Review Article

Indian J Med Res 148, November 2018, pp 539-547
DOI: 10.4103/ijmr.IJMR_1775_18

Quick Response Code:

Prevention & control of fluorosis & linked disorders: Developments in the 21st Century - Reaching out to patients in the community & hospital settings for recovery

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Received September 24, 2018

The review on fluorosis addresses the genesis of the disease, diagnostic protocols developed, mitigation and recovery through nutritional interventions. It reveals the structural and functional damages caused to skeletal muscle and erythrocytes, leading to clinical manifestations in fluorosis. Hormonal derangements resulting in serious abnormalities in the health of children and adults are discussed. Fluoride toxicity destroys the probiotics in the gut, resulting in vitamin B_{12} depletion, an essential ingredient in haemoglobin (Hb) biosynthesis. The article provides an overview of National Technology Mission on Safe Drinking Water and its contributions to fluorosis control. National Programme for Prevention and Control of Fluorosis is presently in operation in India and its focus cited. Major emphasis has been laid on a variety of disorders surfacing in India due to fluoride toxicity/fluorosis as 'fluorosis-linked disorders', *viz.* anaemia in pregnancy, schoolchildren, thyroid hormone abnormalities, hypertension, iodine deficiency disorders/goitre, renal failure and calcium+vitamin D-resistant rickets in children. The major action taken by the Indian Council of Medical Research (ICMR), Government of India in establishing a Centre of Excellence for Fluorosis Research in India and its contributions are highlighted.

Key words Anaemia - diagnosis - hypertension - interventions - recovery - status fluorosis - stillbirth

Introduction

This is a story of a disease, detected in cattle first and then in human beings in Nellore district in 1937[1], then in Madras Presidency now a part of the Telangana State of the former Andhra Pradesh. During the 81 years of its journey in the country of its origin, the investments made by the Government of India (GOI)/ State Governments, various National and International grant agencies including International Development Research Centre (IDRC), Canada, on 'fluorosis (India)' focussed on diverse aspects of research, in animal models and human patients. As a result, it has been possible to suspect the disease with clinical complaints and to get the disease diagnosed through a well-defined protocol at the earliest onset of the condition. The first

diagnostic test developed[2] was well received. The test emanated based on the bone matrix molecules, *i.e.* glycosaminoglycans (GAG, proteoglycans) and sialic acid (SA, glycoprotein) in fluorosis, and the derangements caused due to fluoride toxicity. One of the merits of the test was that differentiation of fluorosis from the rest of the bone disorders, *viz.* ankylosing spondylitis, osteoporosis, idiopathic backache and osteoarthrosis, was possible. However, it had its limitations of taking long duration to extract GAG and finally to assess the ratio of GAG to SA in the blood. The SA:GAG ratio was reduced by one-third in fluorosis compared to other bone diseases which had overlapping health complaints with fluorosis. The longer duration to provide a test report defeated the merits of the test. Efforts, therefore, continued to develop a simpler procedure for diagnosis, when a report can be provided to a patient within 24-48 h. The second diagnostic test was based on assessing fluoride levels in body fluids, water consumed and with an X-ray film of interosseous membrane covering radius and ulna which gets calcified in fluorosis. The disease is correctly diagnosed through a well-defined protocol at the earliest onset of the disease, and it fulfilled the needs of the patients as well as the doctors who suspected the disease and referred the patient(s) for diagnosis. Patients get relief from the disease within a short interval when fluorosis diagnosed early[3-5]. The recovery is not through prescription of drugs or surgical interventions but through simple, easy to practice dietary interventions[6]. Nutrition played a key role in mitigation of the disease. A disease considered to be incurable during the 19th and 20th centuries and patients were denied admission in hospitals for fear of blocking the beds except when a patient needed a surgical or other interventions. During the initial phase of 35 yr in the life of the disease in India (1937-1972), investigations were focussed on calcified tissues, *viz.* bone and tooth, and the abnormalities, such as discoloured teeth with a pattern and stiff joints with a change in the gait of walking, which led to dental and skeletal fluorosis detection both in human patients and animal models[3]. However, it was too late for recovery from the disease. Publications emerged from different institutions in the country, including those from ICMR-National Institute of Nutrition (NIN), Hyderabad, during a century, are truly the milestones in the understanding of fluorosis.

