Iodine repletion, thyrotoxicosis and atrial fibrillation in Isfahan, Iran

Ashraf Aminorroaya, MD; Sina Rohani, MD; Goshtasb Sattari, MS; Sasan Haghighi, MD; Masoud Amini, MD

Background: Iodized salt was reintroduced in Iran in 1989. Just before distribution of iodized salt, thyrotoxicosis was observed in 3.7% of the patients with atrial fibrillation (AF) in university teaching hospitals in Isfahan, a centrally located city in Iran. As repletion of iodine may increase the rate of autoimmune thyroid diseases and toxic multinodular goiter, this study was designed to evaluate the rate of thyrotoxicosis in patients with AF in the same hospitals after about a decade of iodized salt consumption.

Methods: In a case-control study with convenience sampling, 100 patients with AF and an equal number of age- and sex-matched subjects taking the same medications were selected as case and control groups, respectively, in university hospitals in 1997.

Results: Eight percent of patients with atrial fibrillation had overt thyrotoxicosis versus one percent in the control group (odds ratio=8.6, 95% CI= 6.5 to 10.7, $P<0.02$). Thyrotoxicosis in patients with AF was 8 times higher than in the control group without AF. In comparison with the period before use of iodized salt, AF more than doubled (8% vs. 3.7%).

Conclusion: Thyroid function should be evaluated in all patients older than 40 years of age with AF. The benefits of iodine supplementation are great, but more attention should be paid to the complications of iodine repletion, including thyrotoxicosis and its frequent accompaniment, AF.

Key words: Thyrotoxicosis, hyperthyroidism, atrial fibrillation, iodine repletion, Iran

From Isfahan Endocrine and Metabolism Research Center, Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Correspondence to:
Ashraf Aminorroaya, MD
Isfahan Endocrine Research Center
Sedgheh Tahereh Hospital
Khoram St., Isfahan
Iran
E-mail: aminorroaya@med.mui.ac.ir

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Atrial fibrillation (AF) is the most common of cardiac arrhythmias in thyrotoxicosis.[1] In some studies, 10% to 22% of thyrotoxic patients had AF and 15% of new cases with AF were hyperthyroid.[2,3] The prevalence of hyperthyroidism in patients with atrial fibrillation is different in various countries—1% in Japan, 2.7% in the USA, 4.5% in Israel, 17% in Denmark and 24% in France.[4-8] In areas with low prevalence, screening for hyperthyroidism is not recommended, but in countries with high prevalence, such as France, screening has been suggested, particularly because half of patients do not have clinical manifestations of thyrotoxicosis. Even when the cause of AF is known, hyperthyroidism may complicate the problem.[9] In some studies, hypothyroidism was more common in patients with atrial fibrillation than controls.[1, 10, 11] The most important complications of AF accompanying hyperthyroidism are arterial embolism, exacerbation of heart failure and resistance to cardiac management.[1-3] Therefore, early diagnosis and treatment of thyrotoxicosis in AF is crucial. The management of AF, whether caused by or exacerbated by hyperthyroidism, is difficult.

In the 1980s, a few studies showed the existence of various forms of iodine deficiency disorders in Iran.[12-14] A nationwide survey performed in Iran under the supervision of the Iranian National Committee for Control of Iodine Deficiency Disorders (INCCI) in 1989 showed that urinary iodine excretion was below 100 µg/L in all five provinces and <20 µg/L in many localities.[15] In the same year (1989), iodized salt was introduced throughout the country and in 1992, INCCI announced universal salt iodization. All salt factories were obliged by the law to produce only iodized salt for household use in 700- to 1000-gram packages.[15] In 1996, a second national survey was conducted in 2917 schoolchildren. The median urinary iodine excretion was 20.5 µg/dL.[16] In 1997, a study in Isfahan, a centrally located city in Iran, conducted eight years after iodized salt distribution throughout the country, found that iodine intake was sufficient in 94% of 3000 randomly selected students 6 to 18 years of age.[17] An uncontrolled study done before extensive use of iodized salt in Isfahan showed that 3.7% of patients with atrial fibrillation in university hospitals had hyperthyroidism.[18] Our study was conducted about one decade later in the same location to determine if iodine sufficiency had increased the rate of thyroid dysfunction in patients with atrial fibrillation. In iodine-repleted areas, the chance of autoimmune thyroid diseases such as Grave's disease may increase and multinodular goiters might change to a toxic form.[9] We expected that the incidence of AF due to or exaggerated by thyroid dysfunction might be increased.

