Vitamin C: Prevention of Chronic Diseases and Optimal Doses

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ABSTRACT
The role of vitamin C in prevention and treatment of scurvy is well accepted. In spite of having long history as the candidate of alternative therapy for the prevention and treatment of cancer, still there is no common conclusion on the topic. However, its biochemical reaction as an antioxidant and its immunostimulating effects drew further attention towards its health beneficial effects. Current official recommended dietary allowance in most of the countries is higher than what is needed for the prevention of scurvy, but research result suggested that it is far less to obtain optimum health. Therefore, especially for the prevention of chronic illness such as cancer, hypertension, Alzheimer’s diseases etc., it is recommended to consume more fruits and vegetables together with the vitamin C supplements. Evaluating the vitamin C efficiency and safety with current literature, up to 1 g/day supplement of vitamin C has been suggested to be needed for optimal health. In addition, male population compared to female population, older population compared to younger population, smoking population compared to non-smoking population and stressed population compared to non-stressed population need larger amounts of vitamin C to obtain health beneficial effects.

INTRODUCTION
It has been known for a long time that absence of fresh fruit and vegetables in the human diet leads to scurry, a fatal disease widely described throughout written history (Lind, 1753). Later, it was discovered that ascorbic acid in fresh fruits and vegetables prevents scurry and that is why it is a vitamin for humans and must be a part of human diet (Mandl et al., 2009). Among the long list of people who contributed to the knowledge regarding vitamin C, three Nobel prize-winners are in the forefront. Albert Szent-Györgyi discovered vitamin C as an anti-scorbutic factor (Svirbely and Szent-Györgyi, 1932). Walter Norman Haworth used the material from Szent-Györgyi and elucidated the structure and synthesized vitamin C (Haworth and Hirst, 1933). For their contributions, Szent-Györgyi and Haworth were rewarded with Nobel prizes in medicine and chemistry in 1937, respectively. The third person, Linus Pauling is perhaps the most renowned advocate of vitamin C. Pauling believed that high doses of vitamin C can cure or prevent several mental illnesses, chronic diseases such as heart diseases and cancer, including common cold (Pauling, 1970; Cameron and Pauling, 1973; Cameron and Campbell, 1974; Pauling, 1974; Cameron and Pauling, 1979; Cameron and Pauling, 1993). The knowledge contributed by these three great scientists and many others led to the foundation for research on vitamin C.

Although the role of vitamin C in the prevention and treatment of scurvy is well accepted, immunomodulatory effect of vitamin C, its role as an antioxidant to prevent or treat chronic illness and official recommended dietary allowance (RDA) are under critical discussion (Deruelle and Baron, 2008; Mandl, 2009). In this review, the effect of vitamin C on cancer and other diseases and optimal doses are discussed.

MAIN MESSAGE
Vitamin C (ascorbic acid) is one of the essential components in human physiology working as a water-soluble antioxidant and enzyme cofactor. Humans do not synthesize ascorbate, therefore we need to administer it through diet or supplements. We must assure a sufficient intake of vitamin C in order to define its role for the prevention or treatment of various diseases.

UNIQUE CHEMICAL FEATURE AND BIOLOGICAL FUNCTION OF VITAMIN C
Vitamin C (C₆H₈O₆) is named as ascorbic acid because of its anti-scorbutic property (Latin word scorbūtus = scurry). In solution, it releases a proton to give an anion called ascorbate. Ascorbate easily transfers one electron and one additional proton and can remain in the stable radical form as semidehydroascorbate (SDA), a state in between dehydroascorbic acid (DHA) and ascorbate in the physiological condition (figure 1).

Because of the unique electron transferring capability, ascorbate plays a vital role in living cells. Our body synthesizes collagen to strengthen connective tissue. For this, prolyl residue must be hydroxylated and the reaction is carried out by the enzyme prolyl hydroxylase with the support of vitamin C (figure 2). The hindrance of this biochemical reaction is the cause of scurvy. In spite of having its vital role in physiology, human is unable to synthesize ascorbate due to the absence of the enzyme, gulonolactone oxidase (GLO) as found in most animals and those animals including human unable to produce GLO, need external supplement of ascorbate as vitamin to carry out normal physiological functions (Lunter and Van Schaftingen, 2007).

