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The Association Between Nitrite and Nitrate Levels in Drinking Water and Thyroid Dysfunction Biomarkers in Patients with Hypothyroidism: A Cross-Sectional Study in Iran

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Abstract

Introduction: Nitrate and nitrite are prevalent drinking water contaminants that can interfere with iodine uptake and thyroid hormone synthesis, acting as potential endocrine disruptors. Chronic exposure, even at concentrations within international safety limits, has been linked to autoimmune thyroid disorders. This study aimed to assess the association between drinking water nitrate and nitrite levels and serum thyroid autoantibodies—thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb)—in patients with hypothyroidism.

Methods: This cross-sectional study analyzed data from 2015 to 2019, integrating water quality records from the Fars Water and Wastewater Company and clinical data from hypothyroid patients attending the Jahrom endocrinology clinic. Serum TPOAb and TGAb levels were measured using chemiluminescent and ELISA methods, respectively.

Results: A total of 32 hypothyroid patients (9 males, 23 females; mean age 33.2 ± 9.9 years) were included. Median TPOAb and TGAb levels were 297.9 and 41.1 IU/mL, respectively. The median nitrate and nitrite concentrations in drinking water were 25.1 and 0.02 mg/L, both within the WHO limits. A significant positive correlation was observed between nitrate levels and TPOAb concentrations ($r = 0.714$, $P = 0.001$), whereas no significant correlation was found between nitrite and TPOAb concentrations.

Conclusion: The findings suggest that long-term exposure to nitrate, even below regulatory limits, may contribute to autoimmune thyroid activation in hypothyroid patients. Continuous monitoring of nitrate in drinking water and future population-based, longitudinal studies are warranted to clarify causal mechanisms and inform public health interventions.

Keywords: Hypothyroidism, Drinking water, Environmental exposure

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Introduction

The issue of the spatial distribution of diseases and their attribution to specific geographic areas is a well-established concept that has given rise to the field of medical geography (1). Large medical knowledge has been utilized and benefited from geographical research, and we can discover disease patterns in the geographic context of the relationship between disease and economic and social conditions (2-4). Ecological and geospatial studies are valuable tools for examining how environmental and socioeconomic factors influence human health outcomes, particularly through variables such as climate, land use, and water quality (5,6). The high capacity of medical geography modeling enables health policymakers to analyze the environmental agents of some diseases (4,6). As the incidence of infectious diseases declines and life expectancy increases, non-communicable and autoimmune disorders are becoming more prevalent, particularly in developing countries (7). Antibodies are proteins produced by the immune system to combat foreign invaders like viruses and bacteria. However, in some cases, antibodies can erroneously target the body's own cells, tissues, and organs (8). In the case of thyroid autoimmunity, antibodies such as thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) attack thyroid cells, leading to thyroid dysfunction and hypothyroidism. Among these disorders, Hashimoto's thyroiditis is a common autoimmune condition characterized by elevated TPOAb and TgAb levels (9-12). Recent evidence has indicated that exposure to environmental pollutants, especially nitrate and nitrite compounds in drinking water, may play a significant role in thyroid dysfunction. These compounds can compete with iodide for uptake by the sodium/iodide symporter in the thyroid gland, thereby reducing iodine availability for hormone synthesis and potentially contributing to hypothyroidism (13,14). Evidence shows that serum NO is significantly different between the control and case groups, and there is a positive correlation between nitrate concentration in drinking water and serum nitric oxide in the case and control groups (15). Globally, several studies have highlighted a possible relationship between nitrate/nitrite exposure and thyroid dysfunction, although the results remain inconsistent. A study in China found a positive association between higher water iodine and thyroid antibody levels in adults (16), while a study in Iran reported that even fluoride concentrations as low as 0.5 mg/L affected thyroid hormone levels (17). Nitrate contamination of groundwater is largely due to agricultural activities, the use of chemical fertilizers, and improper wastewater management. The World Health Organization (WHO) and the United States Environmental Protection Agency (EPA) have set the maximum contaminant level (MCL) for nitrate in drinking water at 50 and 45 mg/L (as NO_3^-), respectively. The Iranian national standard also adheres to a 50 mg/L threshold (18-20). According to previous studies, exposure to high levels of nitrate has been associated not only with methemoglobinemia and increased cancer risks but also with autoimmune thyroid disorders. Although some studies suggest a positive correlation between nitrate exposure and increased thyroid autoantibodies, others report inconsistent or insignificant associations (11,21). Such inconsistent findings emphasize the importance of regional studies considering local water composition, iodine intake, and genetic susceptibility. Given the limited regional data and the inconsistency of international findings, this study was designed to investigate the association between nitrate and nitrite concentrations in drinking water and thyroid autoantibodies (TPOAb and TgAb) in patients with hypothyroidism in Jahrom, Iran. The results of this research are expected to contribute to the understanding of environmental risk factors for autoimmune thyroid disorders and to provide a scientific basis for preventive measures and public health interventions in water quality management.

