EXCESS FLUORIDE INGESTION AND THYROID HORMONE DERANGEMENTS IN CHILDREN LIVING IN DELHI, INDIA

AK Susheela,[a] M Bhatnagar,[b] K.Vig,[c] NK Mondal[d]

Delhi, India

SUMMARY: Ninety children with dental fluorosis, aged 7–18, living in fluoride endemic, non-iodine deficient areas of the National Capital Territory of Delhi, India, where iodized salt has been promoted for over a decade, were investigated, along with 21 children in two control groups without dental fluorosis living in non-endemic areas, to determine their levels of free T_4 (FT_4), free T_3 (FT_3), and thyroid stimulating hormone (TSH). The drinking water fluoride of the 90 children in the sample group ranged from 1.1 to 14.3 mg F^-/L (mean 4.37 mg F^-/L); their serum ranged from 0.02 to 0.41 mg F^-/L (mean 0.14 mg F^-/L); their urine ranged from 0.41 to 12.8 mg F^-/L (mean 3.96 mg F^-/L).

The drinking water fluoride of the control I group (n = 10) ranged from 0.14 to 0.81 mg F^-/L (mean 0.23 mg F^-/L) and that of the control II group (n = 11) ranged from 0.14 to 0.73 mg F^-/L (mean 0.41 mg F^-/L). In control I, only 3 children had serum fluoride below the normal upper limit of 0.02 mg F^-/L. The remaining 7 children, even though they were consuming "safe" water, had elevated serum fluoride. In control II, only one child had serum fluoride below the normal upper limit. The remaining 8 children who were tested also had elevated serum fluoride. In control I, only 3 children had urine fluoride samples in the normal range (0.09–0.10 mg F^-/L); in the remaining 7 children they were above normal. In control II, only one child had urinary and serum fluoride within the normal range. In the remaining 8 children who were tested it was high, suggesting they had excess F^- exposure from sources other than drinking water.

The hormonal status of the 90 sample children indicated that 49 (54.4%) had well-defined hormonal derangements. In the remaining 41 children the findings were borderline. The hormonal deviations among the affected 49 children fall into the following five categories: (1) high TSH with normal FT_4 and FT_3 (46.9%); (2) normal TSH and FT_4 with low FT_3 (32.7%); (3) high TSH and FT_3 with normal FT_4 (14.3%); (4) high TSH with normal FT_3 but low FT_4 (4.1%); and (5) high TSH with normal FT_4 but low FT_3 (2.0%). In control I and control II, similar hormonal deviations were detected in as many as 50% and 45.4% of the children, respectively.

These findings indicate that children with or even without dental fluorosis from exposure to excess fluoride, either through drinking water or through other sources, may have thyroid hormone derangements that may not be clinically overt until late stages. Determining free T_3, free T_4, and TSH is therefore important for a proper diagnosis of potential health problems. Withdrawal from fluoride sources along with measures to correct the thyroid hormonal status may be necessary to promote better health in such children living in fluoride endemic areas.

Keywords: Children; Delhi, India; Fluoride in drinking water; Hypothyroidism; Serum fluoride; Thyroid gland function; Thyroid hormones; Urinary fluoride.

[a]For correspondence: Dr AK Susheela, Fluorosis Research and Rural Development Foundation, C-103, Saransh, 34 IndraPrasth Extension, Delhi-110092, India;
Email: susheela@bol.net.in; [b]Registry of Pathology, Safdarjung Hospital, New Delhi-110029, India; [c]Dept. of Zoology, University of Delhi, Delhi-110007, India; [d]Fluorosis Research and Rural Development Foundation, Delhi-110092.

INTRODUCTION

In India, both iodine deficiency disorders (IDD) and fluorosis (due to consumption of excess fluoride) are the two most prevalent endemic diseases which coexist in certain regions in the country. Though goiter—an enlarged thyroid gland—is commonly recognized as a visible sign of iodine deficiency, the health effects of iodine deficiency reach far beyond those of goiter, and the significant impact of iodine deficiency on brain function in the foetus, the newborn, and the child are now well documented.[1-6] As early as 1928 Stocks[7] observed that children consuming well water in the village of Somerset, England exhibited both goiter and mottled enamel (dental fluorosis). Some years later, Wilson[8,9] found dental fluorosis associated with goiter and cretinism among children living in areas of Punjab where fluoride was recognized geologically.

Besides dental fluorosis and cretinism, children in endemic fluorosis areas of India often have low IQ, deaf mutism, knock-knee, and bow-legs.[10] Obviously, these are serious public health problems of great concern. Since fluoride is known to interfere with thyroid gland function and to cause degenerative changes in the central nervous system, impairment of brain function, and abnormal development in children,[11-17] further investigation is clearly needed, even where iodine intake is not deficient.

