Frequency of Abnormal Thyroid Function Tests in Kuwaiti Arabs with Autoimmune Diseases

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Key Words

Abnormal thyroid functions · Thyroid autoantibodies · Autoimmune diseases

Abstract

Objectives: The purpose of this study was to examine the frequencies of abnormal thyroid function tests and serum thyroid autoantibodies in healthy Kuwaitis and those with autoimmune diseases. **Subjects and Methods:** Serum concentrations of sensitive thyrotropin, and free thyroxine were measured in 577 apparently healthy controls, 177 patients with rheumatoid arthritis (RA), 60 with systemic lupus erythematosus (SLE) and 25 with primary Sjogren's syndrome (pSS) using the immunochemiluminescent assay method on IMMULITE 1000. Serum microsomal and thyroglobulin autoantibodies were also measured by passive hemagglutination assay. For analysis of the thyroid function tests, the subjects were classified into five categories: normal, subclinical hypothyroidism, overt hypothyroidism, euthyroid sick syndrome and biochemical hyperthyroidism. **Results:** Subclinical hypothyroidism was seen in 1.7% of healthy controls, 10.2% of RA, 13.3% of SLE, and 16% of pSS patients. Among RA patients, the frequency of subclinical hypothyroidism in females (11.4%) was significantly higher than among males (5.4%; $p < 0.01$). In SLE and pSS patients, all those with subclinical hypothyroidism were females. Overt hypothyroidism was seen in 1.4% of controls, 10.2% of RA, 8.3% of SLE,

and 4% of pSS patients. Biochemical hyperthyroidism was seen in 0.2% of controls, 4.5% of RA, 5% of SLE and none of pSS patients. The euthyroid sick syndrome was seen in 0.4% of controls, 13.6% of RA, 16.7% of SLE and in none of pSS patients. Thyroid autoantibodies were present in 3.1% of controls, 12.4% of RA, 18.3% of SLE, and 12% of pSS patients. **Conclusion:** Our data show that abnormal thyroid function tests and thyroid autoantibodies occur frequently in Kuwaitis with autoimmune diseases. Therefore, ordering these tests in these diseases is recommended.

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Introduction

Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS) and Graves' disease are often seen among Kuwaitis [1] and they therefore constitute a health challenge to the community. What is perhaps more important is that thyroid autoimmune disorders, which may be life-threatening, are often associated with these autoimmune diseases as exemplified in RA, scleroderma, pSS, vasculitides and SLE [2–10]. However, the prevalence of these thyroid disorders differs from population to population [11–15] and the prevalence of thyroid autoantibodies in different populations is somewhat variable.

Table 1. Demographic data of the different groups investigated

Characteristics	Controls	RA	SLE	pSS
Total subjects	577	177	60	25
Males	200	37	1	2
Females	377	140	59	23
Female:male ratio	1.9:1	4:1	59:1	11.5:1
Age, years	36.8 ± 10.3	38.3 ± 12.8	42.3 ± 10.8	45.8 ± 15.2

Values for age are expressed as mean ± SD.

There have been no detailed reports in the literature on the frequency of abnormal thyroid function tests and the presence of thyroid autoantibodies in healthy Kuwaitis or in those with autoimmune diseases other than our previous short report limited to the prevalence of hypothyroidism in patients with RA [16], but there are detailed reports on other Arabs [17, 18]. Therefore, the present study was designed to investigate the frequency of abnormal thyroid function tests in healthy Kuwaiti Arabs and in those with RA, SLE, and pSS.

Subjects and Methods

Patients

One hundred and seventy-seven (37 males, 140 females) consecutive ambulatory patients with RA, 60 (1 male, 59 females) with SLE and 25 (2 males, 23 females) with pSS from Al-Amiri and Mubarak Al-Kabeer Hospitals in Kuwait fulfilling the American College of Rheumatology criteria for RA [19], SLE [20] and pSS [21] were recruited into the study. The RA and SLE patients were not in a flare of their disease based on the DAS-28 score (less than 2.4) for RA and the SLE Disease Activity Index (less than 3) for the SLE group.

Controls

Five hundred and seventy-seven apparently healthy controls (200 males and 377 females) aged 18 years and older were recruited from a house to house survey of the Kuwaiti households carried out according to our previous publication [22]. The mean age ± standard deviation of this group was 36.8 ± 10.3 years. None of the controls had any prior history or clinical diagnosis of rheumatic disease, or acute systemic disease and none was on any medications known to affect thyroid function tests. Informed consent was obtained from each subject and the study was approved by the Ethical Committee, Faculty of Medicine, Kuwait University, Kuwait.

Thyroid Function Tests

Blood (10 ml) samples were collected from the patients and controls, serum separated and kept frozen at -80°C until ready for assay.

