Prevalence of thyroid dysfunction with adequate and excessive iodine intake in Hebei Province, People's Republic of China

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Abstract

Objective: To explore (i) the prevalence of thyroid dysfunction in populations with adequate and excessive iodine intakes and (ii) the effect of iodine exposure on the prevalence of thyroid dysfunction.

Design: Cross-sectional study was conducted in Hebei in 2010. The population was classified as having adequate or excessive iodine intake according to the iodine concentration in drinking water. Demographic information was collected by questionnaire. Levels of serum thyroid hormones, thyroid autoantibodies and iodine in drinking water and urine were measured.

Setting: Villages with adequate or excessive drinking water iodine in Hebei Province, People's Republic of China.

Subjects: A total of 854 men and women aged 20–50 years who had lived in the surveyed areas for over 5 years, including 348 from the adequate iodine area (AIA) and 506 from the excessive iodine area (EIA).

Results: Median urinary iodine concentration was 185 µg/l in AIA and 1152 µg/l in EIA. The prevalence of thyroid dysfunction in AIA was 10·3 %, which included 1·1 % with hypothyroidism and 8·1 % with subclinical hypothyroidism; and 20·6 % in EIA, which included 3·6 % with hypothyroidism and 13·6 % with subclinical hypothyroidism. The positive rates of thyroglobulin antibody were 16·1 % in AIA and 11·9 % in EIA; the positive rates of thyroperoxidase antibody were 20·7 % in AIA and 16·4 % in EIA.

Conclusions: Excessive iodine intake may lead to increased prevalence of biochemical thyroid dysfunction, especially biochemical hypothyroidism. This is not related to an increase in prevalence of thyroid antibodies. Women are more susceptible to iodine excess.

Iodine is an essential trace element for the synthesis of thyroid hormones and thyroxine is also critical for brain development. Iodine deficiency may cause hypothyroidism and results in severe developmental delay in infants and stillbirth in pregnant women[1–3]. WHO, UNICEF and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) endorse the policy of iodine supplementation for pregnant and breast-feeding women in iodine-deficient countries where salt iodization is not regulated or is ineffective, in order to improve the nutritional status of iodine[4].

However, iodine deficiency and excessive exposure to iodine due to environmental or artificial factors may lead to thyroid dysfunction[5]. Recommended by WHO, ICCIDD and UNICEF, the optimal iodine intake is 150–300 µg/d (median urinary iodine concentration (UIC): 100–199 µg/l)[6]. Iodine intake exceeding the optimal level will increase the risk of thyroid dysfunction. Chronic iodine intake in the form of iodide is associated with an increase in goitre and subclinical hypothyroidism due to the inhibition of thyroid hormone synthesis[7]. Excessive iodine intake can also trigger an immune response, resulting in autoimmune thyroiditis[8], thyroid inflammation, sensitive reaction or acute toxicity[5,7]. It has been reported that excessive iodate intake has a minimal impact on thyroid hormones. Hypothyroidism or hyperthyroidism was induced in some

individuals receiving iodine supplementation. Most abnormalities disappeared after 4–12 weeks[7,9]. However, in our previous study, we found that thyroid dysfunction induced by excessive iodine intake can last for a longer period. The issue regarding the safety of iodine exposure is still controversial and further studies on excessive iodine exposure are highly desired[10].

Universal salt iodization was first introduced in China in 1996, and iodine deficiency disorders are currently under control in most areas[11–13]. However, there are still more than ten provinces with waterborne excessive iodine. In these endemic areas, more than 30 million people are exposed to excessive iodine exposure[11–14]. With the help of universal salt iodization, iodine intake has increased nationwide[15]. However, only a few data have demonstrated the epidemiological characteristics of populations with chronic, more than adequate or excessive iodine intake[15–17].

In order to understand the effect of excessive iodine intake on thyroid health, a cross-sectional survey was conducted in two regions with different iodine intake levels. Excessive iodine in water was 841 µg/l and 394 µg/l in Haixing County; adequate iodine in water was 13 µg/l in the same county, as control. The effect of persistent local excessive iodine intake on the prevalence of thyroid diseases was evaluated.

