Prevalence of Palpable Thyroid Nodule in Isfahan, Iran, 2006: A Population Based Study

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Key words
- thyroid nodule
- anti thyroglobulin antibody
- thyroid function tests

Abstract

Subjects: This cross-sectional study enrolled 2523 of adult general population (age > 20 years) of Isfahan city. History taking and thyroid exam was performed by seven trained general practitioners. The concentration of TSH was measured in all, TgAb and TPOAb in approximately one in six and urinary iodine concentration in one fourth of them, randomly. We recalled people with any suspicious abnormality in thyroid exam or whose TSH levels were not normal at present or past. They were re-visited by an endocrinologist to confirm or rule out the diagnosis and second serum sample was obtained to measure T4, T3, T3RU and TSH.

Results: Thyroid nodule was identified in 62 (17 men and 45 women) out of 2523 participants (2.5%; 95% CI: 2–3). Single and multiple nodules were found in 56 (2.2%; 95% CI: 1–2.5) and 6 (0.24%; 95% CI: 0.07–0.5) out of 2523 persons, respectively. The prevalence of nodule was higher in females (3.5%) than in males (1.3%) (OR = 2.72, 95% CI, 1.53–5.06, P = 0.001). It was significantly higher in patients older than 35 years in comparison with younger people (3.3% vs. 1.3%; OR = 2.5; 95% CI, 1.3–4.7; P = 0.002).

Conclusion: The prevalence of thyroid nodule in our study is less than what has been reported in other countries. It is due to lower prevalence in female population. Its prevalence in males is similar to other studies. It seems that geographical and racial differences or higher prevalence of deeper location of some nodules in female Isfahani population could explain this finding.

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Abbreviations

TSH	Thyroid Stimulating Hormone
TgAb	Anti Thyroglobulin antibody
TPOAb	Anti Thyroid Peroxidase antibody
T3RU	T3 Resin Uptake test
FT4I	Free T4 Index

Introduction

The prevalence of thyroid nodule by palpation has been reported between 4% and 7% in the general population of North America (Rojeski and Gharib, 1985). The prevalence is higher in autopsy reports (50%) (Mortenson et al., 1995). Twenty three percent of solitary nodules are dominant nodules in the background of multinodular goiter (Walsh et al., 1999). Thyroid nodules are four times more common in females than in males (Mazzaferri, 1993). It occurs more frequently in geographic areas with iodine deficiency; it also increases with advancing age (Tan and Gharib, 1997; Rojeski and Gharib, 1985).

Deep or posterior located thyroid nodules are difficult to palpate (Tan et al., 1995). In short neck patients, they are more difficult to be detected (Christensen and Tibblin, 1985).

Several studies have reported different prevalence of palpable thyroid nodules, for example, 8.9% in healthy population of Gdansk, Gdynia and Sopot, 27% in southern Finland,19% in Belgium (Karaszewski et al., 2006) and 21% in one study in North America (Ezzat et al., 1994).

Because of different prevalence of thyroid nodules in various geographic areas and lack of enough information in this regard in our population, we designed this study to investigate its prevalence in Isfahan, a centrally located city in Iran, with almost two million populations.

Objective

We designed this largest epidemiologic study in Iran to investigate the prevalence of thyroid nodule, in Isfahan, an iodine-replete area since 15 years ago for the first time.

Methods

Subjects

This cross-sectional study was performed from January to April 2006. We selected 40 blocks of Isfahan city, then addresses of all the homes on that blocks were asked from post office and 960 addresses (24 homes in each block) from the list were selected randomly (random cluster sampling). In this way, 2600 adult (age >20 years) were invited. The invitation rate was 97% (n=2523), 1275 male (50.5%) and 1248 female (49.5%). Their mean age was 39 (12.4) years, (range 20–86 years).

People were invited to Isfahan Endocrine and Metabolism Research Center. Consents were obtained from all participants before enrollment.

Seven trained general practitioners examined the invited people and filled out the questionnaires, including demographic data, medications taking, and personal history of thyroid disorders (e.g., Hashimoto's thyroiditis and Graves' disease).