Materials and Methods

Study area

This study was conducted in Jahrom City, located in Fars Province, southern Iran, characterized by a semi-arid climate with an average annual temperature of 25°C and mean precipitation of approximately 250 mm. The topography is mostly flat, and groundwater is the conventional source of drinking water. The city is divided into 11 municipal zones, each supplied by a distinct groundwater well. Based on residential postal codes, each participant's household was linked to the corresponding groundwater well, allowing estimation of water source–specific nitrate and nitrite exposure.

Study population and participants

This cross-sectional ecological study was conducted on patients diagnosed with hypothyroidism who referred to the Endocrinology Clinic of Jahrom City in 2018. Participants were selected using convenience sampling. The inclusion criteria were: Confirmed diagnosis of hypothyroidism by an endocrinologist, currently under levothyroxine therapy or newly diagnosed, and no residential relocation during the previous four years. The exclusion criteria included a history of other autoimmune diseases such as celiac disease, lupus erythematosus, rheumatoid arthritis, collagen vascular diseases, or type 1 diabetes mellitus. A total of 32 patients with hypothyroidism were enrolled (female/male ratio: 23/9; mean age: 33.18 ± 9.9 years). Written informed consent was obtained from all participants before data collection, and ethical approval was granted by the Research Ethics Committee (IR.SUMS.REC.1399.379).

Sampling and water quality analysis

To estimate long-term exposure, groundwater nitrate and nitrite data were obtained from the local health authority for the years 2015–2019. In addition, 50 grab samples were collected seasonally from the main drinking water sources across 11 municipal zones. The concentrations of nitrate and nitrite were analyzed according to the Standard Methods for the Examination of Water and Wastewater (APHA, 4500-NO_3^-, 4500-NO_2^-) using a DR 6000 UV-Vis spectrophotometer (HACH, USA). The samples were stored at 4°C and analyzed within 24 hours of collection to minimize degradation.

The water quality data were spatially matched with each participant's residence zone, ensuring accurate assignment of exposure based on the local groundwater characteristics.

Biomarker and hormone analysis

Blood samples (5 mL) were collected from each participant after overnight fasting. Thyroid peroxidase antibodies (TPOAb) were measured using the chemiluminescent IMMULITE 2000 XPi analyzer (Siemens, Eschborn, Germany). Thyroglobulin antibodies (TgAb) were measured by enzyme-linked immunosorbent assay (ELISA) using a Diesel kit (Germany), following the manufacturer's instructions. Thyroid-stimulating hormone (TSH) levels were determined using the Cobas ECLIA system (Roche Diagnostics GmbH, Mannheim, Germany). Participants with TSH > 3.6 mIU/L were classified as hypothyroid, but the primary outcomes of interest were TPOAb and TgAb levels.

Data analysis

Statistical analyses were performed using IBM SPSS version 213.0 (IBM Corp., USA). Descriptive statistics (mean, standard deviation, percentage) were calculated for demographic and exposure variables. Due to non-normal distribution of data (verified by the Shapiro–Wilk test), Spearman's correlation was used to assess the associations between nitrate/nitrite concentrations and thyroid autoantibody levels. A P-value < 0.05 was considered statistically significant.

Results

A total of 1,066 individuals were recorded in the environmental dataset, including 927 women (86.9%) and 139 men (13.1%). Environmental water quality monitoring data were obtained from the National Water and Wastewater Engineering Company of Iran, and were used to describe the general chemical profile of Jahrom's drinking water during the past decade.

Heavy metals

As shown in Table 1, the measured concentrations of heavy metals in the drinking water of Jahrom between 2012 and 2019 were in full compliance with both Iranian national standards and the World Health Organization (WHO) guidelines. The mean concentrations of all metals were well below the maximum permissible limits, indicating no evidence of heavy metal contamination in the groundwater-based drinking water system during the studied period.

Physicochemical properties of drinking water

The physicochemical characteristics of drinking water during 2011–2019 also remained within acceptable the national and WHO limits (Figure 1). The mean concentrations of nitrate (19.76 mg/L) and nitrite (0.016 mg/L) were below standard. Major cations such as sodium, magnesium, and calcium were moderate and consistent with typical semi-arid aquifer compositions. The mean electrical conductivity (360 µS/cm) and TDS (352 mg/L) values indicated moderate salinity, while total hardness (243 mg/L) classified the water as moderately hard, typical for limestone-rich aquifers.