To gain a better understanding of the problem, the present study was undertaken to determine the fluoride status and the free T_4, free T_3, and thyroid stimulating hormone (TSH) levels of children with and without dental fluorosis living in an endemic fluorosis area where iodized salt intake has been popularized for over a decade.

MATERIALS AND METHODS

A sample group of 90 male and female children 7 to 18 years old exhibiting dental fluorosis and consuming fluoride-contaminated water in endemic fluorosis areas of the National Capital Territory of Delhi, India, were selected through a school dental fluorosis survey. Children (n = 21) of the same age range and socioeconomic status residing in non-endemic areas, who did not exhibit dental fluorosis, formed control I (n = 10) and control II (n = 11) groups. Their drinking water was deemed to be "safe" (<1.0 mg F^-/L). Like the sample group, these control children were also investigated for thyroid gland function.

Fluoride sample collection and analysis: Samples of drinking water, urine, and blood were collected in plastic bottles and investigated for fluoride levels. Fluoride determination in the drinking water was carried out potentiometrically with an Ion 85 Ion Analyzer Radiometer (Copenhagen) and a fluoride ion specific electrode. Urinary fluoride was estimated by the method of Hall et al.[18] using the Ion 85 Ion Analyzer.

Blood samples were left to clot at room temperature, and serum was separated by centrifugation. Serum fluoride was also estimated by the method of Hall et al.[18]

Thyroid gland function tests: The serum samples of children were investigated to assess free T_4 (FT_4), free T_3 (FT_3), and TSH hormone levels using Immuno Chemiluminiscence Microparticle Assay (ICMA) with the Bayer Centaur Autoanalyzer. A few samples that were cross checked using the Radio immunoassay (RIA) method of hormone estimation did not reveal any appreciable difference in the test results.

RESULTS

Table 1 shows that the 90 children in the sample group are ingesting naturally occurring fluoride in groundwater over a wide concentration range of 1.1 to 14.3 mg F^-/L. The data also reveal that they have a higher-than-normal fluoride content in their body fluids.

Table 1. Fluoride content of drinking water, urine, and serum in the sample group children

Sample	Total no. of children investigated	Age range (years)	Range of fluoride content (mg/L)		
			Drinking water[a]	Urine[b]	Serum[c]
Children from endemic areas consuming fluoride contaminated water	90	7-18	1.1-14.3 (4.37)*	0.41-12.8 (3.96)*	0.02-0.41 (0.14)*

[a] Drinking water fluoride guideline in India: not more than 1.0 mg/L; lesser the better.
[b] Fluoride in urine: normal upper limit 0.1 mg /L.
[c] Fluoride in serum: normal upper limit 0.02 mg/L.
*Value in parenthesis indicates mean value.

Results for all 10 children in control group I and the 11 children in control group II are reported in Tables 2 and 3, respectively. Although these 21 children are consuming "safe" drinking water, only 3 children in control I have normal fluoride concentration in their urine and serum, and in control II, only one child has a normal fluoride level in urine, and only one child has normal serum fluoride. It is also evident from Tables 2 and 3 that thyroid hormonal derangements are present in the children of the control groups.

Results reported in Table 4 reveal deviations in FT_3, FT_4, and TSH in the children of the sample and control groups. In the sample group, over twice as many children have FT_3 below the normal range compared to those with FT_3 above the normal range. In 4.1% of the sample children, FT_4 is below the normal range, but in none is FT_4 above normal. Two-thirds of the sample children have elevated TSH, but none are below normal. In the control groups I and II, about half the children have below normal FT_3. Although all TSH levels are normal in control I, they are below normal in 18.2% of the children in control II and above normal in 27.3% of these children. Table 5 records the combined percentage of children in each group with abnormally low or high thyroid hormonal levels.

Table 2. Children in control I group from non-endemic areas showing fluoride content in drinking water, body fluids, and thyroid hormone levels

S. no.	Age/Sex	Fluoride content in mg/L			Thyroid Function Test		
		Water	Urine	Serum	FT_3[a] pg/mL	FT_4[b] ng/dL	TSH[c] µIU/mL
1.	20/M	0.81	1.23	0.14	2.2†	1.5	2.1
2.	17/M	0.17	0.09*	0.04	2.3	1.5	1.2
3.	20/M	0.21	0.96	0.07	2.7	1.7	1.6
4.	13/M	0.19	0.59	0.08	2.2†	1.5	1.6
5.	8/M	0.14	0.09*	0.02*	2.0†	1.2	1.9
6.	8/M	0.17	0.10*	0.02*	1.9†	1.2	2.0
7.	9/F	0.14	0.34	0.02*	1.8†	1.1	2.0
8.	18/F	0.15	1.32	0.03	2.4	1.7	1.8
9.	20/M	0.14	0.43	0.03	2.8	1.8	1.6
10.	17/M	0.15	0.54	0.03	2.6	1.7	1.4
Range	8-20	0.14-0.81	0.09-1.32	0.02-0.14	1.8-2.8	1.1-1.8	1.2-2.1