During the next 25 years (1973-1998), scientific investigations focussed on soft body tissues, besides bone and tooth, as it was intriguing to note that fluoride did bind with each and every soft tissue, wherever the negatively charged F^- ion, found a binding site. The involvement of tissues such as the musculature, which has the highest calcium content, though not calcified in fluorosis, was studied in great detail. The actin and myosin filaments, the two muscle proteins, were not laid down; protein metabolism deranged due to inhibition of enzymes by fluoride[7]. Muscle atrophied, leading to weakness and unable to perform routine activities[8]. The atrophy was myogenic without fascicular atrophy ruling out the possibility of neuronal involvement at early onset of the disease.

The red blood cells were also subjected to extensive investigations to understand the vagaries of fluoride action. The erythrocyte membrane due to influx of F^- into systemic circulation, lost calcium ions, leading to the formation of echinocytes, a structurally and functionally deranged RBC, which had a short life span and was phagocytosed and eliminated from the bloodstream[9,10]. Erythrocyte count was reduced along with reduced Hb levels. This is one of the reasons for patients of fluorosis suffered from anaemia. There are other reasons such as reduced free triiodothyronine (FT_3) and free tetraiodothyronine (FT_4) production without providing impetus to haemopoietic organs for the production of blood cells. Besides, F^- destroyed probiotics (the good bacteria in the gut) leading to non-production of vitamin B_{12}, which is an essential requirement for Hb biosynthesis. While more and more scientific data were emerging on soft tissue involvement in fluorosis[8], a national programme on safe drinking water was launched by GOI in the late 1980s and it had its inputs to the health issues.

National Drinking Water Mission (1987-1997)

A programme 'Control of Fluorosis', a sub-mission in the Water Mission for safe drinking water, was introduced in 1987 by the GOI. During the Water Mission era, only 13 States were known to be endemic for fluoride and fluorosis as opposed to 21 States in the 21st century. The number of States endemic for fluorosis increased because of bifurcation of some of the large States into smaller States at three different time intervals since 2000. The endemic States for fluorosis bifurcated for administrative reasons are Uttar Pradesh, Bihar and Madhya Pradesh, besides Andhra Pradesh, and the number of endemic States for fluorosis[11] thus increased to 21.

Extensive training programmes for professionals in water supply and health sectors were introduced.

Fluorosis disease was addressed as a serious health problem due to consumption of fluoride-contaminated groundwater. Infrastructure was developed for testing fluoride in groundwater in all districts in the endemic States. Two water treatment procedures, *viz*. Nalgonda Technology using lime with alum for removal of fluoride and Activated Alumina Technology for adsorption of fluoride from groundwater, emerged as very useful scientifically sound technologies for de-fluoridation of water[3]. The hand pump, tube well, open well water samples for drinking and cooking purposes were tested to assess the chemical constituents and appropriate technology applied for F^- removal. Different systems for delivery of safe water, *i.e.* domestic filters, hand pump attachments and large community installations, were set-up in villages in endemic States for fluoride/fluorosis. It was the decision of the government that after commissioning the plant, operation and maintenance in the first year would be the mandate of the Public Health Engineering Department (PHED). All systems were then operational. At the end of the first year, the PHED was handed over the responsibility of maintenance to the Village Water and Sanitation Committee. The treatment technologies both Nalgonda and Activated Alumina, though excellent on scientific merits, failed miserably due to scientific inputs required to maintain the functioning of the systems could not be provided by the village committee[3]. The community installation, the remnants of which are still visible in many villages in the country, is a painful reminder of the past efforts and investments[12]. The disillusioned population continued to consume the groundwater with high fluoride content (>1.0 mg/l) as water with high F^- content does not change colour, odour or taste. Health problems prevailed as young and old, men and women besides pregnant women and schoolchildren were unwell with a variety of deformities and ill-health problems. It was then reverse osmosis filters (RO filters) (domestic and community installations) became popular among the rural and urban communities. There was an apprehension that RO removes all the essential nutrients from water. RO filters gained acceptability and also became an investment opportunity under the corporate social responsibility schemes of the GOI. It has also created employment opportunities for local population especially for women for manning community RO plants.

