Egypt J Pediatr Allergy Immunol 2011;9(2):87-92.

Original article

Subclinical hypothyroidism among Egyptian children with systemic lupus erythematosus

Background: *Thyroid autoimmune diseases have been associated with systemic lupus erythematosus (SLE). Both hypothyroidism and hyperthyroidism are seen, but hypothyroidism is the most common abnormality. Subclinical hypothyroidism (SCH) has been reported among adult lupus patients. SCH is not without risk as it might contribute to a pro-atherogenic state.* ***Objectives:*** *This study was aimed to assess the frequency of SCH in a group of Egyptian children with SLE and its effects on the serum lipids.* ***Methods:*** *Forty patients with pediatric SLE who regularly follow up at our center were enrolled in this study. They were subjected to routine laboratory investigations of SLE and measurement of serum lipids (serum triglycerides, cholesterol, LDL and HDL) as well as free thyroxine (T4), thyroid stimulating hormone (TSH) and anti-thyroperoxidase antibody (anti-TPO-ab) titre. SLE activity was assessed using the systemic lupus erythematosus disease activity index (SLEDAI).* ***Results:*** *Six patients (15%) were found to have SCH while the remaining 34 patients (85%) had normal thyroid function. Anti-TPO-abs were positive in 4 out of the 6 (66.6 %) SLE patients with SCH and in 20 out of the 34 (58.8%) SLE patients with normal thyroid function. In SLE patients with SCH, TSH correlated positively yet insignificantly with anti-TPO-ab titre and the duration of SLE (p= 0.17, p= 0.12, respectively). There were no statistically significant correlations between the serum lipids of SLE patients with SCH and their thyroid function or anti-TPO-ab titre.* ***Conclusion:*** *SCH is not uncommon among children with SLE. This SCH does not seem to affect serum lipids. However, further longitudinal studies on wider scales are needed to assess the long term effects of SCH in those patients.*

Keywords: SLE, anti-thyroperoxidase antibodies, subclinical hypo-thyroidism.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibodies directed against self-antigens and resulting in inflammatory damage to target organs including the kidneys, blood cells and central nervous system[1].

Thyroid autoimmune diseases have been associated with a variety of rheumatological diseases, including SLE[2]. Both hypo- and hyperthyroidism are seen in association with SLE, but hypothyroidism is more common. Up to 35% of pediatric SLE patients have antithyroid antibodies, with 10% to 15% of patients developing overt hypothyroidism[3].

The vast majority of hypothyroidism in SLE results from autoimmune thyroiditis. The autoimmune process is believed to begin with activation of CD4+T-helper lymphocytes specific for thyroid antigens. Activated CD4+T lymphocytes recruit cytotoxic (CD8+) T cells as well as B cells into the thyroid gland. Thyroid cell destruction occurs through multiple mechanisms: cytotoxic T cells that induce apoptosis; cytotoxic antibodies that fix complement and cause thyroid cell lysis; and antibody-dependent cell-mediated cytotoxicity involving natural killer cells[4].

Subclinical hypothyroidism (SCH) is a condition characterized by normal thyroid hormones' levels (total and unbound thyroxine and triiodothyronine) in the presence of elevated TSH and absence of symptoms[5]. SCH is associated with a pro-atherogenic dyslipidemias and increased risk of cardiovascular disease[6]. These effects are being greater at higher TSH levels[7].

With this as a background, we aimed to study the frequency of subclinical hypothyroidism among

a group of Egyptian children with SLE, and whether it is associated with increased serum lipids.

METHODS

Study population:

This cross-sectional study was conducted on 40 children with SLE, fulfilling the revised classification criteria of the American College of Rheumatology for diagnosis of SLE[8] during the period from January 2009 to June 2009. The children were regularly followed up at the Pediatric Allergy and Immunology Clinic, Children's Hospital, Ain Shams University. They were 36 females and 4 males with a female to male ratio 9:1. Their ages ranged between 6 and 17 years with a mean of 13.6 ± 2.2 years. Their duration of illness ranged from 4 to 119 months with a median of 18 months.

An informed oral consent was taken from the patients and/ or their care givers before enrolment in the study. The study protocol gained acceptance of the Pediatric Department's Ethical Committee.

