

CLINICAL STUDY

Chronic iodine excess does not increase the incidence of hyperthyroidism: a prospective community-based epidemiological survey in China

Fan Yang¹, Zhongyan Shan, Xiaochun Teng, Yushu Li, Haixia Guan, Wei Chong¹, Di Teng¹, Xiaohui Yu¹, Chenling Fan¹, Hong Dai¹, Yang Yu¹, Rong Yang¹, Jia Li¹, Yanyan Chen¹, Dong Zhao¹, Jinyuan Mao¹ and Weiping Teng

Department of Endocrinology and Metabolism, First Affiliated Hospital, China Medical University, No.155 Nanjing Bei St., Heping District, Shenyang, China and ¹Institute of Endocrinology, First Affiliated Hospital, China Medical University, Shenyang, China

(Correspondence should be addressed to W Teng; Email: twpendocrine@yahoo.com.cn)

Abstract

Objective: An increasing incidence of hyperthyroidism has been observed when iodine supplementation has been introduced to an iodine-deficient population. Moreover, the influence of chronic more than adequate or excessive iodine intake on the epidemiological features of hyperthyroidism has not been widely and thoroughly described. To investigate the influences of different iodine intake levels on the incidence of hyperthyroidism, we conducted a prospective community-based survey in three communities with mild-deficient, more than adequate (previously mild deficient iodine intake), and excessive iodine intake.

Subjects and methods: In three rural Chinese communities, a total of 3761 unselected inhabitants aged above 13 years participated in the original investigation and 3018 of them received identical examinations after 5 years. Thyroid function, levels of thyroid peroxidase antibody (TPOAb), thyroglobulin antibody and urinary iodine excretion were measured and thyroid ultrasound examination was also performed.

Results: In three communities, median urinary iodine excretion was 88, 214, and 634 $\mu\text{g/l}$ ($P < 0.05$) respectively. The cumulative incidence of hyperthyroidism was 1.4, 0.9, and 0.8% ($P > 0.05$) respectively. Autoimmune hyperthyroidism was predominant in thyroid hyperfunction in all the three cohorts. Either positive TPOAb (> 50 U/ml) or goiter in original healthy participants was associated with the occurrence of unsuspected hyperthyroidism in 5 years (logistic regression, OR = 4.2 (95% CI 1.7–8.8) for positive TPOAb, OR = 3.1 (95% CI 1.4–6.8) for goiter).

Conclusion: Iodine supplementation may not induce an increase in hyperthyroidism in a previously mildly iodine-deficient population. Chronic iodine excess does not apparently increase the risk of autoimmune hyperthyroidism, suggesting that excessive iodine intake may not be an environmental factor involved in the occurrence of autoimmune hyperthyroidism.

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Introduction

As one of the most important trace elements in the human body, iodine is required for the synthesis of thyroid hormones which regulate metabolic activities and growth of the brain during fetal as well as early postnatal life. Severe iodine deficiency results in iodine deficiency disorders (IDDs), including endemic goiter, hypothyroidism, cretinism, decreased fertility rate, increased infant mortality and mental retardation (1). Thus the level of iodine intake may play a critical role in influencing public health. Recommended by World Health Organization (WHO), International Council for Control of Iodine Deficiency Disorders (ICCIDD) and United Nations Children's Fund (UNICEF), the interval of optimal iodine intake is 150–300 $\mu\text{g/day}$ (median

urinary iodine concentration 100–199 $\mu\text{g/l}$) (2). IDD was once a global health problem and has now been largely corrected by iodine supplementation programs advocated by WHO, ICCIDD and UNICEF (3).

However, it has been demonstrated in quite a number of studies that iodine-induced hyperthyroidism (IIH) may occur after the introduction of iodine supplementation to iodine-deficient populations (4, 5). The occurrence of IIH, which related to the thyroid autonomy due to the long-term iodine deficiency, was transient and its peak appeared in the third to the fifth year after iodine introduction (6, 7). In addition, after iodine supplementation programs, the iodine intake levels of some countries (such as China) have been more than adequate or excessive (8). However, only a few studies have investigated the epidemiological features of

hyperthyroidism in populations with chronic, more than adequate or excessive iodine intake by a prospective method (9). Thus, the influence of long-term iodine enrichment on the epidemiology of hyperthyroidism should be further investigated.