Normal range for thyroid hormones: [a]FT_3: 2.3–4.2 pg/mL; [b]FT_4: 0.89–1.8 ng/dL;
[c]TSH: 0.5–2.5 µIU/mL.
* In urine and serum, the normal fluoride levels: 3 in each category.
† Abnormal values in hormone levels: below normal FT_3 = 5.

Table 3. Children in control II group from endemic area showing fluoride in drinking water, body fluids, and thyroid hormone levels

S. no.	Age/Sex	Fluoride content in mg/L			Thyroid Function Test		
		Water	Urine	Serum	FT_3[a] pg/mL	FT_4[b] ng/dL	TSH[c] µIU/mL
1.	17/F	0.28	1.41	0.10	2.2†	1.5	1.0
2.	17/F	0.34	0.1*	0.29	2.2†	1.15	1.9
3.	17/M	0.14	0.55	0.29	2.55	1.15	1.9
4.	13/F	0.68	4.2	0.16	2.2†	1.3	0.2‡
5.	–	0.72	–	–	2.0†	1.4	0.4‡
6.	13/F	0.73	2.08	0.14	3.14	1.04	3.82§
7.	13/F	0.14	0.14	0.05	2.52	0.97	1.54
8.	–	0.72	–	–	3.7	1.36	0.94
9.	18/M	0.42	3.22	0.04	3.06	1.0	1.66
10	17/F	0.19	0.19	0.03	2.0†	1.3	3.2§
11.	18/M	0.21	0.34	0.02*	3.85	1.08	2.87§
Range	13-18	0.14-0.73	0.1-4.2	0.02-0.29	2.0-3.85	0.97-1.5	0.2-3.82

*Fluoride content in: Urine normal = 1; Serum normal = 1.
Abnormal values in hormone levels:†FT_3 below normal = 5; ‡TSH below normal = 2; §TSH above normal = 3.

Table 4. Derangement in FT_3, FT_4, and TSH levels in serum in children of sample and control groups

	FT_3 range (pg/mL)	%	FT_4 range (ng/dL)	%	TSH range (μIU/mL)	%
Sample (n=90) 54.4% (49/90)	< 1.8–2.2 (17/49)*	34.7	<0.78–0.84 (2/49)*	4.1	< None	–
	> 4.28–4.9 (7/49)*	14.3	>None	–	>2.55–6.97 (32/49)*	65.3
Control I (n=10)	<1.8–2.2 (5/10)*	50.0	1.1–1.8 (10/10)*	100	1.2–2.1 (10/10)*	100
	> None	–				
Control II (n=11)	<2.0–2.2 (5/11)*	45.5	0.97–1.5 (11/11)*	100	< 0.2–0.4 (2/11)*	18.2
	> None	–			> 2.87–3.82 (3/11)*	27.3

*Total number of children showing either deviation in hormone level or normal hormone level.

Table 5. Percentage of children in each group with deranged thyroid hormone levels

Groups	S. No.	Thyroid hormonal level			No. of children in each categories	Percentage of children with abnormal hormonal level
		Normal	Low ⇓	High ⇑		
Sample	1	FT_3 + FT_4	–	TSH	n = 23	46.9
	2	FT_4 + TSH	FT_3	–	n = 16	32.7
	3	FT_4	–	FT_3 + TSH	n = 7	14.3
	4	FT_3	FT_4	TSH	n = 2	4.1
	5	FT_4	FT_3	TSH	n = 1	2.0
Control I	1	FT_4 + TSH	FT_3	–	n = 5	50.0
Control II	1	FT_4 + FT_3	–	TSH	n = 2	18.2
	2	FT_4 + TSH	FT_3	–	n = 2	18.2
	3	FT_4	FT_3 + TSH	–	n = 2	18.2
	4	FT_4	FT_3	TSH	n = 1	9.1

DISCUSSION

Although it has long been suggested that dental fluorosis is associated with IDD and thyroid dysfunction,[7-9,14] this study, to our knowledge, is the first to investigate dental fluorosis in relation to TSH and the thyroid hormones FT_4 and FT_3, the latter now confirmed to be the biologically active thyroid hormone.[19]

As evident from the data in Table 5, deviations in thyroid hormone levels in the 49 affected children of the sample group fall into five distinct categories, which are discussed below. It is also evident that even in some of the children in the two control groups consuming "safe" water (<1.0 ppm F^-), fluoride levels in their blood and urine are above current upper limits, indicating other sources of fluoride ingestion, such as from foods and beverages, dental products, drugs, air, or salt. In those children disturbances in thyroid hormone ratios are observed as well.

