A Systematic Analysis on Possibility of Water Fluoridation Causing Hypothyroidism

Abstract

Background: Community water fluoridation is widely used worldwide and its role in preventive dental health care is well established. However, there is sufficient evidence of the ill effects of excessive fluoride content in water, causing skeletal and dental fluorosis. Alongside, there was also extraskeletal and dental manifestations of excessive fluorides reported. They include the effect on thyroid function, but the literature regarding this is sparse. Aim: The present systematic review aims to analyze the data from controlled studies about the effect of fluoride on thyroid function. Materials and Methods: A systematic literature search was performed using PUBMED, MEDLINE, EMBASE, COCHRANE Library, EBSCO search, and the internet search, with language restriction to English. The search included published studies which dealt with the association of fluorine with hypothyroidism, from January 1981 to November 2015. Literature search was done using keywords: fluoride and hypothyroidism, dental fluorosis and thyroid disorders, systemic fluorosis and thyroid disease, excessive water fluoridation and hypothyroidism, thyroid and fluoride, fluorosis and its adverse effects. Results: Out of 166 publications, related to search strategy, 37 full articles which were related with the association of fluoride and hypothyroidism were acquired for further inspection. Out of the 37 articles, 10 articles met the inclusion criteria. The data were extracted and placed in an excel sheet and were analyzed. The analysis suggested a positive correlation of excess fluoride and hypothyroidism. Conclusion: The present systematic review suggests a positive correlation between excess fluoride and hypothyroidism. This calls the need for further well-controlled studies in this otherwise emerging alarming issue. It also calls for considerable community network through health informatics for problem sensitization.

Keywords: Hypothyroidism, systematic analysis, water fluoridation

Introduction

Community water fluoridation to drinking water supply holds a controversial position till date since its introduction in 1950. Henri Mossan discovered fluoride in 1886. It is an unstable molecule having reactivity with all organic and inorganic substances. It has been found in soil, air, and food in varying amounts. In addition, this compound is found useful in industrial settings producing pesticides, ceramics, and pharmaceuticals.

The influence of fluoride on teeth was well recognized in 1909 in Colorado, USA. It was concluded that water containing fluoride of more than 1.0 ppm offered significant caries prevention, alternatively reducing the effect on dental enamel. The beneficent evidence for introduction of fluorides in drinking water still remained weak.[1]

The consequence of such intervention on overall health has been pointed out by some studies though none could delineate the direct effect of fluoride in causation of such adverse effects.[2‑4] Literature focused on many adverse effects of fluoride on general health and more particularly on thyroid status continued to be raging debate.

There were a number of animal studies pointing out toward possible hypothryoid effects of fluorides. Similarly, there were also few human interventional studies which had risen that such relation existed altogether and those which did not support such a hypothesis. In the 1950s, fluoride was used pharmacologically to overactive thyroid as a thyroid suppressant and supported by few studies claiming to have improved the gland function in such intervention. Reviews also indicated that fluoride is an endocrine disruptor of tissues competitively requiring iodine at levels

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as low as 0.01 mg/kg/day at iodine-deficient settings.\[5\] The other side of the issue being stated is that there was absolutely no relation between such findings pointing out that hypothyroidism is, predominantly an autoimmune disorder, strongly associated with age and gender. There were many confounding factors of such association and could not be attributed to one element altogether.

With such a polarizing issue on the debate of no effect on thyroid gland versus possible hypothyroid status, the present literature search was intended to compile various evidences from published studies quoted in medical databases, thereby analyzing such an evidence for further exploration.

Furthermore, there appeared to be some information on monitoring of fluoride levels in water at community level. Sometimes, high fluoride endemic belts can lead to its excessive consumption invariably resulting in skeletal and dental fluorosis in resource-limited countries without proper monitoring of the system. Probably, a reasonable argument can be drawn on the association of fluorosis and thyroid effects.

Materials and Methods

Search strategy

A systematic literature search was performed using PubMed, Medline, Embase, Cochrane Library, EBSCO search, and the internet search, with language restriction to English. The search included published studies which dealt with the association of fluorine with hypothyroidism, from January 1981 to November 2015. Literature search was done using keywords: fluoride and hypothyroidism, dental fluorosis and thyroid disorders, systemic fluorosis and thyroid disease, excessive water fluoridation and hypothyroidism, thyroid and fluoride, fluorosis and its adverse effects.

Out of the total search of 166 articles related to fluoride and hypothyroidism, none were randomized control trials. To accommodate the available literature, we included case–control studies, according to Hadorn criteria.\[9\] Inclusion criteria had articles that were published in only English language plus those related to case and control groups and those which evaluated the association between water fluoridation and thyroid disorders. Again, only those articles that could be fully retrieved were considered in the analysis.

