

# Arsenic Toxicity, Vitamin C and PON1

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## Abstract

Arsenic exposure affects millions of people worldwide. It increases the formation of Reactive oxygen species (ROS), oxidative stress and decrease antioxidant cell defense. Because of the role of ROS in the development of atherosclerosis disease, use of using antioxidants such as vitamin C (increasing PON1 activity as an antioxidant and its atheroprotective and anti-inflammatory effects) for prevention and treatment of cardiovascular disease is important. The aim of this review was to investigate effects of vitamin c on arsenic induced oxidative stress and PON1. In this article, the role of arsenic in the production of oxidative stress and its reducing agents, including vitamin C will be discussed.

**Keywords:** Arsenic; PON1; Vitamin C

## Introduction

Oxidative stress is impairment in equilibrium between free radical generation and the antioxidant defense system in cell that causes deleterious effects on cell. Excessive production of the free radicals reacts with most biomolecules (DNA, Lipids, Proteins) and damages them [1-4].

Oxidative stress affects intracellular signaling and its regulation. ROS have important roles in physiological concentration as secondary messengers, activation of transcription factors such as NF- $\kappa$ B and the AP-1 family factors [1,2,5-11]. Exogenous and endogenous sources of ROS are UV and  $\gamma$  irradiation, drugs, pollutants, toxins and neutrophils, direct production of ROS, enzymes (e.g., xanthin oxidase), mitochondria and disease [1,2,12,13].

Some ROS that induce oxidative damage include: hydroxyl radical ( $\bullet$ OH) [14,15], hydrogen peroxide ( $H_2O_2$ ) [16,17], superoxide radical ( $\bullet O_2$ ) [1,5], nitric oxide ( $\bullet$ NO) [1,18], perhydroxyl radical (ROO) [5]. Many studies have shown that exposure to inorganic arsenic lead to oxidative stress and many diseases such as types of cancer, cardiovascular disease, diabetes and neurological disorders [19-23]. This review will provide an overview of the effects of vitamin c on the arsenic induced oxidative stress and PON1 activity.

## Literature Review

### Oxidative stress and cellular defense

ROS such as the hydroxyl radical can damage DNA (cleavages of DNA, oxidation of purines, (8-OHdG), double strand break (DSB), single strand break (SSB), damaging the deoxyribose. These oxidative damages to DNA is related to damage to its mitochondria [13,24-26]. Polyunsaturated fatty acids in cell membrane because of their double bond are sensitive to radical attack (lipid peroxidation). The major products of lipid peroxidation are Malondialdehyde (MDA) and Hydroxynonenal (HNE) [2,5,13,27,28]. Products of lipid peroxidation are ligands for a peroxisome proliferator-activated receptor (PPAR)

[29]. Increasing MDA could be related to the GSH (glutathione) depletion. GSH as an essential antioxidant molecule is responsible for the metabolism and detoxification of arsenic [30-32]. MDA is mutagenic and Carcinogenic in mammalian cells and rats respectively. Lipid peroxidation causes oxidation of LDL-C and formation of atherosclerotic plaques (oxidized LDL has cytotoxic or chemotactic action on monocytes and the inhibition of macrophage motility [33-36]. Therefore prevention or decrease of lipid peroxidation is very important.

ROS react with amino acids residues such as cysteine and methionine that may lead to form modified nonfunctional protein. Products of protein oxidation [Advanced glucation end products] are pentosidine and carboxy methyl lysine (CML) [5,13,37-39].

The cellular antioxidant defenses are the best mechanisms against oxidative stress [40]. Antioxidant defenses include enzymatic antioxidants {superoxide dismutase (SOD), Catalases (CAT), Glutathione peroxidase (GPx)} and non-enzymatic antioxidants, vitamin c (free radical chain terminator) [2], protective cell membrane from oxidation [41-47], and regulator of gene expression [48] and lower serum LDL, triglycerides, cholesterol [49,50], vitamin E, Glutathione (GSH), carotenoids, and flavonoids [1,2,5,13,41-49].

### Arsenic and oxidative stress

Arsenic is a metalloid that exists in nature and groundwater in two forms: inorganic (arsenite As (III) and arsenate As (V) in combination with  $O_2$ , sulfur, and chlorine) and organic (in combination with hydrogen and carbon) compounds [50,51]. Studies have reported that it is released in to the environment through industrial processes and agricultural usage [52]. Sodium arsenite is the inorganic compound and the sodium salt of arsenous acid. It is used as an antiseptic, in insecticides and herbicides to preserve hides and making dyes. Toxic effects of arsenic are attributed to production of ROS and oxidative stress [5].

