

Association of Iodine and Iron with Thyroid Function

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Abstract Iodine and iron are essential elements for healthy thyroid function. However, little is known about the association of iron and iodine with thyroid function in the general US population. We investigated iron and iodine status in relation to concentrations of thyroid hormones. We included 7672 participants aged 20 and older from three surveys (2007–2008, 2009–2010, and 2011–2012) of the National Health and Nutrition Examination Survey. Serum thyroid measures (including free and total T3 and T4, and TSH), serum iron concentration, and urinary iodine concentrations were measured. Multivariate linear regression models were conducted with serum thyroid measures as dependent variables and combinations of serum iron concentration and urinary iodine concentration as predictors with covariate adjustment. Logistic regression models were performed with TSH levels (low, normal, and high) and combinations of serum iron concentration and urinary iodine concentration. Overall, 10.9% of the study population had low iron; 32.2 and 18.8% had low or high iodine levels, respectively. Compared with normal levels of iron and iodine, normal iron and high iodine were associated with reduced free T3 and increased risk of abnormal high TSH. Combined low iron and low iodine was associated with reduced free T3 and increased TSH. In addition, high iodine was associated with increased risk of abnormal high TSH in

females but not in males. Thyroid function may be disrupted by low levels of iron or abnormal iodine, and relationships are complex and sex-specific. Large prospective studies are needed to understand the mechanisms by which iron interacts with iodine on thyroid function.

Keywords Iodine · Iron · Thyroid function · Trace elements · Thyroid cancer

Background

The incidence of thyroid cancer has been rising steadily over the past few decades in most countries [1], particularly among women. This increase may be explained partly by improved detection of papillary tumors and modification in diagnostic criteria [2]. Changes in environmental risk factors also likely play important roles in development of thyroid cancer [3]. Previous history of benign thyroid disease (e.g., nodule/adema, goiter) is one of the few well-established risk factors for thyroid cancer [4]. To shed light on the possible causes for rising thyroid cancer rates, we need to study and understand factors influencing thyroid function.

The thyroid gland plays important roles in regulating metabolism and promoting normal development of cardiovascular, reproductive, and nervous systems. Normal thyroid function depends on the presence of many trace elements for both synthesis and metabolism of thyroid hormones. For example, iodine is a critical element for healthy thyroid hormone production [5]. Iodine deficiency is a risk factor for goiter, development of thyroid nodules and follicular thyroid cancer, whereas papillary thyroid cancer (the most common type of thyroid cancer) seems to be more common in areas with high iodine intake (using WHO criteria for median urinary iodine

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concentration ≥ 300 $\mu\text{g/L}$) [6]. These findings indicate that the relationship between iodine and thyroid function may be non-linear and complicated [7].

Apart from iodine, other trace elements, such as iron, selenium, copper, and calcium, are also involved in regulation of this hormone network [8–10]. Iron is essential for efficient iodine utilization and thyroid hormone synthesis. The interaction between iron and iodine on thyroid function has been reported although the exact pathways are still unclear [9, 11–13]. Iron deficiency is the most common nutritional disorder affecting about 20–25% of the world's population, predominantly children, and women [14]. Iron-deficient women have lower levels of TSH, free T4, and free T3 than the levels of controls [15, 16], as well as higher risk for isolated hypothyroxinemia [17]. Iron deficiency will impair thyroid hormone synthesis, storage, and secretion even by reducing activity of heme-dependent thyroid peroxidase if iodine intake is adequate [9, 13].

The evidence of the iron and iodine interaction has led to several randomized clinical trials in populations with elevated prevalence of goiter and iron deficiency anemia [18–23]. All studies showed greater improvement in thyroid function indices and/or thyroid volume in groups with iron and iodine treatment compared to groups with iodine treatment alone. However, all of these trials were conducted in children or in areas with elevated prevalence of goiter.

Little information is available about the possible combined effects of iron and iodine on thyroid function in the general population. We hypothesized that healthy thyroid function will occur in the presence of adequate iron intake coupled with normal range of iodine intake. People with abnormal levels of either of these elements may experience disrupted thyroid function. The present analysis investigated the combined association of serum iron concentration and urinary iodine concentration with serum thyroid hormone measures using a nationally representative sample, the National Health and Nutrition Examination Survey (NHANES).