Exclusion criteria included case reports, reviews, studies based on animals, and in vitro studies. Articles that were not published in English or where the full text could not be acquired were also excluded from the study [Table 1].

Two separate coordinators were involved in retrieving and analyzing the articles, based on inclusion and exclusion criteria. The principal investigator had evaluated and analyzed those articles retrieved and sorted by the two coordinators. Any discrepancy in the search was corrected and reported back to the coordinators for review of such data and the eligibility of inclusion.

Data extraction

Principal investigator and two co-investigators were involved in data extraction. Co-investigators 1 and 2 were allotted the task of scrutinizing studies related to the association of fluoride and hypothyroidism. Both the co-investigators report to the principal investigator and the principal investigator supervised and further analyzed the data.

All the articles were analyzed and the data were extracted utilizing the eligibility, validity, and design of the study. A total of 10 articles that met the inclusion criteria were analyzed and a systematic review was performed.

Results

Results of search strategies

Out of 166 publications, related to search strategy, 37 full articles which were related with association of fluoride and hypothyroidism were acquired for further inspection. For two articles only abstract was available, one article was translated from Chinese and hence were excluded from the study. Out of the 37 articles, 10 articles met the inclusion criteria. The following table shows complete analysis of the literature search [Tables 2 and 3].

Discussion

Fluoride and hypothyroidism

Dental caries is still a significant oral health issue in many countries. The effect of fluoride on dental caries is much studied. Various water fluoridation schemes and milk fluoridation have been implemented worldwide for decades.\[7,8\] There were many studies which showed a positive correlation between significant decreases in dental caries with the use of optimal water fluoridation. Recent studies have shown that fluoride of ≥0.7 ppm in water is significantly lowering the caries prevalence than in same aged counterparts living in areas with minimal or no water fluoridation.\[9\] Flip side, there are certain adverse effects

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Table 1: Inclusion and exclusion criteria

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Articles only in English language                                                 | Articles not in English language                                                   |
| Articles related to case and control groups with water fluoridation and thyroid abnormalities | Articles with serum thyroid estimation                                               |
| Articles which were fully available-retrievable                                     | Case reports, web news, reviews, studies based on animal and in vitro               |
| Article with serum thyroid estimation                                               | Articles with only abstracts                                                        |

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[Tables 2 and 3]
Table 2: Analysis of various studies employed in the systematic search

| Author and year | Total sample | Age (years) | Sample | Fluoride levels | Hypothyroidism | Hyperthyroidism | Significance | Sample | Fluoride levels | Hypothyroidism | Hyperthyroidism | Significance |
|-----------------|--------------|-------------|--------|-----------------|----------------|-----------------|--------------|--------|-----------------|----------------|----------------|--------------|
| Bachinskii et al., 1985<sup>[9]</sup> | 123 | 18-59 | 71 | 87-184 mol/L (significantly higher than control) | 19 | 22 | Significantly causes thyroid dysfunction. May be hyper/hypothyroidism | 52 | 26-75 mol/L | | | |
| Lin et al., 1991<sup>[6]</sup> | 250 | 7-14 | | 1-6.6 ppm | | | Suggestive T4 significantly elevated | | | Values not available | Values not available | Values not available | Values not available |
| Desai et al., 1993<sup>[7]</sup> | 22,276 | <5-40 | | Values not available | Values not available | Values not available | Significant correlation between the prevalence of goiter and dental fluorosis | | | Values not available | Values not available | Values not available | Values not available |
| Luming Yao et al., 1996<sup>[8]</sup> | 201 | 8-12 | 129 | 2-11 mg/L | Mean value of TSH was significantly high in endemic areas compared to control (value not given) | Nil | Significantly high TSH values | 72 | 1 mg/L | Values not available | Values not available | Values not available | |
| Mathews et al., 1996<sup>[13]</sup> | 70 | 30-50 | 55 | 1.0-6.53 ppm | Values not available | Significant increase in T4 (values not available) | 15 | Values not available | Values not available | Values not available | |
| Susheela et al., 2005<sup>[10]</sup> | 111 | 7-18 | 90 | 1.1-14.3 mg/L | 42 | - | Significantly elevated TSH | 21 | <1.0 mg/L | 4 | Values not available | |
| Yang et al., 2008<sup>[11]</sup> | 1518 | <15 | 1102 | 2.97 mg/L | 42 | - | Significantly elevated TSH | 416 | 0.5 mg/L | 2 | - | |
| Xiang et al., 2009<sup>[12]</sup> | 170 | 8-13 | 82 | 0.62-4.00 mg/L | 16 | - | Significantly elevated TSH | 88 | 0.23-0.76 mg/L | 12 | - | |
| Hosur et al., 2012<sup>[17]</sup> | 75 | 10-18 | 65 | 0.5 ppm-4 ppm | Values not available | Values not available | Elevated TSH Significant elevation of FT3 | 10 | 0.5-0.6 ppm | Values not available | Values not available | |
| Singh et al., 2014<sup>[14]</sup> | 70 | 8-15 | 60 | 1.6-5.5 ppm | 43 | - | Elevated TSH | 10 | 0.98-1 ppm | 1 | - | |