Study measurements:

A- Clinical evaluation was done for each patient with special emphasis on therapeutic history mainly the dose and duration of steroid therapy and assessment of disease activity using the systemic lupus erythematosus disease activity index (SLEDAI), symptoms suggestive of hypothyroidism (pubertal delay, puffy features, swelling in neck, cold intolerance, etc….) or hyperthyroidism (emotional lability, weight loss, and restless sleep, some degree of exophthalmos, etc….). Patients with overt thyroid disease were excluded.

B- The laboratory work up of the study:

Eight ml venous blood were withdrawn from each patient and divided as follows: 2 ml were collected in EDTA tubes for CBC (Coulter Corporation, HIELAS, Florida, U.S.A), 2 ml were collected on sodium citrate for ESR assay (Westergren method) and 4 ml were collected in plain sterile tubes and allowed to clot then centrifuged, and serum was collected and stored at -20°C. Serum was used for the detection of the levels of cholesterol, triglycerides, HDL, LDL and creatinine (on Synchron CX7 autoanalyzer, Beckman Instruments, Brea, California, USA) and ANA and anti-dsDNA by indirect immunofluorescent assay (IMMCO Diagnostics, USA), and for the measurement of C3 using MININEPH™ (Binding Site Group Ltd, Birmingham, UK.), free T4 and TSH using the Immulite 2000 (solid phase, chemiluminescent immunometric assay) and thyroid peroxidase autoantibody (anti-TPO-ab) titre by enzyme linked immunosorbant assay (ELISA) using (Accu-Bind ELISA microwells Monobind Inc. Lake Forest, CA 92630, USA). A reference curve was used to ascertain the concentration of anti-TPO-ab in unknown specimen by utilizing several different serum references of known antibody activity. The presence of anti-TPO-abs is confirmed when the serum level exceeds 40 IU/ml[9].

Normal FT4 reference values (ng/dl) according to the age[10]:

1-5 years: 0.78-2.09 ng/dl.
6-10 years: 1.01-2.09 ng/dl.
11-15 years: 0.78-2.02 ng/d.

Normal TSH reference values (mIU/mL) according to the age[11]:

0-10 years: 0.36-6.0 mIU/mL
>10 years: 0.4- 4.0 mIU/mL

Statistical analysis:

Analysis of data was performed by SPSS (statistical program for social sciences version 12). Numeric data were expressed as mean ± standard deviation and median (range) when appropriate, qualitative data were expressed as frequency and percentage. Mann Whitney test was used to compare between two population medians. Spearman rho non parametric correlation was used to test correlation between quantitative variables. All tests were 2 tailed, p-values less than 0.05 were considered significant.

RESULTS

Frequency of SCH and patient characteristics

Six (15%) patients were found to have SCH while the remaining 34 (85%) patients had normal thyroid function; age and sex distribution were comparable between SLE patients with SCH and those with normal thyroid function. The characteristics of the 2 subgroups are shown in table 1.

Anti-TPO-abs in the 2 subgroups

Anti-TPO-ab positivity was detected in 4 out of the 6 (66.6 %) SLE patients with SCH and in 20 out of the 34 (58.8%) SLE patients with normal thyroid function. There was no statistically significant difference in the anti-TPO-ab titre between SLE patients with normal thyroid function and those with SCH (table 1). Worth mentioning is that the titre of anti-TPO-abs although correlated positively yet insignificantly with the level of TSH among lupus patients with SCH (r=0.67, p=0.17).

The impact of disease activity as assessed by SLEDAI on thyroid function

SLEDAI was comparable in the two groups: SLE patients with SCH and those with normal thyroid function (table 1). Of the 6 patients with SCH, 3 had mild activity (SLEDAI <6) and the remaining 3 had moderate activity (SLEDAI <12).