Production of thyroid hormones is regulated by a negative feedback mechanism, i.e., when the pituitary gland senses a drop in FT_3 levels in circulation, it releases more TSH to stimulate the thyroid gland which in turn accelerates the production of the thyroid hormone T_4, now considered a "pro-hormone". The major source of circulating T_3 is from peripheral deiodination of T_4 and not from thyroid secretion

The enzymes which catalyze deiodination are called iodothyronine deiodinases, of which three have been identified, namely D_1, D_2, and D_3,[20] of which a brief discussion is relevant to the abnormalities detected in the present study. D_1 activity is known to be responsible for conversion of T_4 to T_3 in peripheral tissues, particularly in the liver, and is reflected in plasma T_3 levels, subject of further investigation. D_1 has both outer ring deiodination (ORD) as well as inner ring deiodination (IRD) activity.

D_2 activity reflects conversion of T_4 to T_3 in target tissues (local). This deiodinase has only ORD activity. However, the recent identification of D_2 in human skeletal muscle[21] supports the view that part of plasma T_3 may be generated from tissues other than liver. D_3 activity, on the other hand, converts T_4 into the metabolite reverse T_3 (rT_3) and, further, T_3 into 3,3'-T_2. D_3 has only an IRD activity and is an inactivating enzyme.

Among the three deiodinases, D_1 is expressed in thyroid gland besides the liver and kidney. D_2 is found in the brain, pituitary gland, and skeletal muscle, and D_3 is highly expressed in brain, placenta, and fetal tissues.

While our investigations have focused on thyroid hormones rather than the deiodinases, fluoride is known to interfere with the activity of the deiodinases.

For example, Lin et al.[13] found increased reverse T_3 (rT_3) levels, formed by excessive D_3 activity, in children. The balance of active T_3 and inactive rT_3 in the serum, according to these authors reflects "thyroid hormone economy". Interestingly, the "high" fluoride water levels investigated by Lin et al. included concentrations below the current "optimal" 1 ppm, deemed "safe" and "beneficial" by public health authorities for the reduction of dental caries. These authors concluded that excess fluoride ion affects normal deiodination and that the children

in endemic fluorosis areas are afflicted with such physiological derangements. Since deiodinase activities are considered to be under external TSH control, this could account for many of the thyroid hormone derangements observed in the present study. Fluoride is a TSH analogue, and may be active in both the presence and absence of TSH. In light of the findings discussed below, further studies on deiodinases are considered vital for an in-depth understanding of the problem in fluorosis in children.

In the current investigation 46.9% of the children in the sample group have elevated TSH and normal FT_4 and FT_3 levels, while a similar derangement is also observed in 18.2% of the children in control II. This is our first category and is usually the first indication of thyroid dysfunction, termed sub-clinical hypothyroidism. The largest US study ever conducted on the effects of maternal iodine deficiency showed that mild sub-clinical hypothyroidism in the mother resulted in lowered IQ in the offspring.[22] Besides low IQ, hearing impairment in children ingesting high fluoride and living in endemic areas of iodine deficiency is also reported.[13] Since the development of hearing is controlled by thyroid hormone, thyroid dysfunction in late fetal and early postnatal life has severe adverse effects on the development and function of the acoustic organ, as evidenced from the deafness associated with congenital hypothyroidism.

Because our investigation examined FT_3 levels, which are not routinely tested to assess thyroid gland function, it has been possible to detect low FT_3 in a high percentage of children in both the sample (32.7%) and control groups (7/21 = 33.3%), while FT_4 and TSH values were within normal limits. This is our second category, often described as "Low T_3 syndrome", which has also been observed in workers exposed to fluorides.[14] When the raw data for the 90 sample children in the present series were examined more closely, borderline low FT_3 levels were seen in many of the children (data not shown). It is important to note, therefore, that if only FT_4 and TSH are tested for, these children would elude proper diagnosis.

The third category of children in the sample group (14.3%) show high FT_3 and TSH values with normal FT_4 levels. As the FT_4 levels are seen in the lower end of the reference range, this could indicate T_3 toxicosis. Both T_3 toxicosis and the low T_3 syndrome are associated with disturbances in deiodination.

