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Thyroid Function and Auto-antibodies in Egyptian Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

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ABSTRACT

The present study was designed to investigate the frequency of thyroid dysfunction in Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) and whether these dysfunctions could be an additional risk factor for the development of cardiovascular diseases. Our study included 132 SLE patients (128 females, 4 males) and 217 RA patients (174 females, 43 males). All patients underwent clinical examination and tests for thyroid function and thyroid autoimmunity (antithyroglobulin or Tg and antiperoxidase or TPO antibodies). One hundred and twenty (90 females, 30 males) from the same geographical area, acted as controls. TPO abs were found in 26 SLE patients (19.7%), 22 RA patients (10.1%) and 7 controls (5.8%) while Tg abs were found in 11 (8.3%) SLE, 13 (6%) RA and 2 controls (1.6%). Abnormal thyroid functions were found in 21 (15.9%) SLE, 18(8.3%) RA patients compared to 5 (4.2%) controls ($p<0.05$). Of those patients with thyroid dysfunction, 17 SLE, 12 RA and 4 controls were positive for TPO abs. The most common abnormality was clinical hypothyroidism (8.3 SLE, 4.1% RA patients) then subclinical hypothyroidism (5.3 SLE, 1.8% RA patients). Subclinical hyperthyroidism was found in 2 (1.5%) SLE and 4 (1.8%) RA patients. Hypothyroid patients had significantly higher blood pressure, low density lipoprotein, C-reactive protein, lipoprotein (a) anti TPO and anti TG abs than euthyroid patients. In conclusion, SLE and RA patients had higher prevalence of anti-thyroid antibodies and hypothyroidism, compared to our normal population. SLE and RA patients with hypothyroidism are at increased risk for CVD compared to those with normal thyroid function.

Key words: Thyroid function, auto-antibodies, rheumatoid arthritis, systemic lupus erthymatosus

INTRODUCTION

Autoimmune Thyroid Disease (AITD) affects About 2 to 4% of women and up to 1% of men worldwide and the prevalence rate increases with advancing age (Canaris *et al*., 2000), (Helvaci *et al*., 2006). AITD are often associated with a number of autoimmune diseases as Systemic Lupus Erythematosus (SLE) (Pyne and Isenberg, 2002), Rheumatoid Arthritis (RA) (Chan *et al*., 2001), Sjogren syndrome (Perez *et al*., 1995), scleroderma, vasculitides (Gordon *et al*., 1981) and alopecia areata (El-Gayyar *et al*., 2011).

The association between AITD and rheumatic diseases has been well accepted and blamed for precipitating or exacerbating their symptoms (Delamer *et al*, 1982). However, the prevalence of these thyroid disorders differs from population to population and the prevalence of thyroid autoantibodies in different populations is somewhat variable (Vanderpump *et al.*, 1995; Peterson *et al.*, 1991; Parle *et al.*, 1991; Tomimori *et al.*, 1995).

Although, the prevalence of thyroid disorders is probably greater in SLE than in the general population, controversial results were reported (Pyne and Isenberg, 2002). Rheumatoid Arthritis (RA) occurs with high incidence in association with positive antithyroid antibodies (Del Puente *et al.*, 2003). Hypothyroidism (subclinical and overt) was the most frequent thyroid disease associated with RA in previous studies (Miller *et al.*, 1993; Caron *et al.*, 1992). Raterman *et al.* (2008) found fourfold higher risk of Cardiovascular Disease (CVD) in RA patients with clinical hypothyroidism in comparison with euthyroid RA patients. Also, thyroid disorder found to be another risk factor for premature menopause, miscarriage and preterm delivery in women diagnosed with SLE (Mansourian, 2010; Stagnaro-Green *et al.*, 2011). Therefore, the present study was designed to investigate the frequency of thyroid dysfunction in two non organ specific autoimmune diseases; Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) and whether these dysfunctions could be an additional risk factor for the development of CVD.

MATERIALS AND METHODS

Our study included 132 SLE patients (128 females, 4 males) and 217 RA patients (174 females, 43 males) all fulfilling the American Rheumatism Association criteria for SLE (Tan *et al.*, 1982) and RA. They were selected from the rheumatology outpatient clinic of Mansoura University hospital during their regular visits.