Thyroid Stimulating Hormone (TSH) level was measured in all people. Anti Thyroglobulin antibody (TgAb) and Anti Thyroid Peroxidase antibody (TPOAb) concentrations in approximately one in six (n=450) and urinary iodine concentration in one fourth (n=702) of them were assayed, randomly.

Those with any suspicious abnormality in thyroid exam or TSH levels at present or past and people who were known cases of thyroid disorders (n=319) were recalled. Second blood samples were obtained to measure Thyroxine (T4), Triiodothyronine (T3), TSH, and T3 Resin Uptake (T3RU), after visiting by an endocrinologist (AA) to confirm or rule out the diagnosis of thyroid nodule and thyroid dysfunction. The number (single or multiple) and location of thyroid nodules were determined by physical examination.

Serum TSH, T3, T4 and T3RU assays

Blood samples were obtained from all participants and serum was stored at −20 °C, in the Isfahan Endocrine and Metabolism Research Center laboratory.

TSH was measured by IRMA (Kavoshyar kits, Tehran, Iran). The intra-assay and inter-assay CV was 1.5 and 1.9%, respectively. Its normal range was 0.3–4 mIU/L.

Serum T4 concentration was measured by radio-immunoassay (Kavoshyar kits, Tehran, Iran). Its intra- and inter-assay CV was 4.7 and 4.9%, respectively. Its normal range was 4.5–12 µg/dl.

Serum T3 was assayed by radio-immunoassay, (Kavoshyar kits, Tehran, Iran). Its intra- and inter-assay CV was 5.2 and 3.9%, respectively. Its normal range was 80–190 ng/dl.

T3RU was measured by radio-immunoassay, (Kavoshyar kits, Tehran, Iran). Its intra- and inter-assay CV was 3.6 and 4.4%, respectively. Its normal range was 25–35%.

Free T4 Index (FT4I) was calculated by T4*T3RU. Its normal range was 1.3–4.8 µg/dl.

Elevated TSH (>4 mIU/L) with normal FT4I and T3, and high TSH with low FT4I (<1.3 µg/dl) at second measurement were considered as subclinical and overt hypothyroidism, respectively (Cooper, 2001). The same criteria were used for the diagnosis of subclinical and overt hypothyroidism in treated hypothyroid patients (n=96) according to their previous medical documents, regardless of present TSH concentrations.

Depressed TSH (<0.3 mIU/L) with normal FT4I and low TSH with high FT4I (>4.8 μg/dl) at second measurement were considered as subclinical and overt hyperthyroidism, respectively (Tan and Gharib, 1997).

TPOAb and TgAb assays

TgAb and TPOAb levels were measured by rapid ELISA technique (Genesis Diagnostic Co).

The intra-assay and inter-assay CV for TgAb was <12%. The intra-assay and inter-assay CV for anti TPOAb was 7% and 5%, respectively. TgAb and TPOAb levels more than 100 IU/ml and 75 IU/ml were considered positive, respectively.

Urinary iodine measurement

Urinary iodine concentration was measured using a method based on a modification of Sandell-Kolthoff reaction technique. its intra- and inter-assay CV was 1.25 and 2.2%, respectively (WHO, UNICEF, 2001; Pino et al., 1996). The urinary iodine concentrations less than 10 μg/dl were considered as iodine deficiency (Pino et al., 1996; WHO, UNICEF, 2001).

The protocol was approved by Institutional Review Board of Isfahan University of Medical Sciences.

Statistical analysis

We used Chi-square test in order to compare prevalence of thyroid nodule between gender and two age groups (less or more than 35 years). The Fisher exact test was used for the frequency tables when more than 25% of the expected values were less than 5 (e.g. comparison of medication taking between males and females). Student T test was used to compare the mean of age, FT4I, T3, T3RU levels in people with and without nodules.