Methods

Participants

Haixing County, a county in Cangzhou City, is located in the south-east of Hebei Province. It is a coastal city with 0·22 million permanent residents and a total area of 960 km^2. The study was carried out in April 2010. The criteria for evaluating regions with excessive waterborne iodine, or endemic areas, were according to the national standards (GB/T19380-2003) of China. According to the records of the local Center for Disease Control and Prevention, of the villages in Haixing County, Zhaogao Village and Fuzhuangzi Village were in the excessive iodine area (EIA) and Xiaoshan Village was in the adequate iodine area (AIA).

All inhabitants living in the research areas completed questionnaires concerning the history and medication of thyroid disease. Comparison of demographic characteristics between questioned inhabitants and examined participants did not reveal any significant differences (Table 1). The age of all participants was in the range of 20–50 years and these people had lived in the surveyed areas for over 5 years.

Research protocols were approved by the Medical Ethics Committee of Tianjin Medical University. All participants provided written informed consent after the research protocols were carefully explained to them.

Sample collection

Blood samples were collected from all participants during 08.00–12.00 hours. Serum samples were separated and stored at − 20°C until analysis. Casual morning (between 08.00 and 10.30 hours) urine samples were collected from all participants in clean plastic specimen containers and stored at 4°C. The drinking water of all three villages was extracted underground and supplied by the local government through a pipe network system. Every village owns its particular underground water source. Peripheral drinking water samples were collected in five different positions such as south, north, east, west and middle of every surveyed village. Two drinking water samples were sampled from two different families in each position. The salt was not analysed because the iodized salt was not regulated in these counties.

Concentrations of iodine in drinking water and urine

The concentrations of iodine in drinking water and urine were measured by the national standard method as described previously[10].

Thyroid hormones and autoantibodies

The contents of free thyroxine (FT$_4$), free triiodothyronine (FT$_3$) and thyroid-stimulating hormone (TSH) in serum from all participants were measured by an automated chemiluminescent immunoassay using diagnostic kits from Bayer Health Care, Siemens. The normal ranges were 11·5–23·5 pmol/l for FT$_4$, 3·5–6·5 pmol/l for FT$_3$ and 0·3–5 mIU/l for TSH[10].

The contents of thyroperoxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) in serum were measured by RIA kits from Beijing North Institution. TPOAb and TgAb assays were completed using the standard reference materials that were produced by Tianjin Nine Tripods Medical & Biological Co. Ltd[10].

Diagnostic criteria

The diagnostic criteria for thyroid diseases were as follows: hypothyroidism (TSH > 5·0 mIU/l and FT$_4$ < 11·5 pmol/l); subclinical hypothyroidism (TSH > 5·0 mIU/l, 11·5 pmol/l < FT$_4$ < 23·5 pmol/l and 3·5 pmol/l < FT$_3$ < 6·5 pmol/l); hyperthyroidism (TSH < 0·3 mIU/l, and FT$_4$ > 23·5 pmol/l or FT$_3$ > 6·5 pmol/l); subclinical hyperthyroidism (TSH < 0·3 mIU/l, 11·5 pmol/l < FT$_4$ < 23·5 pmol/l and 3·5 pmol/l < FT$_3$ < 6·5 pmol/l)[10].

Statistical analysis

All tests were two-tailed and a statistically significant difference was considered at $P < 0.05$. Quantitative data were expressed as mean and standard deviation, except the data on urinary iodine and serum TSH that were expressed as median and interquartile range (IQR; 25th–75th percentile). R × C categorical data were analysed by the χ^2 test. The 2 × 2 table was analysed by Fisher's exact test (without Bonferroni correction). Differences between the two areas for age, body weight, height, iodine intake, and serum FT$_3$, FT$_4$ and TSH contents were tested by using independent sample t tests, and UIC was analysed through

the Kruskal–Wallis test. Statistical analyses were conducted using the SPSS statistical software package version 13·0.

Results

Participants
The concentration of iodine in drinking water from Fuzhuangzi Village, Zhaogao Village and Xiaoshan Village was 841, 394 and 13 μg/l, respectively. After being screened by questionnaires, a total of 854 inhabitants, including 348 (112 males and 236 females) in AIA and 506 (185 males and 321 females) in EIA, were investigated. The two populations were similar with respect to age, sex, economic status, accessibility to health care and smoking rate.

Concentration of urinary iodine
Median UIC was 185 (IQR 147–240) μg/l in AIA and 1152 (IQR 753–1539) μg/l in EIA. The distribution of the individual values within categories is reported in Table 1.

Thyroid hormones and autoantibodies
Mean serum FT_3 concentration was significantly lower and mean serum TSH concentration was significantly higher in EIA than in AIA. Mean serum FT_4 was similar in both areas (Table 2).

