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Original Research Article

Cytomorphological alterations of thyroid gland consequent upon fluorosis

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ABSTRACT

Background: Study aimed at assessing the impact of elevated fluoride from drinking water on thyroid gland structure and function in fluorosis prone areas. Iodine is incorporated in the thyroid synthesis by thyroid gland but in the presence of low Iodine levels fluoride is likely to interfere with the concentrating capacity of thyroid of iodine in thyroid production, consequently reflecting changes in thyroid parameters and also cytomorphological features manifesting hypothyroidism in association with different pathological entities.
Methods: Prakasam district in Andhra Pradesh is fluorosis prone zone and subjects are picked up from highly vulnerable zone in this district and their specimens are collected to study cytomorphological changes of the thyroid gland and biochemical parameters of blood samples for thyroid function test were considered. Cytological study by way of Fine Needle Aspiration Cytology (FNAC) of thyroid gland, biochemical parameters pertaining to function of thyroid gland namely Free triiodothyronine (FT3), Free Thyroxine (FT4) and Thyroid stimulating hormone (TSH) were assessed in the subjects from fluorosis prone zone.
Results: The results were statistically significant with concurrent association of different cytological alterations of thyroid gland in these subjects like Hashimoto's thyroiditis of hypothyroidism, adenomatous goitre, colloid goitre and few of follicular adenoma/neoplasm. FNAC makes cytological changes evident showing different morphological features that comprise different pathological entities largely with an evidence of hypothyroidism in most of the cases in the given study.
Conclusions: The results of the study strongly suggest assessing the magnitude of the problem of fluorosis and also magnitude of its influence on thyroid structure and function that warrants assessment of the thyroid function by biochemical and cytological studies.

Keywords: Fluorosis, Fine needle aspiration cytology, Hypothyroidism, Iodine uptake, Thyroid function tests

INTRODUCTION

The study has a bearing on the uptake of iodine by the thyroid gland in the presence of high fluorine content as there is affinity of the thyroid gland for the other halogens beside iodine. As fluoride is more electronegative than iodine, it easily displaces iodine within the body, thereby affects the functioning of thyroid gland.[1] Fluoride is implicated in thyroid dysfunction that is reflected in changes in certain biochemical parameters in addition to certain cytological changes following under different pathological entities.[2]

Thyroid production depends on thyroid status of the individual under physiological conditions. According to previous studies thyroid gland is found to have higher concentrating ability of these elements than any other tissues in the body. Decline in thyroid production concurrent with low iodine uptake is the possible sequence in the presence of high fluoride content, as there is a competitive inhibition of iodine uptake by fluoride.[3] Over the past decade, several studies have focused on the effects of environmental toxins on the human endocrine system including the impact of fluoride on the thyroid gland.[4,5]

Significant population suffers from thyroid associated problems worldwide and its dysfunction is reflected pathologically and biochemically. Pregnant women are more vulnerable with rise of high blood pressure and miscarriage and there is a potential rise of affliction of the brain of the growing foetus consequently.[6-8] High fluoride ingestion from different sources is found with abnormal thyroid function in both animals and humans with low levels of thyroid hormones and high TSH production.[9] Some studies reported a reduction in the FT4 and FT3 levels as well as an abnormal increase in the TSH levels.[10-16] Even at 1mg/L of fluoride in water, that effect on thyroid hormones on learning memory was investigated in rats by Basha PM et al.[17] They found that fluoride reduces the T4 and T3 levels and has generational and cumulative effects on the development of the offspring. Several villages in Prakasam district located in Andhra Pradesh of India which uses groundwater as the primary water source. The chosen area for the study in and around Prakasam district of Andhra Pradesh is found with high fluoride levels in ground water and consequently in drinking water.

