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Thyroid dysfunction and fluoride exposure: Epidemiological and mechanistic insights

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Abstract
Fluoride is an essential environmental element known for its preventive role in dental caries; however, excessive exposure has been linked to multiple systemic effects, including thyroid dysfunction. The thyroid gland, central to metabolic regulation and development, is sensitive to halide interference, particularly from fluoride due to its chemical similarity to iodine. This review comprehensively evaluates current evidence on fluoride exposure and its impact on thyroid physiology in humans. Data from epidemiological, clinical, and experimental studies suggest that high fluoride exposure—especially in iodine-deficient populations—can impair thyroid function by altering hormone synthesis, secretion, and metabolism. Conversely, populations exposed to optimally fluoridated water generally exhibit no major adverse thyroid outcomes. Mechanistic studies indicate that fluoride may inhibit thyroid peroxidase, interfere with iodide transport, and induce oxidative stress, leading to hypothyroxinemia and elevated thyroid-stimulating hormone (TSH) levels. The review emphasizes that iodine status, nutritional factors, and renal efficiency are key modifiers of fluoride toxicity. Continuous monitoring of fluoride exposure, iodine intake, and thyroid health, particularly in vulnerable groups such as pregnant women and children, remains critical to balancing dental benefits against potential endocrine risks.

Keywords: Fluoride, thyroid function, hypothyroidism, iodine, endocrine disruption, public health

Introduction

Fluoride is a naturally occurring halogen present in varying concentrations across soil, water, air, and biological materials. It is widely recognized for its role in preventing dental caries and strengthening enamel; hence, many countries have adopted water fluoridation programs (Peckham *et al*., 2015) [10]. Despite these benefits, concerns regarding fluoride's potential systemic toxicity have persisted, especially regarding skeletal fluorosis and possible effects on soft tissues, including endocrine glands. Among these, the thyroid gland—responsible for maintaining metabolic homeostasis—has received particular attention due to fluoride's potential to interfere with iodine metabolism (Barberio *et al*., 2017; Hall *et al*., 2023) [1, 7].

The human thyroid is uniquely vulnerable to environmental perturbations, and even small hormonal changes can influence metabolism, growth, and neurological development (Vanderpump, 2011) [15]. Fluoride exposure may therefore represent an underappreciated risk factor for thyroid disorders in certain populations, particularly where iodine intake is marginal. This review explores fluoride sources and metabolism, outlines thyroid physiology, summarizes mechanistic and epidemiological evidence, and discusses public health implications and research priorities.

Sources of Fluoride Exposure and Metabolism

Fluoride enters the human body through multiple routes: drinking water, food, dental products, air, and pharmaceuticals. The most significant contributor is drinking water, particularly in regions with high natural fluoride concentrations in groundwater (Kheradpisheh *et al*., 2018) [8]. Levels can vary from <0.1 mg/L in surface waters to >4 mg/L in arid regions of India, Iran, and China. Chronic ingestion of water containing fluoride concentrations above 1.5 mg/L may result in fluorosis (Singh *et al*., 2014) [13].

Once ingested, fluoride is rapidly absorbed in the stomach and small intestine, with bioavailability influenced by dietary calcium and pH. Approximately 50–80% of absorbed fluoride is incorporated into calcified tissues, primarily bone and teeth, while the remainder circulates in plasma and is excreted via the kidneys (Taher *et al*., 2024) [14]. Impaired renal clearance can thus increase systemic fluoride levels. Urinary fluoride concentration is commonly used as a biomarker of exposure (Goodman *et al*., 2022) [4].

Epidemiological studies vary widely in exposure assessment methods, with some relying on community water levels and others on urinary or plasma fluoride. This heterogeneity complicates comparison across studies and contributes to inconsistent conclusions about thyroid effects (Griebel-Thompson *et al*., 2023) [5].

Overview of Thyroid Physiology

The thyroid gland produces thyroxine (T4) and triiodothyronine (T3), hormones crucial for regulating metabolism, growth, and neural development. The hypothalamic–pituitary–thyroid (HPT) axis maintains circulating hormone levels through a feedback mechanism: thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the release of TSH from the anterior pituitary, which in turn regulates thyroid hormone synthesis (Pearce *et al*., 2013) [11].