The fourth category of children in the sample group (4.1%) have high TSH and low FT_4 levels while FT_3 values are normal, the classic indicator for primary hypothyroidism and iodine deficiency. Such a condition may also be caused by abnormal deiodinase activity.

The fifth distinct category of children (2.0%) have low FT_3 and high TSH values, with FT_4 being within the normal range. This again is an indication of disturbed hormone conversion, with inhibition of deiodinases by fluoride a possibility.

With our observation of the above series of derangements in thyroid hormone status in children with dental fluorosis, the association of excess fluoride intake and thyroid hormone disturbances leading to IDD appears to be highly significant

in the understanding of the health problems of children living in endemic areas. Fluorosed children with short stature (cretinism), deaf-mutism, low IQ, knock-knee, and bow-legs seen in endemic areas in India and elsewhere do not respond to any treatment, and they lead a semi-vegetative life.

Thyroid hormone deficiency and/or excess arising from fluoride toxicity leading to IDD such as low IQ, deaf-mutism, and cretinism in children have been reported from elsewhere[11,12] and need to be taken into consideration so that follow-up studies could be directed in a more meaningful manner.

Our findings further strengthen the possibility that fluoride is often responsible for thyroid hormone alterations normally ascribed to IDD. Iodine supplementation for control of IDD is widely practiced in Delhi state and in other parts of India as well as in certain other countries where fluorosis is endemic.[23,24] The monitoring of consumption of iodized salt by school children in Delhi was carried out earlier, and the results showed an upward trend in the consumption of iodized salt at the household level from 76.7% in 1994–1995 to 96.4% in 1996 – 1997.[25] A level of 15.0 ppm iodine was tested in the salt consumed and was considered satisfactory.

The present study therefore provides evidence that fluoride in excess may be inducing diseases normally attributed to iodine deficiency. Fluoride itself has been effectively used as an anti-thyroid drug.[26] The history of fluoride/iodine antagonism has been documented by PFPC.[14]

Adverse effects of excessive fluoride ingestion on the intelligence of children born to mothers in China living in endemic areas of fluorosis and iodine deficiency throughout the period of pregnancy indicate that the deleterious effects are especially critical in brain tissue if exposure occurs very early in development.[15-17]

In light of our findings, the analyses by Burgstahler[27,28] on the association of fluoridated water with Down Syndrome, which were confirmed by Takahashi,[29] clearly appear worthy of further consideration and investigation. Cretinism, like Down Syndrome, shares many similar features with thyroid hormone disturbances as those described here.[30]

Fetal iodine deficiency caused by iodine deficiency in the mother, neonatal iodine deficiency, iodine deficiency in infants and children, and resulting health problems such as endemic cretinism, mental deficiency, deaf-mutism and retarded brain development have been amply demonstrated in the WHO literature.[3] However, the role of excess fluoride in aggravating health problems in children by inducing iodine deficiency disorders appears to be either overlooked or has remained largely unnoticed.

In view of the serum and urinary fluoride levels in the two control groups in the present study, wherein the likelihood of fluoride ingestion from food and other sources is apparent, a good number of reports from India highlighting high fluoride intake through food and dental products have appeared.[31–38] It is evident, therefore, that analysis of fluoride in body fluids besides drinking water is highly relevant and necessary for understanding potential health implications.

Results of the present investigation indicate that better improvement in the health of the children would likely be achieved if management strategies incorporate emerging knowledge to address both fluoride toxicity and iodine deficiency in the same individual, even if residing in non-iodine deficient areas.

Iodine supplementation may not be adequate to reduce IDD when excess fluoride is being consumed. Removal of fluoride from ingestion needs to precede iodine supplementation. The present study, in the light of the observations made, questions the validity of fluoridation of drinking water, milk, fruit juices, and salt by public health authorities in the uncertain hope of preventing dental caries. The damage these programs are causing to the well-being of the children is perhaps unquantifiable.

Some of the conclusions and recommendations we draw from this study are:

- Children with dental fluorosis living in endemic fluorosis areas and IDD may have thyroid derangements that require special care and attention.

- The primary cause of IDD may not always be iodine deficiency, but it might be induced by fluoride poisoning.

- Testing of drinking water and body fluids for fluoride content, along with FT_3, FT_4, and TSH—even in children without dental fluorosis—is desirable for recognizing thyroid derangements.

- Prevention and control of fluorosis and IDD require an integrated approach for diagnosis and patient management, contrary to prevailing practices.

- The results of this study question the validity of the fluoridation of drinking water, milk, fruit juices, and salt by public heath authorities.

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