Review

Is Vitamin C supplementation beneficial in asthmatic patients?

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SUMMARY
As asthma prevails worldwide, nutritional hypotheses appear to suggest that vitamin C supplementation may have a positive effect in asthma management. However, scientific community has not reached an agreement concerning the association between vitamin C and asthma. In this review, we provide evidence of several in vitro and in vivo studies in mouse, rat and pig models that implicate vitamin C in immune response and also as an anti-inflammatory agent with antiviral properties. Finally, whether vitamin C supplementation in asthmatics is beneficial or not, a number of systematic reviews and meta-analyses have tried to shed more light in this controversy, but no robust assessment concerning the use of vitamin C in the management of asthma is available.
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INTRODUCTION

Asthma is one of the most prevalent diseases worldwide with high economic burden, causing a major public health concern. According to the Global Initiative for Asthma, bronchial asthma is a chronic inflammatory disorder that is related to airways hyperresponsiveness and leads to repeated episodes of wheezing, dyspnea, chest tightness, and cough.[1-6] As asthma is a complex and heterogeneous syndrome, risk factors contributing to its etiology are multiple genetic and environmental or lifestyle factors, including dietary intake. Indeed, a "dietary inflammatory index" (DII) was associated with asthma, reduced lung function and increased IL-6 plasma level in a case-control study of adults.[7]

Among nutritional hypotheses, it has been reported that a reduction in fruit intake in "western diet" could be associated with the increase in prevalence and severity of asthma in the developed countries.[8,9] This association comes from the reduction of dietary antioxidants such as vitamin C. In specific, western diet, which is low in fruits and vegetables, and high in refined grains and saturated fat, has been suggested to increase the risk of asthma, whereas a "Mediterranean diet", which is rich in fruits and

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vegetables, and low in refined grains and saturated fat, could protect against the development of asthma or asthma symptoms.[10,11] However, this topic remains still controversial as several studies that have evaluated the association between antioxidant vitamins (A, C and E) and asthma (1-10) have not reached an agreement.[12-16]

This report aims to demonstrate evidence of studies of meta-analysis of vitamin C supplementation that may or may not have a positive effect in asthma management.

VITAMIN C OVERVIEW

Vitamin C is an exogenous nonenzymatic antioxidant. Some mammals including humans, some primates and guinea pigs cannot produce vitamin C by themselves, while most other mammals can. As a result, humans have to be supplemented with exogenous vitamin C by taking fresh fruits and vegetables, and/or supplementary pills, because deficit of vitamin C leads to the scurby.[14]

Lungs are exposed to a range of substances, which directly or indirectly might cause production of oxidants. Vitamin C is abundant in the extracellular and intracellular lining fluid of the lungs, participates in the primary lung defense against the reduction of oxidative damage[17,18] and also helps to reduce airway hyperresponsiveness.[19] Studies have shown that exogenous vitamin C supplementation may restore the imbalance of oxidative damage.[17,20] In specific, oxidative stress in asthma may be initiated by many aerial hazardous substances, such as cigarettes, pollutant particles, or respiratory viruses, resulting in asthma morbidity and pathogenic exacerbations as some patients have a deficiency in anti-oxidative mechanisms.[21] Moreover, due to generation of oxidative stress when heavy physical exertion occurs, it has been suggested that the effects of vitamin C might be more manifest in people who exercise regurarly.[22,23]

Other mechanisms of the protective effects of vitamin C concerning asthma have been proposed, as an effect on the arachidonic acid pathway[24] as well as antiviral properties.[25] Since studies have established that asthmatic patients suffer from oxidative stress due to abnormal airway inflammation[26,27], Jeong et al hypothesed that vitamin C could be used for the treatment and/or management of asthma as an antioxidant and/or as a Th1-shifting agent, when considering asthma pathophysiology. In their experimental mouse model, they concluded that vitamin C did not change Th1/Th2 balance in asthma, but it exerted some anti-inflammatory effects against lung inflammation.[28] The anti-inflammatory effect of vitamin C has been ascribed not only to its anti-oxidant property, but also to direct inhibition of IkB kinase phosphorylation leading to eventual inhibition of NF-kB activation, which plays a critical role in inflammation.[29]

