**[Toxicol Appl Pharmacol.](http://www.ncbi.nlm.nih.gov/pubmed/?term=Das+S%2C+Santra+A%2C+Lahiri+S+and+GuhaMazumder+D.+N.Implications+of+oxidative+stress+and+hepatic+cytokine+%28TNF+alpha+and+IL-6%29+response+in+the+pathogenesis+of+hepatic+collagenesis+in+chronic+arsenic+toxicity.+Toxicology+and+Applied+Pharmacology+204%3A+18-26%2C+2005." \o "Toxicology and applied pharmacology.) 2005 Apr 1; 204(1):18-26.**

**Implications of oxidative stress and hepatic cytokine (TNF-alpha and IL-6) response in the pathogenesis of hepatic collagenesis in chronic arsenic toxicity.**

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**Abstract**

**INTRODUCTION:**

Noncirrhotic portal fibrosis has been reported to occur in humans due to prolonged intake of arsenic contaminated water. Further, oxystress and hepatic fibrosis have been demonstrated by us in chronic arsenic induced hepatic damage in murine model. Cytokines like tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6) are suspected to play a role in hepatic collagenesis. The present study has been carried out to find out whether increased oxystress and cytokine response are associated with increased accumulation of collagen in the liver due to prolonged arsenic exposure and these follow a dose-response relationship.

**METHODS:**

Male BALB/c mice were given orally 200 microl of water containing arsenic in a dose of 50, 100, and 150 mug/mouse/day for 6 days a week (experimental group) or arsenic-free water (<0.01 microg/l, control group) for 3, 6, 9 and 12 months. Hepatic glutathione (GSH), protein sulfhydryl (PSH), glutathione peroxidase (GPx), Catalase, lipid peroxidation (LPx), protein carbonyl (PC), interleukin (IL-6), tumor necrosis factor (TNF-alpha), arsenic and collagen content in the liver were estimated from sacrificed animals.

**RESULTS:**

Significant increase of lipid peroxidation and protein oxidation in the liver associated with depletion of hepatic thiols (GSH, PSH), and antioxidant enzymes (GPx, Catalase) occurred in mice due to prolonged arsenic exposure in a dose-dependent manner. Significant elevation of hepatic collagen occurred at 9 and 12 months in all the groups associated with significant elevation of TNF-alpha and IL-6. However, arsenic level in the liver increased progressively from 3 months onwards. There was a positive correlation between the hepatic arsenic level and collagen content (r = 0.8007), LPx (r = 0.779) and IL-6 (r = 0.7801). Further, there was a significant negative correlation between GSH and TNF-alpha (r = -0.5336)) and LPx (r = -0.644).

**CONCLUSION:**

Increasing dose and duration of arsenic exposure in mice cause progressive increase of oxystress and elevation of cytokines associated with increasing level of collagen in the liver.