We have previously reported in a cross-sectional survey that the prevalence of overt hyperthyroidism was not remarkably different among three communities with different iodine nutritional status: borderline iodine deficiency, more than adequate iodine intake and iodine excess (10). The study was also designed prospectively to acquire the incidence of overt as well as subclinical hyperthyroidism of the three populations, and the final results offered by the present paper may provide information about the relationship between different levels of iodine intake and epidemiological pattern of hyperthyroidism.

Subjects and methods

Communities and cohort populations

Panshan, Zhangwu, and Huanghua are three Chinese rural communities whose iodine nutritional status was mild to borderline deficient (median urinary iodine excretion 88 µg/l), more than adequate (median urinary iodine excretion 214 µg/l) and excessive (median urinary iodine excretion 634 µg/l) respectively (11). The Panshan community had a longstanding iodine deficiency because most of the inhabitants have taken self-made salt with a low content of iodine for many years. The Zhangwu community was previously mildly iodine deficient and had been covered by iodine supplementation programs for at least 8 years at the follow-up time point of the survey. Data from the Endemic Department of Liaoning Province show that the mean urinary iodine excretion in the 1980s and 1990s was between 70 and 90 µg/g creatinine among residents in both Panshan and Zhangwu until 1996, but that it had increased in Zhangwu after 1996 (12). Huanghua has been discovered as a community with severely excessive iodine intake since the 1970s until the 1980s due to iodine-rich drinking water (96–228 µg/l; mean urinary iodine excretion from the 1970s to 1980s, 509–757 µg/g creatinine).

In the original study, a total of 3761 unselected residents received questionnaire investigation and biochemical as well as ultrasonic examinations, covering history of thyroid disease, thyroid function, thyroid autoantibodies and thyroid volume. We examined these subjects by identical means in the follow-up investigation 5 years later. In the meantime, iodine intake levels of the three populations were assessed by measuring the median urinary iodine excretion in all participants as well as an extra number of school-aged children.

Research protocols were approved by the Medical Ethics Committee of the China Medical University. All

subjects provided written informed consent after the research protocols were carefully explained to them.

Laboratory and ultrasonic examinations

The methods and reagents of laboratory examination were identical to those employed in the original survey. Blood samples were obtained and sera were separated and stored at -20°C until further analysis. Serum thyrotropin (TSH), thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) were measured by immunochemiluminescent assay (IMMULIT, DPC, Los Angeles, CA, USA) in all subjects. The reference range of serum TSH was 0.3–4.8 mIU/l and the detection limit was 0.002 mIU/l. If serum TSH was below 0.3 mIU/l, serum-free thyroxine (FT₄) and free tri-iodothyronine (FT₃) concentrations were also tested with an immunochemiluminescent assay (IMMULIT) and serum thyrotropin receptor autoantibody (TRAb) concentration was measured as well (¹²⁵I, RRA Kit, Diasorin, Stillwater, MN, USA). The reference range of FT₄ and FT₃ was 10.3–24.5 and 2.3–6.3 pmol/l respectively, according to the standards provided by the manufacturer. Serum TRAb > 2 U/l was scored as positive. The intra- and inter-assay coefficient of variation (CV) for serum TSH was 1.23–1.38% and 1.57–4.93%, for serum FT₄ was 3.44–5.82% and 6.55–9.38%, and for serum TPOAb was 3.51–4.65% and 6.22–8.29% respectively.

Fasting urine samples were collected from all subjects and measured for iodine excretion by the method based on Sandell–Kolthoff reaction. The intra- and inter-assay CV values were 2.14–6.68 and 2.01–2.52% respectively. Thyroid ultrasonic examinations were performed in all subjects (SA600, Medison, Seoul, Korea). The volume of each lobe was assessed by the formula: width × length × thickness × 0.479. Goiter was diagnosed in adults if the thyroid volume was above 25.6 ml (mean + 2s.d.) for male and 19.4 for female (mean + 2s.d.).

Diagnostic criteria

The diagnosis of overt hyperthyroidism was based on the following: (i) serum TSH < 0.3 mIU/l and (ii) serum FT₄ > 24.5 pmol/l or FT₃ > 6.3 pmol/l. In subjects with overt hyperthyroidism, Graves' disease (GD) was diagnosed accompanied by one of the following: (i) serum TPOAb > 100 IU/ml, (ii) a diffuse enlarged thyroid under ultrasonic examination and (iii) serum TRAb > 2 IU/l. Positive TPOAb and positive TgAb were diagnosed by serum TPOAb > 50 IU/ml and TgAb > 40 IU/ml respectively.