The lipid profile of the two subgroups

Lupus patients with SCH had borderline significantly higher serum cholesterol but comparable serum triglycerides, HDL and LDL to those with normal thyroid function (table 1). Of the 6 patients with SCH, 4 (66.6%) had hyper-cholesterolemia with a median (range) of 287 (270-300), while 6 (18%) patients of those with normal thyroid function had hypercholesterolemia with a median (range) of 314 (285-364) and only one (0.03%) had mild hypertriglyceridemia (179 mg/dl). The lipid profile (serum cholesterol, triglycerides, HDL and LDL) of SLE patients with SCH correlated insignificantly with their thyroid function (TSH and FT4) and the anti-TPO-ab titre (table 2).

Disease characteristics and SCH

TSH levels correlated positively yet insignificantly with the duration of SLE (r= 0.7, p= 0.12). While, anti-TPO-ab titre had borderline significant correlation with SLE duration (r= 0.81, p=0.05). Both TSH levels and anti-TPO-ab titre did not vary significantly with the SLEDAI or the cumulative steroids dose (table 3).

Table 1. Demographic and laboratory data of the studied SLE patients**.**

	SLE patients with normal thyroid function (n=34)	**SLE patients with subclinical hypothyroidism (n=6)**	**p**
Age(years) Range Mean ± SD	 6-17 13.5 ± 2.21	 10-17 14.3 ± 2.4	0.4
Sex Female Male	30 (88.2%) 4 (11.8%)	6 (100%) 0	1
SLEDAI Score Median (Range)	4.5 (0-10)	5 (2-7)	0.93
Duration of the disease (months) Median (Range)	 18(4-119)	 19 (7-72)	0.84
Cumulative steroid dose (grams) Median (Range)	 10.5 (1-107)	 14.9 (5-22)	0.57
ESR Median (Range)	46 (7-130)	68 (40-96)	0.16
ANA Positive Negative	27 7	4 2	0.6
Anti-dsDNA (N:<117Iu/ml) Median (Range)	 206 (10-678)	 257 (158-416)	0.57
C3 (N: 89-189) Median (Range)	90 (27-246)	116 (30-184)	0.9
Free T4 (ng/dl) Median (Range)	1.4 (0.5-2.0)	1.6 (1-2)	0.16
TSH (mlu/ml) Median (Range) Mean ± SD	 2.5 (0.33-4) 2.67 ± 1.03	 4.5(4.4-4.9) 4.56 ± 0.17	<0.001
Anti-TPO-ab titre (N:≤ 40 Iu/ml) Positive Median (Range)	 20 60 (20-240)	 4 45(20-100)	0.73
S.CHOL (N: 150-250 mg/dl) Median (range) Mean ± SD	 202 (130-364) 222.2 ± 53.3	 277 (207-300) 260.33 ± 41.31	0.05
TG (N: 65-165 mg/dl) Median (range) Mean ± SD	 122 (49-291) 130.4 ±40.3	 112 (95-155) 120.8± 25.5	0.53
HDL (N: > 35 mg/dl) Median (range) Mean ± SD	 45 (20-114) 46.7 ±18	 46 (35-60) 47± 9.27	0.53
LDL (N: 70-188 mg/dl) Median(range) Mean ± SD	 144 (70-188) 142.2 ± 30	 152 (105-185) 151.16 ± 29.53	0.47

SLE: Systemic lupus erythematosus, SLEDAI: Systemic lupus erythematosus disease activity index score, ESR: Erythrocyte sedimentation rate, C3: complement-3, Anti-dsDNA: Anti-double stranded DNA, ANA: Antinuclear antibodies, Free T4: Free thyroxine hormone, TSH: Thyroid stimulating hormone, anti-TPO-ab: Anti-thyroid peroxidase antibody, S.CHOL: Serum cholesterol, TG: Triglycerides, HDL: High density lipoproteins, LDL: Low density lipoproteins, SD: Standard deviation.

Table 2. The relationship between the lipid profile (serum cholesterol, triglycerides, HDL and LDL) and TSH, FT4 and anti-TPO-ab titre among SLE patients with subclinical hypothyroidism.