During the first quarter of the 21st century (1998-2018), efforts continued to investigate fluorosis to understand different dimensions of the disease and the major focus was on soft tissue involvement in the disease process. These efforts paid the dividends in achieving the primary goals, *viz.* suspect fluorosis through early manifestations, confirm the diagnosis through laboratory tests, dietary interventions to practice and recovery to attain normalcy within a short interval of a fortnight[4]. It was also that during these years, the commonalities of fluoride action at the molecular level in bone and tooth detected[13,14]. Besides, the gastrointestinal (GI)[15-18] and endocrine systems[19] were investigated. The newly emerged information led to the understanding of fluoride toxicity causing a variety of other disorders associated with fluorosis. Many patients did not respond to treatment when the drugs were orally administered. The fluoride toxicity destroyed the GI mucosa leading to loss of microvilli, cell surfaces denuded, resulted in non-absorption of the drugs. Change of drug(s) to a different brand or dosage would not help in treating the disease. It is necessary to assess urine fluoride, and if found high, intake of fluoride was withdrawn, and within a few days, GI mucosa regenerated and absorption of the drugs administered commenced to get relief from the treatment. Rectification of the damage caused to mucosa was evident as Hb enhanced upon withdrawal of F^- intake and lowering of urine F^- levels <1.0 mg/l[20-22]. These developments assisted the physicians to address the disease effectively.

Fluorosis: National Programme on Prevention & Control of Fluorosis (NPPCF)

Another programme of GOI on Prevention and Control of Fluorosis [National Programme on Prevention & Control of Fluorosis (NPPCF)] focusing on community health was launched during the 11th five-Year Plan period[23]. Reach out to the community in rural India in almost all endemic districts of fluorosis in a phased manner became possible since 2008. A new revelation emerged during this phase that a substantial number of patients attending hospital outpatient departments (OPDs) with classical health complaints due to F^- toxicity were consuming safe water from the existing groundwater sources or through use of RO filters. However, high fluoride levels were detected in their body fluids. This was possibly derived through consumption of F^- through a variety of sources in food, beverages, chewing habit-forming substances (*churans*), chewing tobacco with high fluoride, use of fluoridated toothpaste and drugs containing F^- prescribed for the treatment of disease(s)[24,25]. Patients from rural areas suspected of fluorosis brought

samples of water for testing, and invariably, a safe water source(s) was detected to shift the patient(s) to fetch water from existing safe source(s) in a village[26]. This led to the realization that PHED only tested a few samples from each village and not 100 per cent water sources. The country does not have a mapping of all water sources for F^- except a few States. Promotion of nutrient-rich diet upon withdrawal of fluoride source(s) to rectify the damages caused and improvement of health was achieved. The interventions practiced were through a standardized dietary regime, *i.e*. diet editing and diet counselling. A well-researched and field tested protocol for improving nutrients through daily diet, simple and easy-to-practice procedure for use by all sections of the society was developed[6]. Counselling of the patients led to attitude and behaviour related changes and accepted dietary approach for recovery from the painful disease[3].

Fluorosis & linked disorders

In spite of the fact that fluorosis has become an easily preventable disease, it continues to bother the nation for its widespread prevalence in different formats, *i.e*. the 'linked disorders' which is an integral part of fluorosis. Fluoride being a highly reactive ion and fluorine being a highly powerful oxidizing element interact with cellular and sub-cellular constituents of the body tissues and a new entity 'linked disorders' has emerged. This is largely due to the fact that fluoride being an enzyme inhibitor, a hormone disruptor and a neurotoxin is causing life-threatening health problems. The information reported in recent years is discussed below:

Association of fluorosis with low haemoglobin (Anaemia), premature babies, stillbirth & abortions

Prevention of anaemia has been confirmed by elimination of fluoride consumption or use of fluoridated products. Anaemia may be due to erythrocyte/Hb deficiency and not necessarily due to iron and folic acid deficiency. It was during 2004 the Foundation ventured into correction of anaemia in pregnancy using the know-how already developed in the country to increase Hb in patients with fluorosis, who were anaemic with low Hb levels. In the effort, to address anaemia in pregnancy, only up to 20 wk pregnant women with low Hb, high urinary fluoride and not ailing from any other diseases were included through antenatal clinics (ANCs). Of the pregnant women (n=205) attending ANCs during first and second trimesters, the sample and control groups were selected through a reliable sampling procedure. Sample group comprised of 90 pregnant women and the remaining 115 pregnant women comprised the control group. The former was introduced to two interventions, *viz*. (*i*) provided safe water and safe food without F^- contamination and cross-checked with the urine fluoride levels, (*ii*) promoted, *viz*. calcium, iron, folic acid, vitamins C, E, other antioxidants through dairy products, vegetables, fruits and cross-checked the Hb content during ANC visits. There was no intervention for the control group. Both groups were provided iron+folic acid tablets. Pregnant women were re-assessed for urinary fluoride level (UFL) and Hb during their visit to ANCs. When delivered, delivery details and birth weight of newborn noted from labour room register. It was observed that in pregnant women who attended ANCs during first and second trimesters, the UFL was reduced by 67 and 53 per cent, respectively; Hb was increased in 73 and 83 per cent pregnant women, respectively; body mass index (BMI) was also increased; pre-term deliveries decreased in sample group; newborn weight increased in 80 and 77 per cent of pregnant women in first and second trimesters. However, in control group, it was only 49 and 47 per cent, respectively; and newborn with <2.5 kg birth weight was 20 and 23 per cent, respectively, in contrast to 51 and 53 per cent in control groups[21].