Characteristics of hypothyroid patients

A total of 32 hypothyroid patients were enrolled in the clinical component of the study (female/male ratio: 23/9; mean age: 33.18 ± 9.9 years). The main biochemical characteristics are summarized in Table 2. Median TPOAb and TgAb levels were 297.90 IU/mL (IQR: 455.48) and 41.05 IU/mL (IQR: 359.25), respectively. The median nitrate and nitrite concentrations corresponding to the patients' residential zones were 25.11 mg/L (IQR: 23.93) and 0.02 mg/L (IQR: 0.004), respectively.

Correlation between nitrate/nitrite exposure and thyroid autoantibodies

The Spearman's correlation analysis was used to evaluate

Table 1. Heavy Metal Concentrations in Jahrom's Drinking Water Distribution Network (2012–2019), reported by the National Water and Wastewater Engineering Company of Iran.

Element (Heavy Metal)	Unit	WHO Guideline (µg/L)	Iranian Standard Limit (µg/L)	Min	Max	Mean	No. of Tests	Compliance with Standard
Arsenic (As)	µg/L	10	10	0	0	0	3	Yes
Lead (Pb)	µg/L	10	10	0	2	0.45	6	Yes
Cadmium (Cd)	µg/L	3	3	0	2	0.433	6	Yes
Mercury (Hg)	µg/L	6	6	0	0	0	3	Yes
Cyanide (CN)	µg/L	70	70	0	0	0	3	Yes
Nickel (Ni)	µg/L	70	70	3	9	4.783	6	Yes
Copper (Cu)	µg/L	2000	1000	38	223	110	6	Yes
Zinc (Zn)	µg/L	—	3000	38	295	157.167	6	Yes

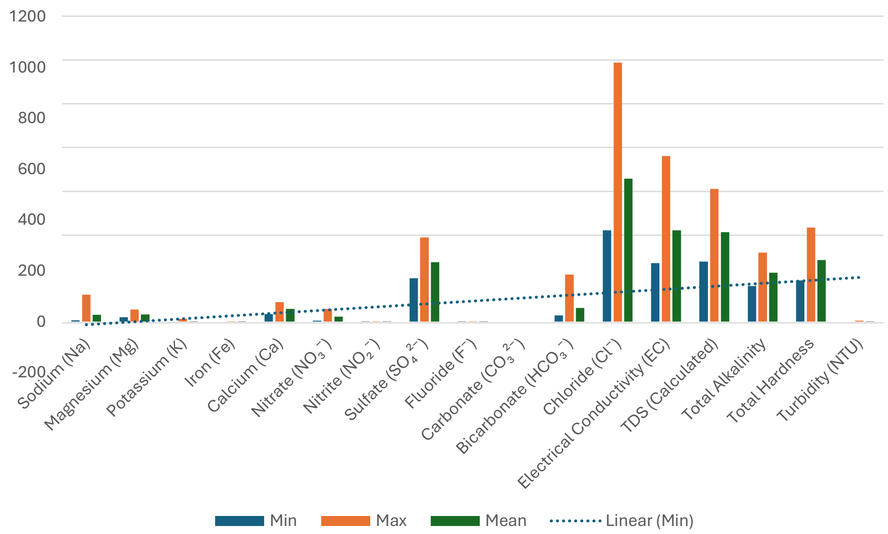

Figure 1. Comprehensive Assessment of Physicochemical Properties of Drinking Water in Jahrom, Iran During 2011–2019

Table 2. Characteristics of clinical variables and drinking water quality

Characteristics	Hypothyroid Patients (n = 32)	
	Median	IQR
Age (year)	33.00	9.75
TPOAb (IU/mL)	297.90	455.48
TGAb (IU/mL)	41.05	359.25
NO_2 (mg/L)	0.02	0.004
NO_3 (mg/L)	25.11	23.93

Table 3. Correlation of thyroid autoantibodies and nitrate/nitrite

Variable	Vs.	Correlation coefficient	*P-value
Nitrite	TPOAb	0.193	0.548
	TGAb	-0.151	0.576
Nitrate	TPOAb	0.714	0.001
	TGAb	0.039	0.879

*Spearman's correlation test.

the associations between drinking water nitrate/nitrite levels and thyroid autoantibody concentrations (TPOAb and TgAb). As shown in Table 3, there was a strong and statistically significant positive correlation between nitrate concentration and TPOAb levels ($r = 0.714$, $P = 0.001$). No significant correlations were observed either between nitrite levels and antibody, or between nitrate levels and TgAb.