	TSH (mIu/ml)		Free T4 (ng/dl)		Anti-TPO-abs titre (Iu/ml)	
	r	p	r	p	r	p
S. CHOL (mg/dl)	0.21	0.68	-0.08	0.87	0.46	0.35
S.TG (mg/dl)	0.15	0.77	0.6	0.21	-0.2	0.7
S. HDL (mg/dl)	-0.69	0.12	-0.43	0.38	-0.23	0.66
S. LDL (mg/dl)	0.03	0.95	-0.08	0.87	0.32	0.54

S.CHOL: Serum cholesterol, S.TG: Serum triglycerides, S. HDL: Serum high density lipoproteins, S.LDL: Serum low density lipoproteins. Free T4: Free thyroxine hormone, TSH: Thyroid stimulating hormone, anti-TPO-ab: Anti-thyroid peroxidase antibody. P>0.05: non-significant

Table 3. The correlation between thyroid profile (TSH & FT4) and anti-TPO-ab titre of SLE patients with subclinical hypothyroidism and their SLEDAI score and cumulative oral prednisone dose.

	SLEDAI		Cumulative steroids dose (grams)	
	r	p	r	p
TSH (mIu/ml)	0.47	0.35	-0.19	0.73
Free T4 (ng/dl)	-0.03	0.96	-0.2	0.7
Anti-TPO-ab titre (Iu/ml)	0.57	0.24	0.25	0.63

SLEDAI: Systemic lupus erythematosus disease activity index, Free T4: Free thyroxine hormone, TSH: Thyroid stimulating hormone, anti-TPO-ab: Anti-thyroid peroxidase antibody. P >0.05: non-significant.

DISCUSSION

In this series, six SLE patients (15%) had SCH, none had subclinical hyperthyroidism. A number of previous studies reported that the prevalence of subclinical hypothyroidism among adult SLE patients were 13%, 5.7%, 10%, 10%, 13.7%, 11.5% and 12% respectively[12-18].

In the present study, the increased frequency of anti-TPO-ab positivity among lupus patients whether those with SCH or those with normal thyroid function suggests that anti-TPO-abs might have a pathogenic role in thyroid dysfunction in lupus children. It might herald the development of autoimmune thyroid disease in those with normal thyroid function, but this remains to be verified with longitudinal follow up studies. Another possibility is that anti-TPO-abs might be a part of the polyclonal hypergammaglobulinemia observed in lupus patients. It has been reported that antithyroglobulin and antimicrosomal (anti-TPO) antibodies were present in two thirds of patients with clinical or laboratory evidence of thyroid disease, but antibodies to thyroglobulin and microsomes were present, respectively, in 30% and 60% of euthyroid children with SLE[3]. The frequency of anti-TPO-abs observed in our studied children with SLE seems similar to that in their adult counterparts where a previous study showed that 70% of the studied adult SLE patients who developed autoimmune thyroid disease at follow-up had previously positive thyroid antibodies[17]. Also, the frequency of anti-TPO-abs in patients with autoimmune thyroid disease was found to be about 85%-100%[19]. However, the prevalence of anti-TPO-abs in previous studies conducted on adult SLE patients were found to be 27%, 23.2%, 3.7%, 15%, 25.6%, respectively[12-14,16,20].

In this study, anti-TPO-ab titre correlated positively, albeit insignificantly with the levels of TSH among SLE patients with SCH. This suggests that the former is directly involved in thyroid injury with subsequent thyroid dysfunction and elevated TSH levels. The lack of significance could be attributed to the small sample size.

The subclinical hypothyroidism observed in two of the studied SLE patients with negative anti-TPO-abs suggest that other mechanisms might come into play, possibly anti-thyroglobulin antibodies, immune mediated thyroid injury through other mechanisms or non-immune thyroid injury.

This study revealed that SLE activity as measured by SLEDAI did not affect the thyroid profile (TSH and FT4) and anti-TPO-ab titre of

studied SLE patients with SCH. This can be explained by the fact that SLE flare affects different organ variably. Therefore, disease activity does not necessarily affect the thyroid gland. This was in accordance with previous studies which found no significant correlation between lupus flare and titre of thyroid autoantibodies and thyroid function (FT4 and TSH) among their studied adult lupus patients[15,17,21,22]. Also, SLE disease activity did not predict the occurrence of hypothyroidism in adult lupus patients[16].