Recently, Bansal et al hypothesed that supplementation of might have a therapeutic effect. In their study of a mouse model of airway disease, the combination of vitamin C with both choline chloride and selenium had the strongest effect against allergic airway disease[30] as intranasal treatment with vitamin C (alone or in combination with choline chloride and selenium) decreased oxidative stress, AHR, airway inflammation, IL-4 and IL-5, IL-10, IgE, and NF-κB. Moreover, Nounou et al in a rat model of bronchial asthma suggested that a combination of antioxidant vitamins may be effective in the treatment of asthma, considering their reported effects on lowering malondialdehyde, IL-4, and IgE levels.[31] Several studies have also suggested vitamin C implication in inflammation[32-34], however, some authors denied its anti-inflammatory role.[35-37]

Furthermore, it has been reported that vitamin C affects lung function by influencing various prostanoids in lung tissues and that vitamin C deficiency increases the level of bronchoconstrictor Prostaglandin F2α (PGF2α).[38-40] In guinea pigs on a diet deficient in vitamin C, an increase in airway hyper-responsiveness to histamine was observed[26] and in isolated guinea pig trachea smooth muscle, vitamin C decreased the contractions caused by PGF2α, histamine and carbamylcholine.[22,41,42] The role of vitamin C in prostaglandin metabolism has also been strengthened by another study in humans, where a 2-week vitamin C diet reduced post-exercise increase in the urinary markers for the bronchoconstrictors leukotriene C4–E4, 9a and 11b-PGF2 as well as exhaled nitric oxide when compared to placebo and usual diet.[43]

Furthermore, another study reported that in vivo administration of vitamin C modulates T cell proliferation and cytokine secretion[44], associating vitamin C with the immune response. Khassaf et al concluded that vitamin C-supplemented subjects, showed attenuation of adaptive responses to oxidants, however suggesting that this may only reflect an increased baseline expression of potential protective systems against oxidative stress.[45] Another study concluded that mega-dose vitamin C administration in mice shifted immune responses toward Th1 lineage with concomitant suppression of the Th2 responses.[46] Conversely, Lee et al showed that inadequate vitamin C supplementation in L-gulono-γ-lactone oxidase deficient

mice which cannot synthesize vitamin C by themselves resulted in a decreased Th1 response against *H. pylri* infection.[47] Considering all the above as well as asthma pathophysiology, some authors have suggested vitamin C as an antioxidant and/or as a Th1-shifting agent for the treatment and/or management of asthma.[27] However, the beneficial effect of vitamin C in asthma remains a subject in controversy.[30,48,49] Recently, an interesting clinical trial on pregnant smokers (n=179) suggested that vitamin C supplementation (500 mg/d) may be an inexpensive and simple approach to decrease the effects of smoking in pregnancy on newborn, based on the improvement of pulmonary function and decreased risk of wheeze in their newborns, up to age 1 year.[50] Besides, another recent study on the same group of pregnant smokers, demonstrated that vitamin C prevents offspring DNA methylation changes associated with maternal smoking in pregnancy.[51]

Besides asthma, there has been evidence that vitamin C may have a treatment effect on some cardiovascular disorders.[52-56] Furthermore, in a recent meta-analysis, vitamin C decreased the risk of contrast-induced acute kidney injury in patients undergoing coronary angiography.[57] Also, concerning common cold, upper and lower respiratory tract infections[58,59] and pneumonia[60], several controlled trials have indicated potential physiological effects for vitamin C as a non-scorbutic effect, still further evidence is needed.

VITAMIN C SUPPLEMENTATION IN ASTHMATICS, SYSTEMATIC REVIEWS AND META-ANALYSES

Several epidemiological studies and meta-analysis in adults and children have focused on the role of vitamin C supplementation in asthma or asthma-related symptoms with inconsistent results[49,61-63] (Table 1).