Statistical analysis

Data processing was performed with SPSS software version 11.5 (SPSS Inc., Chicago, IL, USA). A comparison

of proportions for the three cohorts was performed by χ^2 -test and Fisher's exact test in the case of small numbers ($\alpha=0.05$). When comparing the total incidence rate, the analyses were performed after standardizing the age of the population cohorts. Risk factors analysis was performed with the use of logistic regression. The level of significance was set to 5%.

Results

Follow-up information

All subjects from the original study had been invited for the examinations without any special selection. Characteristics of subjects in original and follow-up surveys are shown in Table 1. The follow-up rate is 80.2% and there are no remarkable differences in age and gender profile among the three communities.

Iodine nutritional status

Table 2 demonstrates the iodine nutritional status of Panshan, Zhangwu and Huanghua communities in the original and follow-up surveys. No significant difference is found in median urinary iodine concentrations of school children or examined adult subjects among communities. It shows that the iodine intake levels had been relatively stable and the iodine nutritional status, which was a mild deficiency in Panshan, more than adequate in Zhangwu and excess in Huanghua, had not remarkably altered during the study interval in all communities.

Incidence of overt hyperthyroidism

Figure 1 shows the cumulative incidence of hyperthyroidism, GD and subclinical hyperthyroidism in the three cohorts. The number of subjects who developed overt hyperthyroidism is 12, 12 and 7 in Panshan, Zhangwu and Huanghua respectively. The cumulative incidence of hyperthyroidism is 1.4, 0.9 and 0.8% correspondingly. At follow-up, seven female subjects in Panshan, seven female subjects in Zhangwu and five subjects (four females, one male) in Huanghua were diagnosed with GD; therefore, the cumulative incidence of GD is 0.8, 0.6 and 0.6% respectively. The cumulative

Table 1 Demographic characteristics of cohorts in original and follow-up surveys.

Cohorts	Numbers original/follow-up	Mean age original/follow-up	Male:female original/follow-up	Follow-up rate (%)
Panshan	1103/884	36.2/41.8	1:2.9/1:3.2	80.1
Zhangwu	1584/1270	39.8/45.4	1:3.2/1:3.4	80.2
Huanghua	1074/864	36.9/43.2	1:2.9/1:3.2	80.4
Total	3761/3018	38.4/43.4	1:3.0/1:3.3	80.2

incidence of subclinical hyperthyroidism is 1.4% (12/884) in Panshan, 2.0% (25/1270) in Zhangwu and 1.0% (9/864) in Huanghua. No significant difference was found in the incidence of overt hyperthyroidism, GD or subclinical hyperthyroidism among the three communities after standardizing the age distributions.

In subjects diagnosed with incident overt hyperthyroidism, 10, 11 and 6 subjects were identified as overtly hyperthyroid at the time point of follow-up in Panshan, Zhangwu and Huanghua communities respectively. During the 5-year interval, the number of unsuspected hyperthyroidism cases diagnosed by the other hospital was two in Panshan, one in Zhangwu and one in Huanghua.

In subjects from the original survey who were TPOAb-positive but without any history of thyroid disease, the incidence rate of hyperthyroidism was 3.5% (3/85) in Panshan, 2% in Zhangwu (3/148) and 3.1% (3/97) in Huanghua respectively ($P>0.05$). However, no suspected hyperthyroidism occurred in subjects with merely positive TgAb.

Outcome of subclinical hyperthyroidism

Out of 115 subjects with subclinical hyperthyroidism detected in the original survey, 92 participated in the follow-up examination and none had received medical treatment during the 5 years. At follow-up, there was no significant difference in the proportion of turning overtly hyperthyroid, remaining subclinically hyperthyroid and recovering euthyroid subjects among the three cohorts (Table 3). Five out of the ninety-two subjects were found with overt thyroid hyperfunction, and therefore the accumulative incidence of overt hyperthyroidism was 5.4%.