METHODS

The study was conducted to evaluate and correlate the effect of chronic excess fluoride intake on thyroid structure and function among subjects residing in fluorotic prone zones. The villages with high fluoride levels in the drinking water in the Prakasam district of Andhra Pradesh, India were included. This study was aimed at determining the correlation between fluoride levels in the drinking water, thyroid hormones and cytomorphological features (FNAC) of thyroid gland in fluorosis prone zones of Prakasam district of Andhra Pradesh. All the methods were carried out in accordance with the relevant guidelines and regulations. A total of 342 subjects included in the study sparing for one year from December 2016 to September 2018. To ensure that the subjects are from the fluorosis prone zone, water samples from the areas in question are collected for analyzing fluoride levels. The samples of drinking water were collected in plastic bottles. Fluoride determination in the drinking water was carried out by using spectrophotometrically by SPADNS method. Irrespective of the age and sex blood samples are obtained from the subjects hailing from the established fluorotic zones and blood samples were left to clot at room temperature by centrifugation serum was separated for assessing the serum fluoride levels (Negoita S et al) in correlation with the fluoride content of the potable water in the respective areas.[20] In these subjects serum fluoride levels were estimated by using manual titration method and automatic fluoride ion 85 Ion Analyzer and radiometer with Hall et al, and ASTDM method. The serum samples were investigated to assess FT4, FT3 and TSH hormone levels using Immuno Chemiluminescence Microparticle Assay (ICMA) with the Bayer Centaur Auto Analyzer. Following the ethical committee approval samples for the cytological study obtained by fine needle aspiration of thyroid gland in additions to the blood samples for assessing thyroid function tests and serum fluoride levels. These specimens were collected from the patients attending to institutional hospital that caters to the medical needs of the neighboring fluorosis prone areas.

The subjects from fluorotic zone with or without thyroid dysfunction were included in the study and the subjects with pre-existing thyroid disorders with supplementation of thyroxine were excluded.

RESULTS

The present study was carried out in Central Laboratory of Government medical institution, Ongole, Prakasam District among the cases which presented from December 2016 to September 2018. FNAC were included in the study, 22-gauge needle attached to 10ml syringe was used for aspiration. On an average 2 to 3 passes were made in the lesion and the aspirate was smeared in clean glass slide and air-dried smear. May Grunwald Giemsa (MGG) staining was done and using DPX mountant slide was prepared for cytological study.

To evaluate the distribution of fluoride levels in the drinking water samples from Prakasam area 20 mandals as distinct locations were chosen according to the difference in the concentration of fluoride in drinking water and samples were taken from 58 villages of Prakasam district to determine the fluoride concentration.

Table 1 shows age distribution in different pathological entities of thyroid gland, mean age was calculated for all the subjects included as many as 342. Mean value of the age of included subjects ranged from 30.31 to 41.46years.

Table 2 shows serum fluoride levels tabulated in association with different thyroid pathological entities among 342 subjects where highest mean levels of 0.1309mg/l were found in association with lymphocytic thyroiditis and with a lowest mean value of 0.0473mg/l in association with follicular adenoma. Table 3 shows classification of fluorotic villages basing on the concentration limit, among the 58 villages twenty villages found to show fluoride content of water >2mg/L while least concentration of <0.5mg/L was found in 3 villages, while rest of the villages had the range in between. The fluoride levels of the water content in the concerned areas are found to be more than the acceptable levels, in some areas as high as 12.7mg/L ranging from 0.23mg/L.

Table 1: Age distribution in different pathological entities of thyroid gland.

Age	n	Mean	Std. deviation	P value	%
Euthyroid	42	30.31	9.267	0.0001	12.3
Hashimoto's thyroiditis	105	36.03	9.719	0.0001	30.7
Lymphocytic thyroiditis	33	30.64	11.093	0.0001	9.6
Autoimmune thyroiditis	25	36.92	8.907	0.0001	7.3
Adenomatous goitre	48	41.46	11.828	0.0001	14.0
Nodular goitre	48	40.15	11.888	0.0001	14.0
Colloid goitre	26	30.5	11.247	0.0001	7.6
Follicular adenoma	15	36.6	10.091	0.0001	4.4

Table 2: Serum Fluoride distribution in different pathological entities of thyroid gland.

Serum fluoride (mg/l)	n	Mean	Std. Deviation	P value
Euthyroid	42	0.0636	0.04487	0.0001
Hashimoto's thyroiditis	105	0.1015	0.05571	0.0001
Lymphocytic thyroiditis	33	0.1309	0.05965	0.0001
Autoimmune thyroiditis	25	0.0948	0.05386	0.0001
Adenomatous goitre	48	0.0471	0.02361	0.0001
Nodular goitre	48	0.0685	0.0464	0.0001
Colloid goitre	26	0.0492	0.02331	0.0001
Follicular adenoma	15	0.0473	0.0252	0.0001

Table 3: Classification of fluorotic villages basing on the concentration limit.

