Int J Clin Exp Med 2014;7(9):2836-2843
www.ijcem.com /ISSN:1940-5901/IJCEM0001698

Original Article

Subclinical hypothyroidism is a risk factor for delayed clinical complete response in patients with systemic lupus erythematosus (SLE)

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Received August 4, 2014; Accepted August 28, 2014; Epub September 15, 2014; Published September 30, 2014

Abstract: The objective of the study was to investigate whether subclinical hypothyroidism is a risk factor for a delayed clinical complete response in patients with SLE. This study included 363 patients with SLE classified according to the ACR classification criteria. These patients were divided into three groups: those who had subclinical hypothyroidism, a euthyroid state, and clinical hypothyroidism. The first group contained 41 cases with SLE and subclinical hypothyroidism, the second group contained 7 cases with SLE and clinical hypothyroidism, and the third group contained 315 positive control cases with SLE and a euthyroid state. Patients were observed for general observational parameters, and an efficacy assessment was performed using SLEDAI, PGA, and SLICC. Results: Patients in the subclinical hypothyroidism group without supplementary treatment had no higher immune activity indicators, SLE activity, and organ damage than those SLE with euthyroid state. These parameters were also no higher than in those who were given treatment in the SLE with clinical hypothyroidism group at 6 months; Immune activity indicators, SLE activity, organ damage, and remission rate were improved after 3 months' supplementary treatment in 14 subclinical hypothyroidism cases that did not display remission non-remission cases at 6 months. Additionally, no significant difference in remission rate was observed in comparison with the group of SLE patients with a euthyroid state after 6 months' supplementary treatment. Conclusion: Subclinical hypothyroidism can the slow remission rate of SLE. Supplementary treatment should be performed earlier to improve the remission rate.

Keywords: Subclinical hypothyroidism, systemic lupus erythematosus, clinical complete response, SLEDAI

Introduction

The thyroid is a target organ of systemic lupus erythematosus (SLE). SLE patients are often present with a thyroid manifestation such as autoimmune thyroid disease, central hypothyroidism, euthyroid sick syndrome, thyroid nodules, hyperthyroidism, clinical hypothyroidism, or subclinical hypothyroidism. Among these manifestations, subclinical hypothyroidism has the highest incidence.

Many studies have shown that the incidence of subclinical hypothyroidism in SLE patients is higher than in the general population. SLE combined with subclinical hypothyroidism is associated with specific relative risk factors, and potential mechanisms have been clarified [1, 5]. However, whether subclinical hypothyroidism makes it more difficult for SLE patients to achieve clinical remission and whether early supplementary thyroid treatment is needed have not been clarified.

Therefore, we conducted this prospective study on the effect of subclinical hypothyroidism on the clinical remission effect of SLE.

Subjects and methods

Subjects

This study was a prospective observational study that included a total of 547 cases that were diagnosed with systemic lupus erythematosus at the Affiliated Hospital of Guilin Medical University from July 2003 to May 2012 in the Division of Rheumatology. Of these cases, the 363 cases with regular follow-ups were enrolled in the study. All patients underwent blood sam-

ple collection and testing for FT3, FT4 and TSH at 3 days after admission. Color Doppler ultrasound examinations of the patients' thyroids were also assessed. Every 3 months, FT3, FT4, and TSH were re-tested. According to the Thyroid Disease Laboratory Diagnostics Guide [6], subclinical hypothyroidism, a euthyroid state and clinical hypothyroidism were defined as follows: subclinical hypothyroidism patients had thyroid-stimulating hormone levels between 2.5 and 20 mIU/L, patients with a euthyroid state had thyroid-stimulating hormone levels between 0.44 and 2.5 mIU/L, and patients with clinical hypothyroidism had thyroid-stimulating hormone levels greater than 20 mIU/L. Out of these three hundred sixty-three cases, 41 (11.3%) were diagnosed with SLE and subclinical hypothyroidism; these patients included 2 males and 39 females and were aged 17-78 years with a median age of 35 years and a mean of 34.69 ± 17.34 years. In addition, 7 cases (1.9%) presented SLE and clinical hypothyroidism. Study inclusion standards were as follows: (1) SLE diagnosis based on the 1997 American College of Rheumatology standard, (2) approval by the Ethics Committee at our hospital, (3) signed informed consent and willingness to attend follow-up visits. The exclusion criteria included the following: (1) the emergence of other rheumatological and immunological diseases; (2) histories of cerebrovascular events associated with clinical cardiovascular disease, such as angina pectoris, myocardial infarction, hyperthyroidism, or pregnancy; (3) cases without the hospital Ethics Committee's approval; and (4) incomplete or missing data from follow-up visits.