Risk factors for development of hyperthyroidism

In subjects without history of thyroid disease or overt thyroid dysfunction, the risk factors for developing overt hyperthyroidism by the time of follow-up were assessed using logistic regression analysis after correction for the influence of age and gender (Table 4). The results show that positive TPOAb and diffuse goiter, which were found in the original survey, were the risk factors of hyperthyroidism within 5 years.

Discussion

We present data on the incidence of hyperthyroidism obtained from a prospective and comparative community-based survey in the present paper. No significant difference in the incidence of overt hyperthyroidism was found among the three investigated communities with iodine nutritional status of mild deficiency, more than adequate and excess, whereas the demographic

Table 2 Iodine nutritional status of Panshan, Zhangwu and Huanghua in original and follow-up surveys.

Group	Median urinary iodine excretion of school children ^a		Median urinary iodine excretion of study cohorts ^a		Iodine content of drinking water ^a		Iodine content of salt ^b		Iodine nutritional status	
	Original	Follow-up	Original	Follow-up	Original	Follow-up	Original	Follow-up	Original	Follow-up
Panshan	83.5	87.6	103.1	96.7	8.2	10.0	<3.4	<3.4	Mildly deficient	Mildly deficient
Zhangwu	242.9	213.9	374	362.5	7.2	7.8	54.5	45.6	More than adequate	More than adequate
Huanghua	650.9	633.5	614.6	596.9	180.1	201.8	23.3	25.0	Excessive	Excessive

^aUnit = µg/l.^bUnit = mg/kg.

characteristics, genetic background and medical service as well as social condition are similar amongst them. The iodine intake levels of the populations explored remain stable during the interval of the survey. Although the number of female subjects is about three times higher than males in each community, the imbalance does not seem to affect the reliability of the results as we employ a method of comparison.

It has been well documented that there may be a transient increase in the incidence of hyperthyroidism due to IIH after iodine supplementation to iodine-deficient populations, but eventually the incidence of hyperthyroidism would fall to a lower level with long-term stable iodine intake (6, 7). In our original survey, the prevalence of hyperthyroidism was not remarkably different among the three communities and the data acquired from a retrospective investigation also showed no significant increase after iodine supplementation (10). In the present paper, there was no statistical difference in the incidence of hyperthyroidism between Panshan and Zhangwu communities. It was reported that IIH was commonly observed in populations with severe iodine deficiency (6), but Zhangwu was mildly iodine deficient before the introduction of iodine supplementation. Hence, we can conclude that the occurrence of IIH was influenced by the previous iodine-deficient status. The absence of increasing incidence of hyperthyroidism in Zhangwu after iodine supplementation was due to its mildly iodine-deficient background.

Comparing to the optimal iodine intake level suggested by WHO and ICCIDD, some populations are still exposed to an excessive iodine intake background (13, 14). There is a question to be discussed about how chronic excessive iodine intake would influence the incidence of hyperthyroidism. Several community-based surveys have given data on the incidence of hyperthyroidism at different levels of iodine intake, including mild to moderate iodine deficiency and iodine sufficiency (9, 15, 16). It is hard to compare the results directly because age composition, ethnicity, methodology and diagnostic standards differed in these studies. A Danish comparative survey provided data on the incidence of hyperthyroidism and found a significantly higher incidence of hyperthyroidism due to a high proportion of toxic multiple nodular goiter in a mild to moderate iodine deficiency area (Jutland, urinary iodine

excretion 40–80 µg/24 h) in contrast to that in a mild iodine excess area (Iceland, ~300 µg/24 h) in which GD was dominant (11). In our study, the incidence of hyperthyroidism in Panshan (mild to borderline iodine deficiency) was not significantly higher than that in Huanghua. Moreover, GD was predominant in the cause of hyperthyroidism in both the communities in accordance with the pattern of the disease found in Iceland (9). The results of our survey suggest that long-term excessive iodine intake may not have an obvious influence on the incidence and pattern of overt hyperthyroidism when compared with that of mild to borderline deficient iodine intake but approaches optimal level. Thus, we may speculate that the risk of hyperthyroidism would not elevate with the increase in iodine intake at a starting point approaching the optimal iodine intake level.