Interpretation of findings

The observed positive association between nitrate exposure and TPOAb levels suggests that higher nitrate concentrations in drinking water may contribute to enhanced autoimmune thyroid activity, consistent with the hypothesis that nitrate can act as a competitive inhibitor of iodide uptake in the thyroid gland. However, the absence of association with TgAb implies that the autoimmune response may be antibody-specific, potentially reflecting different immunological mechanisms.

No significant role of nitrite was detected, likely due to its low concentration and rapid biological instability in environmental and physiological systems. Scatter plots (not shown) demonstrated an upward trend between nitrate and TPOAb values, supporting the correlation results.

Additional context

Although heavy metals and other physicochemical parameters were within safe limits, these data were presented to contextualize the overall environmental safety of the study area and exclude confounding effects from other contaminants.

Summary of key findings

Drinking water in Jahrom showed excellent chemical quality with no exceedance of regulatory limits. A significant positive correlation was observed between nitrate levels and TPOAb concentrations, suggesting potential environmental modulation of thyroid autoimmunity. No significant correlations were found for nitrite or TgAb. Further research using larger, controlled, and longitudinal designs is recommended to confirm these findings.

Discussion

Drinking water is usually locally supplied and largely affected by local geochemistry. According to the World Health Organization (WHO), water is considered a nutritional source; however, excessive intake of certain inorganic compounds through drinking water can cause toxic effects. In recent years, nitrite and nitrate have accumulated in soil and water, particularly in arid and semi-arid regions, due to prolonged drought, over-irrigation, and intensive fertilizer use. These compounds raise significant health concerns due to the potential for nitrate conversion into nitrosamines, which are carcinogenic (22,23). Beyond their carcinogenic potential, nitrates may also function as endocrine-disrupting agents, interfering with iodine uptake and thyroid hormone synthesis through inhibition of the sodium-iodide symporter (NIS), thereby increasing serum TSH and autoantibody titers in predisposed individuals (21,24).

In addition to the observed correlations between nitrate and TPO antibody levels, physicochemical analysis of drinking water in Jahrom between 2011 and 2019 showed that the overall water quality remained within national and international safety limits. The study results showed that concentrations of heavy metals, including arsenic, lead, mercury, and cadmium, were consistently below the maximum permissible levels, with full compliance reported in all samples tested. This suggests that chronic exposure to toxic heavy metals is unlikely to be a confounding factor in thyroid dysfunction in this region. Rafiei et al. conducted a large-scale survey and reported inconsistent associations between heavy metal exposure and non-cancerous thyroid disorders in different populations. This finding is consistent with our findings, where measured concentrations of these metals were consistently below the permissible limits, suggesting that they are unlikely to contribute to thyroid dysfunction in the study area (25). The results of the study by Rezaei et al. were in contrast to the findings of our study (26). Furthermore, Kheradpisheh et al. found that even fluoride levels below 0.5 mg/L can significantly alter TSH and T3 concentrations in humans, highlighting that not only nitrates, but also multiple water-borne inorganic compounds can modulate thyroid function. This finding emphasizes the importance of comprehensive water monitoring and supports our conclusion that subtle environmental exposures may have endocrine impacts even below the established guideline limits (17). Although all measured parameters, including nitrate and nitrite, were within the WHO safety limits, their detectable presence, particularly nitrates, may still pose subtle health risks, as suggested by the observed association with elevated TPO antibodies. Sokal-Dembowska et al. emphasized that even low-level nitrate and nitrite exposure, particularly from dietary and environmental sources, may contribute to thyroid dysfunction findings that align with our observation of elevated TPO antibodies despite compliance with safety thresholds (27). Also, García Torres et al. reported that nitrates may disrupt thyroid function by impairing iodine uptake, which aligns with our findings (28). Similar results were reported by Kasiyan et al. who observed that TPOAb and TgAb titers were significantly associated with drinking water iodine concentrations among women with hypothyroid Hashimoto's thyroiditis. They concluded that variations in water composition could modulate autoimmunity progression, especially in females with additional iodine intake. These findings support our results and suggest that subtle environmental factors whether nitrate or iodine can modulate thyroid autoantibody responses (29).