Methods

Patient Groups: The 547 SLE patients initially considered for this study included 5 cases taking levothyroxine, 2 cases taking carbimazole, 52 cases lost to follow-up and with 3 deaths after 6 months, 122 cases that did not sign the informed consent or comply with the exclusion criteria, and 363 patients who were included in this study. These patients were divided into 3 groups: one group containing 41 patients with SLE and subclinical hypothyroidism, a second group of 7 patients with SLE and clinical hypothyroidism, and a third group of 315 patients with SLE and a euthyroid state. All patients had 5-10 mL of intravenous blood collected in the early morning after fasting 72 hours after they were hospitalized. This blood was treated with heparin sodium for anticoagulation and serum was centrifuged and stored at -80°C for testing of FT3, FT4, and TSH. Following a diagnosis of SLE and clinical hypothyroidism, patients were given thyroid therapy and we retested these patients FT3, FT4, and TSH levels every 3 months and assessed SLE disease activity. Patients in the SLE and subclinical hypothyroidism group were not given thyroid therapy in the first 6 months, but we retested their FT3, FT4, and TSH levels every 3 months and assessed SLE disease activity at the sixth month. At that point, if patients still had a thyroid-stimulating hormone level less than or equal to 2.5 or SLE disease without remission, these patients received thyroid supplementary treatment. All patients were followed for 12 months, at which time the study was ended.

General observation protocol

The general observation protocol included multiple variables, such as demographic variables (age, gender), blood pressure, menstrual history, a routine blood test, a routine urine test, tests of liver and kidney functions, and erythrocyte sedimentation rate (ESR). In addition, this protocol included measurement of the levels of complement (C3, C4), immunoglobulins (IgA, IgG, IgM), rheumatoid factor (RF), anti-ANA antibodies, anti-ds-DNA antibodies, anti-Sm antibodies, anti-SSA antibodies, anti-SSB antibodies, anti-AnuA antibodies, anti-AHA antibodies, FT3, FT4, TSH, and performing an EKG, chest X-rays, and 24-hour urine protein measurements.

Efficacy evaluation

A disease activity assessment was performed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) with a total score of 105 points with 0 to 9 points indicating stable disease and ≥ 10 points indicating active disease.

The patients' global assessment (PGA) was performed for a global assessment of the patients' current disease severity using the VAS score (0-100 mm).

The SLE organ or organ system damage was evaluated using the modified SLICC/ACR dam-

Table 1. Patient characteristics

Item	SLE-SH (n = 41)	SLE-ES (n = 315)	SLE-CH (n = 7)
Age	31.77 ± 13.14	30.89 ± 12.90	31.56 ± 13.26
Gender (male/female)	1/41	4/315	0/7
Hypertension, n (%)	6 (14.6)	45 (14.2)	1 (14.2)
Smoking rate, n (%)	2 (4.8)	11 (3.5)	0 (0)
TC (mmol/L)	8.03 ± 0.57*	4.98 ± 0.59	9.09 ± 0.63*
TG (mmol/L)	3.56 ± 0.48*	1.68 ± 0.51	3.87 ± 0.53*
HDL-C (mmol/L)	1.05 ± 0.11	1.07 ± 0.17	1.12 ± 0.14
LDL-C (mmol/L)	2.99 ± 0.37	3.23 ± 0.43	3.27± 0.47
VLDL-C (mmol/L)	0.57 ± 0.13	0.61 ± 0.17	0.59 ± 0.18
APOB	0.94 ± 0.26	0.88 ± 0.27	0.96 ± 0.31
FT3 (pmol/L)	3.75 ± 0.86	3.81 ± 0.89	0.79 ± 0.24
FT4 (pmol/L)	13.66 ± 3.28	14.11 ± 3.38	7.23 ± 1.57
TSH (mIU/L)	6.42 ± 1.97	1.35 ± 0.71	37.42 ± 8.73

Values are expressed as the means ± SD or number of individuals. TC: total cholesterol, TG: total triglyceride, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, VLDL-C: very low-density lipoprotein cholesterol, FT3: free triiodothyronine, FT4: free tetraiodothyronine, TSH: thyroid-stimulating hormone. *P < 0.05 (vs. SLE-ES).

Table 2. Comparison of patient indicators

Item	SLE-SH (n = 41)	SLE-ES (n = 315)	SLE-CH (n = 7)
24 h urine protein (g/d)	1.76 ± 0.28	1.64 ± 0.31	1.87 ± 0.3.26
Anti-dsDNA antibodies, n (%)	31 (75.6)	242 (76.8)	6 (85.7)
Anti-Sm antibodies, n (%)	12 (29.3)	94 (29.8)	2 (28.6)
ESR (mm/h)	43.7 ± 11.8	47.8 ± 12.8	44.9 ± 12.2
CRP (mg/L)	8.71 ± 2.32	7.95 ± 2.44	8.46 ± 2.27
C3 (g/L)	0.51 ± 0.25	0.46 ± 0.24	0.49 ± 0.26
SLEDAI	9.14 ± 3.67	8.75 ± 3.28	8.47 ± 3.86
PGA	62.50 ± 18.94	63.43 ± 19.33	64.58 ± 20.12
SLICC	5.5 ± 1.7	5.7 ± 1.5	5.9 ± 1.7

ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; SLEDAI, systemic lupus erythematosus disease activity index; PGA, patient's global assessment; SLICC, Systemic Lupus International Collaborating Clinics and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee Damage Index.

age index of 1997 [SLICC/ACR DI (Systemic Lupus International Collaborating Clinics and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee Damage Index)]

Statistical analysis

The SPSS 16.0 statistical software was used to conduct analyses. Data were expressed as x ± s to indicate single factor variance, and the SNK-q test was adopted for multiple comparisons. The Dunnett T3 test was used for comparisons of nonparametric data. Differences were considered significant when P < 0.05.

Results

Comparison of patients' demographic characteristics between groups. By comparing the patients' demographic characteristics, hypertension, and smoking rate, we showed that there were no statistically significant variations between the 3 groups with regard to any indicator (P > 0.05). This finding indicates that the indicators were balanced among each group, and the groups were comparable (**Table 1**).

Comparison of clinical characteristics between groups: Next, we compared the 24 h urine protein analysis, anti-dsDNA antibodies, anti-Sm antibodies, ESR, CRP, and C3 levels of the 3 groups of patients. The SLEDAI scores of the groups were 9.14 ± 3.67 in the SLE-SH group, 8.75 ± 3.28 in the SLE-ES group, 8.47 ± 3.86 in the SLE-CH group. We observed a PGA of 62.50 ± 18.94 in the SLE-ES group, 63.43 ± 19.33 in the SLE-CH group, and 64.58 ± 20.12 in the SLE-ES group. Based on these data, we concluded that all patients were in the active disease stage and had a similar level of disease activity. The SLICC values were 5.5 ± 1.7 in the SLE-ES group, 5.7 ± 1.5 in the SLE-CH group and 5.9 ± 1.7 in the SLE-ES group, indicating patients had a similar degree of organ damage (**Table 2**).

Change in ESR, CRP, C3, 24-hour urine protein levels, and CR in each group after 6 months

Next, we measured the ESR and CRP of the SLE-SH group, which was statistically signifi-

Table 3. Change in ESR, CRP, C3, 24-hour urine protein levels, and CR in each group after 6 months

Group	0 month				3 month				
	ESR	CRP	C3	24U	ESR	CRP	C3	24U	CR, n (%)
SLE-SH (n = 41)	43.7 ± 11.8	8.71 ± 2.32	0.51 ± 0.25	1.76 ± 0.28	41.3 ± 9.4	7.95 ± 2.47	0.55 ± 0.28	1.65 ± 0.43	19 (46.3)
SLE-ES (n = 315)	47.8 ± 12.8	7.95 ± 2.44	0.46 ± 0.24	1.64 ± 0.31	21.5 ± 8.6**,#	4.11 ± 1.76*,#	0.67 ± 0.15*,#	0.67 ± 0.29*,#	213 (67.6)#
SLE-CH (n = 7)	44.9 ± 12.2	8.46 ± 2.27	0.49 ± 0.26	1.87 ± 0.32	35.4 ± 10.1*	5.33 ± 2.09*	0.61 ± 0.13	1.03 ± 0.27	4 (57.1)
	6 month								
	ESR	CRP	C3	24U	CR, n (%)				
SLE-SH (n = 41)	26.7 ± 6.5	5.17 ± 3.36*	0.53 ± 0.36	1.12 ± 0.32	27 (65.8)				
SLE-ES (n = 315)	12.4 ± 9.1*,#	3.03 ± 1.25**,#	0.85 ± 0.22**,#	0.19 ± 0.47**,#	287 (91.1)#				
SLE-CH (n = 7)	14.6 ± 8.7*,#	4.12 ± 1.57*	0.76 ± 0.24**,#	0.26 ± 0.31**,#	6 (85.7)#				

*P < 0.05 (vs. 0 m); **P < 0.01 (vs. 0 m); #P < 0.05 (vs. SLE-SH).

