Environmental Toxicology and Pharmacology 56 (2017) 157–162

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Review

The genetic influence in fluorosis

Sreemanta Pramanik*, Depanwita Saha

Kolkata Zonal Centre, CSIR-National Environmental Engineering Research Institute, i-8 Sector-C, East Kolkata Area Development Project, Kolkata 700107, India

ARTICLE INFO

Keywords:
Exposure
Fluorosis
Candidate genes
Genetic polymorphisms
Genetic association

ABSTRACT

Fluorosis, caused by ingestion of excess fluoride, is endemic in at least 25 countries across the globe, China and India being the worst affected among them. Dental, skeletal and non-skeletal are the major types of fluorosis affecting millions of people in these countries. A number of genetic epidemiological studies carried out by investigators have shown the evidence for association between genetic polymorphisms in candidate genes and differences in the susceptibility pattern of different types of fluorosis among individuals living in the same community and having the same environmental exposure. These studies have pointed out that genetic variants in some candidate genes like *COL1A2* (Collagen type 1 alpha 2), *CTR* (Calcitonin receptor gene), *ESR* (Estrogen receptor), *COMT* (Catechol-o-methyltransferase), *GSTP1* (Glutathione S-transferase pi 1), *MMP-2* (Matrix metallopeptidase 2), *PRL* (Prolactin), *VDR* (Vitamin D receptor) and *MPO* (Myeloperoxidase) could increase or decrease the risk of fluorosis among the exposed individuals in endemic areas. So, it is increasingly becoming evident that an individual's genetic background could play a major role in influencing the risk to fluorosis when other factors like specific environmental exposures including dietary patterns of fluoride intake and other nutrients remain the same. The current manuscript presents an up-to-date critical review on fluorosis, focusing mainly on the genetic association studies that have looked at the possible involvement of genetic factors in fluorosis.

1. Introduction

Fluoride is an essential element which is physiologically essential for normal development and growth of human beings. Fluorine exists abundantly in earth's crust in combination with other elements as fluoride compounds. Fluorosis is caused by ingestion of excess fluoride and the major sources of systemic fluoride exposure in humans occur through diet (water, food and beverages), fluoride supplements and fluoride-containing dental products. It is endemic in at least 25 countries across the globe, and among them India and China are the worst affected. East and North Africa, Mexico and Latin America are also endemic regions for fluorosis. Fluorosis is an untreatable disease, although if diagnosed early, it can be easily prevented and controlled by keeping fluoride intake within safe limit (Susheela and Bhatnagar, 2017). According to World Health Organization, the permissible level of fluoride consumption is 1.5 mg/l. Fluoride is considered as a double-edged sword because it can prevent dental caries at recommended doses, but at the same time its excessive consumption can lead to deleterious effects in mineralized tissues like teeth and bones and soft tissues causing fluorosis (Mehta, 2013).

1.1. Types of fluorosis

There are several different forms of fluorosis such as dental, skeletal and non-skeletal (Majumdar, 2011).

1.1.1. Dental fluorosis

Dental fluorosis is very common among the children and young people and is caused by consumption of fluoride at slightly higher level than optimal. It is a developmental defect characterized by hypo-mineralization of tooth enamel that occurs during the critical periods of tooth development. It can affect the appearance and structure of the tooth enamel. Mild fluorosis appears as fine lacy markings on the enamel of a tooth; usually the appearance is not markedly different from normal enamel. On the other hand, moderate and severe forms of dental fluorosis are characterized by greater hypo-mineralizaion and more pronounced porosity of enamel. Clinically, affected teeth could appear to have white spots, yellow to brownish discoloration, and/or pitting or mottling of enamel, depending on severity. Based on the degree and severity of hypo-mineralization and condition of enamel, dental fluorosis can be classified according to Dean's Index as normal (0), questionable (1), very mild (2), mild (3), moderate (4), severe (5) (Dean, 1993).

* Corresponding author at: Kolkata Zonal Center, CSIR-NEERI, Kolkata 700107, India.
E-mail addresses: sr_pramanik@neeri.res.in, sreemanta@gmail.com (S. Pramanik).

http://dx.doi.org/10.1016/j.etap.2017.09.008
Received 27 June 2017; Received in revised form 7 September 2017; Accepted 14 September 2017
Available online 15 September 2017
1382-6689/

1.1.2. Skeletal fluorosis

Skeletal fluorosis is caused by high fluoride exposure over extended period of time and results in discomfort, pain and rigidity of neck, back, knee, shoulder, bones and joints (Susheela and Bhatnagar, 2017). It leads to bone deformities, increases risk of fracture and other allied problems and affects young as well as elderly people. It is often marked by osteoporosis, osteomalacia or osteopenia (Wang et al., 2007). Skeletal fluorosis is a more serious health concern than dental fluorosis because it has the potential to cause permanent disability.

1.1.3. Non-skeletal fluorosis

Non-skeletal fluorosis affects all the soft tissues and organs of the body. It is now a well-established fact that excessive fluoride due to chronic intoxication could affect cells from soft tissues, e.g., renal, gonadal, endothelial and neurological (National Research Council, 2006). Several studies have reported adverse effects of fluoride on liver and kidney (Xiong et al., 2007), endocrine (Susheela et al., 2005) and reproductive systems (Zhou et al., 2012) from endemic fluorosis areas as well as in cell lines (Riksen et al., 2011). Pain in stomach, loss of appetite, polyuria/polydipsia, muscle weakness, constipation followed by diarrhea are some of the important diagnostic criteria of non-skeletal fluorosis (Majumdar, 2011).