Those who are in a flare of their diseases or had other autoimmune diseases (type 1 diabetes mellitus, vitiligo, alopecia, other rheumatologic disorders and inflammatory bowel disease) or a history of thyroid disease were excluded.

All patients underwent clinical examination for thyroid size and tests for thyroid function and thyroid autoimmunity: antiperoxidase (anti-TPO) and antithyroglobuhn (anti-Tg) antibodies. Lipid profile, C-Reactive Protein (CRP), serum creatinine, lipoprotein (a) and Erythrocyte Sedimentation Rate (ESR) were also assessed.

Controls: One hundred and twenty healthy subjects (90 females, 30 males), from the same geographical area, were taken as a control. The study protocol was approved by our hospital's Ethics committee. None of our patients or controls was taking antihypertensives or medications to lower cholesterol.

Thyroid functions: Free T4 (FT4), free T3 (FT3) and Thyroid-stimulating Hormone (TSH) serum levels were determined by immunometric assays (Immulite TM 2000 Third Generation, DPC Diagnostic Products Corporation, Los Angeles, CA, USA). Within- and between-run coefficients of variation was less than 12.5% for u-TSH, less than 7.5% for FT4 and less than 9.1% for FT3. The normal range of thyroid hormones and TSH were, respectively, FT4 0.8-1.9 ng dL^{-1}, FT3 1.9-4.8 pg mL^{-1} and u-TSH 0.4-4.0 IU mL^{-1}. Subclinical hypothyroidism was defined as TSH level >4.0_IU mL^{-1} together with normal serum thyroid hormone levels. Overt hypothyroidism was defined as raised TSH together with a decreased serum thyroid hormone level. Subclinical hyperthyroidism: normal FT 4 and low TSH (<0.23 mU L^{-1}). Hyperthyroidism: Normal or high FT 4 and low TSH. Euthyroid sick syndrome: Normal/low FT 4 but normal TSH.

Serums anti TPO and anti TG antibodies were assayed by ELISA method supplied by Calbiotech Inc 10461 Austen Dr, Spring Valley, CA, 91978. Levels <100 mIu mL^{-1} for antithyroglobulin and <50 mIu mL^{-1} for antiperoxidase antibodies were considered negative. Lipid profile was assessed using commercially available kits supplied by human (Germany). Low density lipoprotein cholesterol (LDL-C) was calculated according to Friedewald formula: LDL-C = Total cholesterol-{triglycerides (TG)/5+high density lipoprotein cholesterol (HDL-C)}. lipoprotein (a) concentrations were determined in serum by nephelometry (N latex Lp (a) reagent, Behring Diagnostics). Quantitative determination of CRP was performed according to the method of Muller *et al.* (1985) using kits purchased from spinreact, S.A. (Saint Estere de bas, Spain).

Statistical analysis: Variables are given as mean and Standard Deviation (SD) unless stated otherwise. The significance of difference between 2 sets of variables was assessed by the student t- test and chi square. The X_2 test and Fisher exact test were used to compare the frequency of the variables for the three groups.

RESULTS

The male/female ratio was 1:32 in SLE, 1:4 in RA and 1:3 in controls. The mean age range was from 30.2±10.8 in SLE patients, 36.3±12.8 in RA and 36.7±10.3 in controls (Table 1).

Anti-TPO abs were higher in frequency than anti-Tg abs (Table 2). Anti-TPO abs were found in 26 SLE patients (19.7%), 22 RA patients (10.1%) and 7 controls (5.8%) while anti-Tg abs were found in 11(8.3%) SLE, 13 (6%), RA and 2 controls (1.6%). In general, more TPO or Tg abs were found in SLE and RA patients than control and SLE compared to RA.