In line with this, Zhou et al. conducted a large cross-sectional study in China involving over 2,500 adults and found that individuals in areas with higher median iodine concentrations in drinking water had significantly higher positivity for both TPOAb and TGAb, along with elevated TSH values. This provides further evidence that the composition of drinking water, even within permissible limits, can influence thyroid autoimmunity markers (16). Human exposure to nitrate occurs via multiple environmental pathways, especially through food and drinking water. Nitrate and nitrite are highly soluble in aquatic environments, and anthropogenic activities, such as wastewater discharge, agricultural runoff, and leachate infiltration, can introduce them into surface and groundwater sources (19). Despite drinking water standards set by organizations like the WHO and the EPA, nitrate contamination remains a challenge in many regions, including Iran (30-32). Zhu et al. further demonstrated that increased iodine concentrations in drinking water were associated with a higher prevalence of thyroid nodules among Chinese adults, reinforcing that trace elements in water systems, like nitrate, fluoride, and iodine, may exert long-term effects on thyroid structure and function (33). Our study revealed a significant positive correlation between nitrite concentrations in drinking water and serum levels of thyroid peroxidase (TPO) antibodies, suggesting a potential relationship between environmental exposure and autoimmune thyroid responses. Several studies have investigated the impact of nitrate exposure on thyroid function. García-Torres (2022) evaluated families in rural Mexico and found a high prevalence of subclinical hypothyroidism associated with chronic consumption of nitrate-contaminated water, suggesting that long-term nitrate exposure may contribute to thyroid dysfunction through autoimmune mechanisms (14). In a comprehensive review, García-Torres et al. (2020) highlighted that nitrates in drinking water can disrupt iodine uptake by the thyroid gland, acting as endocrine disruptors that may induce hypothyroidism and impair metabolic functions at all stages of development (21). Furthermore, Street et al. (2023) emphasized that environmental contaminants such as nitrates and nitrites negatively affect thyroid function, contributing to increased incidence of thyroid disorders and cancer. Their review also pointed to the complex interactions between environmental pollution, nutritional factors, and endocrine disruptors in altering thyroid hormone synthesis and action (24). Similarly, Sachdeva et al. argued that excess fluoride intake through water fluoridation policies may also contribute to thyroid dysfunction and suggested that thyroid disorders should be recognized as non-communicable diseases (NCDs) of public health concern. Their work supports the broader perspective that cumulative exposure to waterborne inorganic contaminants can trigger subtle but significant endocrine effects (34). Despite these findings, most studies in Iran have focused on the relationship between nitrate and gastrointestinal cancers, such as esophageal and gastric cancers, rather than on thyroid disorders (35,36). Moreover, environmental factors specific to the study area, including water resource management, agricultural practices, and seasonal nitrate fluctuations, should be further examined to understand their role in thyroid health. Future studies should also integrate genetic predisposition, dietary iodine and fluoride intake, and lifestyle factors to better elucidate the multifactorial pathways linking water quality to thyroid autoimmunity. Genetic predisposition, dietary iodine intake, and exposure through food sources were not considered in this study, which are limitations worth addressing in future research.

Limitations of the study

The study was limited by the absence of a control (healthy) group, primarily due to financial and logistical constraints. This limitation prevents definitive causal inference between contaminant exposure and disease occurrence. Additional challenges include high sampling costs, restricted access to certain wells, and limited patient cooperation during data collection. Future studies are recommended to include larger sample sizes, matched control groups, and longitudinal designs to confirm these findings.

Conclusion

This study demonstrates a statistically significant association between nitrate levels in drinking water and elevated thyroid peroxidase antibody (TPOAb) concentrations among hypothyroid patients in Jahrom, Iran. These findings suggest that even nitrate exposure within the range of the WHO and national standards may contribute to autoimmune thyroid activation. The absence of heavy metal contamination strengthens the hypothesis that nitrate is a key environmental factor. Although the observed effects are subtle, they raise important public health concerns about chronic, low-level exposure to nitrates in vulnerable populations. Future investigations should adopt longitudinal or case-control designs including both hypothyroid patients and healthy controls, integrate dietary and genetic data, and evaluate cumulative exposure across multiple pathways. Comprehensive risk assessments are also needed to guide water quality management and preventive public health interventions.

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Authors' Contribution

Conceptualization: Hassan Hashemi.
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Funding acquisition: Hassan Hashemi.
Investigation: Salma Ahi and Naser Hatami.
Methodology: Salma Ahi and Naser Hatami.
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Supervision: Hassan Hashemi and Mahdieh Ardaneh.
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Visualization: Hassan Hashemi and Mahdieh Ardaneh.
Writing – original draft: Salma Ahi and Naser Hatami.
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Competing Interests

The authors declare no conflict of interest.

Ethical Approval

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Ethical code: IR.SUMS.REC.1399.379).

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