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The effects of vitamin C supplementation on oxidative and immune response and post exercises inflammation

Vitamin C in health and physical performance - critical review

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Summary

Ascorbic acid, also called vitamin C is the one of the exogenous vitamins, functioning in human body as ascorbate and affecting many body systems. In presented revive we try to show most of the well-known, and importance proprieties of this compound focusing mainly on its role in health and physical activity.

Interaction of this antioxidant with many other compounds and body tissues revels its free radicals scavenging properties and the main possible role in body functioning. However, the benefits of using this vitamin are still controversial and the presented properties, like those of many other antioxidants, are questioned. On the other had high safety of use and vilely known properties sill indicate that this vitamin may have potential use in sport and health.

In presented work we tried to focus mainly on the properties of this vitamin in context of exercise depended demands and how high vitamin C consumption affects general health of different population and how it can be useful type of supplementation in physical activity.

Keywords: ascorbic acid, ROS scavenging, antioxidant enzymes, inflammation

I. Introduction

Ascorbic acid, commonly known as vitamin C, is a water-soluble nutrient that has garnered significant attention in both the realm of sports performance and health care. due to its powerful antioxidative and anti-inflammatory properties. Since its discovery in 1928 by Albert Szent-Györgyi its powerful antioxidative and anti-inflammatory properties its importance and knowledge about its role is constantly growing (Gęgotek & Skrzydlewska, 2022; Svirbely & Szent-Györgyi, 1933). It has been established that ascorbic acid is essential for the growth and repair of body tissues, plays a kay role in immune system functioning, collagen synthesis, and the iron absorption. All combined together proves its multifaceted influence on overall human health.

All biological properties of ascorbic acid are result from its specific chemical structure. In single vitamin C compound, we find double bonds at the C2 and C3 carbons, as well as four hydroxyl groups in positions C2, C3, C5, and C6. All combined together crats the fact that this compound is an ideal hydrogen or electron donor (Davey et al., 2000; Nishikimi & Yagi, 1991) am may play kay role in many enzymatic cascades (Davey et al., 2000).

May research since the late 80's has highlighted its capacity to mitigate oxidative stress, which is particularly crucial for athletes who experience heightened physical demands that can lead to increased free radical production during activity and competition (Bendich et al., 1986; Benjamin Adams et al., 2014; Braakhuis, 2012; Frei et al., 1989; Sies et al., 1992).

Additionally, by combating inflammation, ascorbic acid may aid in faster recovery from intense exercise, thus enhancing athletic performance. The overarching importance of ascorbic acid in managing oxidative and inflammatory responses underscores its potential as a key nutrient for both physical performance and health care contexts, inviting further exploration into its therapeutic applications (Benjamin Adams et al., 2014; Braakhuis, 2012).

2. Ascorbic acid – pharmacokinetics, activity

In human due the lack of enzyme L-gulonolactone oxidase, ascorbic acid must be supplied with the diet, with the recommendations from 75, to 90 mg per day (Institute of Medicine Panel on Dietary & Related, 2000). There are many significant dietary sources of vitamin C, from various citrus fruits (ex. Ginger lime, Citron, Lemon) through wide range of other fruits' (ex. Chokeberry, Backcurrant, Cranberry), vegetables, and even meats (Granger & Eck, 2018; Mazurek & Pankiewicz, 2012; Valente et al., 2011).

Under physiological conditions, ascorbic acid (as an ascorbate anion), is absorbed from the intestinal lumen by enterocytes, and enters the blood stream reaching different tissues of the human body (Levine et al., 1996). There is additional transdermal pathway of ascorbic acid entering human body, but amount of absorbed vitamin is relatively low (Pinnell et al., 2001). During normal, physiological nutritional state conditions the concentration of ascorbate in the blood stream varies between 10–100 μM (Institute of Medicine Panel on Dietary & Related, 2000). As ascorbate exhibits solubility in water, its movement across lipid plasma membranes is significantly restricted (Levine et al., 1996).

Consequently, the primary ascorbate transport include mainly through: glucose-sensitive transporters, active transport by sodium-dependent transporters SVCT1 and SVCT2, transmembrane channels diffusion, diffusion through exocytosis within secretory vesicles (Levine et al., 1996).

