

# The Protective Role of Vitamin C on Endothelial Dysfunction

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A major function of endothelium is the secretory control of smooth muscle vascular tone. The principal vasodilator substance excreted is nitric oxide (NO), a molecule that is under thorough investigation. There is sufficient evidence that its bioavailability is reduced in many diseases such as coronary artery disease, heart failure, dyslipidaemias, obesity, diabetes, renal failure, and others. The interactions of this molecule with reactive oxygen species are believed to constitute an important pathophysiological pathway. Consequently, intensive research is under way to evaluate the efficacy of various antioxidant interventions against endothelial dysfunction. Vitamin C is an outstanding hydrophilic antioxidant, which is able to scavenge many reactive oxygen species. When infused or chronically ingested in pharmacological doses it substantially improves the defective endothelium-dependent vasodilation involved in the above-mentioned clinical conditions. Several molecular mechanisms have been proposed for this protective effect including scavenging of superoxide anion, inhibition of LDL-oxidation, inhibition of inflammatory cell adhesion, stabilization of NO-synthase through reduction of tetrahydrobiopterin, NO-release from plasma nitrosothiols and preservation of guanyl cyclase activity. Although the experimental evidence is promising, further human clinical trials are necessary before preventive and therapeutic interventions using vitamin C become an established clinical practice. *J Clin Basic Cardiol* 2003; 6: 3–6.

**Key words:** endothelium, vitamin C, oxidative stress, antioxidants

Endothelial dysfunction is being widely recognised as a critical step in the pathophysiology of several cardiovascular and metabolic diseases such as coronary artery disease (CAD), hypertension, heart failure, hypercholesterolaemia, obesity, diabetes, and renal failure [1–3]. This dysfunction occurs during the early disease states before clinical symptoms become overt, and seems to have detrimental consequences on the regulation of vascular tone as well as adverse long-term effects on vascular remodeling [4]. From the clinical point of view it appears to carry negative prognostic impact on long-term outcome of CAD, and perhaps of other vascular diseases [5].

## Endothelium and Nitric Oxide

The study of endothelial dysfunction has mainly focused on the vasodilation achieved by release of nitric oxide (NO) [6], although current reports examine additional processes, such as interactions of endothelium with monocytes, platelets, and coagulation factors [3, 7]. Particularly the vascular tone depends on the balance between vasodilating (NO, prostacyclin, bradykinin, hyperpolarizing endothelial factor etc.) and vasoconstricting factors (thromboxane A<sub>2</sub>, endothelin angiotensin II, prostaglandin H<sub>2</sub> etc.). Nitric oxide, apart from its vasodilatory action, can inhibit adhesion of monocytes, neutrophils and platelets, as well as smooth muscle cell proliferation [8]. On the vessel wall, it derives from the enzymatic action of endothelial NO-synthase (isoenzyme eNOS) and diffuses toward smooth muscle cells, provoking dilation through production of cyclic guanosine monophosphate (cGMP) [8]. A variety of stimuli including shear stress and pressure, thrombin, adenosine diphosphate (ADP), acetylcholine, serotonin, bradykinin, and others, induce NO-release which acts locally on adjacent cells [6]. Substantial bibliographic evidence suggests that reduced bioavailability of NO is present in all the above-mentioned pathological conditions [1, 2]. Subsequent events lead to impaired tissue

perfusion and paradoxical vasoconstriction of vessels, including coronary arteries [9].

## Oxidative Stress and Endothelial Dysfunction

Plenty of experimental and clinical studies have yielded a significant amount of data concerning free-radical mediated injury in the vasculature [10, 11]. Because of the existence of unpaired electrons in their external orbital, these molecules are highly reactive, provoking oxidative damage in various cellular biomolecules such as lipids, proteins, nucleic acids, and others [11, 12]. Specifically, oxidized low-density lipoproteins (LDL) after oxidative modification are taken up by macrophages transforming them to foam cells (early stage of atherosclerosis) but also inactivate NO, provoking direct damage to endothelium [2, 13].

The reaction of NO with superoxide anion (O<sub>2</sub><sup>•-</sup>) is of specific gravity since it gives rise to the formation of highly reactive-toxic molecules such as peroxynitrite (ONOO<sup>-</sup>) [14, 15]. During the development of oxidative stress many inflammatory cells are abstracted and induction of several adhesion molecules allows them to pass through the endothelium [7, 11]. The activation of these cells increases free radical production leading to a vicious cycle. In respect to the formation of free radical species, many factors contribute, such as NADH/NADPH oxidase enzymatic system, xanthine oxidase enzyme, mitochondrial enzymes, and eNOS (under specific conditions) [10, 16]. The relative contribution of these factors to the evolving oxidative stress has not been elucidated yet.

