ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Review Article

# FLUORIDE INDUCED NEPHROTOXICITY: APOPTOSIS, ULTRASTRUCTURAL CHANGES AND RENAL TUBULAR INJURY IN EXPERIMENTAL ANIMALS

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**ABSTRACT**

Fluorosis is endemic in many countries across the globe. Most of the Indian states are endemic for fluorosis. Fluoride is known to cause many types of health complications and affects skeletal & soft tissues. The kidneys are one of the highly exposed organs for all the ingested toxins including fluoride. Therefore fluoride exposed subjects are highly vulnerable to fluoride induced nephrotoxicity. In recent years it has been demonstrated that the prevalence of renal impairment is remarkably high in different fluorosis endemic areas. Higher prevalence of CKD observed in central dry zone of Sri Lanka, a fluorosis endemic region. The prevalence of renal tubular dysfunctions is significantly high in residents of El Quel, which is also an endemic fluorosis area in Southern Algeria. On the basis of previous research reports it may be concluded that fluoride induces renal impairments and renal tubular injuries, cellular and sub-cellular ultrastructural changes. But all the research reports available are confined to animal models only. The data available on fluoride associated renal impairment in human is scant and limited to case reports and epidemiological studies. Due to the variation in types of animal models used in the studies, variations in quantity of fluoride administered and variations in route of fluoride administration, the generated insight cannot be translated to clinic. Therefore there is need to adopt a direct holistic approach to evaluate the adverse effects of fluoride on kidney structure and function in human subjects.

**KEYWORDS:** Fluorosis; Nephrotoxicity; Tubular injury; Oxidative stress; Apoptosis; Ultrastructural changes.

## INTRODUCTION

Fluorosis, a clinical manifestation due to fluoride poisoning through drinking water, food and other sources, has emerged in the recent past as a major public health problem in India. At least 21 Indian states are endemic for fluorosis due to high fluoride concentration in underground drinking water.[1] Increased exposure to fluoride may occur from natural sources, industrial sources and from misuse of fluoride containing products.[2] Organic forms of fluoride ranks as third most prevalent class of industrial air pollutants and ground water is the thirteenth most abundant element in the earth's crust. Other sources of fluoride include fluoride containing drugs, Spice, black salt, fluoride containing tooth paste, fluoride addition in drinking water supply, black tea / coffee and many Ayurvedic & herbal preparations. The most common toxic effects of fluoride on humans are dental, skeletal and soft tissues fluorosis and are endemic in areas where drinking water contains high level of fluoride. Toxic level of fluoride exposure also affects vital organs including kidneys.[2]

**Fluoride induced nephropathy:** It has been reported that fluoride-treated rats develop hyperglycemia along with statistically significant increase in concentrations of serum creatinine, blood urea and a decrease in the level of protein and calcium in the blood. The results indicate that fluoride will induce renal impairment and may interfere with renal function.[3] Kidneys are one of the sensitive organs for many toxic element and excessive amount of fluoride exposure to kidney induces histopathological and functional impairment.[4] Kidneys are the main machinery for the excretion and retention of fluoride after fluoride exposure.[5] Therefore numerous renal structural, ultrastructural and functional changes have been reported in animal models after receiving increased amounts of fluoride exposure.[6] Al-Hiyasat et. al., has observed a significant amount of increase in kidney weights as compared to controls in adult female rats exposed to sodium fluoride. Increased level of fluoride exposure to mice remarkably affects serum and urinary parameters including 24-hour urine output, serum creatinine levels and creatinine clearance rate.[7] This phenomenon is most likely induced by inhibition and /or alteration of salt, electrolyte and water reabsorption in the renal proximal tubules[8] and also in thick ascending limb of Henle's loop,[9] by elevated blood flow to the renal medulla.[10] In addition to it fluoride induced pathological changes in the proximal, distal, and collecting tubules have been demonstrated in experimental animals.[11] Fluoride induced effects on glomerular functions are less pronounced, on the other hand, proximal tubular injury is more pronounced in experimental animal models.[12] In case of fluoride toxicity and fluorosis, fluoride-induced polyuria occur due to renal impairment and it may be the manifestation of fluoride induced lipid peroxidation.[13] The same also has been demonstrated in rabbits exposed to high doses of sodium fluoride through food or drinking

water.[14] Fluoride is highly permeable and easily cross cell membranes and can enter into deeper soft tissues such as the liver, brain, and kidney[15] and therefore, nephrotoxicity is may be due to retention and accumulation of inorganic fluoride in the renal tubules.[16]