Iodine, obtained from dietary sources such as iodized salt and seafood, is a vital substrate for T3 and T4 synthesis. The sodium-iodide symporter (NIS) transports iodide into follicular cells, where thyroid peroxidase (TPO) catalyzes hormone formation. Fluoride, sharing halide characteristics with iodine, can compete for binding sites and interfere with TPO activity, potentially altering T4 and T3 production (Ferreira *et al*., 2024) [3].

Deiodinase enzymes (DIO1 and DIO2) convert T4 to active T3 in peripheral tissues. Any disturbance in this conversion—through oxidative stress or enzyme inhibition—can lead to functional hypothyroidism even when total hormone levels appear normal (Gupta *et al*., 2020) [6].

Mechanisms of Fluoride-Induced Thyroid Dysfunction

1. Competition with Iodine

Fluoride competes with iodide for NIS transport due to its similar ionic radius, thereby reducing iodine availability for thyroid hormone synthesis. Laboratory studies have shown that high fluoride exposure decreases iodide uptake in thyroid tissues (Ferreira *et al*., 2024) [3].

2. Inhibition of Thyroid Peroxidase (TPO)

Fluoride can directly inhibit TPO, the enzyme catalyzing iodination of tyrosine residues in thyroglobulin (Goodman *et al*., 2022) [4]. Inhibition of TPO disrupts T3 and T4 synthesis and may lead to compensatory TSH elevation.

3. Oxidative Stress and Immune Modulation

Excess fluoride generates reactive oxygen species (ROS), leading to oxidative damage in thyroid cells (Gupta *et al*., 2020) [6]. Chronic oxidative stress may promote autoimmune thyroiditis, linking fluoride exposure to increased thyroid antibody levels in susceptible individuals (Chatterjee *et al*., 2023) [2].

4. Central Regulatory Effects

Animal studies indicate that fluoride may also act on the hypothalamus and pituitary, altering TRH and TSH secretion and disturbing the feedback loop that regulates thyroid function (Taher *et al*., 2024) [14].

5. Interaction with Micronutrients

Iodine deficiency amplifies fluoride toxicity by weakening thyroid resilience, while selenium—important for deiodinase activity—can mitigate some of fluoride's adverse effects (Griebel-Thompson *et al*., 2023) [5]. Populations deficient in either nutrient show heightened vulnerability.

Epidemiological Evidence

Epidemiological data assessing the fluoride–thyroid relationship is mixed, reflecting differences in design, exposure level, and confounder control. The principal findings are summarized in Table 1.

1. Ecological Studies

Peckham *et al*. (2015) [10] analyzed data from 7935 general practice clinics in England and observed a higher prevalence of hypothyroidism in areas with elevated fluoride concentrations (>0.7 mg/L). However, ecological designs cannot control for individual confounders such as iodine intake, socioeconomic factors, or healthcare access, limiting causal inference (Newton *et al*., 2017) [9].

2. Cross-Sectional Surveys

Barberio *et al*. (2017) [1] evaluated 6,914 Canadians and found no significant association between fluoride exposure and abnormal thyroid hormone levels after adjusting for age, sex, and iodine intake. Similar results were obtained by Shaik *et al*. (2019) [12] in Indian children consuming water with fluoride levels between 0.2–1.4 mg/L, where adequate iodine appeared protective.

3. Studies in High-Fluoride Endemic Regions

In Iran, Kheradpisheh *et al*. (2018) [8] reported elevated TSH and altered T3 levels in residents consuming water with <0.5 mg/L fluoride, suggesting even low concentrations might impact thyroid function under specific physiological conditions. In contrast, Singh *et al*. (2014) [13] and Chatterjee *et al*. (2023) [2] observed significant thyroid dysfunction only in individuals from areas where fluoride exceeded 3 mg/L.

4. Pregnancy and Developmental Studies

Pregnancy increases iodine demand and susceptibility to thyroid disruption. Hall *et al*. (2023) [7] found an association between drinking water fluoride and elevated TSH among pregnant women, though other maternal studies (Goodman *et al*., 2022) [4] did not replicate these findings consistently. Fluoride may indirectly affect fetal neurodevelopment by altering maternal thyroid hormones.

5. Systematic Reviews

Systematic reviews by Ferreira *et al*. (2024) [3] and Taher *et al*. (2024) [14] concluded that fluoride exposure may impair thyroid function in high-exposure, iodine-deficient populations but is unlikely to cause clinical hypothyroidism at optimal fluoridation levels. Both reviews emphasized the need for longitudinal designs and better exposure biomarkers.