Methods

In a case–control study with convenience sampling, 100 patients with atrial fibrillation according to EKG changes

with or without pre-existing cardiac diseases were selected in teaching hospitals of Isfahan University of Medical Sciences during one year from 1 January through 31 December 1998. The control group consisted of 100 age- and sex-matched patients taking the same medications (for any reason) as the case group. Those who were taking medications with known effects on thyroid function tests, such as amiodarone, estrogens, clofibrate, androgens, glucocorticoids, niacin, salicylate (>100mg/d), phenytoin, phenylbutazone or dopamine, and those with diseases such as hepatitis, primary biliary cirrhosis, nephrotic syndrome, renal failure and acute psychosis were excluded in both groups.[20-24] Other cardiac disease was not an exclusion criteria, since thyrotoxicosis can precipitate or exaggerate AF.[5]

Symptoms and signs of thyroid dysfunction were sought and a thyroid examination was done by one of us (S. R.). A 10-mL blood sample was obtained from each patient. The serum concentration of TSH was measured by the immunoradiometric assay (IRMA) method using a commercial kit from Orion Diagnostica, Finland. Commercial kits were used for measuring serum T4 and T3 levels by radioimmunoassay (RIA) (Beckman Coulter, Czech Republic) and T3 resin uptake (Kavoshyar, Iran). Reference ranges for serum parameters for euthyroid adult subjects were as follows: for T4, 54.1-154.4 nmol/L (4.2-12 µg/dL); for T3, 1.3-3.1 nmol/L (80-200 ng/dL) and for TSH, 0.3-3.5 mU/L (0.3-3.5 µU/mL).

Overt thyrotoxicosis was defined as a serum TSH concentration below the normal range and serum concentrations of T4 and T3 above normal ranges.[20] A serum TSH concentration less than the normal range with serum T4 and T3 within normal ranges was considered subclinical hyperthyroidism. Serum TSH concentration above the upper limit of normal range with serum T4 and T3 concentrations below the lower limit of normal ranges was defined as overt hypothyroidism. If serum TSH levels were above the upper limit of normal, but T4 and T3 were within normal limits, the condition was called subclinical hypothyroidism.[25]

Data are reported as mean±SD unless stated otherwise and were statistically analyzed by Student's *t* test and the *chi*–square test using SPSS software. The odds ratio was used to determine the correlation between AF and hyperthyroidism. To extend the results of the study to the society of Isfahan, a confidence interval of 95% was taken into account. *P* values less than 0.05 were considered statistically significant. The results were compared with the findings of a similar study conducted just before extensive iodine distribution. Methodology, diagnostic criteria of AF and thyroid dysfunction were the same in the two studies, but the earlier study had no control group.

The appropriate human research review committee approved this study and patients gave informed consent.

Table 1. Comparison of thyroid function in patients with atrial fibrillation and control group

Thyroid function	Case group (n=100)	Control group (n=100)	P value
Overt hyperthyroidism	8	1	0.02*
Subclinical hyperthyroidism	6	6	NS
Overt hypothyroidism	1	0	NS
Subclinical hypothyroidism	7	6	NS
Euthyroid	78	87	—

*Odds ratio=8.6, 95% confidence interval 6.5 to 10.7

Results

The mean age of patients with atrial fibrillation was 61.5±14.8 vs. 60.4±14.6 years for the control group (difference not statistically significant). The age ranges were 20 to 85 years and 19 to 85 years, respectively. Eight patients with atrial fibrillation were younger than 40 years. The two groups had similar numbers of men and women (51 men and 49 women), even though sex was not a factor in selecting the case group. There were 8 patients with overt hyperthyroidism in the case group compared with 1 patient in control group (odds ratio 8.6, 95% CI, 6.5 to 10.7, $P<0.02$) (Table 1). Subclinical hyperthyroidism was observed in 6 patients in each group. Subclinical hypothyroidism was observed in 7 patients in the case group and 6 patients in control group. Neither of these differences were statistically significant (Table 1). Table 2 shows the serum thyroid hormone concentrations in the case and control groups.