Besides acting as a cofactor in several metabolic reactions, it serves primarily as a biologic antioxidant and free radical scavenger in aqueous environment. Free radicals produced by enzymatic and non-enzymatic reactions inside and outside cells have been suggested as a major cause of aging process (Harman, 1956; Harman, 1994). This theory was further supported by the discovery of superoxide dismutase (SOD) (McCord and Fridovich, 1969). Since then, a great deal of evidences has been accumulated implying free radical reactive oxygen and nitrogen species in the pathology of a number of chronic diseases and age associated functional decline (Knight, 1998, Ratten 2006; Viña et al., 2007; Gruber et al., 2008; Ljubunic and Reznick 2009). Ascorbate readily scavenges many physiologically relevant reactive oxygen...
and nitrogen species and is the most effective endogenous aqueous phase antioxidant in human plasma under many different oxidizing conditions (Frei et al., 1989). Although other endogenous antioxidants are able to decrease the rate of lipid and protein oxidation in plasma, only ascorbate is reactive enough to intercept oxidants before they can cause detectable oxidative damage. Due to its role as an antioxidant and by having immunomodulatory functions, vitamin C is one of the most promising molecules of health beneficial effects. For this purpose, more than 86,000 metric tons of vitamin C was consumed only in 2003 which is more than 50 % of all the other vitamins. In addition, consumption rate is expected to increase by more than 2000 metric tons per year (Asard et al., 2004).

RECOMMENDED DIETARY ALLOWANCE FOR VITAMIN C

The US Food and Nutrition Board has prepared RDAs for vitamin C since 1941. Initially, the RDA was based on the amount needed to prevent people from getting scurvy with a safety margin but numerous research results suggested that this may not be sufficient for optimal health (Pauling 1974; Levine et al., 1996; Food and Nutrition Board, 2000). Moreover, the RDA for vitamin C is based on estimates of rates of absorption, depletion, turnover and catabolism (Levine et al., 1999; Food and Nutrition Board, 2000). For vitamin C, however, the information is unavailable, incomplete, or flawed. Currently, RDA requirements for vitamin C differ among countries, with the highest value being 110 mg/day (Food and Nutrition Board 2000; Levine et al., 2001). According to Norwegian Social and Health Affairs, the RDA for vitamin C are 75 mg per day for the adult and 100 mg per day for the women during lactating period. Pauling suggested the daily intake of vitamin C of 250–4000 mg (Pauling, 1970; Pauling 1974). Challem concluded that the RDAs might be seriously inadequate guidelines for health (Challem, 1999). However, high doses of vitamin C, as proposed by previous authors, are not supported by all literature. A meta-analysis on a potential effect of vitamin C on the common cold showed that there seems no justification for routine mega dose vitamin C supplementation, 1–3 g/day, in the normal population (Hemilä et al., 2007a). Moreover, without reaching the mega doses of vitamin C consumption, numerous reviews suggest that intakes of vitamin C much higher than the RDA may reduce the risk or risk factors for chronic diseases such as heart disease and certain types of cancer (Hathcock, 1997; Ames 2004; Ames 2005; Ames 2006). In this connection, two studies demonstrated that current RDA for vitamin C should be re-evaluated and increased to 200 mg daily (Levine, 1996; Graumlich et al., 1997).

ROLE OF VITAMIN C IN CANCER THERAPY

For the prevention of cancer, the US department of Agriculture and the National Cancer Institute has recommended five servings of fruits and vegetables daily. Further analyses have suggested that this consumption should be even higher (Lachance and Langseth,
Navyticated that vitamin C inhibits tumor growth with the treatment of high doses (Cameron and Pauling, 1973). Cameron and Campbell reported beneficial effect of vitamin C based on the response of 50 consecutive patients with advanced cancer to continuous i.v. infusions (5–45 g/day) and/or oral doses (5–20 g/day) (Cameron and Campbell, 1974). Cameron and Pauling compared survival time between 100 patients with terminal cancer treated with i.v. and oral vitamin C, usually 10 g/day and 1,000 comparable patients not given vitamin C (Cameron and Pauling, 1976). Patients treated with vitamin C survived approximately four times longer than controls. A follow-up study reported that patients given vitamin C had a mean survival time almost 1 year longer than matched controls (Cameron and Pauling, 1978).

The National Cancer Institute sponsored two randomized, placebo-controlled, double-blind trials with vitamin C and advanced cancer at the Mayo Clinic (Creagan et al., 1979; Moertel et al., 1985). In both trials, patients were given 10 g/day vitamin C or placebo. Survival rates were essentially the same for all groups. Plasma concentrations of vitamin C were not measured in these studies and vitamin C was given only orally. In retrospect, the Mayo Clinic trials may have failed to properly evaluate the clinical efficacy of vitamin C in cancer because of insufficient plasma concentrations of vitamin C attained with oral supplementation (Padayatty et al., 2004).

In spite of several controversies, two phase I clinical trials with vitamin C have recently been published that demonstrated remarkable tolerance and safety for high i.v. doses up to 1.5 g/kg in patients (Riordan et al., 2005; Hoffer et al., 2008). Additionally, a series of case reports indicated that high-dose i.v. vitamin C was associated with long-term tumor regression in three patients with advanced renal cell carcinoma, bladder carcinoma, or B-cell lymphoma (Hoffer et al., 2008).