Free thyroxine (FT₄) and sensitive thyroid stimulating hormone (TSH) were measured in the serum samples by immunochemiluminescent assay on the IMMULITE 1000 (Diagnostic Products Corporation, Los Angeles, Calif., USA) and compared with the normal reference ranges in our laboratory for FT₄: 9.2–23.8 pM, and TSH: 0.23–4.0 mU/l. Passive hemagglutination assays, Thymune-M and Thymune-T (Remel Europe Ltd, Kent, UK) were used to measure thyroid microsomal antibody and thyroglobulin autoantibody, respectively.

For analysis, the subjects were classified into the following five groups: (a) normal: normal FT₄ and normal TSH levels; (b) subclinical hypothyroidism: normal FT₄, but high TSH (>4.0 mU/l); (c) overt hypothyroidism: low FT₄ (<9.2 pmol/l), but high TSH; (d) euthyroid sick syndrome: normal/low FT₄ but normal TSH; and (e) biochemical hyperthyroidism: normal or high FT₄ (>23.8 pM) and low TSH (<0.23 mU/l).

Statistical Analysis

Group data were analyzed for statistical significance using the Scheffé test in the computerized ANOVA program for multiple comparisons. The χ^2 and Fischer exact tests were used for comparison of percentages. A p value of < 0.05 was accepted as significant.

Results

Demographic Data

The demographics of the study group are given in table 1. In general, the females outnumbered the males with as low a ratio of 1.9:1 in control to 59:1 in SLE patients. The mean ages were from 36.8 ± 10.3 in controls to 45.8 ± 15.2 in pSS patients. Patients with pSS are rare in Kuwait, hence the small number studied.

The frequency of abnormal thyroid function tests in the different groups are listed in table 2. Subclinical hypothyroidism was seen in 10 (1.7%) controls, 18 (10.2%) RA, 8 (13.3%) SLE and 4 (16%) pSS patients. The frequency of subclinical hypothyroidism in pSS, SLE, and RA were significantly higher ($p < 0.01$) than in the control group, with that in pSS being the highest. The frequency of subclinical hypothyroidism in females was significant-

Table 2. Frequency of thyroid function tests in the different groups investigated

Types of thyroid functions	Controls			RA			SLE			pSS		
	females	males	total	females	males	total	females	males	total	females	males	total
Subclinical												
hypothyroidism	8 (2.1)	2 (1)	10 (1.7)	16 (11.4)	2 (5.4)	18 (10.2)	8 (13.6)	0	8 (13.3)	4 (17.4)	0	4 (16)
Overt												
hypothyroidism	8 (2.1)	0	8 (1.4)	16 (11.4)	2 (5.4)	18 (10.2)	5 (8.4)	0	5 (8.3)	1 (4.3)	0	1 (4)
Euthyroid sick syndrome	2 (0.5)	0	2 (0.4)	20 (14.3)	4 (10.8)	24 (13.5)	10 (17)	0	10 (16.7)	0	0	0
Biochemical												
hyperthyroidism	1 (0.3)	0	1 (0.2)	6 (4.3)	2 (5.4)	8 (4.5)	3 (5.1)	0	3 (5)	0	0	0
Subtotal	19 (5)	2 (1)	21 (3.6)	58 (41.4)	10 (27)	68 (38.4)	26 (44)	0	26 (43.3)	5 (21.7)	0	5 (20)
Normal thyroid function	358 (95)	198 (99)	556 (96.3)	82 (58.6)	27 (73)	109 (61.5)	33 (55.9)	1 (100)	34 (56.7)	18 (78.3)	2 (100)	20 (80)

Figures in parentheses are percentages.

Table 3. Frequency of thyroid autoantibodies in the different groups investigated

Thyroid autoantibody	Controls			RA			SLE			pSS		
	females	males	total	females	males	total	females	males	total	females	males	total
Microsomal antibody (normal <75 IU/ml)	8 (2.1)	4 (2.0)	12 (2.1)	11 (7.9)	1 (2.7)	12 (6.7)	4 (6.8)	0	4 (6.7)	1 (4.3)	0	1 (4.0)
Thyroglobulin antibody (normal <115 IU/ml)	3 (0.8)	1 (0.5)	4 (0.7)	4 (2.9)	2 (5.4)	6 (3.4)	4 (6.8)	0	4 (6.7)	2 (8.7)	0	2 (8.0)
Both antibodies	2 (0.5)	0	2 (0.3)	3 (2.1)	1 (2.7)	4 (2.3)	3 (5.0)	0	3 (5.0)	0	0	0
Total	13 (3.4)	5 (2.5)	18 (3.1)	18 (12.9)	4 (10.8)	22 (12.4)	11 (18.6)	0	11 (18.3)	3 (13)	0	3 (12)

Figures in parentheses are percentages.

ly higher than in male control subjects and RA patients ($p < 0.01$). Its frequency among females was 13.6% in SLE and 17.4% in pSS. Also the frequencies of subclinical hypothyroidism in females with RA, SLE and pSS were significantly higher than in female controls ($p < 0.01$). Overt hypothyroidism was more frequent among RA patients (18; 10.2%) than healthy controls (8; 1.4%). It was seen in 5 (8.3%) in SLE and 1 (4%) in pSS. The frequency of this condition was higher among females with RA than among females with SLE, pSS, or healthy females ($p < 0.01$).