Water fluoride conc. limit (mg/l)	Frequency	%
<0.5	3	5.2
0.51-1.5	22	37.9
1.51-2.0	13	22.4
>2.0	20	34.5
Total	58	100

In this study, twenty distinct mandals were chosen according to the difference in the concentration of fluoride in drinking water. These distinct locations include HM Padu, Kanigiri, Podili, Kandukuru, Jarugumalli, Singarayakonda, Kovuru, Marturu, CS puram, SN padu, Korisipadu, Kondepi, PC palli, Addanki, Gudluru, Cheemakurthy, Naguluppalapadu, Maddipadu, Inkollu, Chinnaganjam, kothapatnam. The frequency distribution of fluoride was statistically significant for the cases (P<0.005). Table 4 shows the levels of thyroid hormones and mean TSH of different thyroid entities where highest mean TSH levels of 73.65µIU/ml were found in association with Hashimoto's thyroiditis and with a lowest mean TSH value of 3.35µIU/ml in association with follicular adenoma. In the present study 87.720% of subjects had thyroid problems, while 47.65% had hypothyroidism and among the subjects who had Euthyroid as 12.28%. The distribution of different kinds of thyroid diseases in the 342 cases include 163 (47.65%) with hypothyroidism, 11 (3.22%) with hyperthyroidism. As per the scope of this study, 163 (47.65%) participants with hypothyroidism were selected for the cases. The average amount of TSH and FT3 hormones based on the fluoride levels in the range of 34.58µIU/ml and 2.59 Pg/ml was significant.

Figure 1 shows microscopic picture of thyroid gland (Euthyroid), characterized by fibrous septa extending in to the gland and divides in to lobules. Each lobule was with aggregation of follicles and was lined by follicular epithelium on a basement membrane. The follicular cavity filled with homogenous colloid material. The follicular cavity filled with homogenous colloid material.[21]

Figure 2 shows microscopic picture of Hashimoto's thyroiditis characterized by lymphoid infiltrate destroying the thyroid follicles. Moderately cellular with aggregates of hurthle cells, finely granular cytoplasm, large hyperchromatic nuclei, variable pleomorphism and mature lymphocytes. Extensive lymphocytic infiltrate with germinal center formation, and with reduced or no colloid material. Increased fibrosis but does not extend beyond capsule. Epithelium may have enlarged or overlapping nuclei with partial nuclear clearing. Figure 3 shows microscopic picture of lymphocytic thyroiditis with plenty of lymphocytes admixed with few thyroid follicular epithelial cells and hurthle cells. Focal aggregates of lymphocytes in inter or intralobular fibrous tissue, no oxyphilic metaplasia, no follicular atrophy, no follicular disruption. Figure 4 shows microscopic picture of autoimmune thyroiditis was characterized by diffuse lymphocytic infiltration with occasional germinal centers, thyroid follicles of reduced size containing sparse colloid and fibrosis. Although the follicles are small, the individual thyroid cells often appear enlarged and contain granular cytoplasm.

Table 4: Levels of thyroid hormones and mean TSH of different thyroid disorders.

Thyroid disorders	Free triiodothyronine (FT_3) pg/ml	Free thyroxine (FT_4) ng/ml	Thyroid stimulating hormone (TSH) µIU/ml	n	Mean TSH
Euthyroid	1.4-4.0	0.19-1.51	2.18-4.15	42	3.73
Hashimoto's thyroiditis	0.7-3.9	0.08-1.56	52.89-115.54	105	73.65
Lymphocytic thyroiditis	0.9-2.1	0.17-0.78	34.45-51.12	33	50.97
Autoimmune thyroiditis	0.89-4.1	0.19-1.65	36.64-72.64	25	67.23
Adenomatous goitre	2.7-4.1	0.96-1.16	2.43-5.12	48	3.79
Nodular goitre	1.40-4.1	0.19-1.62	2.42-4.92	48	5.05
Colloid goitre	2.8-4.0	1.03-1.54	2.45-4.95	26	3.81
Follicular adenoma	2.8-4.01	0.98-1.35	2.74-3.75	15	3.37