No statistically significant differences were observed in the mean age of patients with overt hyperthyroidism (63.1±12.4 years), subclinical hypothyroidism (63.9±13.5 years), overt hypothyroidism (60.5±15.1 years), or in euthyroid patients (60.5±15.1 years). The mean age of patients with atrial fibrillation, regardless of thyroid function, was 61.5±14.8 years. The age range of those patients with both atrial fibrillation and hyperthyroidism was 47 to 70 years.

Five of the 8 patients with atrial fibrillation who had overt hyperthyroidism based on thyroid function tests did not show clinical manifestations of thyrotoxicosis, and 3 out of 8 patients had borderline symptoms and signs. Overall, none of the patients with atrial fibrillation had typical manifestations of hyperthyroidism.

Discussion

We evaluated the rate of hyperthyroidism, one of the side effects of iodized salt distribution in an iodine-repleted area, in patients with atrial fibrillation. The patients in our case group were similar to subjects in studies performed in

Table 2. Mean±SD of serum thyroid hormone concentrations by thyroid function in patients with and without atrial fibrillation.

	T4 nmol/L (µg/dl)	T3 nmol/L (ng/dl)	Free thyroxine index*	TSH mU/L (µU/ml)
Case group with atrial fibrillation (n=100)				
Overt hyperthyroidism (n=8)	221.4 ± 57.5 (17.2 ± 4.5)	4 ± 0.9 (258.4 ± 56.5)	6.4 ± 1.9	0.06 ± 0.03 (0.06 ± 0.03)
Subclinical Hyperthyroidism (n=6)	100.4 ± 27 (7.8 ± 2.1)	1.9 ± 0.6 (125.8 ± 40.3)	2.4 ± 0.6	0.19 ± 0.06 (0.19 ± 0.06)
Overt Hypothyroidism (n=1)	45.1 (3.5)	1.4 (92.1)	1.3	5.3 (5.3)
Subclinical Hypothyroidism (n=7)	82.4 ± 25.7 (6.4 ± 2)	1.7 ± 0.5 (110.9 ± 29.6)	1.9 ± 0.6	7.2 ± 4.3 (7.2 ± 4.3)
Overt and subclinical hypothyroidism (n=8)	77.9 ± 27 (6.05 ± 2.1)	1.7 ± 0.4 (108.6 ± 28.2)	1.8 ± 0.6	7 ± 4.4 (7 ± 4.4)
Euthyroid (n=78)	105.6 ± 23.2 (8.2 ± 1.8)	1.8 ± 0.4 (117.7 ± 27.8)	2.33 ± 0.49	1.3 ± 0.78 (1.3 ± 0.78)
Control group without atrial fibrillation (n=100)				
Overt hyperthyroidism (n=1)	167(13)	3.4(221.3)	3.6	0.1(0.1)
Subclinical hyperthyroidism (n=6)	123.6 ± 27 (9.6 ± 2.1)	2 ± 0.6 (130.1 ± 36.4)	2.7 ± 0.65	0.18 ± 0.1 (0.18 ± 0.1)
Hypothyroidism (n = 6)	77.2 ± 12.9 (6 ± 1)	1.8 ± 0.7 (119 ± 24.7)	1.74 ± 0.37	8.6 ± 6.9 (8.6 ± 6.9)
Euthyroid (n = 78)	105.5 ± 23.2 (8.2 ± 1.8)	1.8 ± 0.4 (117.7 ± 27.8)	2.33 ± 0.49	1. 3 ± 0.8 (1.3 ± 0.8)
Normal range	54.1-154.4 (4.2-12)	1.3-3.1 (80-200)	1.3-4.2	0.3-3.5 (0.3-3.5)

*Total T4 x T3 uptake

other countries except that the mean age of patients was 10 years less than in studies carried out in the USA, Israel, Denmark and Brazil.[5, 7, 27-29] However, our case patients were similar to those in a study performed in Isfahan (Iran) approximately one decade ago.[18] According to Malek Afzali and colleagues' study, which was published in a local journal in 1986, life expectancy in Iran in men and women is 69 and 72 years, respectively. This shorter life expectancy may explain the difference between the mean ages of patients with atrial fibrillation in this study compared with studies done in other countries.

