Fluoride as a Carcinogen: A Myth or Fact? 24

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Abstract

Fluoride is an naturally occurring element and enters the human body principally through food, water, and respiration. Currently, the largest source of fluoride is water that is fluoridated to eliminate pathogens. Fluoride in concentrations present in beverages and products for dental hygiene is reported to be safe. However, at high concentrations, fluoride can be extremely toxic to myriad tissues. In this regard, the dose, duration, and age of the individual being exposed also is of cardinal importance. Existing data is inconclusive in ascertaining an association between fluoride and carcinogenesis. However, reports based on preclinical and clinical study models do suggest that fluoride triggers oxidative stress by triggering multiple mechanisms. This short review addresses these aspects.

Keywords

Fluoride · Cancer · Oxidative stress · Free radical production

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Introduction

Fluorine is the 13th most abundant element and occurs ubiquitously as fluorides in nature. It is the most electronegative element and highly reactive, showing reaction with virtually organic and inorganic substances (IPCS 1984). Though fluoride has beneficial effects in the form of prevention of dental caries, the beneficial effects are overshadowed by toxic effects. Fluoride easily crosses through the cellular components and gets distributed in the organs (Carlson et al. 1960; Jacyszyn and Marut 1986). Fluorosis is endemic in many areas of the world. The toxicity of fluoride, fluorosis is endemic in many areas of the world. Fluoridation, in which the increase in the level of fluoride in human community can spread though several resources like water system, food, atmosphere, drugs, cosmetics, tooth paste and dental caries (IPCS 1984; Jacyszyn and Marut 1986).

Excessive fluoride intake directly affects the public health and can cause fluorosis through the consumption of groundwater rich in fluoride. In fact, reports indicate that consuming water contaminated with fluorine is responsible for 60% of fluoridation (Shivarajashankara and Shivashankara 2012). Mainly, a certain level of fluoride is dissolved and can be found in rocks and soil in a wide variety, which presents in the form of minerals such as fluorspar (CaF2), cryolite (3 NaF AlF2), apatites (3 Ca2 [PO4] 2 Ca[F] 2), mica, and hornblende. Alkaline and calcium-deficient water components consist of more amount of fluoride (IPCS 1984; Jacyszyn and Marut 1986; Carlson et al. 1960). According to the WHO consideration, the fluoride level in water is 0.5 to 1.0 PPM, although higher levels of fluoride exist in the regions of interior and arid areas than coastal, moist areas (IPCS 1984). The optimum level is required to prevent dental caries. When it is above the optimum level, it may cause fluorosis (Browne et al. 2005; IPCS 1984).

Several studies have revealed the toxicity and role of fluoride in various components and reported that high level of fluoride can cause skeletal and non-skeletal fluorosis. Studies involving experimental animals have demonstrated the deleterious effects of fluoride on cell morphology, activities of enzymes, metabolic pathways, oxidant-antioxidant balance, and virtually all physiological processes of the body (IPCS 1984; Buzalaf and Whitford 2011; Lu et al. 2017; Chlubeka 2002; Perera et al. 2018; Tsunoda et al. 2005; Shivarajashankara et al. 2001; Shivarajashankara and Shivashankara 2012). Similar findings of altered homeostasis and pathological changes have been reported with human beings in fluorosis endemic areas (IPCS 1984; Shivarajashankara and Shivashankara 2012; Rawlani et al. 2010; Blaylock 2004; Aravind et al. 2016; Green et al. 2019).

Fluoride and Cancer

Several epidemiology investigations have correlated the link between exposure to fluoride and the risk of carcinogenesis. Various behavioral evaluations have been carried out to understand how cancer risks are associated with fluoride deposits in

drinking water. One such cohort analysis is that of fluoride and aluminum-rich mineral element (cryolite) production employees and with four case-control studies with osteosarcoma. The editorial of the journal "fluoride" in 1969 drew the attention of researchers towards paradoxical action of fluoride; on one hand fluoride promotes growth and on the other, it inhibits growth. Epidemiological investigation correlates between fluoride effects in drinking water and the risk of cancer rates among the population was shown by International Agency for Research on Cancer (IARC) with inadequate indication of carcinogenicity progression (IARC 1987). Diverse other epidemiological approaches have not been found with any proof showing the relationship between cancer and water fluoride level (IPCS 2002; NRC 1993). Even the subsequent analysis of data on animal studies by International Programme on Chemical Safety (IPCS) revealed inadequate evidence of carcinogenicity of fluoride (Kim et al. 2011).