Methods

Database

The present study analyzed measurements from three surveys (2007–2008, 2009–2010, and 2011–2012) of the National Health and Nutrition Examination Survey (NHANES) data. NHANES is an ongoing cross-sectional survey that assesses the health and diet of nationally representative samples of the US civilian non-institutionalized population [24]. It uses a complex, stratified, multistage sample design. In NHANES, participants undergo a detailed home interview, followed by a physical examination and laboratory evaluation at a local mobile examination center. Methods for survey data collection are described in detail elsewhere [24].

Study Population

The analytic sample was restricted to survey participants aged 20 and older who had information on thyroid, iron and iodine measures. There were 8436 participants who met these inclusion criteria. We then excluded 84 women who were pregnant, 597 participants with a reported history of thyroid disease, and 83 with data missing for other covariates (age, sex, race/ethnicity, body mass index (BMI)). This resulted in 7672 total subjects available for analysis.

Serum Thyroid Measures

Serum thyroid measures in the NHANES include free and total T3 and T4, and TSH. Measures were based on immunoenzymatic assays as described in the NHANES website [24]. The distribution of TSH was right skewed and was log transformed for analysis. Since TSH analysis is the most common for diagnosing both hyperthyroidism and hypothyroidism, we also categorized TSH as below normal level (<0.45 $\mu\text{IU/mL}$), normal level (0.45 – 3 $\mu\text{IU/mL}$), or above normal (>3 $\mu\text{IU/mL}$) [25].

Measurement of Iron and Iodine

Serum iron concentration was abstracted from standard biochemistry profile data in the NHANES. The iron concentration was measured by the DcX800 method. The DcX800 method is a timed-endpoint method [24]. Urinary iodine concentrations in the NHANES were determined by ICP-DRC-MS (inductively coupled plasma dynamic reaction cell mass spectroscopy) [24]. There were no changes for both measurements among the three time periods in equipment, lab methods, or lab site.

Serum iron concentration was categorized based on sex-specific reference levels (55 – 160 $\mu\text{g/dL}$ in men and 40 – 155 $\mu\text{g/dL}$ in women) [26]. Only 3% of the study population had increased iron levels; therefore, we categorized serum iron concentration into only two categories: low (male < 55 $\mu\text{g/dL}$ and female < 40 $\mu\text{g/dL}$) and normal. Urinary iodine concentration was categorized as low, normal, and high based on reference ranges suggested by the WHO (low (<100 $\mu\text{g/L}$), normal (100 – 299), and high (≥ 300)) [27].

Covariates

We considered age in years, sex (male, female), race/ethnicity (Mexican American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, others), and BMI (kg/m^2) as potential confounding variables.

Statistical Analysis

Descriptive analyses examined baseline characteristics by serum iron and urinary iodine concentrations. Differences were tested using chi-squared statistics for categorical variables and ANOVA for continuous variables.

We included stratum and cluster weights to account for the complex and multistage study design of NHANES data. We also used 2-year examination sample weights for individual probabilities drawn for laboratory examination.

Multivariate linear regression models were conducted with serum thyroid measures (TT3, FT3, TT4, FT4, and TSH) as dependent variables and combinations of serum iron concentrations and urinary iodine concentrations as predictors after adjusting for age, sex, race/ethnicity, and BMI categories. Further, logistic regression models were performed with TSH levels (low, normal, and high) and combinations of serum iron concentrations and urinary iodine concentrations after adjusting for potential confounders. Models were run overall and by sex. Data analysis was performed using SAS software version 9.4.

Results

In the study population, 48.8% were females with mean age of 46.5 ranging from 20 to 80 years and mean BMI of 28.4 (SD = 7.2). Among males, the mean age was 46.0 ranging from 20 to 80 years and mean BMI was 28.6 (SD = 5.9).

Overall, 10.9% of the study population had low serum iron concentrations (10.9% in men and 10.8% in women); 32.2, 49.0, and 18.8% of the study population had low, normal and high urinary iodine concentrations, respectively. The distributions of low, normal and high iodine concentrations were 28.4, 50.2, and 21.4% in men, and 36.3, 47.8, and 16.0%, in women, respectively.