Abnormal thyroid functions were found in 21 (15.9%) SLE, 18(8.3%) RA patients compared to 5(4.2%) controls ($p<0.05$). they were 100% females in SLE and control and 83.3% in RA. Of these patients 17 SLE, 12 RA and 4 controls were positive for TPO abs, respectively. The most common abnormality was clinical hypothyroidism (8.3% SLE, 4.1% RA patients) then subclinical hypothyroidism (5.3% SLE, 1.8% RA patients). Subclinical hyperthyroidism was found in 2 (1.5%) SLE, 3 (1.4%) RA patients and 2 (1.7%) controls. One SLE patient had clinical hyperthyroidism. TPO abs showed high frequency among those with different thyroid abnormalities. In 9 out of 111 SLE, 10 out of 199 and 3 out of 115 controls with normal thyroid function TPO abs were positive (Table 3). The characteristics of subchinical and clinical hypothyroid patients in comparison with euthyroid patients with either SLE or RA are shown in Table 4. Hypothyroid patients (clinical and subclinical) had significantly higher blood pressure, LDL, CRP, anti TPO, anti TG abs and antibodies levels than euthyroid patients. Clinically hypothyroid patients had significantly higher TG than euthyroid patients.

Table 1: Demographic data of patients and control

Parameters	SLE	RA	Control
Total	132	217	120
Males (M)	4	43	30
Female (F)	128	174	90
M/F ratio	1:32	1:4	1:3
Age (years)	30.2±10.8	36.3±12.8	36.7±10.3

Age is expressed as Mean±Standard deviation

Table 2: Frequency of both thyroid antibodies in patients and control

Parameters	SLE	RA	Control
Anti-TPO abs	26*+x (19.7%)	22* (10.1%)	7x (5.8%)
Anti-Tg abs	11*+ (8.3%)	13* (6%)	2 (1.6%)
Both abs	9* (6.8%)	13*(6%)	(0%)

*p<0.05 compared to control. +p<0.05 compared to RA patients. xp<0.05 compared to anti Tg abs. SLE: Systemic lupus erythematosis, RA: Rheumatoid arthritis, Anti-TPO abs: Antiperoxidase antibodies, Anti-Tg abs: Antithyroglobulin antibodies

Table 3: Frequency of thyroid dysfunction and anti-TPO in patients and control

Parameters	SLE	RA	Control
Thyroid dysfunction (%)	21* (15.9%)	18* (8.3%)	5 (4.2%)
Anti-TPO	17/21	12/18	4/5
Females	21/21	15/18	4/5
Hypothyroidism			
Clinical	11* (8.3%)	9* (4.1%)	1 (0.8%)
Anti-TPO	11/11	7/9	1/1
Subclinical	6* (5.3%)	4 (1.8%)	2 (1.7%)
Anti-TPO	5/6	3/4	½
Hyperthyroidism			
Clinical	1(0.75%)	0	0
Subclinical	2 (1.5%)	3 (1.4%)	2 (1.7%)
Anti-TPO	½	2/3	2/2
Euthyroid sick syndrome	1	2	-
Anti-TPO	0	0	-
Normal thyroid function	111 (84.1%)	199 (91.7%)	115 (95.8%)
Anti-TPO	9/111	10/199	3/115

*p is significant if p<0.05 in compared with control subjects, Anti-TPO: Thyroid peroxidase antibodies

Table 4: Characteristics of subclinical and clinical hypothyroid patients in comparison with euothyroid patients with either SLE or RA

Parameters	Subclinical hypothyroidism (n = 10)	Clinical hypothyroidism (n = 20)	Euthyroid (n = 311)
Female (%)	90	100	85.9
Age (years)	34.3±10.3	33.7±9.3	34.1±11.9
Disease duration (years)	4.9±2.1	5.2±1.8	6.1±2.3
BMI (kg m^{-2})	23.9±1.7	24.6±4.1	23.1±4.8
SBP (mmHg)	134.7±14*	137.7±17.5*	118.5±6.5
DBP (mmHg)	91.5±8.8*	92.3±9.1*	86±4.98
TG (mg dL^{-1})	113.7±25.5	136±54.1*	96.25±18.9
HDL-c (mg dL^{-1})	41.2±7.7	40.06±9.2	43.77±8.2
LDL-c (mg dL^{-1})	103.5±38.11*	126.4±39.2*	69.35±23.18
ESR (mm/h)	64±5.3	67±6.2	61.8±4.9
CRP (ng mL^{-1})	7.4±3.1*	10.2±1.3*	4.7±1.1
Serum creatinine (mg dL^{-1})	0.89±0.27	0.91±0.16	0.86±0.17
Lipoprotein (a) (mg dL^{-1})	28.3±10.2*	34.6±12.7*	13.1± 4.2
Anti-TPO abs (Iu mL^{-1})	96.68±102.83*	105.76±112.34*	63.16±132.2
Anti-Tg abs (Iu mL^{-1})	68.4±71.7*	79.2±83.9*	44.18±36.7