**Fluoride induced histopathological and ultrastructural changes in kidneys:** Bruce reported that two fold increase in chronic renal disease as a cause of death among anesthetists in the period when the fluorinated anesthetic agents were introduced.[17] Chang demonstrated that in silver staining, silver get deposited in the renal proximal convoluted tubular cells of animals exposed to fluoride, suggesting cellular injury. While no significant silver deposit was observed in the glomeruli.[18] And the hematoxylin & eosin and PAS staining also demonstrated exfoliation of epithelial cells with the formation of cellular casts in the lumen of the proximal convoluted tubules. They also observed ultrastructural changes in the kidneys of the rats after toxic level of exposure to fluoride.[17] The uncoupling effect of halothane on the mitochondria has also been reported. The rapid degeneration of the mitochondria presumably gives rise to the large numbers of membranous bodies in the renal tubular cells. Accumulation and fusions of lysosomes to form irregularly shaped dense bodies was observed in many proximal convoluted tubule cells. Similar dense bodies have also been described in methoxyfluorane exposed patients. However, it was also suggested that abnormality in renal tubular structure might be directly or indirectly related to an alteration in lysosomal function.[18] Formation and aggregation of defined clusters of smooth endoplasmic reticulum in the cells of renal tubule has also reported in many types of nephrotoxicity. It may be explained that the aggregation and/or clustering of SER represents the detoxification response of the kidney tubule cells.[19] Initially focal cytoplasmic degradation was described in hepatic cells induced after various types of toxicity.[20] And focal cytoplasmic degradation observed within the proximal convoluted tubule epithelial cells after halothane intoxication also. Zhan et al, has also observed various renal histological changes in experimental animals exposed to toxic level of fluoride. These changes include necrosis of tubules, tubules dilatation and severe tubular leakage appeared in study group exposed to highest level of fluoride.[21] Moreover it is also observed that fluoride can induce various degrees of damage to the architecture of proximal tubular epithelia, such as cell swelling, cytoplasmic and mitochondrial vacuolations, nuclear membrane breakdown, cell shrinkage, nuclear condensation, apoptosis, and necrosis.[21]

**Fluoride induced renal tubular injury:** Since the kidney is a main target organ of mammalian fluoride systemic exposure and renal toxicity can occur after acute and chronic fluoride intoxication.[22-24] Numerous structural and functional changes have been noted in kidneys of animals receiving increased amounts of fluoride under different conditions.[6] In humans, only a few reports pertaining to kidney involvement in endemic fluorosis are available. Kono *et al* reported impaired renal functions in fluoride-exposed workers.[25] In rats exposed with high concentration of fluoride in their drinking water, renal tubular injury was observed.[3] Other changes including, tubular degeneration, inflammation, fibrosis, parenchymatous nephritis, cloudy swellings, and dilatation of convoluted tubules also has been reported in experimental animals.[26] Chronic fluoride toxicity at a level of 14 mg F/kg bw/day and higher has been claimed to result in a renal tubular lesions in animal models.[27] Fluoride induced nephrotoxicity causes pathological changes in the proximal, distal, and collecting tubules.[11] Its effects on glomerular function are less severe, whereas proximal tubular injury is more evident by analysis of urinary markers such as; α-glutathione-Stransferase, and creatinine.[12] Shupe et al, found fatty degeneration and focal calcification in the stroma and tubules of the bovine kidneys[28]

Rioufol et al, also observed that guinea pigs fed with 20 ppm NaF in their diet for 12 months incurred dilatation of the proximal convoluted tubules with inflammatory infiltration in the cortical region. In the tubules cystic dilatation occurred along with hyaline cylinders.[29] All these findings indicate fluoride induces renal tubular injury in various experimental animal models.

**Fluoride induced apoptosis:** Apoptosis is a pathway of cell death, and excessive apoptosis leads to various kinds of organ injury.[30] *In vivo* liver lesions from fluoride through apoptosis have been reported but few studies are available that show fluoride induces kidney lesions through apoptosis.[31] Fluoride caused various renal histological structure changes such as necrosis of glomeruli and tubules, atrophic glomeruli, glomerular capsule and tubules dilatation; moreover, severe tubular leakage appeared in group of animal given high concentration of fluoride in drinking water and food.[32] Tubular damage can result from ischemic or nephrotoxic injury to the kidney[33] The nephrotoxic and ischemic damages are generally most severe in the early proximal tubule (S3 segment) and the thick ascending limb of the loop of Henle.[34] Poor oxygenation leads to a variety of secondary factors that promote the development of tubular injury, including the intracellular accumulation of calcium, the generation of reactive oxygen species, depletion of adenosine triphosphate, and apoptosis.[35] Apoptotic and/or necrotic tubular cells, exfoliating into the lumen due to either cell death or defective cell-to-cell or cell-to-basement membrane adhesion, obstruct the flow of urine and give rise to a back pressure limiting glomerular filtration. However, the presence of tubular epithelial cells in the urine represents an advanced damage of the renal tubule, whereas the absence of these findings does not exclude renal tubular injury and urinary sediment lacks sensitivity in detecting tubular injury at an early stage.[36] Tubule cells are bizarre, large cells with a single nucleus containing one or more fluid-filled vesicle and accompanied by oval fat bodies observed.[37]

