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IMPLICATIONS OF FLUORIDE TOXICITY ON THE MALE REPRODUCTIVE SYSTEM: A REVIEW

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Abstract

Element fluorine and its bonded-form fluoride were reviewed in accordance with the available recent literature. Generally regarded as safe, fluoride's toxicity has been unappreciated, un-scrutinized, and hidden for over seven decades. Incidents of fluoride toxicity are increasing daily regardless of its being acute or chronic. It arises from the upper layer of earth crust and is largely dissolved in the drinking water. Fluoride is usually essential for the animal body but its excess is equally detrimental and cause severe damage to various systems of our body, especially male reproductive system. The current epidemiological investigations have determined that reproductive system is more vulnerable to the fluoride toxicity and need much attention. Fluorides had deleterious effects on the process of spermatogenesis and the hormones related to sperm productions. Almost all the hormones related with male reproductive system are negatively affected by the excess intake of fluorides in the body. Hence, owing to their importance, we reviewed the current literature pertaining to fluoride toxicity on the male reproductive system and presented a brief account.

INTRODUCTION:

Fluoride is an essential nutrient element and fluorine is the part of fourteen elements which are physiologically essential for the development of humans (Dhar and Bhatnagar, 2009). The main fluoride source for intake is the drinking water (Murutu et al., 2012). At low concentrations, fluoride stimulates bone formation (Richards et al., 1994) and small concentrations have beneficial effects on the teeth by hardening the enamel and reducing the incidence of caries (Fung et al., 1999). However, the increase in the concentration of the fluoride in drinking water could be detrimental to health (WHO, 1984). Maximum acceptable concentration of fluoride may range between 1.0 - 1.5 mg/l (Meenakshi et al., 2004; Misra and Misra, 2007). Any elevation in concentrations may result in dental and skeletal fluorosis, along with lesions of the endocrine glands, viz. thyroid and liver (Czarnowski et al., 1999). At low levels (<2 ppm) soluble fluoride in the drinking water may cause mottled enamel during the formation of the teeth, but at higher levels other toxic effects may be observed. Severe symptoms lead to death when fluoride doses reach 250–450 ppm (McDonagh, 2000).

Elevated fluoride levels in drinking water may risk adverse pregnancy outcome. For instance, human pregnancy exposure to drinking water with 12–18-times the recommended fluoride concentration may cause impaired development of the infant's deciduous (baby) teeth (Reprotox, 2004). Increased fluoride contents could have hazardous effects on the nervous system. Fluorides given to rats in their drinking water at a concentration producing a plasma level of fluoride equivalent to that found in humans consuming water with 4 ppm of fluoride developed symptoms resembling attention deficit-hyperactivity disorder (Mullenix et al., 1994).

Fluorides especially target reproductive system, especially male. Epidemiological investigation indicates that fluoride can lead to detrimental effects in the reproductive system of males living in fluorosis endemic areas (Ortiz-Perez, 2003). In a study to determine the effects of fluoride containing drinking water on human birth rates revealed an association of decreasing total fertility rate with increasing fluoride levels (Freni, 1994). Heindel et al., (1996) studied the developmental toxicity of fluoride and found no adverse effect of sodium fluoride on the embryonic and foetal developments in rats or rabbits at doses of 27 mg/kg/day in the rat and 29 mg/kg/day in rabbits. Testosterone concentrations in skeletal fluorosis male patients were found to be largely decreased, (whereas and no clinical manifestations of the disease compared with those of normal, healthy males living in areas non-endemic for fluorosis (Susheela and Jethanandani, 1996). Furthermore, *in vitro* exposure of human sperm to fluoride (250 mM) resulted in altered lysosomal activity, altered glutathione levels and morphological anomalies leading to a significant decline in sperm motility (Chinoy and Narayana, 1994). These investigations suggest that fluoride toxicity may be specifically detrimental to the reproductive system of males living in fluorosis endemic areas. Increasing evidence of fluoride toxicity on the humans, especially male reproductive systems was the reason to review the literature available on the fluoride toxicity and its implications on the male reproductive system.