The total positive rates of TgAb and TPOAb were not statistically different between EIA and AIA (16·1 % *v.* 11·9 % for TgAb and 20·7 % *v.* 16·4 % for TPOAb). However, there was a significant difference in autoantibodies between genders, with the positive rates of autoantibodies in females being significantly higher than in males. Specifically, in AIA, the positive rate of TgAb in females was 6·1-fold higher than in males (22·0 % *v.* 3·6 %; $\chi^2 = 19\cdot174$, $P = 0\cdot000$) and

the positive rate of TPOAb was 2·4-fold higher (25·4 % *v.* 10·7 %; $\chi^2 = 10\cdot015$, $P = 0\cdot002$). In EIA, the positive rate of TgAb in females was 2·9-fold higher than that in males (15·6 % *v.* 5·4 %; $\chi^2 = 11\cdot616$, $P = 0\cdot001$) and the positive rate of TPOAb was 1·8-fold higher (19·6 % *v.* 10·8 %; $\chi^2 = 6\cdot651$, $P = 0\cdot010$). However, the positive rates of autoantibodies were not significantly different between AIA and EIA when comparing by gender (Table 3).

The percentage of positive thyroid antibodies (TgAb and TPOAb) was similar in both areas (with adequate iodine and with excessive iodine). This percentage was at least twice greater in women than in men (Table 3).

Prevalence of thyroid dysfunction
Thyroid dysfunction was two times more frequent in EIA than in AIA (20·6 % *v.* 10·3 %). Frequency of subclinical hypothyroidism (elevated TSH and normal FT_4; 13·6 % *v.* 9·0 %) and subclinical hyperthyroidism (decreased TSH and normal FT_4; 2·2 % *v.* 0 %) differed significantly between both areas. Hypothyroidism (decreased TSH and elevated FT_4; 3·6 % *v.* 1·3 %), but not hyperthyroidism (decreased TSH and elevated FT_4), was more frequent (not statistically significant) in EIA than in AIA. In men, the proportion of thyroid dysfunction was similar in AIA and EIA. By contrast, it was more than two times greater in females from EIA than in females from AIA (Table 4). As a result, there was no significant difference in thyroid dysfunction frequency by gender in AIA, but a highly significant difference in EIA (Fisher's exact test, $P = 2\cdot3 \times 10^{-4}$).

More than 10 % of euthyroid participants showed at least one positive thyroid antibody test and 8·1 % were positive for both thyroid antibodies. In the hypothyroid participants, this percentage of positive anti-thyroid test was more or less double (Table 5). Due to the small number of

Table 1 Urinary iodine concentration and distribution in men and women aged 20–50 years who had adequate or excessive drinking water iodine, Hebei Province, People's Republic of China, 2010

	UIC (μg/l)		UIC < 100 μg/l		UIC ≥ 300 μg/l	
	Median	IQR	n	%	n	%
AIA (*n* 348)	185	147–240	45	12·9	87	25·0
EIA (*n* 506)	1152	753–1539	0	0·0	471	93·1
Comparison: AIA *v.* EIA	Wilcoxon: $P < 0\cdot001$		χ^2: $P < 0\cdot001$		χ^2: $P < 0\cdot001$	

UIC, urinary iodine concentration; IQR, interquartile range; AIA, adequate iodine area; EIA, excessive iodine area; Wilcoxon, Wilcoxon rank sum test; χ^2, χ^2 test.

Table 2 Levels of thyroid hormones in men and women aged 20–50 years who had adequate or excessive drinking water iodine, Hebei Province, People's Republic of China, 2010

	Serum FT_4 (pmol/l)		Serum FT_3 (pmol/l)		Serum TSH (mIU/l)	
	Mean	SD	Mean	SD	Median	IQR
AIA (*n* 348)	14·75	2·71	4·93	0·60	2·40	1·58–3·56
EIA (*n* 506)	14·68	3·35	4·77	0·94	2·71	1·73–4·56
Comparison: AIA *v.* EIA	*t* test: $P = 0\cdot729$		*t* test: $P = 0\cdot003$		Wilcoxon: $P = 0\cdot002$	

FT_4, free thyroxine; FT_3, free triiodothyronine; TSH, thyroid-stimulating hormone; IQR, interquartile range; AIA, adequate iodine area; EIA, excessive iodine area; *t* test, Student's *t* test; Wilcoxon, Wilcoxon rank sum test.

