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Original Research Article

Fluorosis and its impact on thyroid hormones: a cross-sectional study in Bankura District, West Bengal, India

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ABSTRACT

Background: Fluorosis is an important public health problem in India. Fluoride ions can interact with iodide which can leads to abnormal thyroid function.
Methods: The present descriptive, community based study was conducted over a period of 1 year and 6 months in the endemic and non-endemic areas of Bankura district with the sample size of 200. High serum fluoride level (≥0.02 mg/L) was also noted in fluorosis endemic areas (39%) with respect to non-endemic areas (3%). Thyroid profiles were investigated among the participants.
Results: Hypothyroidism was found to be higher in proportion in endemic regions (34%) with respect to non-endemic regions (20%). The levels of serum TSH, fT4 and fluoride in endemic areas were correlated significantly with non-endemic areas. Fluoride level was found to be in significant positive correlation with TSH level and in negative significant correlation with fT4 and fT3.
Conclusions: High fluoride level could produce hypofunctioning of thyroid gland and so hypothyroidism was found to be higher in proportion in fluorosis endemic areas in respect to non-endemic areas.

Keywords: Fluorosis, Free T3, Free T4, Hypothyroidism, Thyroid stimulating hormone

INTRODUCTION

Fluorosis is one of the important public health problems in India.[1] Available data suggests that 15 out of 32 states are fluorosis endemic.[1] Studies showed that approximately 62 million people including 6 million children are suffering from fluorosis due to consumption of high fluoride, especially through drinking water and foods.[2] The upper admissible limit of fluoride in drinking water is 1.5 mg/L [as per Bureau of Indian Standards (BIS)] or 1 mg/L [as per World health Organization (WHO)].[3] In this case, 'Lesser the better' is the dictum to be followed. Fluoride is regarded as 'double-edged sword' because inadequate intake of fluoride can lead to dental caries and it is essential for normal mineralization of bones and formation of dental enamel but prolonged excessive ingestion of fluoride causes dental, skeletal and neurological fluorosis; multi-organ dysfunction abnormal thyroid functions.[1,4,5] Common sources of fluoride are drinking water (60%), foods, drugs, tooth-paste, cosmetics, air with inorganic fluorides etc.[6]

Most of the blocks (17 out of 22) in Bankura district are affected with fluorosis. In this above background, a cross-sectional study was framed to assess the relationship between thyroid profile and serum fluoride level in endemic and non-endemic areas of Bankura district, West Bengal, India.

METHODS

A descriptive, cross-sectional, community based study was conducted over a period of 18 months in the endemic (Simlapal, Taldangra) and non-endemic areas (Bishnupur, Jaypur) of Bankura. Hundred age and sex matched participants were taken from non-endemic as well as from endemic regions, by systematic random sampling method (total participants=200) considering the exclusion criteria. After getting ethical clearance from Institutional ethics committee of Bankura Sammilani Medical College, Bankura and written consent from the voluntarily interested participants, they were interviewed with a predesigned, pretested questionnaire and 5 mL of fasting venous blood sample were collected from each of them, as per the standard protocol of blood collection. Serum was separated by centrifuging the samples at 3000 rpm for 10 minutes. Serum free Triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels were assayed by Enzyme Linked Immunosorbent Assay (ELISA) and serum fluoride were measured by fluoride- Ion Selective Electrode (ISE) (Potentiometric method) at the department of Biochemistry, Bankura Sammilani Medical College. Reference ranges of TSH, fT4 and fT3 were 0.5-5.5 mIU/L, 0.7-1.9 ng/dL, 2.3-4.2 pg/mL, respectively. Desired cut-off limit of serum fluoride was taken <0.02 mg/L. Overt Hypothyroidism is defined as TSH >10 mIU/L with subnormal or low normal fT4; and Subclinical hypothyroidism as TSH level 5.50- 10 mIU/L with normal fT4.

Inclusion criteria

Total 200 participants of age between 12 to 70 years of Bankura district, who were voluntarily willing to take part in the study, were selected from the community by systematic random sampling method.