Compared to people with a normal concentrations of serum iron, people with a low level of iron were more likely to be younger (46.5 vs. 43.3), female (48.5 vs. 51.0%), non-Hispanic black (10.3 vs. 19.4%), or Mexican American (8.1 vs. 10.5%), and have high BMI (28.3 vs. 29.8). In addition, compared with people with high urinary iodine, people with low iodine were more likely to be younger, female, non-Hispanic black, and have lower BMI regardless of iron status (Table 1).

Controlling for covariates, and compared with normal levels of iron and iodine, when serum iron was normal, elevated urinary iodine concentration was associated with reduced level of free T3; when serum iron concentration was low, both low and normal levels of urinary iodine concentrations were associated with reduced level of free T3, and when serum iron concentration was low, low urinary iodine

Table 1 Demographics and anthropometrics of participants in NHANES study by combinations of serum iron concentration and urinary iodine concentration

	Normal serum iron			Low serum iron				
	Total (N = 6838)	Low urine iodine (<100 µg/L) (N = 2242)	Normal urine iodine (100- < 200 µg/L) (N = 3322)	High urine iodine (≥200 µg/L) (N = 1274)	Total (N = 834)	Low urine iodine (<100 µg/L) (N = 227)	Normal urine iodine (100- < 200 µg/L) (N = 440)	High urine iodine (≥200 µg/L) (N = 167)
Age (mean, years) (SD)	46.5 (17.5)	44.8 (16.6)	47.3 (17.8)	47.9 (18.2)	43.3 (17.1)	41.1 (16.6)	44.5 (17.1)	43.0 (17.6)
Female (N, %)	3286 (48.5)	1222 (55.7)	1550 (46.6)	514 (39.4)	398 (51.0)	114 (54.6)	210 (50.8)	74 (47.1)
Race (N, %)								
Mexican American	1123 (8.1)	339 (7.5)	578 (8.5)	206 (8.1)	132 (10.5)	30 (9.0)	78 (10.8)	24 (10.4)
Other Hispanic	766 (6.0)	228 (5.6)	397 (6.3)	141 (5.7)	94 (6.3)	21 (5.6)	52 (6.2)	21 (7.7)
Non-Hispanic White	3125 (68.4)	996 (67.5)	1510 (69.0)	619 (68.8)	299 (57.0)	80 (53.8)	152 (60.4)	67 (52.3)
Non-Hispanic Black	1318 (10.3)	485 (11.3)	619 (10.1)	214 (8.7)	257 (19.4)	82 (24.4)	140 (19.2)	35 (13.8)
Other Race	506 (7.3)	194 (8.1)	218 (6.1)	94 (8.6)	52 (6.7)	14 (6.4)	18 (3.5)	20 (15.8)
BMI (mean kg/m ²) (SD)	28.3 (6.3)	27.7 (6.2)	28.7 (6.3)	28.8 (6.4)	29.8 (8.1)	29.0 (7.8)	30.0 (8.3)	30.4 (7.7)

The numbers of participants in all of the categories are un-weighted. The means or proportions are weighted

concentration was associated with increased TSH level after adjusting for age, sex, BMI and race/ethnicity (Table 2).

When TSH was analyzed as a categorical variable, we found that high urinary iodine concentration was associated with increased risk of having abnormal high TSH when serum iron was normal overall. When performing analysis stratified by sex, we observed that high iodine was associated with increasing risk of having abnormal high TSH for females regardless of iron level, but no significant association was observed for males (Table 3).

Discussion

In the present study, we found that when serum iron concentrations were normal, a high urinary iodine concentration was associated with reduced free T3, and increased risk of having abnormal high TSH. When serum iron levels were low, a low

level of urinary iodine concentrations was associated with reduced free T3 level and increased TSH level. In this study, serum iron concentration modified the association between urinary iodine concentration and thyroid function. In addition, we also observed that high urinary iodine concentration was associated with increased risk of having abnormal high TSH only in females, but not in males. These results suggest that associations between iron, iodine and thyroid function may be sex-specific.