In a cell culture based study Magne et al, examined possible mechanisms involved in fluoride-induced apoptosis in a human epithelial lung cell line (A549). The number of cells with plasma membrane

impairment increased with increasing concentration of fluoride and A549 cell line treated with Deferoxamine, an Al3 chelator almost completely prevented this fluoride - induced responses, which may suggest a role for G protein activation.[38] There is abundant literature reported that fluoride increases the generation of reactive oxygen species (ROS) and free radicals, causes extensive oxidative stress and excessive lipid peroxidation, and reduces antioxidant enzyme activities *in vivo* or *in vitro.*[39,40] The kidney has a prominent role in fluoride metabolism as 50%–80% of fluoride is removed via urinary excretion.[5] Fluoride exposed rats showed increased ROS generation and lipid peroxidation in the kidney.[41]

Fluoride treated cells from kidney proximal tubule showed many types of ultrastructural changes including swollen mitochondria, vacuole formation and apoptosis due to fluoride induced ROS generation and oxidative stress.[42] The ability of oxidative stress to provoke apoptosis as a result of massive cellular damage has been associated with lipid peroxidation and protein and nuclei alterations. Previous studies showed fluoride-induced apoptosis by oxidative stress and suggested the role of oxidative stress in the apoptotic process.[43] Apoptosis is regulated by complex pro- and anti-apoptotic genes. Bcl-2 family members have been demonstrated to be involved in regulation of apoptosis. Bcl-2 inhibits apoptosis and Bax promotes apoptosis, and they are widely present in the mitochondria, nuclear membrane, and endoplasmic reticulum. The mitochondria are one of the most important organelles in apoptotic process. Mitochondrial swelling and rupture may release a large number of apoptosis-promoting factors. Bcl-2 expression was down-regulated in fluoride-treated human gingival fibroblasts.[44] A positive correlation was observed between the fluoride concentration of water and the expression of Bax in liver of fish after fluoride exposure.[45]

**Enzymuria and tubular injury:** Many tubular enzymes have been studied as markers of the necrotic /apoptotic damage or dysfunction of tubular cells.[46-48] Three major origins have been identified: the lysosomes, the brush-border membrane, and the cytoplasm of the cells. Enzymuria may reflect mild injury or injury that is reversible. *Chew et al*,[47] found that elevated levels of ***N***-acetyl-β-d-glucosaminidase (NAG) was associated with tubular injury. Previous studies have demonstrated that tubular enzymuria can detect early tubular injury.[48]

## DISCUSSION

Polyuric nephropathy, a kidney disease characterized by frequent urination, has been established as a major non-skeletal manifestation of fluoride toxicity [49] Like rats subjected to 2.0 to 7.5 mg of fluoride for 18 to 48 weeks, on histological examination revealed vascular, and tubular degeneration leading to interstitial fibrosis. Kaur and Singh[50] reported marked necrosis of tubular cells, atrophy of the glomeruli and areas of interstitial infiltration of round cells of mice subjected to chronic fluoride exposure.

Kidney disease in skeletal fluorosis patients is not uncommon. In persons drinking water containing high level of fluoride, kidney function was found impaired, as indicated by depressed clearance of urea, lowered rate of filtration and enhanced elimination of amino acids,[51,52] and also observed higher incidence of urinary tract calculi in fluorosis endemic areas of Punjab India. Furthermore, the fluorosis patients with urinary tract calculi had significantly higher fluoride level in excretion compared to controls and the urinary tract calculi obtained from these patients also had significantly higher fluoride content compared to calculi from persons of non-endemic area. Previous reports have suggested that kidney stone formation is influenced by levels of fluoride in drinking water.[52] Kidneys are one of the sensitive organs for many toxic element and excessive amount of fluoride exposure to kidney induces histopathological and functional impairment.[4]

## CONCLUSION

All these conclusions are made on exponential animal based finding therefore fluoride associated nephrotoxicity study in human will be of great importance. To best of our knowledge, till now no early specific markers are available to detect fluoride induced renal impairment. Even the widely used renal impairment markers like serum creatinine (Sr. Cr) and blood urea nitrogen (BUN) are very late onset diagnostic markers. Therefore identification and validation of some authentic, reliable and non-invasive diagnostic markers for fluoride induced renal injury may help in early detection of fluoride related kidney impairment.

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**Cite this article as:**
Quadri JA, Alam MM, Sarwar S, Singh S, Shariff A, Das TK. Fluoride Induced Nephrotoxicity: Apoptosis, Ultrastructural Changes and Renal Tubular Injury in Experimental Animals. International Journal of Ayurveda and Pharma Research. 2016;4(8):91-95.

***Source of support: Nil, Conflict of interest: None Declared***

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