Researchers have suggested an association between more fluoride accumulation in drinking water and the incidence of osteosarcoma. Seminal studies by National Toxicology Programme (NTP) has shown that a small increase in the incidence of osteosarcoma occurred in experimental F344/N male rats when fed with high concentrations of fluoride (175 ppm sodium fluoride) through drinking water for 2 years (Bucher et al. 1991). In the tenure of 2 years, the analysis showed that 0, 25, 100, or 175 ppm sodium fluoride (equivalent to 0, 11, 45, or 79 ppm fluoride) was present in drinking water. In addition to that, similar evasive facts of carcinogenic activity due to sodium fluoride in animals were documented based on the occurrence of a small number of osteosarcomas in treated experimental animals (Bucher et al. 1991). However, other studies have found no evidence of carcinogenicity of fluoride in experimental animals. Maurer and coworkers fed rats with a diet containing sodium fluoride (4, 10, and 25 mg/Kg per day) for up to 99 weeks. Though fluorotic changes were observed in these animals, there was carcinogenicity (Maurer et al. 1990).

To understand the mutagenicity of fluoridation, sodium fluoride was used to find out the risk of cancer. Most of these studies have not reported any mutagenic effects of fluoride in vivo or in vitro. Fluoride is shown to cause chromosomal aberrations at cytotoxic concentrations of more than 10 mg/liter (IPCS 2002). It is shown that inhibition of DNA repair and synthesis was influenced by NaF-induced aberrations resulting in risk (Aardema et al. 1989). Further, Grandjean et al. (1992) observed incidence of primary cancers of lungs and urinary bladder among cryolite mill workers at Denmark and attributed it to the exposure to high levels of fluoride dust and observed lack of exposure to other carcinogens in these workers. Follow-up studies indicated the possible role of fluoride as a carcinogen. Cryolite is a salt of fluoride and aluminum, and toxicity manifestations of fluoride and aluminum mimic each other (Grandjean and Olsen 2004). Additionally, Kharb and co workers (2012) have observed in their study that when compared to controls, patients with osteosarcoma had high serum fluoride levels. Further they also observed that the drinking water that they consumed also had high levels of fluoride indicating a link between fluoride and osteosarcoma (Kharb et al. 2012).

Fluoride and Apoptosis

Fluoride's paradoxical action on growth is indicated by studies that reported apoptotic effects of fluoride. Fluoridation in the liver showed increased levels of caspase activity, high expression of BAX protein, and a concomitant decrease in Bcl-2 levels indicating that process of the apoptosis was altered (Song et al. 2015; Zhan et al. 2006; Cao et al. 2013). When experimental mice were exposed to sodium fluoride (NaF) at various concentrations under laboratory conditions (0 mg/kg, 12 mg/kg, 24 mg/kg, and 48 mg/kg) and observed for 42 days, high levels of malondialdehyde with regressed mRNA expression led to decreased enzymatic and non-enzymatic activities in the mice liver. These outbreaks assist with the soaring in TNF-R1, FADD, caspase-8, caspase-3 mRNA, and protein expression levels in the organ in a dose-dependent manner. Together, all these observations indicate that accumulation of fluoride in the liver triggers cellular apoptosis through TNF-R1 signaling pathway and to exacerbate the oxidative stress (Lu et al. 2017).

Conclusions

Fluoride has damaging effects on multiple organs, and the effects of fluoride are mediated by multiple molecular mechanisms. The relationship between fluoride and carcinogenesis is not well established. Fluoride has been inducing oxidative stress as demonstrated by preclinical and clinical studies. However, there are limited numbers of in vitro and in vivo studies reporting carcinogenic action of fluoride. Fluoride has two contradicting actions of inducing carcinogenesis as well as apoptosis. An association between incidence of osteosarcoma and fluorosis, as reported by some researchers, is not adequate to conclude carcinogenicity of fluoride. Future research needs to focus on the detailed analysis of fluoride and cancer with an aim of deciphering the molecular mechanisms involved in proposed carcinogenicity of sodium fluoride. Preclinical studies using animal models and clinical studies in endemic fluorosis patients would be able to shed light on the relationship between fluoride and cancer.

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