Anaemia in pregnancy was further studied in a large number of pregnant women (n=481) attending ANCs in hospitals from different locations in the city, to confirm the observations made in the first case study[20,27].

Fluorosis linked with anaemia in schoolchildren

Nutritional anaemia is also a major public health problem in schoolchildren. Two hundred and fifty adolescent girls, 10-17 yr of age, from a Government senior secondary girls school in Delhi State, participated in the project. Only those girls who were dewormed in the school health programme and not on any medication particularly for malaria were included[28]. The assessments were made on (*i*) Hb level; (*ii*) UFL; and (*iii*) drinking water fluoride from home and school. The anaemic students consuming drinking water with high fluoride level and those with high urine fluoride level made the sample group introduced to interventions, *viz.* diet editing and diet counselling. The students were monitored by re-testing Hb and urine fluoride levels at one, three and six months after the start

of the interventions. There was an inverse relationship in the levels of urine fluoride and Hb. Reduction in the level of urine fluoride led to a rise in the Hb level. Following interventions, the Hb level revealed significant improvement from the anaemic (<12.0 g/dl) to the non-anaemic range 12.0-14.4 g/dl. At six months of follow up, of the 244 girls studied, those with severe anaemia decreased from 3 to 1 per cent, with moderate anaemia from 97 to 58 per cent and the non-anaemic girls increased from 0 to 41 per cent[28].

Non-toxic, nutritive food and water were useful in improving Hb levels in a high percentage of anaemic schoolchildren. Hb level of >12.0-14.4 g/dl was an achievable target in children without iron and folic acid supplementation[28].

The investigations on school children were extended to boys and girls in six more schools in the National Capital Territory to re-confirm the observations made in girl students and to develop a simple, easy to practice treatment procedure for anaemia by focusing on withdrawal of fluoride consumption and promotion of nutrient-rich diet[28].

The simple easy-to-practice treatment procedure for anaemia, by focusing on withdrawal of fluoride consumption and promotion of nutrients through diet, was field tested in rural and urban areas. The study was made on 2420 adolescent students from six schools in Delhi. Fluoride removal through diet editing and improved nutrients through counselling without prescription of drugs led to correction of anaemia[22].

Fluorosis linked with thyroid hormone abnormalities in children: An area of concern

Children born and brought up in the endemic areas of fluoride and fluorosis have commonalities in their disabilities. Children are stunted, with bow legs, knock-knee and mentally retarded (low IQ). These led to investigate the hormonal profiles especially those produced by the thyroid glands. Children (n=90) with dental fluorosis in the age group of 7-18 yr, living in fluoride endemic, but iodine sufficient areas of Delhi, where iodized salt has been promoted for a decade, were investigated as sample group[19]. Children (n=21) in two control groups with and without dental fluorosis living in non-endemic areas were investigated for T4 (FT4), T3 (FT3) and thyroid stimulating hormone (TSH). In the sample group children, F^- ranged from 1.1 to 14.3 mg F^-/l in water; from 0.02 to 0.41 mg F^-/l in serum; and from 0.41 to 12.8 mg F^-/l in urine. In the control I group children (n=10) F^- ranged from 0.14 to 0.81 mg/l and that of the control II group children (n=11) ranged from 0.14 to 0.73 mg/l. The FT4, FT3 and TSH levels of the 90 sample children revealed that 49 (54.4%) had hormonal abnormalities. In the remaining 41 children, the results were borderline. The results suggested that children with or without dental fluorosis might have hormonal abnormalities that may not be overtly evident until late stages. Determining all three hormones in children is necessary to address health issues[19].