The thyroid is an endocrine gland. Measuring the TSH level is considered by the American Thyroid Association as the best way to initially test thyroid function [28]. A high TSH level often indicates that the thyroid gland is failing and does not produce enough thyroid hormones (primary or subclinical hypothyroidism). On the other hand, a low TSH level usually indicates an overactive thyroid that is producing too much thyroid hormone (hyperthyroidism) with an exception of abnormality in the pituitary gland that does not produce enough

Table 2 Multivariate linear regression results for relationship between combinations of serum iron concentration and urinary iodine concentration and thyroid function in both sexes ($N = 7672$)

Overall	TT3				FT3			
	Estimate	Lower limit	Upper limit	P value	Estimate	Lower limit	Upper limit	P value
Normal iron ^a								
Iodine: low (<100 µg/L)	1.20	-0.71	3.12	0.21	0.002	-0.03	0.03	0.90
Iodine: normal (100 ≤ 300 µg/L)	Reference				Reference			
Iodine: high (≥300 µg/L)	-1.04	-3.19	1.11	0.34	-0.04	-0.07	-0.003	0.04
Low iron ^a								
Iodine: low (<100 µg/L)	-3.34	-6.97	0.28	0.07	-0.07	-0.14	-0.003	0.04
Iodine: normal (100 ≤ 300 µg/L)	-1.66	-4.82	1.50	0.30	-0.05	-0.11	-0.001	0.05
Iodine: high (≥300 µg/L)	-2.71	-7.26	1.84	0.24	-0.06	-0.14	0.01	0.11
Normal iron ^a								
Iodine: low (<100 µg/L)	1.20	-0.71	3.12	0.21	0.004	-0.01	0.02	0.60
Iodine: normal (100 ≤ 300 µg/L)	Reference				Reference			
Iodine: high (≥300 µg/L)	-1.04	-3.19	1.11	0.34	-0.01	-0.03	0.003	0.11
Low iron ^a								
Iodine: low (<100 µg/L)	-3.34	-6.97	0.28	0.07	-0.01	-0.03	0.02	0.64
Iodine: normal (100 ≤ 300 µg/L)	-1.66	-4.82	1.50	0.30	0.02	-0.004	0.04	0.12
Iodine: high (≥300 µg/L)	-2.71	-7.26	1.84	0.24	-0.002	-0.04	0.04	0.90
Log TSH								
Normal iron ^a								
Iodine: low (<100 µg/L)	-0.01	-0.06	0.05	0.83				
Iodine: normal (100 ≤ 300 µg/L)	Reference							
Iodine: high (≥300 µg/L)	-0.01	-0.07	0.05	0.71				
Low Iron ^a								
Iodine: low (<100 µg/L)	0.12	0.005	0.23	0.04				
Iodine: normal (100 ≤ 300 µg/L)	0.01	-0.09	0.11	0.86				
Iodine: high (≥300 µg/L)	0.01	-0.15	0.17	0.90				

^a Serum iron: normal: ≥55 µg/dL in men or ≥40 µg/dL in women; low: <55 µg/dL in men and <40 µg/dL in women

Table 3 Multivariate linear regression results for relationship between combinations of serum iron concentration and urinary iodine concentration and blood TSH level

Overall	Low TSH**			High TSH**		
	OR	Lower limit	Upper limit	OR	Lower limit	Upper limit
Normal iron ^a						
Iodine: low (<100 µg/L)	1.33	0.72	2.48	1.11	0.91	1.35
Iodine: normal (100 -< 300 µg/L)	Reference					
Iodine: high (≥300 µg/L)	1.40	0.86	2.29	1.36	1.04	1.77
Low iron ^a						
Iodine: low (<100 µg/L)	0.90	0.32	2.53	1.29	0.72	2.31
Iodine: normal (100 -< 300 µg/L)	1.49	0.85	2.63	1.29	0.90	1.85
Iodine: high (≥300 µg/L)	1.85	0.69	4.95	1.60	0.71	3.60
Males						
Normal iron ^a						
Iodine: low (<100 µg/L)	1.87	0.84	4.17	0.90	0.66	1.23
Iodine: normal (100 -< 300 µg/L)	Reference					
Iodine: high (≥300 µg/L)	1.55	0.62	3.90	1.25	0.91	1.72
Low iron ^a						
Iodine: low (<100 µg/L)	0.82	0.17	4.00	1.34	0.61	2.97
Iodine: normal (100 ≤ 300 µg/L)	2.26	0.98	5.24	1.35	0.63	2.86
Iodine: high (≥300 µg/L)	2.64	0.72	9.77	1.03	0.21	5.09
Females						
Normal iron ^a						
Iodine: low (<100 µg/L)	1.05	0.52	2.11	1.34	0.97	1.85
Iodine: normal (100 -< 300 µg/L)	Reference					
Iodine: high (≥300 µg/L)	1.33	0.70	2.55	1.52	1.04	2.20
Low iron ^a						
Iodine: low (<100 µg/L)	0.88	0.26	2.96	1.30	0.54	3.15
Iodine: normal (100 -< 300 µg/L)	1.05	0.51	2.14	1.27	0.63	2.53
Iodine: high (≥300 µg/L)	1.30	0.31	5.38	2.50	1.06	5.93