EFFECTS OF FLUORIDES ON MALE REPRODUCTIVE SYSTEM

Multiple animal models revealed that fluoride toxicity decreases fertility in most species studied. Fluoride excess in the body can lead to zinc deficiency in testes and the male reproductive system (Krasowska and Wlostowski, 1996). The resultant deficiency of zinc can lead to the repression of the testosterone levels critically necessary for testis development and, more significantly, it enhances oxidative stress in testes leading to poorer quality spermatozoa (El Seweid et al., 2008). Excess of fluoride may also disturb signalling systems, especially those involving capacitation and acrosome reactions of spermatozoa (Dvorakova et al. 2008). In addition, elevated fluoride levels may culminate into decrease sperm head tyrosine phosphorylation and actin polymerization, thereby decreasing capacitation and acrosome reactions in spermatozoa (Izquierdo et al., 2008). Fluoride is also known to block the calcium signalling pathway involved in sperm hyperactivation, which is a type of sperm motility needed for penetration of the zona pellucida (Sun et al., 2009). Disturbance in the calcium signalling pathway as effect of fluoride toxicity could damage sperm hyperactivation leading to dysfunction of spermatozoa. The detail effects of fluorides on the male reproductive system have been listed (Table -1).

EFFECTS OF FLUORIDES ON SPERMATOGENESIS

Fluorides can cross this permeable barrier, which protects both spermatogenic cells and spermatogenesis, during prolonged exposure (Susheela and Kumar, 1991). This is possibly due to the fluoride dependent necrosis of seminiferous tubules in testes (Kour and Singh, 1980). Fluorides after crossing the permeable

Table-1: Table showing the effects of fluorides on various aspects of male reproductive system using rat as test model (DW= Distilled water).

S. No.	Dose	Exposure duration	Effects	Reference
1.	4.5 ppm or 9 ppm NaF DWa	75 Days	Decrease in sperm motility and steroidogenic enzymes	Pushpalatha <i>et al.</i> (2005)
2.	5 mg F/kg bw/day	56 Days	Altered plasma membrane, and decreased ability to undergo acrosome reaction and oocyte fertilization	Izquierdo <i>et al.</i> (2008)
3.	10 mg NaF/kg bw/day	30 or 50 Days	Disturbances in energy metabolism in vas deferens and seminal vesicle	Chinoy <i>et al.</i> (1995)
4.	5 mg F/kg bw/day; F in serum: 0.263±0.024 ppm	56 Days	Oxidative stress and loss of mitochondrial transmembrane potential	Spittle (2008)
5.	5 or 26 mg F/L DW	84 Days	Free radical toxicity in testes	Inkielewicz and Krechniak (2004)
6.	100 or 200 ppm F DW	112 Days	Decreased zinc concentrations in testes	Krasowska and Wlostowsk (1992)
7.	20 mg NaF/kg bw/day	28 Days	Inhibition of spermatogenesis and significant diminution in steroidogenic enzymes (3β-HSD, 17βHSD)	Sarkar <i>et al.</i> (2006)
8.	150 mg NaF/L DW	10 Days	Decreased expression of EGF & EGFR in spermatogenic cells and Leydig cells	Wan <i>et al.</i> , (2006a)
9.	4.5 mg NaF/kg bw/day	60 Days	Decreased diameter of seminiferous tubule	Araibi <i>et al.</i> (1989)
10.	Subcutaneous injection of NaF solution	28 or 38 Days	Decrease in serum estradiol level and apoptosis of spermatogenic cells	Jiang <i>et al.</i> (2005)
11.	10 mg NaF/kg bw/day	50 Days	Significant change in diameter of Leydig cells, reduced steroidogenic enzymes, and disturbance in steroidogenesis	Narayana and Chinoy (1994)
12.	30 or 100 mg F/L DW	56 Days	Disturbed hormone levels of each layer of the hypothalamus-hypophysis-testis axis	Ma <i>et al.</i> (2008)