Fluorosis & hypertension

A study was conducted on 125 individuals (75 patients of hypertension and 50 controls) (mean age 53±10 yr; 52% males), and a food habit score indicating level of fluoride intake was calculated by a questionnaire. Drinking and cooking water, serum and urine fluoride level were estimated. Serum malondialdehyde (MDA) and catalase levels were estimated as markers of lipid peroxidation and oxidative stress. Blood parameters identifying fasting sugar, blood urea, serum lipids (triglycerides, total and low-density lipoprotein cholesterol), Hb and total leucocyte count were also estimated[29]. The results revealed that compared to control, hypertensive patients had worse food score indicating high fluoride score and high serum and urinary but not water fluoride levels. Hypertensives had higher MDA and lower catalase activity. Correlation analysis showed serum and urine fluoride to be directly correlated with serum MDA level and inversely with serum catalase levels[29]. High BP was directly correlated with fluoride in serum and urine and serum MDA levels and inversely with serum catalase levels. The worse food habit score was also directly correlated with SBP and diastolic BP (DBP). Different parameters were recommended in both hypertensive and control groups for five weeks. The hypertensive group showed significantly greater fall in UFL but not in serum fluoride level. There was significant fall in serum MDA and significant increase in serum catalase levels as compared with control group. Dietary interventions led to a significant fall in both SBP and DBP. The Hb level also improved in hypertensive group after practice of interventions. The study led to the conclusion that hypertensive patients had high fluoride level and evidence of increased lipid peroxidation and oxidative stress and BP were related to each other[29].

Animal experiments were conducted in the aorta of rabbits fed sodium fluoride (NaF) for certain

intervals. It was found that the smooth muscle fibres disintegrated in the wall of the aorta in the middle layer, the mitochondria revealed electron-dense granules on the inner surface of the plasma membrane of smooth muscle fibres, matrix vesicles with electron-dense particles were observed, increased calcium content and the Ca/P ratio was enhanced, enhanced GAG with decreased dermatan sulphate, an isomer of GAG, was also recorded. The electron-dense granules in the mitochondria, plasma membrane and matric vesicles suggest the initiation of calcification[30].

In one of the studies from Turkey, an endemic nation for fluorosis, it was reported that plasticity of the ascending aorta was lost in chronic fluorosis patients. The aorta was examined directly by echocardiography and it was shown the aorta lost its pliability in endemic fluorosis[31,32]. Fluoride ingestion and hypertension were correlated in males and females as reported from Amini *et al*[33].

Fluorosis & iodine deficiency disorders (IDDs)

Fluorosis and IDDs, two serious and highly prevalent non-communicable, metabolic disorders, are caused by two elements of the halogen family, fluoride and iodine. The Government of India launched a movement to enrich salt with iodine (15.0 ppm iodine in iodized salt) under the National Goitre Control Programme in 1962[34]. Ideally, this should have eliminated goitre cases in the country. Yet, there are reports of goitre prevalence in people with adequate iodine levels in the body. Interestingly, most of these cases are from fluoride-endemic areas where people are consuming excess fluoride either by way of water, food or beverage. Because excess fluoride can damage the thyroid gland, it can create a deficiency of thyroid hormones (FT_3 and FT_4) even when sufficient iodine is present in the body. A recent review article[35] on fluorosis and IDDs in India discussed the issues to address the diseases with better understanding. Correct diagnosis and management of patients in an integrated manner are the need of the hour.

According to the prevailing norms, fluoride if consumed <1.0 mg/l, is within acceptable limits. Similarly, if the salt has >15 ppm of iodine, it is classified as adequately iodized. There are nine studies from India and another eight studies from other nations reported on goitre prevalence in population with iodine sufficiency, goitre in fluoride endemic areas and goitre in industrial workers exposed to fluorine fumes and dust. Fluoride excess is the reason for persistence of goitre, even in case of iodine sufficiency. The first report on fluoride action on thyroid gland dates back to 1854, appeared in a French journal[36] and correlation of F^- excess and iodine deficiency causing the same disorders remained under the carpet for a long time. The study reported that feeding dogs with NaF (20-120 mg/day) for four months caused goitre. There are studies reported on cows, chicks, mice and their pups, reporting on the goitre induced by feeding NaF or providing mineral supplementation[37-40].

