IM, SC in 3-4 divided doses	N/A
Treatment of chronic recurrent furunculosis in patients with neutrophil dysfunction	100 mg/day PO for 4 to 6 weeks	N/A
Reduction in resuscitation fluid volume requirements in patients with severe burns	66 mg/kg/hr continuous IV for first 24 hours (limited data)	N/A

IV: intravenous, IM: intramuscular, SC: subcutaneous, PO: by mouth, TPN: total parentral nutrition

nutritional supplementation. Vitamin C is also used in patients for the treatment of burns, furunculosis, iron toxicity, and methemoglobinemia, as well as for urinary acidification (Table No. 2)[7].

Deficiency of Vitamin C

Deficiency of vitamin C can cause anemia, scurvy, infections, bleeding gums, muscle degeneration, poor wound healing, atherosclerotic plaques and capillary hemorrhaging. Neurotic disturbances consisting of hypochondriasis, hysteria and depression followed by decreased psychomotor performances have been reported in ascorbic acid deficiency (Kinsman and Hood, 1971). Vitamin C deficiency is often associated with gingivitis.

Vitamin C deficiency, defined as an intake of less than 10 mg/day, leads to scurvy, a disease that was found in sailors who were on long voyages during the 15th to 18th centuries. Scurvy is rare in developed countries due to the availability of foods that are enriched with vitamins[9]. However, despite the availability of vitamin containing foods and vitamin supplements, the National Health and Nutrition Examination Study reported that 10% to 14% of adults in the United States are deficient in vitamin C. Taking this into consideration, a differential diagnosis of scurvy should be taken into account in patients who present with symptoms consistent with scurvy and who report a dietary history with nutritional deficiencies[16].

Scurvy, which can lead to syncope and sudden death, may occur over time and is dependent on the amount of vitamin C stored in one's body. Initial signs and symptoms, including fatigue and malaise, usually appear within 1 month of

vitamin C deficiency with body stores less than 300 mg. Cutaneous findings, such as petechiae, ecchymoses, purpura, poor wound healing, hyperkeratosis, and corkscrew hairs (bent or coiled body hairs) occur due to decreased collagen synthesis and weak connective tissues. Additionally, joint pain and back pain may be present[17]. If an individual has teeth, inflammation and bleeding in the gums may occur as well as the loosening/loss of teeth. Also, hematologic blood work may show iron deficiency anemia and leukopenia[16,17].

In developed countries, the practice of boiling milk for infants is not as common as feeding them breast milk or formula. Boiling cow's milk is not recommended, because heat may destroy the little vitamin C that is present. Additionally, most people are able to obtain the RDA for vitamin C through fruits, vegetables, and other foods; however, there are some people who have limited resources.

At highest risk of vitamin C inadequacy are the elderly, indigent, alcohol- or drug-abusing, and mentally ill populations. Vitamin C inadequacy may also occur due to pathologic conditions, such as intestinal malabsorption, end-stage renal disease, or cancer. These conditions may hinder the body's ability to absorb vitamin C[9].

Vitamin C in adequacy, defined as an intake more than 10 mg/day but below the RDA, is more common than vitamin C deficiency in developed countries. The following populations are at greatest risk of vitamin C inadequacy: smokers/ passive smokers, infants fed with evaporated/ boiled milk, individuals with limited food variety and those with malabsorption, cachexia, or cancer disorders[9,18].

Vitamin C Toxicity

Toxicity, normally, does not occur since vitamin C is water-soluble and is regularly excreted by the body. Excess ascorbic acid excreted in the urine gives a false-positive test for sugar. High levels of vitamin C interfere with copper absorption (Finley and Cerklewski, 1983). Vitamin C should be avoided by those who suffer from kidney stones, as it can convert to oxalate (Piesse, 1985). However some research suggests that vitamin C only undergoes this transformation in urine after the urine has left the body (Wandzilak and D'Andre, 1994).

There are some data that link higher vitamin C doses with increased oxalate excretion and kidney stone formation, including a study that included 51,529 male health professionals aged 40 to 75 years who provided full dietary information every 4 years, unless a kidney stone occurred.

This study did show an association between high vitamin C dietary intake and the increased risk of kidney stones; however, because much of the food with high vitamin C also had high potassium levels, they concluded that there is no strong data that support decreasing dietary vitamin C for the prevention of stones[19].