Depending upon the source of consumption of fluoride, fluorosis can also be classified into three groups- water borne, brick tea-type fluorosis and coal burning fluorosis.

1.1.4. Water borne fluorosis

Among the different source of fluoride, drinking water is the most common source of exposure of fluoride in humans. Consumption of excess fluoride through water can lead to dental, skeletal and non-skeletal fluorosis.

1.1.5. Brick tea-type fluorosis

Brick tea-type fluorosis is an endemic fluorosis caused by habitual consumption of large amounts of brick tea. Brick tea has higher fluoride concentrations as it is made of older leaves and stalks than other kinds of tea. It is mostly prevalent in western and northern segments of China. It is characterized by mild forms of dental fluorosis in children and severe forms of skeletal fluorosis in adults. In China, it is becoming a major public health issue as compared to water borne and coal burning fluorosis which are on the wane.

1.1.6. Coal burning fluorosis

Apart from water borne and brick tea-type fluorosis, there is another type of endemic fluorosis called coal burning fluorosis. Combustion of coal and coal bricks release gaseous and aerosol forms of fluoride into the environment which can enter exposed food products as well as human respiratory tract. This type of fluorosis is severely affecting populations living in many rural areas of China. In China, severity of water and coal burning fluorosis has declined because of schemes launched for improving drinking water quality through defluoridation and new methods and technologies for improving stove and grain baking respectively, but brick tea-type fluorosis still remains a major concern for public health.

1.2. Molecular mechanism of fluorosis

Although the molecular mechanisms responsible for fluorosis pathogenesis are still unknown, but it is well accepted that fluoride has a very high affinity for mineralized tissues like teeth and bones and at elevated concentration, fluoride disturbs this mineralization process of teeth and bones (Everett et al., 2002). Enamel mineralization is highly sensitive to free fluoride ions, so when fluoride gets incorporated into the enamel crystals, it affects the subsequent mineralization by reducing the solubility of mineral and this modulates the ionic composition of the fluid surrounding the mineral (Aoba et al., 2002). The minerals in teeth enamel and bones are composed of mainly hydroxyapatite. In this way, fluoride forms fluoroapatite by displacing hydroxide from hydroxyapatite. Fluoroapatite is slower to undergo rebuilding of bones as it less soluble and more compact than hydroxyapatite. So, excess consumption of fluoride could affect bone metabolism and enamel development which ultimately results into skeletal and dental fluorosis. Fluorides cause their action by Mitogen-activated protein kinases (MAPKs) signaling pathway which results in changes in gene expression, cell stress and cell death (Everett, 2011). In this regard, Aoba et al. (2002) postulated the effects of fluorides into two categories-(i) it can affect intracellular events like gene expression, protein synthesis, secretion and trafficking, resorption and degradation of secreted products and (ii) it can affect extracellular events like interaction among matrix protein, protease, crystals and fluid constituents (Aoba et al.,2002).

2. Evidence for the genetic influence associated with fluorosis

2.1. Inter-individual difference in the susceptibility pattern in humans and mice

Although ingestion of excess fluoride can lead to dental, skeletal and non-skeletal fluorosis, however, it is becoming increasingly clear that there is also considerable inter-individual variation in predisposition to fluorosis. It is hypothesized that fluorosis could result from a complex interplay between candidate genes involved in fluorosis and specific environmental exposures, including dietary patterns of fluoride intake and other nutrients. The severity of fluorosis does not always depend on the amount of fluoride consumed. Genetic factors may contribute to the inter-individual variation in the susceptibility or resistance to the fluoride exposure. Few epidemiological studies have observed that some ethnic groups are more prone to dental fluorosis than other groups (National Research Council, 1993), which could not be explained just by the extent of fluoride in the structure of teeth. Russell (1962) showed that while living in the same community, prevalence of dental fluorosis was higher among African American children as compared to the white children. Existing literature data also indicate that some subgroups of population e.g., elderly people with deficiencies of calcium, magnesium and/or vitamin C and people with cardiovascular and kidney problems are extraordinarily susceptible to the deleterious effects of fluoride.

Several studies have been performed on different laboratory mice strains to find the genetic determinants of dental fluorosis. Everett et al. (2002), showed that different strains of mice having the same level of fluoride in their mineralized tissue could produce variable degrees of dental fluorosis severity with genotype, gender, food, age, housing and drinking water fluoride concentration being controlled. Their study also revealed a strong interrelationship between fluoride level in water and bone. Vieira et al. (2005) in a similar study investigated the relationship between fluoride concentration in tooth, dental fluorosis severity, and tooth property (mechanical and material) in three different strains of mice having different susceptibility to dental fluorosis. Their study demonstrated that both environmental (fluoride level in structure of tooth) and genetic (strains having different susceptibility) factors could influence tooth quality. Mousny et al. (2006) tried to understand the underlying genetic influence on extrinsic factors such as fluoride effect on bone metabolism in another animal study. Their study evaluated the effect of increasing fluoride doses on the bone properties in three inbred mouse strains (susceptible, resistant and intermediate) having different susceptibilities in developing enamel fluorosis. Although the bone mineral density did not change in any of the three strains, but they observed significant alteration in the bone quality in the susceptible, moderate alteration in the intermediate and no alteration in the resistant strains. The findings of the study thus suggest that genetic factors might contribute to the variation in bone quality in response to fluoride exposure.