Table 1: Representative epidemiological studies on fluoride and thyroid function

Author (Year)	Country	Sample size	Exposure range (mg/L)	Main Findings
Peckham *et al*. (2015) [10]	England	7935 clinics	0.1–1.5	Hypothyroidism prevalence higher in fluoridated areas
Barberio *et al*. (2017) [1]	Canada	6914 adults	0.1–1.5	No association between fluoride and thyroid hormone levels
Kheradpisheh *et al*. (2018) [8]	Iran	720 adults	0.01–0.5	Elevated TSH, altered T3 even at low levels
Shaik *et al*. (2019) [12]	India	450 children	0.2–1.4	No thyroid dysfunction with adequate iodine
Hall *et al*. (2023) [7]	Canada	2500 pregnant women	0.2–0.8	Mild TSH increase in fluoride-exposed pregnancies
Chatterjee *et al*. (2023) [2]	India	630 adults	1.5–4.0	Hypothyroxinemia and high TSH in endemic fluorosis areas

Discussion

The interaction between fluoride and thyroid function remains a contentious topic in environmental endocrinology. Mechanistic plausibility is supported by laboratory data demonstrating that fluoride interferes with iodine uptake, TPO activity, and deiodinase enzymes (Ferreira *et al*., 2024) [3]. Nevertheless, human studies yield heterogeneous results.

A major determinant of variability appears to be iodine status. Regions with low iodine intake (e.g., parts of India, Iran, and China) consistently exhibit stronger fluoride–

thyroid associations, whereas iodine-replete populations rarely show significant effects (Goodman *et al*., 2022) [4]. Furthermore, the threshold of fluoride toxicity is influenced by renal function, calcium intake, and overall nutritional status (Taher *et al*., 2024) [14].

Pregnant women and developing fetuses constitute high-risk groups. Maternal hypothyroxinemia—even mild—can impair fetal brain development. Evidence linking fluoride exposure to thyroid changes in pregnancy remains inconclusive but warrants caution (Hall *et al*., 2023) [7].

Table 2: Mechanistic pathways proposed for fluoride-induced thyroid dysfunction

Mechanism	Target Site	Effect
NIS inhibition	Thyroid follicular membrane	Reduces iodide uptake
TPO inhibition	Follicular cell enzyme	Decreases T3/T4 synthesis
Deiodinase alteration	Peripheral tissues	Impairs T4-T3 conversion
Oxidative stress	Thyroid tissue	Promotes cellular damage and autoimmunity
HPT axis interference	Hypothalamus–pituitary	Alters TSH feedback loop

Public Health Implications

The public health implications of fluoride–thyroid interactions are region-specific. In fluoridated countries maintaining fluoride around 0.7 mg/L, the risk of thyroid impairment appears minimal. However, in endemic regions with water fluoride above 2 mg/L, particularly where iodine intake is suboptimal, thyroid dysfunction may become significant (Chatterjee *et al*., 2023) [2].

Policy measures should include:

1. Integrated monitoring of fluoride and iodine levels in community health surveys.
2. Defluoridation programs in high-fluoride regions using activated alumina or bone char filters.
3. Nutritional interventions, ensuring adequate iodine and selenium intake.
4. Targeted screening of thyroid function in pregnant women and children residing in endemic fluorosis areas.

The balance between dental benefits and systemic risks should be periodically re-evaluated, incorporating local exposure data and nutritional profiles.

Limitations of Current Evidence

Current research suffers from several methodological gaps:

- Overreliance on ecological studies lacking individual-level data.
- Poor adjustment for confounders such as iodine, calcium, and renal status.
- Inconsistent laboratory assays for hormone measurement.
- Limited longitudinal data assessing temporal causation. Addressing these issues through standardized protocols and multicentric prospective studies is essential for reaching conclusive evidence.

Conclusion

Fluoride has clear dental health benefits at optimal concentrations but may pose risks to thyroid function when exposure exceeds safe limits, particularly under iodine-deficient conditions. The biological plausibility of fluoride-induced thyroid suppression is supported by mechanistic data, yet epidemiological findings remain mixed. Policymakers must consider both fluoride and iodine nutrition in setting water standards. Future research should emphasize well-controlled prospective studies using precise exposure biomarkers and stratified analysis by iodine status and life stage. In conclusion, maintaining fluoride levels within the recommended range (<1 mg/L) while ensuring adequate iodine intake offers the best safeguard for both dental and endocrine health.

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