Many research indicates that ascorbate is one of the essential vitamins for the optimal functioning of the human body. It plays an important role in regulation of various physiological conditions, ex. collagen synthesis, reduction of blood pressure regulation, fortification and integrity of blood vessels, modulation of microbial uptake by leukocytes, regulation of the cholesterol levels, and many other (Ang et al., 2018; Langlois et al., 2001).

On the other hand, due to its water-soluble nature excessive intake of vitamin C can mainly cause gastrointestinal disorders. Moreover, it may contribute to the formation of kidney stones (Knight et al., 2016).

3. Antioxidant Properties of ascorbate

From the many widely properties of ascorbic acid, its ability to regulate the level of reactive oxygen species and its antioxidant activity is most important. The modulation of the ROS starts on the initial stages of their formation, and primary contributors to their mitochondrial production and the activity of NADPH oxidases (NOXs) and xanthine oxidase (XO) (Sies & Jones, 2020). Supplementation with ascorbate offers significant protection against the hyperactivity and the plasma concentration of xanthine oxidase (Alghamdi et al., 2021; Linani et al., 2022). Moreover, some researchers indicate that supplementation with the vitamin C may be beneficial in prevention of reperfusion injuries or hyperuricemic nephropathy (Li et al., 2021). Excessive NOXs activity can lead to unfavorable for health oxidative stress. It results a cells dysfunction in pro-oxidative systems and may lead to many undesirable changes. Additional ascorbate consumption can down-regulate excessive NOXs activity and restore oxidative system homeostasis (Mason et al., 2020).

In human body system ascorbate is classified as a low molecular weight antioxidants, which activity is mainly limited to the elimination of ROS and interaction with other low molecular weight antioxidants (Yen et al., 2002). It has been proven that ascorbic acid affects the activity of other antioxidant enzymes, such like superoxide dismutase (SOD) (Gęgotek & Skrzydlewska, 2023; Surai, 2016), catalase (CAT) (Gęgotek & Skrzydlewska, 2023). Ascorbate influences the activity of those enzymes in various ways, depending on the type of cells but the observed changes in their activity are health-promoting and beneficial for reducing reactive oxygen species (Gęgotek & Skrzydlewska, 2023; Surai, 2016).

Exploring multipotential properties of ascorbic acid it is impossible not to mention that increased ascorbate concentration can contribute to the changes in the activity of the DNA polymerases (Lan et al., 2004). Moreover, it has been proven that that ascorbate can directly reduce DNA mutations and DNA strand break levels (He & Häder, 2002)and may also affects oxidative modifications of proteins (Pawlowska et al., 2019; Zou et al., 2006). The efficacy of ascorbate in protection of proteins from the oxidative damage is always dependent from the tissue concentration of this vitamin. Unfortunately, ascorbate concentration in case of the most European diets is often insufficient (Hahn et al., 2019).

Additionally, it has been proven that due to the direct correlation of ascorbate concentration and the ROS formation, increased ascorbate tissue content is positively correlated with the decreased concentration of lipid peroxidation products (Krishna Mohan & Venkataramana, 2007; Surapaneni & Venkataramana, 2007). It has been proven that a 1 g per day of ascorbate efficiently reduces the expression of plasma isoprostanes and prevents inflammation mediated by lipid peroxidation (Huang et al., 2002).

4. Anti-Inflammatory Properties of ascorbate

Many researchers proven that ascorbate possess various anti-inflammatory properties (Ellulu et al., 2015; Gęgotek & Skrzydlewska, 2022). However, each time the interpretation of different research results will create serious interpretation problems. This is due to the fact that different authors obtained contradictory research and analysis results in their works. In addition, very often vitamin C supplementation was also based on the supply of other compounds that may in themselves have health-promoting effects (Darnton-Hill et al., 2015; García-Bailo et al., 2012; Jafarnejad et al., 2018).

Ascorbate exerts an influence on inflammatory signaling within cells, as it clearly diminishes the expression of pro-inflammatory mediators, leading to a reduction in the inflammatory response. One of the main kay pro-inflammatory signaling pathway that is influenced by ascorbic acid and connected with its antioxidative properties, including the reduced ROS production is the NFκB/TNFα pathway(Tan et al., 2005). Additionally, some authors indicate that ascorbate may inhibits IL-6 protein release from an active skeletal muscles and significantly reduces IL-6 and TNF-α levels(Kong et al., 2015). On the other hand, it may upregulate anti-inflammatory cytokines release, increasing level of IL-4 and IL-10 (Kong et al., 2015).