FT3=Free triiodothyronine, TSH=Thyroid-stimulating hormone, FT4=Free thyroxine
reported with excessive fluoride content in water, and they include dental and skeletal fluorosis. Furthermore, there are other nondental adverse health effects of fluorides such as hypothyroidism and reduced intelligence quotient (IQ) in children. Literature shows that children in areas of endemic fluorosis had cretinism, low IQ, genu valgum, and genu varum (knock knees and bow legs, respectively). Some studies have attributed abnormal thyroid hormone metabolism as a cause of dental fluorosis. Ha et al., 1989, stated that the interference of fluoride with thyroid function results in degenerative changes in the central nervous system, defective brain function, and abnormal growth in children. The mechanism of action proposed was that as fluorine is more electronegative than iodine, it displaces iodine easily, thus affecting the normal functioning of the gland. This might lead to deranged hormone levels of thyroid within the body. As the level of thyroid within the body is regulated by feedback mechanism, drop in TSH levels; however, similar depression in T3 and T4 was observed. A cross-sectional study done by Bachinskii et al., 1985, included nonendemic region with water fluoride concentration of 0.5–1.4 mg/L. The study concluded that there was no significant difference in thyroid prevalence within the two regions.

A cross-sectional study done by Bachinskii et al., 1985, included nonendemic region with water fluoride concentration of 0.5–1.4 mg/L and that in endemic region with 1.6–3.5 mg/L. The study concluded that there was no significant difference in thyroid prevalence within the two regions.

The present analysis included the studies involving water fluoridation and thyroid function. It tried to correlate thyroid dysfunction particularly hypothyroidism with fluorides. A total of 10 studies fulfilled the inclusion criteria. Among them, seven studies evaluated pediatric population only (Lin et al. in 1991, Luming Yao et al. in 1996, Susheela et al. in 2005, Yang et al. in 2008, Xiang et al. in 2009, Mahadevi et al. in 2012, and Singh et al. in 2014), one study included only adults (Bachinskii et al. in 1985), while two studies included both pediatric and adult population (Desai et al. in 1993 and Michael et al. in 1996). All the studies tested for sample in both fluoride endemic and nonendemic areas. Six studies (Desai et al. in 1993, Luming Yao et al. in 1996, Yang et al. in 2008, Xiang et al. in 2009, Mahadevi et al. in 2012, and Singh et al. in 2014) had dental fluorosis samples. One study (Michael et al. in 1996) was combination of dental and skeletal fluorosis samples.

The analysis revealed that all the studies showed the elevation of TSH and depression of T3 and T4 hormones using free assays except for two studies done by Lin et al. 1991 and Micheal et al. which showed elevated T4 levels. Eight studies (Bachinskii et al. in 1985, Luming Yao et al. in 1996, Michael et al. in 1996, Susheela et al. in 2005, Yang et al. in 2008, Xiang et al. in 2009, Mahadevi et al. in 2012, and Singh et al. in 2014) had dealt using standard case–control analysis, but two studies (Lin et al. 1991 and Desai et al. 1993) had not leading to bias in results.

Overall, six studies had shown a significant elevation of TSH levels; however, similar depression in T3 and T4 levels was underestimated. In most of the studies, the mean value of TSH in dental fluorosis group from the endemic area was significantly higher than that of the control group from the nonendemic area. A significant difference was also found when comparing the test results of the dental fluorosis group in the low versus severely affected endemic fluorosis area. Serum T3 and T4 were within normal range. In the study, a range of 0.5 ppm to 14.3 ppm showed a significant increase in TSH status and depression in T3 and T4 status in combination with fluorosis. However, two studies (Lin et al. in 1991 and Michael et al. in 1996) had shown hyperthyroid status than hypothyroidism. The studies used in the present systematic review were analyzed individually.