Additionally, increased iron absorption leading to iron overload is a possibility with high levels of vitamin C intake; however, data suggest that although this could be an issue in people with blood disorders, it does not increase iron stores in healthy individuals. Therefore, because the studies did not show conclusive evidence of adverse effects of vitamin C in the aforementioned areas, the UL was based on the occurrence of diarrhea and gastrointestinal disturbances[8].

Dietary Sources of Vitamin C

Ascorbate is found in many fruits and vegetables[20]. Citrus fruits and juices are particularly rich sources of vitamin C but other fruits including cantaloupe and honeydew melons, cherries, kiwi fruits, mangoes, papaya, strawberries, tangelo, tomatoes, and water melon also contain variable amounts of vitamin C.

Vegetables such as cabbage, broccoli, Brussels sprouts, bean sprouts, cauliflower, kale, mustard greens, red and green peppers, peas, and potatoes may be more important sources of vitamin C than fruits, given that the vegetable supply often extends for longer periods during the year than does the fruit supply.

Table No.3[9]: Common Vitamin C- Containing Foods

Common Vitamin C- Containing Foods					
> 90 mg per serving		**45-90 mg per saving**		**<45 mg per saving**	
½ cup raw red pepper	95 mg	1 medium orange	70mg	½ cup grapefruit	39mg
¾ cup orange juice	93 mg	¾ cup grapefruit juice	70mg	½ cup raw broccoli	39mg
		1 medium kiwi fruit	64mg	½ cup cantaloupe	29mg
		½ cup raw green pepper	60mg	1 medium baked potato	20mg
		½ cup cooked broccoli	51mg	1 medium raw tomato	17mg
		½ cup fresh strawberries	49mg	½ cup cooked spinach	9mg

Supplements of Vitamin C

Vitamin C supplements fall under the dietary supplement category, manufacturers do not need FDA approval prior to manufacture, and are therefore responsible for the safety and efficacy of their products[21].

According to Natural Medicines Comprehensive Database, there are 12,437 products containing ascorbic acid and 219 of them are United States Pharmacopeia (USP) verified[22].

Nonprescription Vitamin C Supplements

Nonprescription vitamin C dietary supplements typically contain ascorbic acid, which is considered to have bioavailability equivalent to that of naturally occurring ascorbic acid in foods such as orange juice and broccoli, but some supplements contain other forms, such as sodium ascorbate, calcium ascorbate, other mineral ascorbates, and ascorbic acid with bioflavonoids[23,24]. Adult multivitamin supplements typically contain doses of 60 to 100 mg, which are considered to be adequate if supplements are required[2]. Vitamin C is available in several dosage formulations, including capsule, tablet, lozenge, syrup, chewable tablet, effervescent tablet, oral disintegrating tablet, and gummy. According to the *Handbook of Nonprescription Drugs*, the recommended daily upper limit of vitamin C is 2 g[2].

CONCLUSION

Vitamin C is a water soluble vitamin and it is an essential nutrient for human growth and development. It is an antioxidant. Everyone should have the sufficient amount in dietary intake of vitamin C.

It has many vital uses in therapy of diseases like common cold, cancer, asthma. It lowers the blood pressure, it has an antihistamine effect. It is used in cataracts and Preeclampsia.

Vitamin C is help for the relief of back pain and and it is acts as laxative and helps in constipation problem.

The pharmacist should aware about the RDA (Recommended daily allowances) of vitamin C and should give proper counselling to the patient. The RDA varies from normal people to smokers and pregnancy women. The pharmacist should suggest to patients to take the fruits and vegetables which are high sources of vitamin C.

The pharmacist should aware about the symptoms of scurvy disease. The excessive intake or the over supplementation of ascorbic acid cause toxicity including diarrhea, nausea, and abdominal cramps. The pharmacist should

aware about the ADR's of vitamin C and should council the patients about recommended doses.

Some patients will use the vitamin C supplements rather than dietary intake. In these cases the pharmacist should aware about the drug interactions, contraindications and special precautions. The patients should take the recommended supplements by the health care provider.

Vitamin C supplements may interact with chemotherapeutic agents, so patients should be advised to talk to their primary health care provider prior to using these supplements. Some research indicates that vitamin C supplements may also interact with HMG-CoA reductase inhibitors (statins) when taken in combination with other antioxidants, such as beta carotene and vitamin E. This combination may decrease the effectiveness of statins; however, it is not known whether vitamin C alone affects the effectiveness of this drug class. In addition, megadoses of vitamin C may decrease the effectiveness of some agents, such as protease inhibitors, warfarin, estrogens, and niacin[25-28].

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