Exclusion criteria

- Suffering from any thyroid disorders or fluorosis.
- Any acute illness or infectious diseases or malignancy.
- Any therapy that might alter thyroid or hepatic function.
- Known liver or kidney diseases.
- Pregnancy and lactation period.
- Extreme of ages (<12 years or >70 years).

Study Period was from August 2015 to February 2017 (total 18 months).

Study population

Population was selected from the endemic (Simlapal, Taldangra) and non-endemic areas (Bishnupur, Jaypur) of Bankura district of West Bengal, India. Age and sex matched total participants was 200 (100 from endemic and 100 from non-endemic areas).

Study type was descriptive, cross-sectional, community based study.

Statistical analyses

Obtained data were codified in excel spread sheets and analysed by suitable statistical software package (SPSS version 20) as per the need of statistical calculations. Central tendencies (Mean, median, SD, Variance, maximum and minimum values) were calculated of different attributes and the significance of differences between endemic and non-endemic areas were found. Distributions of data of different parameters (thyroid profile and fluoride level) in between endemic and non-endemic areas were determined. As the data were found to be skewed, nonparametric tests were mandate for statistical assessments. Wilcoxon signed ranked tests were performed to evaluate the significance of difference between different attributes. Cross-tabulation between thyroid parameters and fluoride levels of endemic and non-endemic areas were done. Spearman correlation was also done between parameters.

RESULTS

The statistical distributions and central tendencies of different attributes were calculated. It was found that mean age of endemic and non-endemic areas were 32.77 and 34.62 with SE of mean 1.16 and 1.218 with SD 11.604 and 12.175 with medians 31 and 34, respectively. It was also found that mean TSH level of endemic and non-endemic areas were 5.72 and 4.754 with SD 2.635 and 1.834 with medians 5.1 and 4.6, respectively. In case of fT4 in endemic and non-endemic areas means were 1.566 and 1.568 with SD 0.37 and 0.43 with medians 1.6 in both the cases, respectively. In case of fT3 in endemic and non-endemic areas means were 2.629 and 2.825 with SD 0.708 and 0.591 with medians 2.9 and 3.0, respectively. In case of fluoride in serum in endemic and non-endemic areas, means were 0.02112 and 0.01333 with SD 0.0075 and 0.0036 with medians 0.018 and 0.013, respectively (Table 1).

Serum fluoride levels were found to be higher in endemic region than in non-endemic region. Total cases of (subclinical + overt) hypothyroidism in endemic and non-endemic regions were 34% (27%+7%) and 20% (17%+3%), respectively. High serum fluoride levels (≥0.02 mg/L) in endemic and non-endemic regions were 39% and 3%, respectively. One important finding we could observe that low fT3 was more in endemic (34%) with respect to non-endemic areas (22%) (Table 2).

As the data of different parameters were not normally distributed, non-parametric statistical tests were done. Wilcoxon signed ranks tests were done to evaluate the significance of difference between parameters of endemic and non-endemic regions and the differences of TSH, fT3 and serum fluoride levels were found to be significant; i.e., p <0.005 (Table 3).

Table 1: Statistical distributions of different attributes.

Statistics	nAge	Age	nTSH	TSH	nfT4	fT4	nfT3	fT3	nFluoride	Fluoride
	years	Years	mIU/L	mIU/L	ng/dL	ng/dL	pg/mL	pg/mL	mg/L	mg/L
Participants	100	100	100	100	100	100	100	100	100	100
Mean	32.77	34.62	5.720	4.754	1.566	1.568	2.629	2.825	0.02112	0.01333
SE of Mean	1.16	1.218	0.2635	0.1834	0.037	0.043	0.0708	0.0591	0.00075	0.00036
Median	31.0	34.0	5.1	4.6	1.6	1.6	2.9	3.0	0.018	0.013
SD	11.604	12.175	2.635	1.834	0.370	0.430	0.708	0.591	0.0075	0.0036
Variance	134.644	148.238	6.944	3.362	0.137	0.185	0.501	0.349	0.0	0.0
Minimum	15	12	2.3	1.5	0.6	0.6	1.1	1.3	0.012	0.006
Maximum	61	61	17.9	12.8	2.1	2.1	4.0	4.0	0.041	0.023

NB:- n=> Values in Endemic region; SE=> Standard Error; SD=> Standard Deviation, nAge=> Age in endemic region; Age=> Age in non-endemic region; and so on.