Common source of arsenic is the drinking water. Arsenite react readily with sulfhydryl groups of proteins and inhibit various enzymes such as glutathione reductase (GR) [53].

Arsenic produce ROS and that causes oxidative stress (it acts as a co-carcinogen) [43]. Arsenic generates a variety of ROS such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), superoxide radical (•O<sub>2</sub>), nitric oxide (•NO), perhydroxyl radical (ROO), dimethyl arsenic peroxy radicals and dimethyl arsenic radical [2]. Many studies about metal-induced toxicity such as arsenic have shown that they cause various modifications to DNA bases, increasing lipid peroxidation and inhibition of the production of GSH and change in calcium and sulphhydryl homeostasis [54]. The attach of arsenic to mitochondrial enzymes and reaction with thiol groups of enzyme related to tissue respiration results in impaired tissue respiration. Also arsenic induces apoptosis in various human cancer cells *via* alteration mitochondrial membrane potential [55,56]. Arsenic causes atherosclerosis (*via* vascular endothelial dysfunction and hypertension) [57]. Arsenic can be methylated (detoxification mechanism) *via* methyltransferase using SAM (monomethyl arsenic: MMA, or dimethyl arsenic: DMA), that is reactive and more carcinogenic. Methylation of arsenic may deplete methyl and induce DNA hypomethylation and may cause DNA mutation [43,57].

Arsenic decreases citric acid cycle activity and the production of cellular ATP (competition with phosphate for ATP synthesis and reduction of conversion of pyruvate to acetyl COA *via* inhibition of pyruvate dehydrogenase) [53].

Arsenic induces a dysfunction of triglyceride degradation secondary to insufficient mitochondrial  $\beta$ -oxidation of FFA (fatty free acid) Triglyceride hydrolysis by triglyceride lipase resulting in increased plasma FFA. Inhibition of LPL (lipoprotein lipase) occurs due to increased concentration of plasma FFA that causes hypercholesterolemia, decrease in HDL-C and hypertriglyceridemia secondary [58]. Studies have shown that suboptimal vitamin C intake caused increase in cholesterol ester transfer protein (CETP) activity and that may cause a reduction in HDL cholesterol [58-60].

### Vitamin C and PON1

Vitamin c powerful and water soluble antioxidant in human plasma [61,62]. It regulates cholesterol metabolism (activation of 7- $\alpha$  hydroxylase and production of bile acid from cholesterol) and inhibits LDL oxidation as a free radical scavenger, and radical chain terminator [2,47-50,58].

### Discussion

Studies have shown that antioxidants such as vitamin C are effective in protection of DNA, LDL, and increasing PON1 [63-65]. PON1 is synthesized in the liver and the component of HDL cholesterol that inhibits the oxidative modification of LDL [66]. It has antioxidant activity and protects lipoproteins against oxidation probably by hydrolyzing lipid peroxides [67,68]. It has atheroprotective and anti-inflammatory effects [69]. Its activity loses in the oxidative stress. Metals bind to histidine (His) -115, -134, -155 and -243 that are essential amino acid for the esterase activity of PON1 or cysteine (Cys) residues on PON1 in positions 42, 284 and 353, with a disulfide bond between Cys-42 and-353 and a Cys-284 as a free thiol. The disulfide linked Cys-42 and Cys-353 are essential for PON1 hydrolase. Cys-284 is in or close to the active site and it has protective effect against LDL oxidation [70]. Several studies have shown an increase in oxidative stress, decrease concentration of PON1 in some disease such as diabetes, hyperthyroidism, chronic renal failure, atherosclerosis and pancreatitis [71-73].

Some heavy metals such as lead inhibit PON1 activity with binding to the free thiol group of PON1 and reduce its antioxidant function [67]. Arsenic exposure and low PON1 activity may be related to atherosclerosis [73]. It has been reported that vitamin C and folic acid supplementation resulted in an increase of PON1 (antioxidants can increase PON1 activity, possibly by protecting the enzyme from oxidative stress-induced inactivation).

### Conclusion

Reduction of oxidative stress related to vitamin C (complex formation with arsenic, reduction plasma lipid peroxidation levels, inhibiting oxidative modification of LDLs, protective effects on LDL receptors and increasing apolipoprotein A-I concentration) may preserve PO activity. So reduction of arsenic toxicity with vitamin c supplementation and increasing PON1 activity may have beneficial effects on the incidence of atherosclerosis.

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