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### Table 3: Flowchart of the study characteristics identified in the study

The PRISMA Flow chart of Study Methodology
with fluoride <2 mg/L (17.1%). No evidence of functional changes in thyroid activity was noted.\textsuperscript{[10,11]} Luming Yao et al., 1996, conducted a study in China involving schoolchildren between 8 and 12 years from two endemic and one nonendemic areas. Severely endemic area had water fluoride concentration of 11.0 mg/L while slightly endemic area was with 2 mg/L and nonendemic area had 1 mg/L. The mean value of TSH in dental fluorosis group from the endemic area was significantly higher than that of the control group from the nonendemic area. Serum T3 and T4 were within normal range.\textsuperscript{[12]}

In contrast to above studies, a study done by Michael et al. in 1996, where 500 individuals from 52 villages in 2 districts were involved with water fluoride concentration ranging from 1.0 to 6.53 mg/L, there was a significant increase in serum T4 in areas with high fluoride level. There was no significant difference noted in concentrations of serum T3 and TSH.\textsuperscript{[13]} A cross-sectional study was done by Susheela et al., 2005, which included case and control group in endemic (1.1–14.3 mg/L) and nonendemic areas (<1 mg/L), with and without enamel fluorosis, respectively. Forty-nine of 90 children with fluorosis had "well-defined" hormonal derangements. In rest of the 41 children, the findings were on the borderline. They showed low T3 and elevated TSH levels.\textsuperscript{[14]}

Yang et al. in 2008 studied 1102 endemic cases and 216 controls, where fluoride levels in endemic and nonendemic areas were 2.97 mg/L and 0.5 mg/L, respectively. The study showed that the serum levels of T3 and T4 for the children from the high fluoride zone were only slightly higher than the control \((P > 0.05)\), but the level of TSH was clearly elevated \((P < 0.01)\).\textsuperscript{[15]} Another study by Xiang et al. in 2009, done in 82 children from severe endemic and nonendemic areas where fluoride levels were 0.62–4.00 mg/L and 0.23–0.76 mg/L, respectively, showed that T3 and T4 concentrations in children from the two areas were not significantly different. However, the TSH concentration in endemic area was significantly higher than that in nonendemic area.\textsuperscript{[16]}

Mahadevi et al. in 2012 studied 65 participants from endemic area and 10 participants from nonendemic areas, where water fluoride in study group ranged from 0.5 ppm to 4 ppm and that in control group was 0.5–0.6 ppm. The study revealed no significant relationship between fluorosis index and T4 levels. FT3 levels were significantly different between mild and moderate as well as mild and severe fluorosis groups whereas there was no significant difference between moderate and severe fluorosis.\textsuperscript{[17]} Singh et al. in 2014 conducted a study in fluoride endemic and nonendemic areas and found that the children from endemic areas revealed derangement of serum thyroid hormone and TSH levels, along with increased fluoride concentration in body fluids.\textsuperscript{[16–18]}

Monitoring the levels of fluorides and health-care informatics

It is important to carry out an evaluation of quality and performance of fluoridation of public water supplies with regard to structure, process, and outcome. Optimum water fluoridation may help in caries reduction. The prevention of fluoride induced disorders such as skeletal and dental fluorosis. However, additional water fluoridation in endemic areas and presence of high fluorides in ground water coupled with dietary intake of fluoride through beverages and indiscriminate use of pesticides have resulted in derangement of health. The association of hypothyroidism in people consuming fluoride from above sources may or may not be a chance occurrence which needed to be probed. This can be achieved by health information technologies which evaluate (1) documents related to fluoridation research, (2) patient education, and (3) timely scientifically based community water fluoridation. The tracking of such information is the need of hour.

Conclusion

The present systematic review attempted to analyze the effect of fluoride on the function of thyroid. The study has shown a positive correlation between fluoride and hypothyroidism, which is an alarming issue. This calls for the need for further well-controlled studies in large sample sizes, correlating the serum fluoride levels to the amount of fluoride in the water, to establish this relationship. The paucity of data from fluoride endemic areas had resulted in overlooking of this very fact. Public education measures through internet and governmental website portal system (health-care informatics) can reduce such irregularities as well as monitoring the status of fluoride in water.

Limitations

There were hardly any randomized control trials in studying the effect of fluoride on thyroid. Due to the sample size and sampling technique, there could be bias in the study. The studies analyzed the usage of water with high fluoride content and have not included to which supply of water in specific. It may be considered as a limitation as there will be a different amount of fluoride levels in different sources of drinking water.

Mere presence of high TSH levels may not attribute to hypothyroid state. The compounding factors associated with the individual, the state of testing laboratory, and methodology may be implicated which may have led to inconclusive evidence.

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Conflicts of interest

There are no conflicts of interest.
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