Data are expressed as mean±standard deviation, *p is significant if p<0.05 in compared with euothyroid patients, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TC: Total cholesterol, TG: Triglyceride, LDL-c: Low density lipoprotein cholesterol, HDL-c: High density lipoprotein cholesterol, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, Anti-TPO abs: Antiperoxidase antibodies, Anti-Tg abs: Antithyroglobulin antibodies

DISCUSSION

Autoimmune thyroid disease, marked by the presence of antibodies directed against thyroid antigens, has been associated with a number of non-organ specific rheumatic disorders (Pyne and Isenberg, 2002).

In the present study, we investigated the prevalence of thyroid disorders and their possible associated cardiovascular risk factors in patients with RA or SLE. We found an increased prevalence of thyroid auto antibodies in both SLE and RA patients than control subjects. Both anti TPO and anti-Tg antibodies were detected. Overall, there was a trend towards anti-TPO antibodies being found more frequently, this trend has been observed in earlier studies (Pyne and Isenberg, 2002; Porkodi *et al*., 2004). Some population studies have shown variable prevalence of thyroid autoantibodies in the general population (O'Leary *et al*., 2006; Quinn *et al*., 2005; Pederson *et al*., 2005). The frequency of anti-TPO antibodies in our healthy Egyptian was (5.8%) which was low compared to 12.4% found among Australian (O'Leary *et al*., 2006) and higher than 3.1% among Kuwaiti (Al-Awadhi *et al*., 2008). However, nearly close to 5.7% among Omanis (Al-Jabri *et al*., 2003). The reason for these discrepancies cannot be explained clearly but it may be due to ethnic differences, differences in age, gender, anti-TPO assays and unknown genetic or environmental factors.

Twenty one out of our 132 SLE (15.9%) and 18 out of 217 RA (8.3%) patients had thyroid dysfunctions, that was high compared with (4.2%) found in healthy individuals. All were females in SLE group and comprise 83.3% in RA group. Incidence of all thyroid disorders is greater in SLE and RA patients than control subjects. Our data are similar to those reported for other populations (Delamer *et al*., 1982; Thomas *et al*., 1983). In previous, Egyptian study, thyroid disorders were 50% in SLE patients and 15% in RA but it was a small number study and the%age difference could be attributed to patient selection as there was high%age of patients with euthyroid sick syndrome (El-Sherif *et al*., 2004).

The most common abnormality was clinical hypothyroidism which is higher in SLE (8.3%) than RA (4.1%). A number of studies have looked at the frequency of thyroid dysfunctions in SLE, hypothyroidism was reported to vary greatly from 3.9% (Miller *et al*., 1993) and 6.6% (Miller *et al*., 1987) to 24% by Weetman and Walport (1987). The differences may be related to patient numbers and the sensitivity of Enzyme Linked Immunosorbent Assay (ELISA) used to detect TSH. The incidence in RA reported to be 3.1% by Chan *et al*. (2001) and 6.8% in the study of Raterman *et al*. (2008). These percentages together with that shown in our study were found to be higher than the prevalence of clinical hypothyroidism in our healthy subjects as well as in the general population by the Whickham study (1%) (Tunbridge *et al*., 1977).

The follow up study of the Whickham survey showed that clinical (overt) hypothyroidism rarely developed below the age of 45 year and peaked around the age of 80 year. SLE in particular and RA may confer an 'autoimmune locus' for earlier development of hypothyroidism. These patients represent a pool from which cases of organ specific autoimmune diseases emerge (Vanderpump *et al*., 1995).

The study of Chan *et al*. (2001) showed that the prevalence of subclinical hypothyroidism was more than that of clinical cases. However, the present study showed a lower incidence of subclinical hypothyroidism in both SLE and RA than clinical cases. Moreover, Raterman *et al*. (2008) found that the prevalence of subclinical hypothyroidism in RA was lower than in a sex and age matched population. Together with the finding that anti TPO were positive in all our SLE and 7 out of 9 RA patients with clinical hypothyroidism, the lower incidence of subclinical cases might be explained

by the pyramid hypothesis. This hypothesis is based on the observation that subclinical hypothyroidism will develop into clinically manifest hypothyroidism in approximately one quarter of the cases (Diez and Lglesias, 2004). Facilitating factors for this development are old age, female gender and higher titers of anti TPO (Dayan, 1996; Chan *et al.*, 2001). So, SLE and RA may accelerate progression up this disease pyramid by conferring anti TPO positivity.