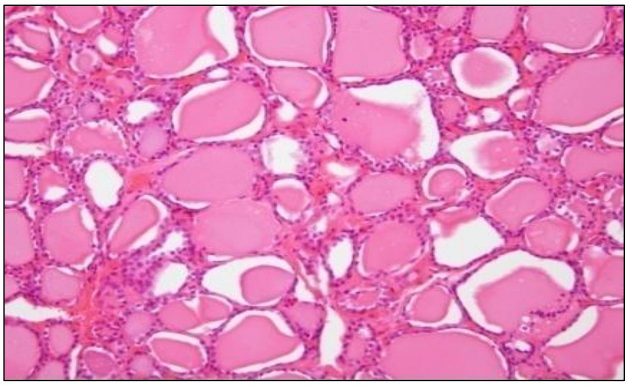

Figure 1: Microscopic picture of FNAC showing euthyroid thyroid epithelial cells arranged in cluster sheets follicles with varying sizes filled with colloid and lined by columnar epithelium.

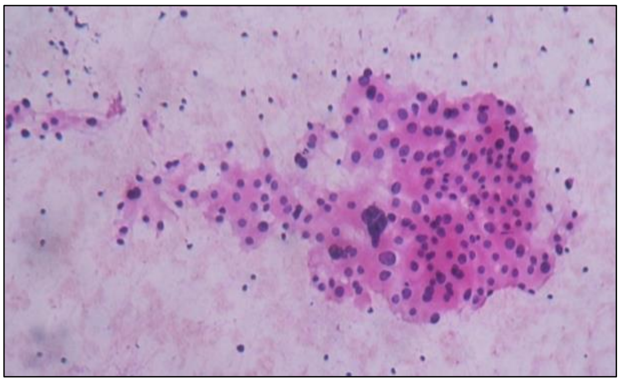

Figure 2: Hashimoto's thyroiditis: hurthle cells admixed with lymphocytes and scanty colloid material.

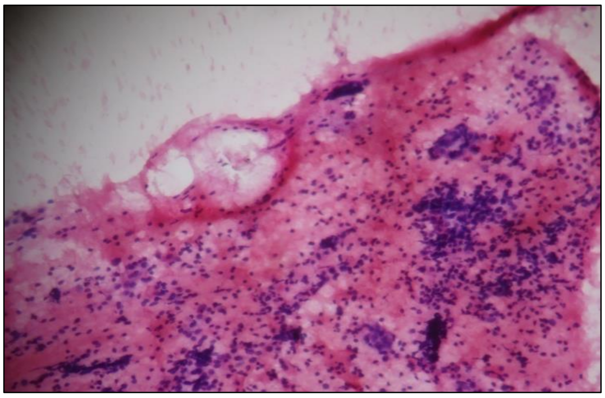

Figure 3: Lymphocytic thyroiditis: plenty of lymphocytes admixed with few thyroid follicular epithelial cells and hurthle cells.

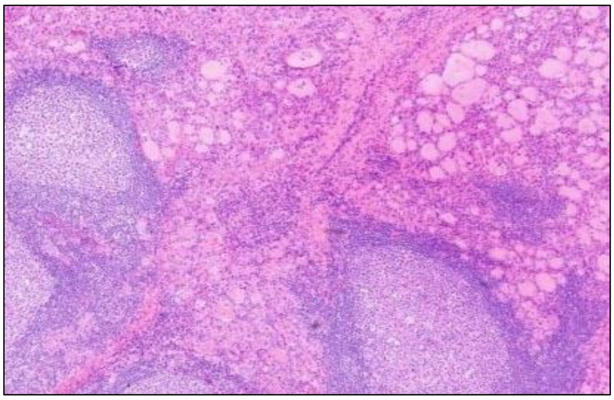

Figure 4: Autoimmune thyroiditis: thyroid follicular epithelial cells admixed with lymphocytes and few hurthle cells and scanty colloid material.

Figure 5 shows microscopic picture of adenomatous goitre showing hyperplastic as well as involutional follicular epithelial cells in cluster sheets and in follicle admixed with oxyphilic cells, occasional few foamy macrophages and admixed with thin colloid material.