Data not normally distributed, using Kolmogorov-Smirnov test, were compared by Median test (TSH, T4, TPOAb and TgAb and urinary iodine concentrations) and expressed as median (range).Values of normally distributed data were presented as mean (SD). P values less than 0.05 were considered statistically significant.

Statistical analysis was performed by Statistics Package for Social Science (SPSS version 13.0, 1 Sep 2004; SPSS Inc., Chicago, IL, USA).

Results

General population data

Baseline characteristics of the general population are shown in **Table 1**.

Mean age of 2523 enrolled adults was 39 (12.4) years.

Clinical nodule was identified in 62 (17 men and 45 women) out of 2523 people (2.5%; 95% CI, 2–3). Their mean age was 44 years (range, 21–71years).

The prevalence of nodule was greater in women than in men (3.5% vs. 1.3%, OR=2.72; 95% CI, 1.53–5.06; P=0.001).

1476 people [48 with and 1428 without nodule(s)] out of 2523 population (58.5%; 95% CI; 56–60%), were older than 35 years and 1047 (14 vs.1033 with and without nodules, respectively) were younger (41.5%; 95% CI, 40–43%). Prevalence of nodule was higher in former (3.3%) than later group (1.3%) (3.3% vs. 1.3%; OR=2.5; 95% CI, 1.3–4.7; P=0.002).

Table 1 Baseline characteristics of Isfahani adult general population (n = 2523) and those with thyroid nodule (n = 62) in 2006.

Characteristics		General population			With nodule		
		Male	Female	P value	Male	Female	P value
	number (%)	1275(50.5)	1248(49.5)	0.6	17(27.5)	45(72.5)	0.001
	age, yr, mean (SD)	41(12.2)	37(12.3)	0.0001	49(9.2)	44.5(12.3)	0.4
medication, n (%)	levothyroxine	9(0.7)	87(7)	0.0001	1(5.9)	9(20)	0.170
	oral contraceptive	0(0.0)	16(1.3)	0.005	0(0)	1(2.2)	0.726
	methimazole	2(0.15)	4(0.32)	0.999	0(0)	1(2.2)	0.726

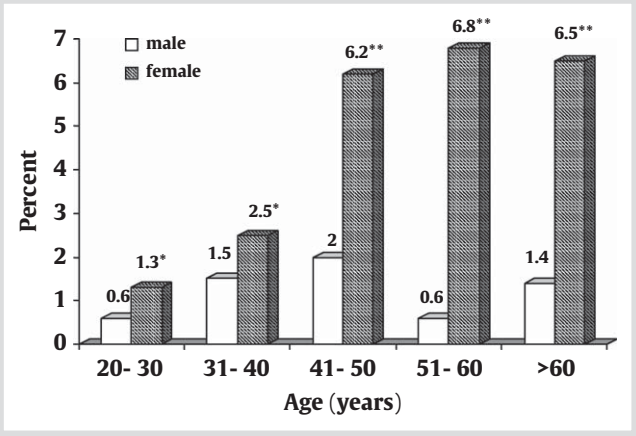

Fig. 1 Prevalence of thyroid nodule in males and females has been stratified by age (10 years intervals). Prevalence of nodule in groups marked by ** was higher than those marked by * (P < 0.05).

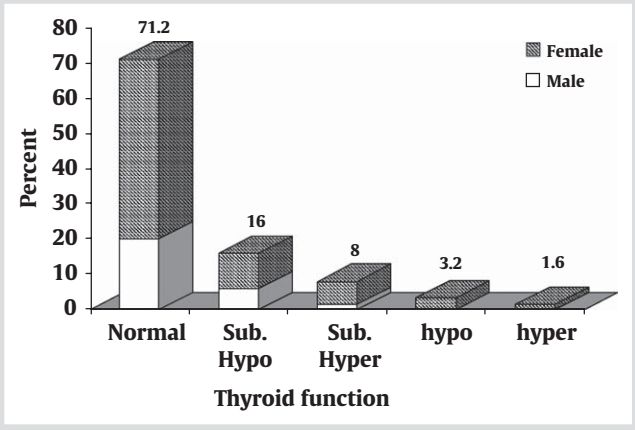

Fig. 2 Distribution of thyroid function (normal thyroid function, subclinical hypothyroidism, subclinical hyperthyroidism, hypothyroidism and hyperthyroidism) in males and females with thyroid nodule.