Table 3 Gender ratio (number of males/number of females) and prevalence of thyroid autoantibodies in men and women aged 20–50 years stratified by adequate/excessive iodine area and gender, Hebei Province, People's Republic of China, 2010

	Gender ratio (male/female)	TgAb				TPOAb			
		Males		Females		Males		Females	
		%	n	%	n	%	n	%	n
AIA	112/236	3·6	4	22·0	52	10·7	12	25·4	60
EIA	185/321	5·4	10	15·6	50	10·8	20	19·6	63
Comparison: AIA v. EIA		Fisher: $P=0.084$				Fisher: $P=0.124$			
Comparison: males v. females		Fisher: $P=4.3 \times 10^{-9}$				Fisher: $P=3.6 \times 10^{-5}$			

TgAb, thyroglobulin antibody; TPOAb, thyroperoxidase antibody; AIA, adequate iodine area; EIA, excessive iodine area; Fisher, Fisher's exact test.

Table 4 Prevalence of thyroid dysfunction in men and women aged 20–50 years who had adequate or excessive drinking water iodine, Hebei Province, People's Republic of China, 2010

	AIA		EIA		Comparison: AIA v. EIA (Fisher's exact test, two-tailed probability)
	%	No. of cases/no. of participants	%	No. of cases/no. of participants	
Thyroid dysfunction	10·3	36/312	20·6	104/506	$P=8.0 \times 10^{-4}$
Hypothyroid biology	1·3	4/312	3·6	18/506	$P=0.073$
Subclinical hypothyroid biology	9·0	28/312	13·6	69/506	$P=0.046$
Hyperthyroid biology	1·3	4/312	1·2	6/506	$P=1.00$
Subclinical hyperthyroid biology	0	no case	2·2	11/506	$P=8.7 \times 10^{-3}$
Thyroid dysfunction in males	10·7	12/112	11·9	22/185	$P=0.852$
Thyroid dysfunction in females	10·2	24/236	25·5	82/321	$P=3.6 \times 10^{-6}$

AIA, adequate iodine area; EIA, excessive iodine area.

Table 5 Prevalence of thyroid autoantibodies in clinical categories of thyroid function among men and women aged 20–50 years who had adequate or excessive drinking water iodine, Hebei Province, People's Republic of China, 2010

Thyroid biology	No. of participants	TgAb-positive		TPOAb-positive		Double-positive	
		%	No. of cases	%	No. of cases	%	No. of cases
Euthyroid (EU)	714	12·2	87	15·6	111	8·1	58
Hypothyroid & subclinical hypothyroid (HypoT)	119	21·0	25	29·4	35	17·6	21
Hyperthyroid & subclinical hyperthyroid (HyperT)	21	19·0	4	42·9	9	14·3	3
χ^2 test (df = 2)		$P=0.026$		$P=1.6 \times 10^{-5}$		$P=0.004$	
Two-tailed Fisher's exact test							
HypoT v. EU		$P=0.013$		$P=6.0 \times 10^{-4}$		$P=0.002$	
HyperT v. EU		$P=0.316$		$P=0.003$		$P=0.407$	
HypoT v. HyperT		$P=1.000$		$P=0.307$		$P=1.000$	

TgAb, thyroglobulin antibody; TPOAb, thyroperoxidase antibody.

cases, there was no statistical difference in the percentage of participants with subclinical hypothyroidism and those with isolated elevated TSH (data not shown). Only twenty-one participants were diagnosed as biological hyperthyroid or subclinical hyperthyroid among the population. In the hyperthyroid participants, the percentage of positive thyroid antibodies was similar to the hypothyroid; however, the TgAb-positive rate was obviously high but without significance because of the limited number of cases.

Relationship between autoantibodies and hypothyroidism and subclinical hypothyroidism

As hypothyroidism and subclinical hypothyroidism accounted for a large amount of the overall prevalence of thyroid dysfunction, the relationships between hypothyroidism and subclinical hypothyroidism and positive rates of single and double autoantibodies were analysed. The positive rates of TgAb ($\chi^2=11.099$, $P=0.001$) and TPOAb ($\chi^2=10.061$, $P=0.002$), as well as the double-positive rate ($\chi^2=14.882$, $P=0.000$), were higher in hypothyroidism than those in euthyroidism. The positive rate ($\chi^2=7.709$, $P=0.005$) and double-positive rate ($\chi^2=4.203$, $P=0.040$) of TPOAb in subclinical hypothyroidism was significantly higher than that in euthyroidism. The positive rates were not significantly different between hypothyroidism and subclinical hypothyroidism (Table 5).