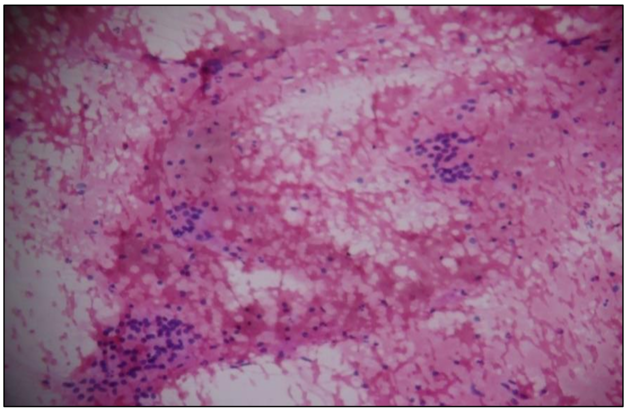

Figure 5: Adenomatous goitre: hyperplastic as well as involutional follicular epithelial cells admixed with colloid material.

Figure 6 shows microscopic picture of nodular goitre presenting variable sized dilated follicles with flattened hyperplastic epithelium, sparse to moderately cellular smears with abundant thin or thick colloid, flat sheets with evenly spaced follicular cells, nodules may be present but without thick capsule, rupture of follicles with granulomatous response, fibrosis, calcification, occasional oxyphilic cells and abundant watery colloid material.

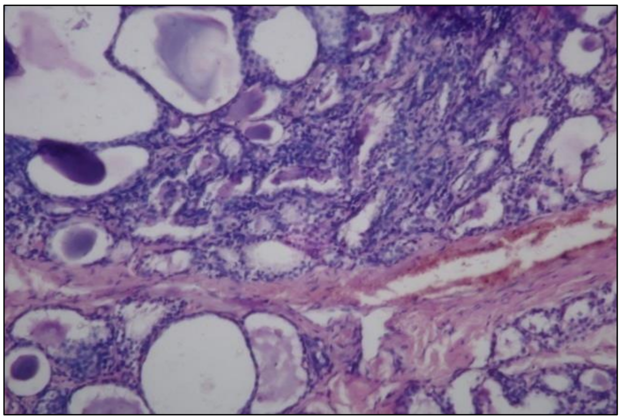

Figure 6: Nodular goitre: hyperplastic and involutional follicular epithelial cells occasionally oxyphilic cells and abundant watery colloid material.

Figure 7 shows colloid goitre with abundant thin colloid material and clusters of follicular epithelial cells. Flattened follicular epithelial lining with low cuboidal to columnar, the follicles are enlarged and filled with abundant colloid, there was hyperplasia of the lining epithelium and columnar cells sometimes may project into the follicular lumen.

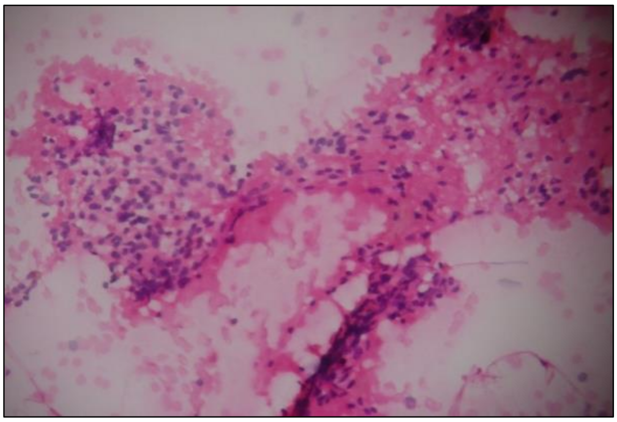

Figure 7: Colloid goitre: abundant thin colloid material and clusters of follicular epithelial cells.

Figure 8 showing follicular adenoma/neoplasm with follicular epithelial cells in repetitive follicular configuration admixed with scanty colloid. Trabecular or solid pattern of follicles with invasion of adjacent thyroid parenchyma, capsule or blood vessels. May have nuclear atypia, no necrosis, no squamous metaplasia and rare lymphatic invasion.

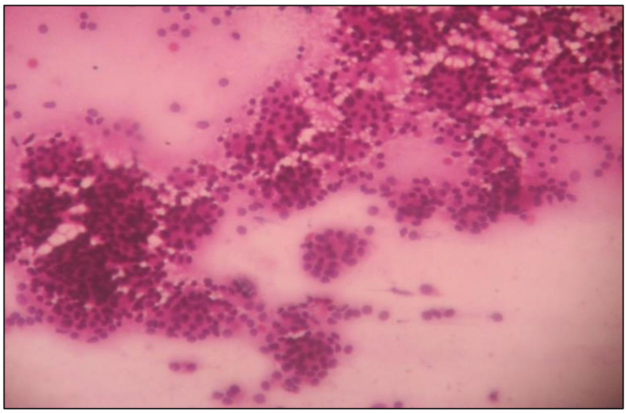

Figure 8: Follicular neoplasm/adenoma: follicular epithelial cells in repetitive follicular configuration admixed with scanty colloid.