Table 2: Distribution of parameters of participants in non-endemic and endemic regions.

Attributes	Values	Non-endemic (%)	Endemic (%)
TSH group (mIU/L)	<5.5	80.0	66.0
	5.5-10	17.0	27.0
	>10	3.0	7.0
FT4 group (ng/dL)	<0.7	3.0	6.0
	0.7-1.9	81.0	86.0
	>1.9	16.0	8.0
FT3 group (pg/mL)	<2.3	22.0	34.0
	2.3-4.2	78.0	66.0
Fluoride group (mg/L)	<0.02	97.0	61.0
	≥0.02	3.0	39.0

Table 3: Wilcoxon Signed Ranks Test.

Total= 100 participants		N	Mean Rank	Sum of Ranks	Z	p value (2-tailed)
nAge ~ Age	Negative Ranks	56a	51.08	2860.50	-1.1154	0.249
	Positive Ranks	44b	49.76	2189.50		
nTSH ~ TSH	Negative Ranks	43c	41.38	1779.50	-2.290	0.022
	Positive Ranks	55d	55.85	3071.50		
nfT4 ~ fT4	Negative Ranks	44e	51.50	2266.00	-0.052	0.958
	Positive Ranks	51f	44.98	2294.00		
nfT3 ~ fT3	Negative Ranks	55g	51.09	2810.00	-1.969	0.049
	Positive Ranks	40h	43.75	1750.00		
nFluoride ~ Fluoride	Negative Ranks	10i	26.65	266.50	-7.235	<0.001
	Positive Ranks	81j	48.39	3919.50		

a. nAge<Age; b. nAge>Age; c. nTSH<TSH; d. nTSH>TSH; e. nfT4<fT4; f. nfT4>fT4; g. nfT3<fT3; h. nfT3>fT3; i. nFluoride<Fluoride; j. nFluoride>Fluoride, *p* value <0.05 was Significant.

Proportionate distribution of hypothyroid cases was found to be significantly higher, in endemic areas with respect to non-endemic areas, when serum fluoride level was ≥0.02 (Table 4 and 5).

In spearman correlation study, it was found that TSH level showed a strong positive significant correlation with the serum fluoride level (correlation coefficient=0.523 and significance; 2-tailed <0.001) but serum fluoride was negatively and significantly correlated with fT3 (correlation coefficient = -0.397 and significance; 2-tailed <0.001) and fT4 (correlation coefficient=-0.170 and significance, 2-tailed 0.016) (Table 6).

Table 4: Cross-tabulation of TSH groups vs. Fluoride groups in Non-endemic area.

TSH level (mIU/L)		Serum fluoride level in non-endemic areas (mg/L)		Serum fluoride level in endemic areas (mg/L)	
		<0.02	**≥0.02**	**<0.02**	**≥0.02**
<5.5	Count	80	0	60	6
	% within TSH group	100.0	0.0	90.9	9.1
5.5-10	Count	15	2	1	26
	% within TSH group	88.2	11.8	3.7	96.3
≥10	Count	2	1	0	7
	% within TSH group	66.7	33.3	0.0	100.0
Total	Count	97	3	61	39
	% within TSH group	97.0	3.0	61.0	39.0
Chi-square, 2 tailed significance of difference among (1) endemic groups of different fluoride levels and (2) non endemic groups of different fluoride levels		<0.001		<0.001	

Table 5: Cross-tabulation of fT4 groups vs. Fluoride groups in Non-endemic area.

fT4 level (ng/dL)		Serum fluoride level in non-endemic areas (mg/L)		Serum fluoride level in endemic areas (mg/L)	
		<0.02	**≥0.02**	**<0.02**	**≥0.02**
<0.7	Count	2	1	0	6
	% within FT4 group	66.7	33.3	0.0	100.0
0.7-1.9	Count	79	2	39	30
	% within FT4 group	97.5	2.5	56.5	43.5
≥1.9	Count	16	0	22	3
	% within FT4 group	100.0	0.0	88.0	12.0
Total	Count	97	3	61	39
	% within FT4 group	97.0	3.0	61.0	39.0
Chi-square, 2 tailed significance among (1) endemic groups of different fluoride levels and (2) non endemic groups of different fluoride levels		0.007		<0.001	

Table 6: Correlation of different parameters.