In this study, SLE and RA patients with clinical or subclinical hypothyroidism had significantly higher blood pressure, LDL-C, CRP and lipoprotein (a) compared with Euthyroid patients. Raterman *et al.* (2008) found higher risk of cardiovascular disease particularly, ischemic heart disease and congestive heart failure in RA patients with clinical hypothyroidism in comparison with euthyroid RA patients; however, these abnormalities were not fully explained by traditional risk factors. Because of the evidence linking raised Lp (a) concentrations with the development of atherosclerosis (Bostom *et al.*, 1996), attention has focused on serum Lp (a) levels in thyroid diseases. Although, the possible role of thyroid autoimmunity per se in the Lp (a) metabolism should be not overlooked (Lotz and Salabe, 1997). Obviously, elevated Lp (a) levels may conspire with the raised LDL-c to enhance cardiovascular risk in hypothyroid patients. In other study, restoration of thyroid status dose not influences the occurrence of CVD (Nyirenda *et al.*, 2005). Hence, the excess of CVD in thyroid disorders is not necessarily due to thyroid hormone abnormalities and the accompanying dyslipidemia but may be mediated by chronic inflammation due to autoimmunity that amplify the cardiovascular risk in the already high risk SLE and RA patients.

Although, most studies have shown that the prevalence of hypothyroidism in SLE and RA is greater than that quoted for the general population, the issue of whether hyperthyroidism is also more prevalent is still debatable. In our study, hyperthyroidism was not significantly higher in SLE and RA compared to our control subjects. Other studies, like ours suggest there is no increase in prevalence of hyperthyroidism in SLE or RA (Miller *et al.*, 1987; Boey *et al.*, 1993; Atenzeni *et al.*, 2008). However, Chan *et al.* (2001) and Porkodi *et al.* (2004) had higher rates in their SLE and RA patients.

Of our patients, 26 SLE and 22 RA had positive anti TPO but only 21 SLE and 18 RA had thyroid dysfunction. On the other hand, of these patients with thyroid dysfunction, 3 SLE and 6 RA had negative anti TPO. The pathogenesis of thyroid disorders in autoimmune disease may have a common pathway. Since autoimmune disease like SLE or RA 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 thyroid activity of one of the autoantibodies produced in these diseases (Scofield, 2004; Szyper-Kravitz *et al.*, 2005). Also, Thyroid auto-antibodies could be a secondary response to thyroid injury; these antibodies increase the diagnostic sensitivity of autoimmune thyroid disease and possibly other diseases as well. Auto reactive t-cells which can cause primary thyroid destruction as well as polyclonal B cell activation in the two autoimmune rheumatic diseases may induce autoimmune thyroiditis and SLE or RA in the same patient. Other factors such as genetic and environmental factors may be involved (Park *et al.*, 1995; Raterman *et al.*, 2008).

In this study, RT3U was not performed. However, we considered low FT4 with normal TSH diagnostic for Euthyroid Sick Syndrome (ESS) and we found one case in SLE and 2 cases in RA patients with ESS, all were negative for thyroid antibodies. In contrast to our study, Al-Awadhi *et al.* (2008) and Kumar *et al.* (2010) demonstrated higher frequencies among patients with SLE and/or RA. The reason for this difference may be the selection of patients who displayed no exacerbation of their disease activity.

CONCLUSION

In conclusion, present results demonstrated that thyroid dysfunctions were detected in 15.9% of SLE and 8.3% of RA patients and this prevalence was significantly higher than that of general population in our locality (4.2%). Most of those with thyroid dysfunctions had hypothyroidism and higher frequency of anti-thyroid antibodies. Cardiovascular risk factors were significantly higher in patients with subclinical or overt hypothyroidism compared to those with normal thyroid function. Those who are at high risk (female gender and those with positive thyroid antibodies) should have thyroid function follow up to identify subclinical and clinical cases and should be treated to improve the symptoms and avoid additional cardiovascular risk.

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