barrier can cause retardation in the maturation and differentiation of spermatocytes along with fragmentation of spermatozoa, and even cessation of spermatogenesis (Kumar and Susheela, 1995). Wan *et al.* (2006a) investigated that fluoride may cause decreased expression of EGF (epidermal growth factor) and EGFR (epidermal growth factor receptor) in spermatogenic cells. Both EGF and EGFR are strong mediators of spermatogenesis and are associated with the mediation of normal spermatogenic proliferation. Hence, any decrease in their counts can lead to the blockage of spermatogenesis pathway. Fluorides are also responsible for the decrease diameter of seminiferous tubules (Wan *et al.*, 2006b). They can cause a considerable disorganization and denudation of germinal epithelial cells of seminiferous along with the decline in the number of seminiferous epithelium cell layers (Wan *et al.*, 2006b). Furthermore, fluoride interferes with spermatogenesis by modifying important cell signal transducers

called G-protein coupled receptors which are used by the pituitary hormone called luteinizing hormone (LH). Thus, fluoride dependent induced modification of G-proteins may repress the release of testosterone, and thereby leading to the impairing spermatogenesis (Zhang et al., 2006).

EFFECTS OF FLUORIDES ON MALE HORMONES:

Fluorides have a major impact on the endocrine system, especially they disturb the production and release of male sex hormones. Usually decline the levels of testosterone and androgen receptor, disturb the level of estradiol, and interfere with thyroid hormones, which are directly related to spermatogenesis and other reproductive activities. Fluorides have also been found interfering with the hypothalamus-hypophysis testis axis (Ma et al., 2008) by altering catecholamine and melatonin levels.

It is much investigated that excess of fluorides decreases the levels of primary hormone of males, i.e., which is much needed for the initiation of spermatogenesis (Susheela and Jethanandani, 1996; Ghosh et al., 2002). In addition, fluorides tend to reduce EGFR and androgen receptor expression (Wan et al., 2006; Huang et al., 2008) and hinder G-proteins in Leydig cells apart from causing alteration in the diameter of Leydig cells (Narayana and Chinoy, 1994; Susheela and Kumar 1997). These structural changes decrease the ability of Leydig cells to synthesize testosterone. Fluorides also interfere with the production of steroids in Leydig cells by suppressing the enzymes required for testicular steroidogenesis. Fluoride interference suppresses the release of testosterone without affecting the level of gonadotropic hormones. These hormones produce proliferative signals for Sertoli cells, which are seemingly counter-balanced by the anti-proliferative signals from the thyroid hormone, tri-iodothyronine (T3). However, any imbalance in these signals can be detrimental and may lead to some consequences, such as testicular tumours (Fukagai et al., 2005). Increase in fluoride concentration may reduce the expression of androgen receptor, (Huang et al., 2008). Since the functional androgen receptors in both Sertoli cells and Leydig cells play a vital role in spermatogenesis and steroidogenesis, respectively, any decrease in the fluoride induced level of androgen receptors impairs the process of spermatogenesis and decreases the level and function of testosterone (Xu et al., 2007). Excess of fluorides also cause decrease in estradiol levels, which can aid apoptosis of spermatogenic cells, culminating in a reduction or cessation of spermatogenesis. Elevated levels of fluoride negatively affect thyroid hormones. There will be a sharp decline in thyroid hormones, especially T3, which simultaneously results in increased aromatase activity, a decrease in the level of androgens, and an increase in the level of estrogens (O'Donnell et al., 2001).

CONCLUSION:

From the above overview, it is widely held that fluorides, for sure, have deleterious effects on the male reproductive system apart from other functional systems. Owing to the excess of exposure in the environment, fluoride exerts its toxic effects by disturbing normal architecture and functions of spermatozoa, affecting the process of spermatogenesis, and negatively affecting hormone levels required for male reproduction. The intensity of damage on the male reproductive system induces an apprehension that other systems including female reproductive system may also be equally affected by elevated fluoride levels. Hence, more research is needed to explicate the molecular pathways involved, and to find out the minimum dose of fluoride required in the blood levels in a bid to have no negative effect of fluoride toxicity.

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