Spearman's Correlations (N= 200)		TSH	fT4	fT3	Fluoride
TSH	Correlation Coefficient	1.000	-0.313	-0.569	0.523
	Significance (2-tailed)		<0.001	<0.001	<0.001
FT4	Correlation Coefficient	-0.313	1.000	0.392	-0.170
	Significance (2-tailed)	<0.001		<0.001	0.016
FT3	Correlation Coefficient	-0.569	0.392	1.000	-0.397
	Significance (2-tailed)	<0.001	<0.001		<0.001

DISCUSSION

Thyroid dysfunction and goiter is one of the endocrine abnormal manifestations of fluorosis.[7] The thyroid gland, being the most sensitive tissue to fluoride has strong capacity for absorbing and accumulating fluoride.[8,9] Being chemically related but more reactive than iodine, fluoride has an inhibitory effect on iodine uptake in thyroid gland.[10] Moreover, fluoride can directly damage thyroid follicles, cause pycnosis, induce rupture of DNA strands of follicular cells and reduce the number of microvilli on cristae of epithelial cells.[11,12] Fluoride also hinders secretion of T4 and interferes with the activity of deiodinase type-I, leading to perturbation of circulating T3.[13,14,15]

Previous studies were corroborative with our findings showing hypothyroidism was in higher prevalence in

fluorosis endemic areas in-spite of adequate iodine intake.[16,17]

Animal study showed high fluoride ingestion might increase VEGF- mRNA expression and NO level in blood and thus weight of thyroid gland (goitrogenesis).[18] Significant decrease in FT4, FT3 and acetylcholine esterase were noted in fluoride-treated animals.[19] Low T3 syndrome (subnormal T3 level with normal T4 and high reverse T3) might occur in fluorosis.[20] Present study was corroborative with this findings ($p < 0.001$). Fluoride might interfere with hypothalamic–pituitary–thyroid axis or sodium–iodide symporter or thyro-peroxidase or receptors for T4/T3/TSH or transport proteins and cause hypothyroidism.[21]

Fluoride-induced cytotoxicity was observed in a study. Exposure to excessive fluoride might enhance LDH leakage, production of Reactive oxygen species, expression of glucose regulated protein-78, Inositol Requiring Enzyme-1, 'CCAAT' Enhancer Binding Protein Homologous Protein (CHOP) and Spliced X-box-Binding Protein-1 or producing cytotoxicity by IRE-1 pathway-induced apoptosis.[22] Some study reported that fluoride increased intracellular cAMP and caused desensitization of the TSH-receptor.[23] A close relationship was found between fluoride intake and the incidence of goiter in endemic areas.[24,25]

CONCLUSION

Hypothyroidism was commonly encountered in fluoride endemic areas. Low T3, T4 and high TSH were associated with the increment of serum fluoride level. So, active screening and follow up of thyroid endocrine function among patients at risk in fluoride endemic region is mandate. To ensure the causal relationship and effects of other confounding factors more extensive study with more number of sample sizes should be done in future.