^a Serum iron: normal: ≥55 µg/dL in men or ≥40 µg/dL in women; low: <55 µg/dL in men and <40 µg/dL in women. TSH (<0.45 low, >3 high)

TSH to stimulate the thyroid (secondary hypothyroidism) [28].

Our data show that both low urinary iodine concentration and excess urinary iodine concentration were associated with high TSH. The high TSH associated with low iodine is well understood, because low iodine leads to a low amount of T4 and/or T3 production, and these stimulate an increase in TSH as an adaptation. However, accounting for the high TSH associated with excess iodine is less apparent, although the acute Wolff-Chaikoff effect (a transient reduction in the synthesis of thyroid hormone in rats exposed to high amounts of iodide) was described in 1948 [29]. In most individuals, the decreased production of thyroid hormones is only transient; however, vulnerable individuals (such as those with autoimmune thyroid disease, a previous history of surgery, or other pre-existing thyroid disease) might have an increased risk of failing to adapt to the acute Wolff-Chaikoff effect [30]. Exposure to high concentrations of iodine might decrease the release of

thyroid hormone, and increase the serum level of TSH to the upper limit of the normal range [5, 31]. TSH is a known thyroid growth factor. Increased serum TSH concentration is associated with increased risk of differentiated thyroid cancer and advanced tumor stage [32]. Therefore, optimization of population iodine intake is an important component of preventive health care to reduce the prevalence of thyroid disorders.

Mechanisms by which iron and iodine mutually influence thyroid function are not well understood. Iron, an essential element in the body, plays a wide variety of physiological and biochemical roles. It is essential for efficient iodine utilization and thyroid hormone synthesis [9]. Iron deficiency anemia could impair thyroid metabolism through decreased oxygen transport [9]. Experimental studies on model organisms have suggested various mechanisms in which iron impacts thyroid function and iodine utilization [9, 11, 12]. For example, iron deficiency in animals alters the central nervous

system control of thyroid metabolism [15], decreases T3 affinity to receptors in hepatocytes [33], lowers oxygen transport [34], and reduces thyroid peroxidase (TPO) activity [35]. TPO is an iron-dependent enzyme bound to the apical membrane of the thyrocyte. It catalyzes two initial steps in thyroid hormone synthesis, including iodination of the thyroglobulin and coupling reaction of the iodotyrosine molecules. Given the crucial role of iron in TPO activity, iron deficiency could decrease TPO activity and thereby interfere with iodine utilization and thyroid metabolism [9].

Sex differences in thyroid disease have been reported. A 2014 review of differences in thyroid disease by sex found that the prevalence of hypothyroidism was increased (two to seven fold) in women compared to men [36]. Subclinical hypothyroidism was the most common, which occurs in up to 20% of postmenopausal women [36]. These sex differences may be partially explained because thyroid function in females may be more sensitive to abnormal concentrations of iron or iodine or both. In addition, these sex differences in thyroid disease may also be because women are more likely to have iron or iodine deficiency as shown in our data.

Strengths of this study include, first, that this is the first large-scale analysis in a nationally representative adult population of combined association of iron and iodine with thyroid function, and second, that NHANES collects a range of potential confounders that we adjusted for in the models. However, several limitations should also be noted. First of all, both urinary iodine and serum iron concentrations were based on a single sample; these measures may represent short term exposure. Second, NHANES is a cross-sectional database; both iron and iodine biomarkers and thyroid function were measured at the same time, making attribution of causal direction difficult.

In conclusion, our study suggests that thyroid function may be disrupted by low levels of iron, low or high levels of iodine, and the relationships are complex and sex-specific. Large prospective studies are needed to better understand the mechanisms by which iron interacts with iodine on thyroid function, so that light may be shed on the complex nature of the associations shown here and in prior research.

Compliance with Ethical Standards

Conflict of Interest There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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