With reference to the cytological changes, observable under different pathological entities in which highest number 105 were found to be associated with Hashimoto's thyroiditis and the least 15 were found to be associated with follicular adenoma. 42 out of 342 were found to be Euthyroid though all the subjects hail from the fluorotic zone.

Cytological study by aspiration cytology revealed association with different wide range of pathological entities of thyroid, largely attributed to autoimmune aetiology of Hashimoto's thyroiditis, adenomatous, nodular goitre, colloid goitre were also found association in these subjects in addition to a few of the subjects showing follicular neoplasm/adenoma. The different entities were graphically represented (Table 1). The data collected from the experimental study was analyzed by using logistic regression models. Thereafter, Microsoft EXCEL 2013 and SPSS 21.0 (statistical package for social sciences) software and to test association, correlation and significance of the study.

DISCUSSION

In the light of the knowledge that iodine uptake by the thyroid and concentrating ability of the thyroid gland in the presence of low levels of iodine with concomitant high levels of fluoride. At the cellular level the pathological changes of the thyroid gland are studied. Fluoride and iodine are both halogens. By virtue of the low atomic weight fluoride displaces iodine interfering with the iodine availability for the uptake by the thyroid gland. The fluoride is a universal G-protein activator/inhibitor. The mechanism of iodine uptake is affected in the presence of high fluoride that can adversely affect the G-protein. The TSH output from pituitary gland is inhibited by fluoride, thus reducing thyroid output from thyroid glands. Fluoride competes for the receptor sites on the thyroid gland which respond to TSH, so that this hormone reaches the thyroid gland and so fewer hormone is manufactured Wilson and DeEds, Susheela AK et al.[14]

In the present study, author found statistically significant relationship between water and serum fluorides. Similar relationships were also observed by Rathee et al. High fluoride content in the water was concurrent with their high levels in the serum in some of the previous studies.[18] Thyroid dysfunction was also apparently seen in the scenario of high fluoride in the serum and drinking water as well. Author observed that high fluoride exposure can cause functional and structural abnormalities of thyroid and significant deviation in the serum thyroid hormone levels, as cited by Xiang Q et al.[19]

It was ensured that the subjects included were from the fluorotic zone by estimating the fluoride levels of potable water from the areas they hail from. Water samples from these endemic zones of fluorosis have shown fluoride levels beyond the acceptable levels. Serum fluoride levels of the subjects hailing from endemic zones have shown variable levels of fluoride. Cytological study showed changes that were consistent with the cytological findings of hypothyroid cases. Among them different fractions of the subjects found to be associated with different pathological entities hypothyroidism being a common finding. More than 45% of the cases were found with an element of hypothyroid aetiology, the major chunk being Hashimoto’s thyroiditis comprising more than 30% of cases. A study conducted by Uma P et al, reported the incidence of 55.53% of Hashimoto’s thyroiditis.[22] The entity found with a least number among the subjects is follicular neoplasm comprising little more than 4% of the subjects. In addition to the neoplastic and autoimmune entities adenomatous goitre, nodular goitre and colloid goitre were also found that comprised about little more than 35% of the cases. About little more than 12% of the subjects were found to be euthyroid (Rathi M et al).[23]

The cytological compensatory changes that was suggestive of hypothyroid state. Fluoride that is absorbed in to the blood is found in higher concentration in the plasma than the cells around. Higher the water content of the fluoride higher the plasma levels of the same are encountered in earlier studies. In chronic disorder of the thyroid gland, subjects were characterized by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy and an eosinophilic change in tissue.

CONCLUSION

The results of the study strongly suggested assessing the magnitude of the problem of fluorosis, where drinking water, milk, fruit juices or any such drinks can be a source of high fluoride content warranting remedial measures as a major public health problem prompting the public health authorities for necessary measures to combat the situation.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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