The outcome of subclinical hyperthyroidism was not significantly different among the three cohorts, which suggests that iodine intake may not powerfully influence the incidence of subclinical hyperthyroidism. A study from the United Kingdom showed that 61% of subclinical hyperthyroidism subjects turned euthyroid after 1 year and only 2% of them progressed to overt hyperthyroidism (17). These findings are compatible with the results of our survey. On the basis of the present survey, we can also conclude that

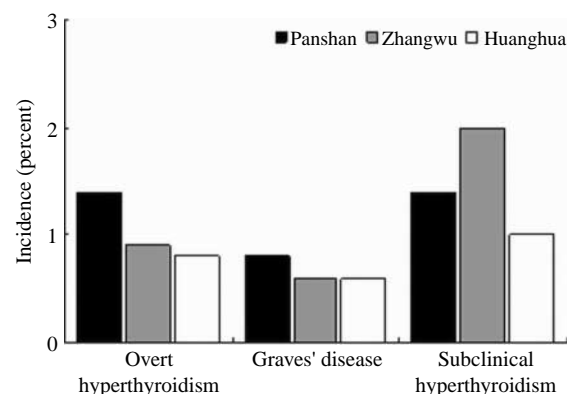


Figure 1 Five-year cumulative incidence of overt hyperthyroidism, Graves' disease and subclinical hyperthyroidism in Panshan (mild iodine deficiency), Zhangwu (more than adequate iodine intake) and Huanghua (excessive iodine intake).

Table 3 The outcome of thyroid function in subjects with subclinical hyperthyroidism in the three cohorts.

Outcome	Panshan ^a		Zhangwu ^b		Huanghua ^c	
	n	%	n	%	n	%
Euthyroid	26	76.5	33	68.8	7	70
Subclinical hyperthyroidism	5	14.7	12	25	1	10
Overt hyperthyroidism	2	5.9	1	2.1	2	20
Subclinical hypothyroidism	1	2.9	2	4.1	–	–
Total	34	100	48	100	10	100

^aMildly deficient iodine intake.^bMore than adequate iodine intake.^cExcessive iodine intake.

only a few of the subjects diagnosed as overtly hyperthyroid had developed from subclinical hyperthyroidism. The majority of those with subclinical hyperthyroidism were transient and would not progress to overt thyroid hyperfunction.

Quite a number of studies demonstrated that chronic excess iodine ingestion would induce thyroid hypofunction and autoimmunity both in humans and in animals (18–20). In an autoimmune-prone animal model of NOD-H2^{h4} mouse, excess iodine intake induces spontaneous autoimmune thyroiditis which exhibits lymphocytic infiltration and a high level of TgAb (21). It was also reported that in areas of Japan where dietary iodine intake is high, the incidence of Hashimoto's thyroiditis is higher than that in areas of low to normal dietary iodine intake (14). The mechanism has not been clarified and may partly attribute to the augmented antigenicity of thyroglobulin by iodine (19). In addition, several epidemiological surveys showed that incidence of GD was higher in regions with long-term iodine sufficiency or iodine repletion in previous iodine deficiency (9, 22). However, the present study has not obtained a significant difference in the incidence of autoimmune hyperthyroidism, in spite of obviously different levels of iodine intake. It has been known in the Whickham study that positive thyroid autoantibody is the risk factor for developing hypothyroidism (23). Similarly, TPOAb (but not positive TgAb) was found as the risk factor for developing hyperthyroidism in the present survey, and iodine excess

Table 4 Risk factors for development of overt hyperthyroidism in the follow-up survey in subjects without history of thyroid disease from the original survey.

Items from original survey	β Value	S _x	Wald χ^2 value	P value	OR value (95% CI)
TPOAb-positive	1.339	0.423	10.009	0.002	3.816 (1.665–8.749)
Goiter	1.116	0.416	7.377	0.007	3.053 (1.364–6.831)
Constant	–4.421	1.126	15.418	0.000	0.012

did not increase the incidence of overt hyperthyroidism in subjects with positive TPOAb. This may suggest that in the comparison of the tendency of hypothyroidism, partly induced by thyroid autoimmunity due to the elevated iodine intake, long-term excessive iodine intake as an environmental factor does not seem to be involved in the occurrence of autoimmune hyperthyroidism.

In conclusion, iodine supplementation may not lead to an increase in hyperthyroidism in previously mildly iodine-deficient populations. Chronic iodine excess does not apparently increase the risk of autoimmune hyperthyroidism or influence the incidence and outcome of subclinical hyperthyroidism, which suggests that chronic excessive iodine intake may not be involved in the occurrence of autoimmune hyperthyroidism as an environmental factor.

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