Fifty six and 6 out of 2523 people had single (2.2%; 95%CI, 1–2.5) and multiple (0.24%; 95% CI; 0.07–0.5%) nodules, respectively. Prevalence of single nodule was higher than multiple ones (P = 0.001).

TPOAb and TgAb levels were measured in 450 of 2523 subjects. Positive anti TPO and anti Tg was observed in 130 (28.9%) and 129 (28.7%) out of 450 people, respectively.

Urinary iodine concentration was measured in 702 out of 2523 subjects. In 167 (23.8%) of whom, urinary iodine concentration was less than 10 µg/dl.

Data of patients with thyroid nodule

Characteristics of patients with thyroid nodule are presented in **Table 1**.

Thyroid nodule was observed in 27.5%. of males and 72.5% of females (P = 0.001).

Forty eight (13males and 35 females) out of 62 persons were older than 35 years and 14 (4 males and 10 females) were younger (27.5% vs. 72.5%; P = 0.9).

Thyroid nodule was more prevalent in people aged 51–60 years (6.8%) in females and 41–50 years (2%) in males. Although the difference between male groups were not statistically significant (p = 0.2) (**Fig. 1**).

Single nodule was found in 56 of 62 subjects (90.3%). Nodule was observed in 38 out of 62 (61.2%; 95% CI, 40–64%) in right lobe versus18 subjects (29.1%; 95% CI, 13–35%) in left lobe. six out of 62 people (9.7%; 95% CI, 8–10%) had multiple nodules.

Six, 44 and 12 subjects had TSH levels < 0.3 mIU/L, between 0.3–4 mIU/L and >4 mIU/L, respectively. Mean of TSH level was 3.1(4.5) mIU/L.

Prevalence of normal thyroid function was more than thyroid dysfunction (P = 0.002).

Distribution of thyroid function test in people with thyroid nodule is shown in **Fig. 2**.

TPOAb and TgAb levels were measured in 45 out of 62 subjects with thyroid nodule (11 men and 34 women). Sixteen (5 men and 11 women) (35.6%) had positive TPOAb and 18 out of these 45 people (6 men and 12 women) (40%) had positive TgAb. Median of TPOAb was 23 IU/ml (1.3–2258) and 122 (5.9–1875) in males and females, respectively. Median of TgAb was 18.5 IU/ml (1–2858) and 52 (2.9–2955) in males and females, respectively.

Positive TPOAb was observed in 45.5% of males and 32.4% of females. However, this difference was not statistically significant (P = 0.43).

Positive TgAb was observed in 54.5% of males and 35.3% of females. It was not statistically significant (P = 0.25).

Urinary iodine concentration was measured in 37 of 62 subjects with nodule, 16 out of 37 people (43.2%) had urinary iodine concentration less than 10 µg/dl.

The prevalence of iodine deficiency was higher in males than in females. However, it was not statistically significant (45.5% vs. 38.5% P = 0.692).

Comparison of people with and without nodule

Mean age of subjects with thyroid nodule was higher than in those without nodule [44 (10.83) vs. 39 (12.43), respectively, P = 0.0001].

Comparison of laboratory findings between people with and without nodule is presented in **Table 2**.

Sixteen (35.6%) people with nodule vs.114 (28.1%) of those without had positive TPOAb (p = 0.298). Eighteen (40%) of people with vs.111 (27.4%) without nodule had positive TgAb level (p = 0.076) (**Fig. 3**).

Table 2 Mean (SD) or median (range) of thyroid function tests, thyroid autoantibodies and urinary iodine concentrations of Isfahani adult population with and without nodules in 2006.