The effect of ascorbate on the regulation of the anti-inflammatory status takes part on a different pathways' and in some cases still remains unclear.

5. Ascorbic Acid and post exercises inflammation and muscle damage

Uncontrolled ROS generation and increased oxidative stress has been described as a one of the main factors contributing to the intensive and long-lasting exercises (Mieszkowski, Stankiewicz, et al., 2021). Thus, a wide number of antioxidants are being used during and pre-competition period to reduces exercises-induced muscle damage and inflammation (Mieszkowski, Borkowska, et al., 2021; Stankiewicz et al., 2023).

Similarly, as it was mentioned early in case of other populations ascorbate supplementation may reduce post-exercises induced inflammatory response, by decreasing post-exercises concertation of IL-6 (Cobley et al., 2015). Additionally, by affecting other antioxidant molecules activity (ex. α-tocopherol) vitamin C together with them may decrease lipid peroxidation (Smirnoff, 2018).

Ascorbate by reducing the formation of pro-inflammatory cytokines and enhancing the regeneration of other antioxidants, contributes to the attenuation of post-exercises inflammation (Table 1). Effective dose of vitamin C supplements clearly indicates that greater protection to during exercise damage is directly related to the higher dose (Goldfarb et al., 2005).

Table 1. Effects of vitamin C supplementation on physical performance and oxidative stress and inflammation.

Author (Year)	Supplementation regiment	Effect on Physical Performance	Effect on Oxidative Stress & Inflammation	Conclusions
BRAAKHUIS (2012) ***(BRAAKHUIS, 2012)***	Vitamin C (500–1,000 mg/day)	No significant improvement.	Reduces oxidative stress and inflammation but may hinder muscle adaptation.	May impair beneficial training adaptations; caution is advised for athletes.
JOOYOUNG KIM (2023) ***(KIM, 2023)***	High-dose Vitamin C (500–2,000 mg) and Vitamin E (400–1,400 IU)	No significant improvement in endurance, strength, or hypertrophy; potential negative impact on training adaptation.	Reduces oxidative stress and muscle damage markers, but may interfere with beneficial redox signaling required for optimal adaptation.	Reduces oxidative stress and inflammation but may hinder muscle growth and strength; a balanced diet is preferable for athletes.
MARTÍNEZ-FERRÁN ET AL. (2022) ***(MARTÍNEZ-FERRÁN ET AL., 2022)***	Acute Vitamin C (1000 mg) + Vitamin E (235 mg)	No significant improvement in running performance.	Antioxidants reduced exercise-induced muscle damage markers but may delay muscle recovery.	Reduce oxidative stress but don't enhance performance and may hinder recovery; a balanced diet is preferable.
JOHNSTON ET AL. (2014) (JOHNSTON ET ***AL., 2014)***	Vitamin C (1000 mg/day for 8 weeks)	Modest increase in physical activity levels (+39.6% compared to placebo, p = 0.10).	Not directly assessed; potential immune support inferred from reduced cold duration and incidence.	May slightly enhance physical activity levels and reduce cold incidence and duration, particularly in individuals with marginal vitamin C status.
THOMPSON ET AL. (2003) (THOMPSON ***ET AL., 2003)***	Vitamin C (200 mg post-exercise, then twice daily for 3 days)	Not specifically assessed.	No significant effect on muscle soreness, creatine kinase levels, myoglobin, IL-6, or lipid peroxidation markers.	Not enhance recovery, suggesting oxidative stress plays a minor role in muscle damage or supplementation is ineffective.
NIEMAN ET AL. (2002) ***(NIEMAN ET AL., 2002)***	Vitamin C (1,500 mg/day for 7 days before and on race day)	Not specifically assessed.	No significant effects on oxidative stress markers (lipid hydroperoxide, F2-isoprostane) or immune responses (cytokines, immune cell counts).	Not mitigate oxidative stress or immune alterations in ultramarathon runners; oxidative stress appears to have minimal influence on post-race immune changes.
EVANS ET AL. (2017) ***(EVANS ET AL., 2017)***	Vitamin C (250 mg every 12 hours for 28 days)	Not specifically assessed.	Reduced oxidative stress, as indicated by a decrease in malondialdehyde (MDA) levels.	Reduces oxidative stress and enhances peak muscular force, suggesting potential benefits for resistance exercise performance.
KHASSAF (2003)	Vitamin C (500 mg/day for 8 weeks)	Not directly assessed.	Increased baseline antioxidant enzymes (SOD, catalase) and HSPs	Vitamin C supplementation elevates baseline antioxidant defenses but may reduce the body's