One of the first systematic reviews and meta-analysis was conducted by Allen et al in accordance with the MOOSE guidelines, in an effort to provide pooled quantitative estimates of the likely magnitude of the effect of dietary intake and serum levels of vitamins A, C and E to asthma development and severity.[62] The authors concluded that even relatively low dietary intakes of vitamin C are associated with statistically significant increased odds of asthma and wheeze. However, a year earlier, Gao et al in their meta-analysis, including 10 studies on asthma, did not support the hypothesis of the effect of dietary intake of the antioxidant vitamins on a lower risk of asthma[63] with the only positive association found concerning lung function being between vitamin C intake and an increase in FEV1. Similarly, a recent Cochrane review of eleven randomized controlled trials including 419 children and adults with asthma concluded that there is insufficient evidence to recommend vitamin C as a therapeutic agent in asthma.[64] According to Hemila Harri, a Cochrane review on vitamin C and asthma that has been withdrawn recently, was misleading readers

TABLE 1. Studies of meta-analyses of vitamin C on asthma and asthma related symptoms

Authors of meta-analyses	Year	No of trials included in meta-analyses	Focus	Conclusions
Gao et al[63]	2008	10	Dietary antioxidants and risk of having asthma	No association
Allen et al[62]	2009	37	Serum levels of vitamin C association with asthma	Low dietary intakes of vitamin C are associated with increased odds of asthma and wheeze
Kaur et al[49]	2009	9	Efficacy of vitamin C in the treatment of asthma	Insufficient evidence to recommend vitamin C as a therapeutic agent in asthma
Hemila et al[61]	2013	3	Vitamin C benefit on FEV1 decline caused by exercise	Consistency of positive findings on vitamin C against EIB
Milan et al[64]	2013	11	Vitamin C supplementation on preventing exacerbations and improve HRQL	Insufficient evidence to recommend vitamin C as a therapeutic agent in asthma

for a decade reporting insufficient data to recommend a specific role for vitamin C in the treatment of asthma.[49] He reported that Kaur et al had substantial errors in the extraction of data and data analysis.[65] Thus, to determine the role of vitamin C in asthma management, the published data on vitamin C should be analyzed carefully and comprehensively. Most of the trials are clinically so heterogeneous in experimental settings such as patient selection criteria, recommended dosage of vitamin C, and parameters assessed. As a result, the positive findings cannot be generalized widely.

As atopic asthma includes the most common phenotype, a systematic review and meta-analysis investigated the potential role of nutrient and food intake in modifying the risk of children developing allergy.[66] Although the available epidemiologic evidence is weak, they found no link between vitamin C and allergic outcomes. Another common phenotype in asthmatics is exercise-induced bronchoconstriction (EIB).[67] EIB is a transient narrowing of the airways that occurs during or after exercise. Recently, Hemila et al in their meta-analysis concerning three randomized placebo controlled double-blind trials on patients with exercise-induced bronchoconstriction, found that vitamin C administration (0.5–2 g) before exercise reduced post-exercise decline in FEV1.[61] Moreover, despite the small size of these trials and given that vitamin C is safe and low cost, they suggested that physically active people could use vitamin C on an individual basis if they have respiratory symptoms such as cough associated with exercise.

CONCLUSIONS AND FUTURE PERSPECTIVES

Finally, is Vitamin C supplementation beneficial in asthmatics? In spite of the controversy reported, there is an indication that vitamin C as a chronic usage may positively affect asthmatics patients. However, currently, there is no available evidence on a robust assessment concerning the use of vitamin C in the management of asthma or exercise induced bronchoconstriction. Besides, there are still no data available to evaluate the effects of vitamin C supplementation on asthma exacerbations in adults. Larger well-designed trials are needed to focus on good quality clinical endpoints, such as exacerbation rates and health-related quality of life scores, in order to address the question of the potential therapeutic or preventive usage of vitamin C on asthma and asthma-related symptoms.

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