Laboratory Findings	with nodule	without nodule	P value
T3, ng/dl	† 134.31(20.75)	††135.25(25.57)	0.848
T4, µg/dl*	† 6.1(1.6–9.8)	†† 6.5(0.1–18.7)	0.847
TSH, mIU/L*	† 3.3(0.5–73.6)	†† 3.3(0.05–200)	0.953
T3RU,%	† 33.66(2.09)	†† 33.48(2.40)	0.720
FT4I, µg/dl	† 2.22(0.664)	†† 2.21(0.73)	0.98
TPOAb, IU/ml*	‡ 21(1–2858)	‡‡ 8.2(0–7809)	0.346
TgAb, IU/ml*	‡ 54(2.9–2955)	‡‡ 24(0–9000)	0.028
Urinary Iodine, µg/dl*	¶ 12(2–40)	¶¶ 18.2(1–80)	0.001

Data were expressed as mean (SD) or median (range)

*Data were not normally distributed

† (n = 62), †† (n = 257)

‡ (n = 45), ‡‡ (n = 405)

¶(n = 37), ¶¶ (n = 665)

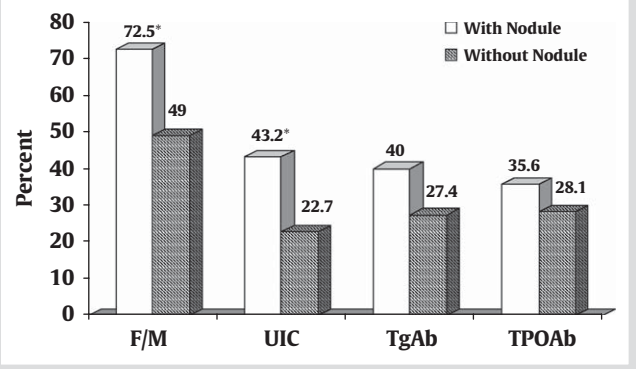

Fig. 3 Distribution of female to male ratio (F/M), urinary iodine concentration (UIC) less than 10 µg/dl, positive TgAb and TPOAb in subjects with and without thyroid nodule.

Urinary iodine concentration was measured in 665 of 2 462 subjects without nodules. 151(22.7%) had urinary iodine concentration less than 10 µg/dl. The prevalence of iodine deficiency was significantly lower in people without nodule (p = 0.004) (**Fig. 3**).

Discussion

Thyroid nodule is a common problem in clinic; we conducted this largest epidemiologic study to investigate the prevalence of thyroid nodule in population of Isfahan in 2006 for the first time.

Palpation of thyroid is the simplest method to detect thyroid nodule. In one study, the sensitivity of the thyroid gland size and nodularity by palpation was 38% (Christensen and Tibblin, 1985).

We observed the prevalence of thyroid nodule in 2.5% of our study population. These findings are in contrast with the higher prevalence (4–21%) of thyroid nodule which, has been described in other clinical studies (Rojeski and Gharib, 1985; Rago et al., 2001; Wong and Wheeler, 2000).

In the Framingham study, which enrolled 5 127 people over 15 years, thyroid nodule was observed in 4.2% of the population (6.4% of the women and 1.6% of the men). In that study, the prevalence of thyroid nodule in men was similar to ours (Vander et al., 1968).

Our results are consistent with findings of Wickham survey (3.2% in a randomly selected population in England) (Turnbridge et al., 1977).

In one study, that thyroid exam was performed by the same examiner; thyroid nodule was found in 13.4% and 2.6% of German and Swedish adult population, respectively (Gutekunst et al., 1986).

Although the prevalence of thyroid nodule in our general population was similar to that of Swedish adults, but iodine deficiency was found in 28% of Isfahani versus 0.3% in Swedish population. Thus, iodine deficiency alone may not explain the pattern of nodule prevalence. Other factors should play a role, such as geographical and racial differences or autoimmunity.

On the other hand, some of these studies (Ezzat et al., 1994) enrolled few subjects (n = 100) to determine the prevalence of nodule. In fact, it has been a clinically rather than a population based study.