There are also human studies which revealed that excess fluoride ingestion caused goitre. The first study was reported from the USA in 1923 stating children aged 12-15 yr after consuming fluoridated water (6 mg/l) in Idaho (USA) developed enlarged thyroid glands[41]. A British scientist had reported in 1941[42] that fluoride played a role in developing endemic goitre in children when he was investigating children living in Punjab. A Chinese report decreased FT_4 and raised TSH were recorded in F^--endemic areas although there was adequate intake of iodine[43].

In patient management for those who have iodine sufficiency but fluoride excess in urine need to be counselled for diet editing for fluoride removal and simultaneously counselled for, promotion of nutrients through diet, to correct the derangements. Similarly, patients who have fluoride excess and iodine deficiency in urine, need diet editing for fluoride removal and diet counselling for the promotion of nutrients besides promoting intake of iodized salt.

Fluorosis linked with renal failure

The literature revealed a direct link of fluoride consumption and renal failure in the population. Reports from India, China, Sri Lanka and Algeria appeared indicating the correlation of fluoride excess consumption and renal failure[44-47].

In patients of fluorosis with renal failure when detected at an early stage, fluoride entry could be forbidden so that the patients may or may not need dialysis or transplantation. Under normal course of events, kidney failure surfaces without much of warning. In an unpublished study on 188 patients of fluorosis at the Foundation, 34 were detected with renal failure. Patients with fluorosis and renal involvement, when tested for fluoride levels in body fluids, revealed higher levels of circulating fluoride compared to normal urine fluoride levels. This is considered as the earliest signs of fluoride toxicity. The clinical manifestations are also identified which overlap with fluorosis patients to suspect renal failure.

ICMR Centre of Excellence for Fluorosis Research: Reach out to rural & urban patients of fluorosis

Besides dental and skeletal fluorosis, the 'linked disorders' cover a range of life-threatening diseases incapacitating the population in both rural and urban settings in the country. The decision of the GOI to set up a Centre of Excellence for Fluorosis Research and address the various issues was a step in the right direction. The mandate of the Centre is to introduce location specific, meaningful strategies for mitigation of the disease. The State of Rajasthan with all its districts severely affected was the first State identified to launch the activities. The Centre and its activities are directed, executed and monitored by the Fluorosis Foundation of India since January 2017[48].

The activities encompass sensitizing policymakers, health administrators and doctors at all levels to view the health issues in its totality and focus on improvement of health of the patients. Most importantly, the programme included sensitization/ awareness generation of grass-root level functionaries, *viz*. Accredited Social Health Activists (ASHAs), Ancillary Nurse Midwifes (ANMs) and the female and male supervisors. Till date, 470 doctors and 925 ASHAs, ANMs have been sensitized in six districts in Rajasthan.

Conclusion

In the 21st century, fluorosis is not a serious health issue. The disease is easily diagnosed, differentiated from other disorders, mitigation is through practice of interventions with focus on nutrition and complete recovery in a fortnight is possible. The problem is the emergence of the 'linked disorders'. The major linked disorders such as anaemia (erythrocyte/Hb deficiency disorder or iron and folic acid deficiency disorder), thyroid hormone abnormalities, GI disorders/irritable bowel syndrome, goitre/IDD, hypertension, vitamin D and calcium-resistant rickets, and renal failure, are the issues that need to be addressed along with fluorosis. Fluoride, an enzyme inhibitor, a hormone disruptor and a neurotoxin plays a dreadful role within the body upon its entry through a variety of sources as a disease causing agent. The revelation of the 'linked disorders' with fluorosis is the milestones in the beginning of a new era which needs attention.

***Acknowledgment*:** The first author (AKS) thanks her Graduate students, Residents, Research Associates, Scientists, who have spent long years conducting research in the National Medical Institute, New Delhi, and thereafter in the Fluorosis Foundation of India, Delhi. She is deeply indebted to her support staff in the Foundation for their involvement in the activities and doing their very best to achieve the goals in each and every project.

***Financial support & sponsorship*:** Authors acknowledge the Funding Agencies in the country, *viz*. Ministry of Environment and Forests, Ministry of Science & Technology, Indian Council of Medical Research/ Department of Health Research, besides International Development Research Centre (IDRC), Ottawa, Canada, UNICEF, WHO Country Representative's office in Ministry of Health and Family Welfare for supporting and funding Fluorosis Research.

***Conflicts of Interest*:** None.

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