Vitamin C can be taken i.v. or orally. Oral absorption of vitamin C can not achieve plasma concentrations comparable to those obtained by i.v. administration (Padayatty et al., 2004). Intravenous doses were used as an alternative therapy to treat patients with advanced cancer (Cameron and Pauling, 1993; Padayatty et al., 2004; Riordan et al., 2005; Hoffer et al., 2008). This can be explained by the fact that i.v. doses raise plasma concentrations as high as 14,000 µmol/L, with doses of 50–100 g/day and concentrations of 1000–5000 µmol/L were found selectively cytotoxic to tumor cells but not to normal cells in vitro (Benade et al., 1969; Bram et al., 1980; Leung et al., 1993; Riordan et al., 1995; Casciaro et al., 2001; Padayatty et al., 2006).

A rosy picture came forward with the recent series works of Chen et al. which showed that high doses (pharmacologic doses) of vitamin C decreased the growth and weight of human, rat, and murine tumor xenografts in athymic nude mice (Chen et al., 2005; Chen et al., 2007; Chen et al., 2008). The results suggested that millimolar concentrations of extracellular vitamin C selectively kill cancer cells but not normal cells in a hydrogen peroxide (H2O2)-dependent manner. Such millimolar concentrations of vitamin C can be achieved in humans by i.v. infusion but not by diet or supplements (Padayatty et al., 2004). Hence, vitamin C is postulated to exert local pro-oxidant effects in the interstitial fluid surrounding tumor cells, killing them or inhibiting their growth, while leaving normal cells intact.

According to Frei and Lawson, ascorbate (ASC–), which is regarded as an antioxidant in general, can act as a pro-oxidant by donating an electron to reductone transition metal ions, such as ferric (Fe3+) or cupric (Cu2+) ions, reducing them to ferrous (Fe2+) or cuprous (Cu+) ions, respectively (Eq. 1) (Frei and Lawson, 2008). In fact, reduction of iron or copper in the catalytic site of certain enzymes underlies ascorbate’s well known biological function as a co-substrate in procollogen, carnitine, and catecholamine biosynthesis (Englard and Seifter, 1986). Reduced transition metal ions, in contrast to ascorbate, readily react with O2, reducing it to superoxide radicals (Eq. 2), which in turn dismutate to form H2O2 and O2 (Eq. 3) (figure 3).

In addition, the reaction of ascorbate with iron and H2O2 produces the extremely reactive pro-oxidant hydroxyl radical (Halliwell 1987). Although scientific rationale for the production of H2O2 and radicals in initiation with ascorbate as shown in figure 3 might be a matter of discussion, it is evident that ascorbate causes cancer cells to undergo apoptosis, pyknosis, and necrosis by H2O2-dependent pathways (Chen et al., 2005). In contrast, normal cells are considerably less vulnerable to H2O2. The reason for the increased sensitivity of tumor cells to H2O2 is not clear but may be due to lower antioxidant defences (Oberley and Oberley, 1997). Whatever may be the exact mechanism, the increased sensitivity of tumor cells to H2O2 may provide the specificity and “therapeutic window” for the antitumor effect of extracellular millimolar concentration (higher doses) of vitamin C.

IMMUNE RESPONSE AND OTHER BIOLOGICAL FUNCTIONS OF VITAMIN C

White blood cells store higher quantities of vitamin C even when levels in the surrounding plasma are low (Hornig, 1994; Guenther et al., 2006). If these recommendations are based on vitamin C and followed, daily intake will be 210 to 280 mg, depending on food type (Levine, 1999). Reports suggest that fresh produce or juice may lose 50–100 % of its vitamin C content due to handling and processing (Severi et al., 1998; Gil et al., 1999; Johnston and Bowling, 2002). Furthermore, more than 500 mg/day of vitamin C would be difficult to obtain from dietary sources alone and therefore would require supplements especially for the prevention of cancer (Levine et al., 1995). In spite of several controversies, two

Figure 3. The possible pathways of vitamin C to generate H2O2 by the reduction of Fe3+ (Frei and Lawson).
delayed-type hypersensitivity response, lymphocyte proliferation, chemotaxis, and natural killer cell activities, immune responses, such as antimicrobial, and that the elderly might require more ascorbate than younger people (Blanchard et al., 1990; Blanchard, 1991; Heseker and Schneider, 1994).