Furthermore, low prevalence of thyroid nodule demonstrated in our study could be due to lower prevalence of this disorder in female group in comparison with other large research such as Framingham study. Their study showed similar prevalence of thyroid nodule in males.

Mean age of our population was less than that of the other studies, for example, in one study mean age of males and females was 43 (25–75 years) and 50 (29–77) years, respectively (Ezzat et al., 1994). On the other hand, in Framingham study persons with 30–59 years old has been enrolled. Lower mean age of females than males in our general population may be an explanation of lower prevalence of thyroid nodule in females than what was expected.

Interestingly, the prevalence of iodine deficiency, positive TPOAb and TgAb was higher in males than in females. Although this difference was not statistically significant (P = 0.692, 0.43 and 0.257, respectively). It can explain lower prevalence of thyroid nodule in female group.

The other reason is probably due to higher prevalence of deep location of some nodules in our females.

We recommend ultrasonographic study to determine locations of the nodules and to investigate whether our hypothesis is true or not.

As it was reported in previous studies, we observed higher prevalence of nodule in women than in men (Karaszewski et al., 2006; Ezzat et al., 1994; Turnbridge et al., 1977; Vander et al., 1968). It was approximately three times more frequent in our female population.

Multiple nodules were observed in 6 of 62 subjects (9.7%). It is lower than reports of the previously published studies. In those studies, 12 of 21 (57%) subjects (Ezzat et al., 1994), and 53 of 199 (27%) people had multiple nodules (Vander et al., 1968). It may be due to differences in populations, which have been selected for the studies.

In one report, single and multiple nodules were found in 4.3% and 1.2% of subjects, respectively (Wong and Wheeler, 2000). However, we observed single and multiple nodules only in 2.2% and 0.2% of general population, respectively (P = 0.001).

As in one previous study (Rago et al., 2001), we also found that the prevalence of thyroid nodule was significantly higher in subjects older than 35 years in comparison with younger people (OR = 2.5; 95% CI = 1.3–4.7; P = 0.002).

In agreement with some previous reports, (Welker and Orlov, 2003; Ezzat et al., 1994) our data showed that thyroid function was normal in most of the subjects with thyroid nodule. It was 71% in our population versus 81% in Ezzat et al., study.

In consistent with another previous report, we observed 6 out of 62 people with thyroid nodule (10%) had depressed TSH levels (Rago et al., 2001).

Prevalence of positive thyroid autoantibodies was higher in people with (40%) than those without nodule (28%). However, it was not statistically significant ($p = 0.2$). Low sample size may be the cause. Therefore, this finding can not rule out the probable role of autoimmunity.

The prevalence of positive autoantibodies has been reported in previous studies (Tomer, 1997; Premawardhana et al., 2000) from 27% to 70%. One study detected positive TPOAb in 13.0%, and positive TgAb in 11.5% of general population. The different prevalence of thyroid autoantibodies may explain the wide range of the reported prevalence of the thyroid nodule.

In this study, the prevalence of iodine deficiency was statistically significant higher ($p = 0.004$) and median urinary iodine concentration was lower ($p = 0.0001$) in subjects with than those without nodule. These findings support the role of iodine deficiency in genesis of thyroid nodules; however iodine deficiency alone may not explain the pattern of nodule prevalence.

We had selected people randomly to measure urinary iodine. By chance, none of them were taking medications like amiodarone or undergone imaging studies, using contrast agents, to have excess urinary iodine. The maximum urinary iodine concentration was 80μg/dl (**Table 2**).

Intra-observer variation of 7 examiners is a limitation of our study, which has not been determined, although, any suspicious in thyroid exam by each of these examiners was re-assessed by the endocrinologist (AA).

Conclusion

The low prevalence of thyroid nodule in our study, especially in females may be due to geographical and racial differences, genetic background, autoimmunity, or other causes such as some local environmental factors, which remain to be identified. Further reason may be due to higher prevalence of deep or posterior nodule location in females.

We recommend ultrasonographic studies to determine the location of nodule and to investigate whether or not our hypothesis is true.

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