Current epidemiological studies exhibit negative relations between consumption of antioxidant vitamins (mainly C and E) and CAD, even though there is not full unanimity [17, 18]. Vitamin C (ascorbic acid) administration seems to have beneficial effects both in primary and secondary prevention of the above conditions [17, 19]. Recently, the levels of ascorbic acid in plasma were proposed to be an independent prog-

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nostic factor for the occurrence of unstable angina in CAD-patients [20].

### Vitamin C as an Antioxidant

Vitamin C is a potent hydrophilic antioxidant [21] able to scavenge a variety of free radicals and oxidative molecules such as hydroxyl radicals ( $\cdot\text{OH}$ ), superoxide anions ( $\text{O}_2^{\cdot-}$ ), sulphhydryl radicals, oxidized LDL, and others [22–24]. The ability of this vitamin to reduce oxidized vitamin E is of special importance because cells can reutilize reduced vitamin E to scavenge free radicals in lipophilic sites. For that reason, some investigators assume that negative results in some experimental interventions studying vitamin E may be attributed to concurrent vitamin C depletion, which permits the former to act as a prooxidant [22]. Also, they propose that the co-administration of these antioxidants is of exceptional benefit. At this point, it is necessary to elucidate a controversy that for some researchers represents an obstacle for the administration of ascorbic acid in humans. Does this vitamin exhibit prooxidant action? It is well documented that *in vitro*, and in the presence of transition metals ( $\text{Fe}^{++}$ ,  $\text{Cu}^+$ ) vitamin C acts as a prooxidant, facilitating the formation of  $\cdot\text{OH}$  [25]. Excluding conditions of pathological accumulation such as haemochromatosis, the organism does not permit the presence of free transition metal ions, through chelation by specific proteins (mainly ferritin, transferrin, and ceruloplasmin). There is a suspicion of possible local release of these ions, especially in inflammation or tissue damage sites. Nevertheless, the majority of published data concerning laboratory animals as well as human beings (healthy or diseased) concludes that the employment of high doses of vitamin C (p.os. or i.v.) is harmless and does not trigger oxidative stress [26, 27]. A recently published striking clinical study showed that even the co-administration of vitamin C with ferrum does not induce oxidative DNA-damage [28].

### Vitamin C and Endothelial Dysfunction

The accumulation of knowledge regarding endothelial dysfunction and oxidative stress interrelationship led to the conduction of well-organized experimental interventions using vitamin C as an effective tool for increasing NO-bioavailability and in extrapolation for protecting the endothelium [22]. Currently, the endothelial dysfunction is being intensively studied *in vivo*, particularly in large conduit vessels of the upper extremities as well as in coronary arteries [2, 29]. It seems that dysfunction in the endothelium of large arteries like the brachial artery correlates with existence of similar dysfunction in coronary circulation [30]. Many experimental observations clearly indicate a vitamin C-induced increase of NO-bioavailability in response to a variety of stimuli. These include acetylcholine, methacholine, L-arginine (substrate for eNOS) and shear stress-pressure [6]. The examined abnormal vessels, in the absence of vitamin C, do not respond to the above stimuli or they reduce their lumen diameter (paradoxical vasospasm). On the contrary, when ascorbic acid is administered before stimulation, vasodilation emerges. These responses are obvious in patients suffering from coronary CAD [31–33], variant angina [34], heart failure [35], hypertension [36–38], hypercholesterolaemia [39], diabetes mellitus type I [40], type II [41], and renal failure [42]. Similar effects were also observed in specific groups of “healthy” individuals, such as smokers [43], obese [44], and people with hyperhomocysteinaemia [45]. The latter conditions have been characterised as independent risk factors for CAD and are also involved in the occurrence of oxidative stress [46,

47]. Furthermore, of special interest is a double-blind study, where ascorbic acid administered p.os. in hypertensive subjects for one month as monotherapy has significantly reduced the systolic blood pressure [48].