Other studies reported an association between thyroid autoimmunity and disease activity in SLE. This was explained in part by the effect of interferons, where elevated interferons, during flares of SLE activity, might lead to aberrant major histocompatibility complex (MHC) expression by thyrocytes, provoking an autoimmune response and the development of antithyroid antibodies[23-25]. Also, the fluctuating course of thyroid autoimmunity observed among a group of adult lupus patients was attributed to the variation of thyroid autoantibodies with SLE activity[21].

In the present study, the duration of SLE correlated positively with borderline significance with anti-TPO- ab titre but insignificantly with TSH levels. Small sample size could interfere with displaying the actual relationship between SLE duration and thyroid function and autoimmunity. Longer duration of SLE would give the altered immune system a greater chance to react against different organs with subsequent organ dysfunction in variable severity ranging from subtle biochemical disturbance to overt clinical disease. This was in agreement with a previous study in adult patients with lupus[26]. Another two studies in adults could not demonstrate such an effect[16,18].

The cumulative dose of oral prednisone given to the subgroup of studied SLE patients with SCH did not affect the thyroid function or the anti-TPO-ab titre. The effect of corticosteroids is controlled by its pharmacogenetics which has individual and ethnic variation. Inter-ethnic differences in glucocorticoids (GCs) response have been observed clinically[27], and the prevalence of many GC-regulated physiological traits differs across human populations[28]. Therefore, it seems that our lupus patients escaped the GC-induced thyroid dysfunction but larger sample and longer duration are needed to verify this suggestion. Similar results have been previously reported among adult lupus patients[17].

The SCH observed in 6 of our studied SLE children appeared to have borderline association with hypercholesterolemia supporting the role of thyroid gland in lipid metabolism particularly LDL and cholesterol clearance. Similarly other studies reported that elevations in TSH above the normal range was significantly correlated with increasing LDL and possibly serum cholesterol levels which might cause or contribute to a pro-atherogenic lipids level[29,30]. A possible explanation is the younger age of our studied SLE patients, and lack of follow up period which would not allow for the effects of thyroid dysfunction to be revealed.

Our study has some limitations due to small sample size and lack of follow up period that would otherwise reveal the actual prevalence of SCH among juvenile onset lupus and its adverse long term effects on serum lipids.

In conclusion, SCH is observed in up to 15% of children with SLE. SCH does not seem to affect serum lipids. Further studies are needed to delineate the long term effects of subclinical hypothyroidism among SLE patients and hence to evaluate the need for thyroxine replacement therapy. The role of anti-TPO-abs in prediction of immune mediated thyroid disorders among pediatric SLE warrants longitudinal studies.

REFERENCES

1. **Klein MS, Miller ML.** Systemic Lupus Erythematosus. In: Behrman RE, Kleigman RM, Jenson HB (eds). Nelson Textbook of Pediatrics, 17th ed. Philadelphia: W B Saunders Inc, 2004. p. 809-13.
2. **Viggiano DP, Saliva NA, Montandon AC, Barbosa VD.** Prevalence of thyroid autoimmune disease in patients with systemic lupus erythematosus. Arq Bras Endocrinal Metab 2008; 52: 531-6 (Abstract).
3. **Eberhard BA, Laxer RM, Eddy AA, Silverman ED.** Presence of thyroid abnormalities in children with systemic lupus erythematosus. J Pediatr 1991; 119: 277-9.
4. **Weetman AP. Chronic autoimmune thyroiditis. In: Braverman LE, Utiger RD** (editors). The Thyroid: A Fundamental and Clinical Text, 8th ed. Philadelphia: Lippincott Williams and Wilkins, 2000. p. 721-32.
5. **McDermott MT, Ridgway EC.** Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001; 86: 4585-90.
6. **Chu JW, Crapo LM.** Should mild subclinical hypothyroidism be treated? Am J Med 2002; 112: 422–3.
7. **Kahaly GJ.** Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 2000; 10: 665-79.