Some of the above-mentioned studies in other countries found no statistically significant difference in the rate of thyrotoxicosis in atrial fibrillation patients in comparison with control groups. But in our study, 8% of patients in the case group had overt hyperthyroidism compared with only 1 patient in the control group. The statistical analysis indicated that the chance hyperthyroidism in patients with atrial fibrillation is 6.5 to 10.7 times more than those without atrial fibrillation. In comparison with the similar study conducted earlier in Isfahan, before extensive iodized salt consumption, the rate of overt hyperthyroidism in patients with atrial fibrillation more than doubled (8% vs 3.7%). Such an increase in the rate of thyrotoxicosis has been reported in some iodine-repleted areas.[30] No increase in the rate of thyrotoxicosis was seen in Australia, but the increase was 7% in Sweden.[19] Overall, in iodine-repleted areas with endemic goiter, the mean increased rate has been 1.7%. About 85% of cases occur in patients with multinodular goiter, and Grave's disease or autonomous thyroid nodules. Iodine repletion also increases the chance of other autoimmune thyroid diseases.[19,31] It is possible that sufficient iodine intake in Isfahan has increased the rate of hyperthyroidism and its consequence, atrial fibrillation, but not the rate of hypothyroidism.

Since an increase in prevalence of hypothyroidism was not observed, it seems that these patients had endemic goiter rather than autoimmune thyroid disease.[19] It should be mentioned that our patients were mostly older than 40 years of age, and the incidence of thyroid nodular disease would be higher than in younger patients. Our results do not imply that iodine repletion has not increased the incidence of autoimmune thyroid disease in Iran. Another study with a community-based population would be required to evaluate this hypothesis.

In the study of Casiglia et al. in Italy, 17.8% of patients with atrial fibrillation were hyperthyroid. Although the

rate of hyperthyroidism was about twice as high as in our study, there was no significant difference from the control group.[31] A study by Schlienger et al in France showed 14% overt hyperthyroidism and 10% subclinical thyrotoxicosis in patients with atrial fibrillation while no patient in the control group had overt hyperthyroidism and 2% of them had subclinical thyrotoxicosis. In the present study, as in the study by Schlienger et al, the rate of overt thyrotoxicosis was higher in patients with atrial fibrillation, but subclinical hyperthyroidism was not more than in the control group. In other studies, an increased rate of hypothyroidism was also reported in patients with atrial fibrillation.[1, 10, 11, 18] Like the previous study in Isfahan [18] that reported the incidence rate of hypothyroidism as 12%, most of these studies did not have a control group. The incidence of 8% in our study was not statistically significant difference from the control group (7%). Therefore, like subclinical hyperthyroidism, hypothyroidism is not considered a cause of atrial fibrillation in Isfahan. It is possible that some patients presumed to be hypothyroid have, in fact, sick euthyroid syndrome,[5, 25] as the mean of their serum TSH concentration was 7±4.4 mU/L, which is just a bit more than the upper limit of normal range (Table 2). All of these patients (TSH>3.5 mU/L) were recalled 8 weeks later but only half of them came to the clinic. Re-evaluation of those patients revealed normal thyroid functions. Thus, at least half of the presumed cases of hypothyroidism actually had sick euthyroid syndrome. The same may be true for the patients classified as having subclinical thyrotoxicosis.

On the other hand, the clinical manifestations of thyroid dysfunction in patients with atrial fibrillation and hyperthyroidism were not in accordance with thyrotoxicosis in the patients in our study. Other investigators have made the same observation.[1, 2, 32-35] Therefore, it is not possible to rely on symptoms and signs of hyperthyroidism in patients with atrial fibrillation for the diagnosis of thyrotoxicosis.

We conclude that a lack of clinical manifestation of hyperthyroidism in patients older than 40 years of age with atrial fibrillation does not exclude the thyrotoxicosis diagnosis. We recommended that thyroid function be evaluated in all patients older than 40 years with atrial fibrillation. It also seems that iodine repletion has more than doubled the rate of atrial fibrillation in Isfahan, by causing hyperthyroidism. This is not a reason to stop iodine supplementation, however, since the benefits to the community from correcting iodine deficiency and avoiding its associated disorders far outweigh the damage from iodine-induced hyperthyroidism.[30]

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