(KHASSAF ET AL., 2003)			(HSP60, HSP70) but blunted adaptive response to oxidative stress and exercise.	adaptive response to oxidative stress, potentially impairing beneficial training adaptations
PASCHALIS ET AL. (2015) (PASCHALIS ET AL., 2016)	Vitamin C (1000 mg/day for 30 days)	Marginal improvement in VO2max in individuals with low baseline vitamin C levels, but no effect in those with high baseline levels.	Reduced oxidative stress (F2-isoprostanes, protein carbonyls) in all participants, with a greater effect in those with low initial vitamin C status.	Decreases oxidative stress and may improve exercise performance only in individuals with initially low vitamin C levels, while those with sufficient vitamin C derive little or no benefit.
BRYER (2006) (BRYER & GOLDFARB, 2006)	High-dose Vitamin C (3 g/day for 2 weeks before and 4 days after eccentric exercise)	Not directly assessed.	Reduced 24-hour muscle soreness and glutathione oxidation but not creatine kinase increase or muscle function loss.	Reduces early muscle soreness and oxidative stress but does not prevent muscle damage or loss of function; it may provide limited benefits for recovery from eccentric exercise.
BOONTHONGKAEW ET AL. (2021) (BOONTHONGKAEW ET AL., 2021)	Vitamin C (1000 mg/day for 6 weeks)	Not assessed.	Reduced oxidative stress markers (malondialdehyde and F2-isoprostanes) and increased nitric oxide levels.	Lowered blood pressure pre- and post-exercise by improving oxidative stress and nitric oxide release, with no added effect from exercise.

The mechanical and metabolic stress occurred during the intensive exercises is mostly related to the increased serum concentration of the intramuscular enzymes, such like creatine kinase (CK), and proteins (CRP), which shows it's main peak 24h post the exercises (Noakes, 1987). Vitamin C supplementation don't show effects on the CRP and CK content. It may be due to the half-life of this antioxidant but the amount of the data is still insufficient to fully confirm such conclusions.

However, it should be remembered that each time intense physical activity is connected with the increased inflammatory response, associated with elevated proinflammatory cytokines secretion (ex. IL-1, IL-6, other) (Mieszkowski, Borkowska, et al., 2021; Stankiewicz et al., 2023). Vitamin C due to the reduction of oxidative stress affects post-exercises concentration of IL-6 (Powers et al., 2011).

Presented findings suggest that athletes might consider vitamin C supplementation as a one of the dietary methods to enhance post exercises recovery. Such supplementation could facilitate adaptation and promote sustained engagement in regular physical activity.

Nonetheless, generalizing these findings to broader exercise or training regimens shouldn't be done due the fact that the repeated stimulation of inflammatory signaling pathways and muscle damage during each workout is essential for muscle adaptation and remodeling especially in professional sport (Cobley et al., 2017; Owens et al., 2019).

Furthermore, it is important to note that uncontrolled intake of antioxidant supplements may adversely affect muscle remodeling and carries the potential risk of hypervitaminosis.

Conclusion

Presented systematic review clearly shows that vitamin C supplementation may contribute to reduced oxidative stress, lipid peroxidation and beneficial decreased inflammatory response (IL-6) especially in response to prolonged physical activity.

However, ascorbate doesn't reduce serum levels of CK, CRP and may only play an additional supplementation role to favor the post-exercises recovery, especially during occasionally prolonged sports competitions and mainly for the beginners.

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Conflict of Interest Statement

The authors declare that we have no conflict of interest. The authors declare that there is no grant support or financial relationships on any stages of the research.

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