SAFETY OF VITAMIN C SUPPLEMENTATION

It has been suggested that vitamin C alone or mixed with N-acetylcysteine could be toxic, acting as a pro-oxidant (Podmore et al., 1998; Childs et al., 2001). However, the literature shows that ascorbic acid is not a pro-oxidant in vivo, even with iron co-supplementation (Carr and Frei, 1999a; Gomez-Cabrera et al., 2008). The literature has also evoked the potential adverse effects of high doses of vitamin C, especially as regards the increase in oxalate and kidney stone formation (Levine et al., 1996; Levine et al., 1999). Indeed, Auer et al. demonstrated that 8 g/day, for 8 consecutive days, can cause harmful calcium oxalate crystalluria secondary to relative hyperoxaluria in persons who have a predisposition for increased crystal aggregation (Auer et al., 1998; Auer et al., 1999a). Wandzilak et al. observed a modest increase in urinary oxalate after administration of high doses of vitamin C (5 and 10 g/day for 5 days) (Wandzilak et al., 1994). Moreover, other work by Auer et al. using 4 g/day of ascorbic acid for 5 days, concluded that ingestion of these doses did not affect the principal risk factors associated with calcium oxalate kidney stone formation (Auer et al., 1998a; Auer et al., 1998b). Furthermore, large doses of vitamin C (1.5 g or more) did not produce kidney stones and the doses of vitamin C above 1.5 g in fact reduced the risk of kidney stones (Curhan et al., 1996; Curhan et al., 1999; Gerster, 1997).

Evidence indicates that high intakes of vitamin C do not increase oxalate excretion or induce the potential formation of kidney stones (Hathcock, 1997; Hathcock, 2005).

Gastrointestinal distress seems to be the most common adverse effect of higher doses of vitamin C intake (Miller and Hayes, 1982). When these symptoms occur, the vitamin C dosage is usually more than 2 g/day. The symptoms generally disappear within a week or 2 with no further consequences, and may have been produced by other components such as sorbitol (Hill and Kamath, 1982).

No consistent and compelling data demonstrating serious adverse effects of vitamin C in humans have been established (Frei and Traber, 2001), although the tolerable upper limit intake has been estimated to 2 g/day (Food and Nutrition Board, 2000).

CONCLUSIONS

Vitamin C is an essential component of human physiology and should be supplied either through fresh fruits and vegetables or through supplements. The clinical benefit of vitamin C known so far is the prevention of scurvy. Intake of as little as 10 mg/day is sufficient for this purpose. In order to potentiate immune function or prevent chronic illnesses such as cancer, hypertension etc., higher doses of vitamin C are needed. Recent clinical updates on the role of vitamin C in tetanus (Hemilä and Koivula 2008) pneumonia (Hemilä and Louhiala 2007), asthma (Kaur et al., 2009), diabetic retinopathy (Lopes de Jesus et al., 2008) and pregnancy (Rumbold and Crowther 2005) are available as Cochrane reviews. Most of these reviews conclude that present knowledge does not allow a strong conclusions on the role of vitamin C, however the weakness of research methodology in vitamin C clinical trial has to be considered before further conclusion (Lykkesfeldt and Poulsen, 2009).
We need more research to explain some of the facts associated with vitamin C such as: lack of vitamin C supply causes decrease number of leukocytes, tobacco smoking lowers the plasma and leukocyte vitamin C level, refined carbohydrate seems to be accelerated the process of depleting vitamin C, women’s vitamin C plasma levels are approximately 20% higher than men’s for any given dietary intake, vitamin C plasma level decreases by aging, etc. in order to get a clearer picture of the biological functions of vitamin C.

A recommendation of five servings of fruits and vegetables daily for the cancer prevention is not sufficient to obtain optimal benefit based on the current evidence. In addition, because of modern farming, handling and processing, more than 500 mg/day vitamin C would be difficult to obtain from dietary sources alone. It should be noted that pharmacokinetics and physiologic responses to vitamin C are known to vary considerably between individuals and optimal intakes for children, older adults and those suffering from acute and chronic diseases remains to be determined. Many studies have demonstrated that higher doses than the RDA for vitamin C can potentiate the immune system and prevent as well as treat a wide range of pathologies.

The need of vitamin C is higher to those who are in continuous oxidative stress. Oxidative stress is the focal point for chronic illnesses in human. The direct evidence and mechanism of action for the role of vitamin C in treating chronic illnesses could not be correlated yet, but results of epidemiologic and indirect studies are in strong support (Myint et al., 2008).

Consequently, even if vitamin C requirements vary greatly among individuals, it is suggested that vitamin C supplementation is not only safe but also necessary to achieve optimal health. Therefore, in agreement with the current literature, it can be suggested, especially to the older population to consume more than five servings of fruits and vegetables daily, added to 1 g of vitamin C supplementation divided in two or three doses during the day, in order to ensure an optimal health. Moreover, male population compared to female population, older population compared to younger population, smoking population compared to non-smoking population and stressed population compared to non-stressed population may need higher consumption of vitamin C to obtain health beneficial effects.

Conflict of interest: None

For references, see www.farmatid.no/id/4002

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