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REFERENCES

1. Arlappa N, Aatif Qureshi I, Srinivas R. Fluorosis in India: an overview. Int J Res Develop Heal. 2013;1(2):97-102.
2. Susheela AK. Fluorosis Management Programme in India. Curr Sci. 1999;77(10):1250-56.
3. WHO. Guidelines for Drinking-water Quality Recommendations. 3rd Ed. Geneva, World Health Organization; 2004:(1).
4. Park K. Textbook of preventive and social medicine. 21st Ed, India: Banarasisdas Bhanot Publishers: Jabalpur: 2011:577.
5. Yaming G, Hongmei N, Shaolin W, Jundong W. DNA damage in thyroid gland cells of rats exposed to long-term intake of high fluoride and low iodine. Fluoride. 2005;38(4):318-23.
6. Passmore R, Nicol BM, Rao MN, Beaton GH, Demayer EM. Handbook on human nutritional requirements. Monogr Ser World Health Organ. 1974;(61):1-66.
7. Yang Y, Wang X, Guo X. Effects of high iodine and high fluorine on children's intelligence and the metabolism of iodine and fluorine. Chung Hua Liu Hsing Ping Hsueh Tsa Chih. 1994;15(5):296-8.
8. Shashi A. Biochemical effects of fluoride on thyroid gland during experimental fluorosis. Fluoride. 1988;21(3):127-30.
9. Monsour PA, Kruger BJ. Effect of fluoride on soft tissue in vertebrates. Fluoride. 1985;18(1):53-61.
10. Durrant-Peatfield B. The effects of fluoride on the thyroid gland. Available at: http://rense.com/general57/FLUR.html.
11. Fang WT, Qao BS, Wang JB, Hu PY, Yang XX, Jiang RJ, et al. Iodine deficiency induces thyroid cancer in rats and mice. Zhonghua Zhong Liu ZaZhi. 1994;16(5):341-44.
12. Bouaziz H, Soussia L, Guermazi F, Zeghal N. Fluoride-induced thyroid proliferative changes and their reversal in female mice and their pups. Fluoride. 2005;38(3):185-92.
13. Bachinskii PP, Gutsakeko OA, Narysaniuk ND, Sidora VD, Shliakhta AI. Action of fluoride on the function of the pituitary-thyroid system of healthy persons and patients with thyroid disorders. Probl Endokrinol (Mosk). 1985;31(6):25-9.
14. Susheela AK, Bhatnagar M, Vig K, Mondal NK. Excess fluoride ingestion and thyroid hormone derangements in children in Delhi, India. Fluoride. 2005;38(2):98-108.
15. Bouaziz H, Ammar E, Ghorbel H, Ketata S, Jamoussi K, Ayadi F, et al. Effect of Fluoride ingested by lactating mice on the thyroid function and bone maturation of their suckling pups. Fluoride. 2005;37(2):133-42.
16. Trabelsi M, Guermazi F, Zeghal. Effect of fluoride on thyroid function and cerebellar development in mice. Fluoride. 2001;34(3):165-73.
17. Zhan XA, Li JX, Wang M, Xu ZR. Effects of fluoride on growth and thyroid function in young pigs. Fluoride. 2006;39(2):95-100.
18. Liu G, Zhang W, Jiang P, Li X, Liu C, Chai C. Role of nitric oxide and vascular endothelial growth factor in fluoride-induced goitrogenesis in rats.

Environmental Toxicol Pharmacol. 2012;34(2):209-17.
19. Piler MB, Rai P, Begum S. Fluoride toxicity and status of serum thyroid hormones, brain histopathology, and learning memory in rats: a multigenerational assessment. Biol Trace Element Res. 2011;144(1-3):1083-94.
20. Alder SM, Wartofsky L. The nonthyroidal illness syndrome. Endocrinol Metab Clin North Am. 2007;36(3):657-2.
21. Boas M. Environmental chemicals and thyroid function. Eur J Endocrinol. 2006;154(5):599-611.
22. Liu H, Zeng Q, Cui Y, Yu L, Zhao L, Hou C, et al. The effects and underlying mechanism of excessive iodide on excessive fluoride-induced thyroid cytotoxicity. Environ Toxicol Pharmacol. 2014;38(1):332-40.
23. Tezelman S, Shaver JK, Grossman RF, Liang W, Siperstein AE, Duh QY, et al. Desensitization of adenylatecyclase in Chinese hamster ovary cells transfected with human thyroid-stimulating hormone receptor. Endocrinol. 1994;134(3):1561-69.
24. Day TK, Powell-Jackson PR. Fluoride, water hardness and endemic goitre. Lancet. 1972;299(7761):1135-8.
25. Desai VK, Solanki DM, Bansal RK. Epidemiological study of goitre in endemic fluorosis district of Gujarat. Fluoride. 1993;26(3):187-90.

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