### Mechanisms of Protection

In the majority of the previous studies vitamin C-administration was performed intravenously and the immediate effects were investigated. In the remaining studies, the administration was accomplished through the oral route, and the effects were studied at diverse intervals (from two hours to four weeks of regular administration). Several researchers taking into account the previous studies as well as relative epidemiological evidence (where ingestion of pharmacological doses  $> 500$  mg/day was investigated), have been disputing the ability of vitamin C to inhibit the reaction between NO and  $\text{O}_2^{\cdot-}$  *in vivo*, when received orally [49]. Vitamin C levels in plasma of healthy individuals exhibit wide variations, but concentrations of 30–60  $\mu\text{M}$  are usually measured. Pharmacokinetic studies [50] have shown that oral doses above 400 mg/day do not provide any additional advantage, and moreover that a dose of 200 mg/day is sufficient to approach maximal levels in plasma (100–120  $\mu\text{M}$ ). However, ascorbic acid levels in the order of mM are necessary for effective competition of  $\text{O}_2^{\cdot-}$  during the reaction with NO, because at pH 7.4 the first reaction (Ascorbic Acid +  $\text{O}_2^{\cdot-}$ ) exhibits a rate constant of  $2 \times 10^5 \text{ M}^{-1} \times \text{s}^{-1}$ , while the second reaction ( $\text{O}_2^{\cdot-} + \text{NO}$ ) a rate constant of  $1.7 \times 10^{10} \text{ M}^{-1} \times \text{s}^{-1}$  [22]. Thus, the matter of the mode of protection in the presence of relatively small concentrations has become apparent.

Currently, this issue has been investigated thoroughly and several possible explanations emerged. These explanations are categorized in two main axes. The first axis refers to the controversy about the appropriate concentration. Particularly, there is a well-documented aspect that vitamin C-concentration intracellularly reaches the level of mM in spite of the lower plasma levels [50]. For example the intracellular concentration in mononuclear leukocytes is 6–8 mM [51] whereas in cultured endothelial cells it is 3–8 mM [52]. Taking into account the previous assumptions regarding rate constants, it is obvious that these concentrations can provide efficient protection. The second axis refers to the probable existence of additional modes of action of vitamin C, beyond the reduction of  $\text{O}_2^{\cdot-}$ , which contribute to NO bioavailability increase [49]. This concrete vitamin, as already mentioned, inhibits LDL-oxidation and hence its toxic influences on endothelial integrity [24, 53]. Moreover, human studies utilising ascorbic acid, revealed reduced adhesiveness of inflammatory cells to endothelium, and suppressed production of mediators such as free radicals [54, 55]. In addition, current research efforts revealed remarkable data regarding the role of vitamin C on eNOS function. It has been observed that vitamin C enhances NO production without induction of eNOS, neither affecting L-arginine engagement [56]. Tetrahydrobiopterin constitutes a very significant co-factor for eNOS enzymatic activity. It is possible that vitamin C, possibly in conjunction with glutathione (GSH), favours tetrahydrobiopterin accumulation through inhibition of its oxidation [57]. When this co-factor becomes oxidised, eNOS can trigger free radical production by itself, provoking detrimental effects [16]. Furthermore, *in vitro* experimental studies have shown that ascorbic acid contributes to NO-release from plasma nitrosothiols, although most NO released into the blood vessel lumen is being scavenged by haemoglobin present in erythrocytes [58]. Another possible mechanism by which ascorbic acid could preserve NO is to directly reduce

nitrite (NO<sub>2</sub><sup>-</sup>) to NO. This reaction takes place at low pH *in vitro* [59] but its occurrence at physiological pH *in vivo* remains controversial. Finally, it has been proposed that vitamin C preserves guanyl cyclase activity, thus enhancing cGMP production. This proposal is supported by clinical observations [60], where administration of this vitamin prevents nitrate tolerance in patients receiving continuous nitrate therapy (a class of vasodilators acting as NO-donors).

## Conclusions

In conclusion, a review of recent literature provides substantial evidence concerning the favourable influence of vitamin C on endothelial dysfunction accompanying several pathological entities. It is reasonable to assume that this dysfunction is derived, at least in part, from a local vitamin C depletion which is a consequence of increased oxidative stress occurring in the abnormal vessel wall. Future therapeutic directions may virtually affect primary and secondary prevention as well as acute therapy of atherosclerotic diseases. Nevertheless, despite hopeful results, much more prospective human studies are required for the improvement of this specific antioxidant intervention and the establishment of contemporary therapeutic protocols.

## Acknowledgements

The authors would like to thank Miss Kalliopi Paila for excellent secretarial assistance.

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