Biochemical hyperthyroidism was seen in 8 (4.5%) RA, 3 (5%) SLE and 1 (0.2%) normal patients. Biochemical hyperthyroidism was not seen in any patient with pSS.

In total, the frequency of abnormal thyroid function tests was seen in 21 (3.6%) healthy controls, 68 (38.4%) RA, 26 (43.3%) SLE, and 5 (20%) pSS patients (table 2). The difference between controls and RA, SLE or pSS patients was statistically significant ($p < 0.01$). Moreover, females had significantly higher frequency of abnormal

thyroid function tests than males in RA (58, 41.4% vs. 10, 27%), SLE (26, 44.3 vs. 0%) and pSS (5, 21.7 vs. 0%) groups (table 2). In general, abnormal thyroid function tests were seen more commonly in patients with autoimmune diseases than in the healthy control subjects. Their frequencies in females are about twice the male frequency.

The frequency of thyroid autoantibodies is listed in table 3. Microsomal autoantibodies were found in 14 (2.4%) of the controls. The microsomal autoantibodies were less in controls than in patients with RA, SLE or pSS. Both microsomal and thyroglobulin autoantibodies were seen in control: 2; RA: 4 and SLE: 3 patients, while microsomal autoantibodies alone were seen in 12 (2.1%) controls, 12 (6.7%) RA, 4 (6.7%) SLE and 1 (4%) pSS. Thyroglobulin autoantibodies alone were seen in 4 (0.7%) controls, 6 (3.4%) RA, 4 (6.7%) SLE and 2 (8%) pSS patients. In general, less microsomal or thyroglobulin autoantibodies were seen in controls than in RA, SLE, or pSS patients. Females had more of these antibodies than males.

Discussion

The frequencies of thyroid dysfunctions in our study are considerably lower than those reported for other populations [11–15], most probably due to the small sample size (577 out of a population of 1 million). Hence, definite inference may not be drawn from this study until a larger sample size has been investigated to confirm the present observations.

In our study, the frequency of subclinical hypothyroidism was higher in patients with autoimmune diseases than in the healthy individuals. All patients were females in SLE and pSS groups and comprised 88.9% in the RA group. Our data are similar to those reported for other populations [5–10]. Previous studies have shown that a number of patients with subclinical hypothyroidism will eventually develop clinical hypothyroidism [12]. The risk factors for this progression are advanced age, female gender and presence of thyroid antibodies [11]. In this study, the mean age of our patients with subclinical hypothyroidism was below 45 in RA (40.5 ± 8.6 years) or SLE (43.5 ± 10 years) patients but above 45 years in pSS (50.6 ± 12.6 years) patients, suggesting that Kuwaiti patients above the age of 45 years with pSS need to be monitored carefully for clinical hypothyroidism.

The mean ages for the overt hypothyroid group in RA (49 ± 5.2 years), SLE (50.6 ± 6.3 years) or pSS (53.5 ± 10.6 years) patients were higher than those of the subclinical hypothyroid group. These results support a 'disease pyramid' in autoimmune thyroiditis in which patients progress from mild thyroiditis to clinical hypothyroidism over time [23, 24].

Punzi et al. [25] found a higher frequency of thyroid disorders in pSS (13.4%) than in RA (3.1%) patients from Italy. However, thyroid dysfunction was lower in our patients with pSS compared with those with RA or SLE. Perez et al. [26] reported higher frequency of thyroid dys-

function in Mexican patients with pSS (45%) compared with our data. These variances may be attributed to different environmental factors of the different populations. Genetic difference could also be a plausible explanation.

Some population studies have shown variable prevalence of thyroid autoantibodies in the general population especially among females [27–30]. However, the frequency of thyroid antibodies in Kuwaiti healthy individuals in our study was low compared with the 12.4% found by O'Leary et al. [27] among Australians and 5.7% among Omanis reported by Al-Jabri et al. [17]. The reason for these discrepancies can not be explained clearly, but it may be due to ethnic differences, and unknown genetic or environmental factors. Our study confirmed that the frequency of autoantibodies is much higher in females than in males both in the control group and in patients with RA or SLE or PSS, suggesting that the development of hypothyroidism is enhanced particularly among females by the presence of thyroid autoantibodies.

The pathogenesis of thyroid disorders in autoimmune disease may have a common pathway. Since autoimmune disease like RA or SLE is a systemic disorder that can affect any organ in the body, it could be speculated that the abnormal thyroid function tests seen in autoimmune diseases are due to the thyroid activity of one of the autoantibodies produced in these diseases [31, 32].

Conclusion

Our study showed that abnormal thyroid function tests, particularly hypothyroidism, occur frequently in Kuwaiti patients with systemic autoimmune diseases. Those who are at high risk (female gender and positive thyroid autoantibody) should have thyroid function test follow-up and should be given appropriate treatment whenever clinical hypothyroidism develops.

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