Discussion

To understand the influence of excessive iodine intake on thyroid function and the prevalence rate of thyroid

dysfunction in China, a cross-sectional investigation in three areas with adequate or excessive iodine intake was carried out. Hebei Province is located downstream of the Yellow River. The EIA in Hebei mainly were scattered around the estuary of the Yellow River. The high iodine concentration in drinking water is an important source of iodine intake by the inhabitants. The water of the surveyed villages is extracted independently underground and supplied to the inhabitants through the pipe network system. The depth of the underground water source is different, from less than 100 m to more than 400 m. So the iodine concentration is different according to the depth of source water.

The results showed that the serum levels of both FT$_3$ and TSH were affected by the excessive iodine intake. The average level of FT$_3$ in EIA revealed a slight decrease when compared with that in AIA, while the level of TSH exhibited a slight increase in EIA. The results suggest a link between increased iodine intake and hypothyroidism. Similar results have been reported in a randomized controlled trial in older people[9]. With a supplementation of 80 µg or >50 mg iodate daily for 8 weeks, ten of forty-three participants exposed to excessive iodate showed hypothyroidism at the end of the trial. A 5-year cohort study on the prevalence of thyroid dysfunction in populations with different iodine intakes such as mildly deficient (median UIC: 84 µg/l), more than adequate (median UIC: 243 µg/l) and excessive (median UIC: 651 µg/l) in China has been completed[15]. An increase in the prevalence of overt hypothyroidism, subclinical hypothyroidism and autoimmune thyroiditis with increasing iodine intake was observed. Another follow-up study in three rural Chinese communities with mild to borderline deficiency, more than adequate and excessive iodine intake, respectively, has been carried out[18]. On the contrary, a follow-up examination has been provided to these inhabitants for 13 years and the results demonstrated that chronic excessive iodine intake does not apparently increase the risk of autoimmune hyperthyroidism. In the present study, although we did not detect a significant difference in the prevalence of hyperthyroidism between AIA and EIA, we found that the prevalence of subclinical hyperthyroidism in EIA was significantly higher than that in AIA. No subclinical hyperthyroidism case was observed in AIA, and eleven inhabitants living in EIA were diagnosed as subclinical hyperthyroidism in our research.

The thyroid dysfunction spectrum of AIA and EIA was also similar. It has been reported that the prevalence of subclinical hyperthyroidism and hyperthyroidism may be increased among people with more than adequate and excessive iodine intake[15]. Similarly, high iodine intake may trigger and aggravate autoimmune thyroiditis, thus increasing the risk of clinical hypothyroidism. Moreover, the titres of autoantibodies, TgAb and TPOAb, in females are sensitive to iodine exposure. Higher levels of autoantibodies in females from AIA and EIA were observed when compared with those in males. In addition, a case–control study has reported that excessive iodine intake may trigger thyroid autoimmunity and hypothyroidism among women[19]. These results indicate that women may be a susceptible population and even a high-risk population to iodine exposure.

Our data did not provide direct evidence that excessive iodine exposure could increase the risk of thyroid auto-immunity. However, the results showed a relationship between the positive rate of autoantibodies and the severity of hypothyroidism. A higher positive rate of autoantibodies was observed in hypothyroidism compared with that in subclinical hypothyroidism and euthyroidism. In Li *et al.*'s study, only an increased positive rate of TgAb with increased iodine intake was reported and individuals with a positive rate of TPOAb and/or TgAb had more frequent development of thyroid dysfunction[20]. These results suggest that autoantibodies such as TgAb and TPOAb are effective parameters associated with the development of thyroid dysfunction, especially hypothyroidism.

Conclusion

In conclusion, excessive iodine intake (iodine concentrations in water were 394 µg/l and 841 µg/l, and median UIC was 1152 µg/l, which is larger than 300 µg/l) is not safe. Excessive iodine exposure may be a risk factor for an increased prevalence of biochemical thyroid dysfunction, especially biochemical hypothyroidism. The iodine supplementation should be tailored according to the level of iodine intake. Women may be a susceptible population to excessive iodine exposure.

Acknowledgements

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