8. **Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al.** The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-7.
9. **Degroot LJ.** Heterogenicity of human antibodies to TPO thyroperoxides. Thyroid Autoimmunity 1990; 207: 177-82.
10. **Hay ID, Bayer MF.** American thyroid association assessment of current free thyroid hormone and thyrotropin measurements and guidelines for future clinical assays. Clin chem 1991; 37: 2002-8.
11. **Baloch Z, Carayon P, Conte-Devolex B, Demer LM, Feldt-Rasmussen U, Henry JF, et al.** Guidelines Committee, National Academy of Clinical Biochemistry (NACB). Laboratory medicine practice guidelines (LMPG). Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003; 13(1): 3-126.
12. **Chan A'l'Y, Soffhr AL, Bucknall RC.** Thyroid disease in systemic lupus erythematosus and rheumatoid arthritis. Rheumatology 2001; 4: 353-4.
13. **Pyne D, Isenberg DA.** Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis 2002; 61: 70-2.
14. **El-Sherif WT, El Gendi SS, Ashmawy MM.** Thyroid disorders and autoantibodies in systemic lupus erythematosus and rheumatoid arthritis patients. Egypt J Immunol 2004; 11: 81-90.
15. **Kakehasi AM, Dias VN, Duarte JE, Lanna CCD, de Carvalho MAP.** Thyroid abnormalities in systemic lupus erythematosus: a study in 100 Brazilian patients. Rev Bras Reumatol 2006; 46: 375-9.
16. **Al-Saleh J, Jassim V, El-Sayed M, Saleh N, Harb D.** Clinical and immunological manifestations in 151 SLE patients living in Dubai. Lupus 2008; 17: 62–6.
17. **Appenzeller S, Pallone AN, Natalin RA, Costallat LT.** Systemic lupus erythematosus, thyroid dysfunction, autoimmunity. J Clin Rheumatol 2009; 15: 117–9.
18. **Kumar K, Kole AK, Karmakar PS, Ghosh A.** The spectrum of thyroid disorders in systemic lupus erythematosus. Rheumatol Int 2010; doi: 10.1007/s00296-010-1556-50.
19. **Engler H, Staub JJ, Althaus B.** Assessment of antithyroglobulin and microsomal autoantibodies in patients with autoimmune thyroid disease: comparison of haemagglutination assay, enzyme-linked immunoassay and radioligand assay. Clinica Chimica Acta 1989; 179: 254-64.
20. **Park DJ, Cho CS, Lee SH, Park SH, Kim HY.** Thyroid disorders in Korean patients with systemic lupus erythematosus. Scand J Rheumatol 1995; 1:13–7.
21. **Kausman D, Isenberg DA.** Thyroid autoimmunity in systemic lupus erythematosus: the clinical significance of a fluctuating course. Br J Rheumatol 1995; 34: 361- 4.
22. **Mader R, Mishail S, Adawi M, Lavi I, Luboshitzky R.** Thyroid dysfunction in patients with systemic lupus erythematosus (SLE): relation to disease activity. Clin Rheumatol 2007; 11: 1891–4.
23. **Ytterberg SR, Schnitzer TJ.** Serum interferon levels in patients with systemic lupus erythematosus. Arthritis Rheum1982; 25: 401-6.
24. **Kim T, Kanayama Y, Negoro N, Okamura M, Takeda T, Inoue T.** Serum levels of interferons in patients with systemic lupus erythematosus. Clin Exp Immunol 1987; 70: 562-9.
25. **Magaro M, Zoli A, Altomonte L.** The association of silent thyroiditis with active systemic lupus erythematosus. Clin Exp Rheumatol 1992; 10: 67-70.
26. **Tsai RT, Chang TC, Wang CR, Chuang CY, Chen CR.** Thyroid disorders in Chinese patients with systemic lupus erythematosus. Rheumatol Int 1993; l3: 9-13.
27. **Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB.** Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000; 18: 3262–72.
28. **Lin SX, Carnethon M, Szklo M, Bertoni A.** Racial/ethnic differences in the association of triglycerides with other metabolic syndrome components: the Multi-Ethnic Study of Atherosclerosis. Metab Syndr Relat Disord 2011; 9: 35–40.
29. **Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, et al.** TSH-controlled l-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double-blind, placebo-controlled trial (Basal Thyroid Study). J Clin Endocrinol Metab 2001; 86: 4860-6.
30. **Ineck BA, Ng TM.** Effects of subclinical hypothyroidism and its treatment on serum lipids. Ann Pharmacotherapy 2003; 37: 725–30.