Table 4. Evaluation of the SLEDAI, PGA, and SLICC score at 6 months in each group

Group	0 m			3 m			6 m		
	SLEDAI	PGA	SLICC	SLEDAI	PGA	SLICC	SLEDAI	PGA	SLICC
SLE-SH (n = 41)	9.14 ± 3.67	62.50 ± 18.94	5.5 ± 1.7	8.43 ± 2.19	53.78 ± 16.57	4.6 ± 1.8	3.76 ± 2.19*	42.24 ± 14.42*	3.1 ± 1.2*
SLE-ES (n = 315)	8.75 ± 3.28	63.43 ± 19.33	5.7 ± 1.5	3.36 ± 1.15**,#	24.39 ± 8.12**,#	2.3 ± 1.1**,#	0.86 ± 0.27**,#	13.68 ± 8.12**,#	0.5 ± 0.3**,#
SLE-CH (n = 7)	8.47 ± 3.86	64.58 ± 20.12	5.9 ± 1.7	5.32 ± 1.47*,#	29.77 ± 9.96**,#	3.3 ± 1.3*,#	1.63 ± 0.56**,#	24.76 ± 8.49**,#	1.2 ± 0.4**,#

*P < 0.05 (vs. 0 m); **P < 0.01 (vs. 0 m); #P < 0.05 (vs. SLE-SH).

Table 5. Fourteen cases of non-remission in SLE-CH patients after supplementary treatment

Time	6 m	9 m	12 m
24 h urine protein	1.43 ± 0.42	0.59 ± 0.24**	0.23 ± 0.21**
FT3	3.65 ± 0.79	3.78 ± 0.83	3.81 ± 0.85
FT4	12.89 ± 3.42	13.90 ± 3.52	13.46 ± 3.78
TSH	5.25 ± 1.47	1.72 ± 0.83**	1.35 ± 0.76**
ESR	46.42 ± 11.8	19.5 ± 8.6**	13.1 ± 8.5**
CRP	8.64 ± 4.37	4.47 ± 1.53**	3.56 ± 1.46**
C3	0.36 ± 0.41	0.68 ± 0.36*	0.86 ± 0.33**
SLEDAI	6.38 ± 3.46	1.23 ± 0.53**	0.93 ± 0.31**
PGA	56.77 ± 18.57	21.43 ± 9.25**	12.48 ± 7.63**
SLICC	4.7 ± 1.5	0.8 ± 0.3**	0.6 ± 0.4**
CR, n (%)		9 (64.2)	12 (85.7)Δ

*P < 0.05 (vs. not treatment); **P < 0.01 (vs. not treatment); ΔP < 0.05 (vs. SLE-ES 6 m CR).

cantly different between the sixth month and the beginning of the study. The ESR, CRP, C3 level, and 24-hour urine protein levels of the SLE-ES group was only statistically significant comparing the 3rd month with the beginning of the study. After supplementary treatment, the ESR and CRP of the SLE-CH group showed a statistically significant difference both at third month and the sixth month, while the C3 level and 24-hour urine protein levels were only statistically significant at the sixth month. Comparing the SLE-ES group with the SLE-SH group, the ESR, CRP, C3 level, and 24-hour urine protein levels showed statistically significant differences both at the third month and the sixth month. While complete remission was observed in 65.8% of the SLE-SH group, 14 cases did not achieve CR, which was statistically different from the result observed in the SLE-ES and SLE-CH groups (**Table 3**).

Evaluation of the SLEDAI, PGA, and SLICC score at 6 months in each group

The SLEDAI, PGA, and SLICC scores of the SLE-SH group of patients at the 6-month and the 0-month time points were statistically significant, but the 3-month time point was not statistically significant. The values for the SLE-ES group at 3 months was statistically significant compared with that at 0 month. The SLEDAI, PGA, and SLICC of the SLE-CH group exhibited a statistically significant difference at 3 months following supplementary treatment, and the two groups were statistically significantly different at 6 months. When we compared the SLE-SH group with the SLE-ES and SLE-CH groups, the SLEDAI, PGA, SLICC, and 24-hour urine protein levels were statistically significant at 3 months and 6 months (**Table 4**).

Fourteen cases of non-remission in SLE-CH patients after supplementary treatment

The ESR, CRP, C3 levels, 24-hour urine protein levels, SLEDAI, PGA, and SLICC of 14 cases of patients who did not undergo remission of SLE symptoms had a significant improvement after 3 and 6 months of supplementary treatment for hypothyroidism. This difference was statistically significant compared with the values observed in patients who did not receive this supplement at 6 months. After supplementary treatment for 3 months, a total of 9 patients underwent clinical remission. After 6 months of supplementary treatment, a total of 12 patients displayed clinical remission; however, the remission rate was still lower than in the SLE-ES group (85.7 vs 91.1), both P < 0.05 (**Table 5**).

Discussion

SLE is a multi-organ, multisystem autoimmune disease that not only has a wide range of clinical manifestations but also results in a range of antibodies in the serum against the nucleus, the cytoplasm, and other non-organ-specific targets. The pathogenesis of subclinical hypothyroidism has been shown to be related to the body's own immune responses [7, 8], meaning that patients with SLE are at high risk for the occurrence of subclinical hypothyroidism. Our clinical studies and the research results of other groups have confirmed that SLE patients have a prevalence of subclinical hypothyroidism that is significantly higher than the normal population. This result also confirms that subclinical hypothyroidism is a risk factors for SLE [1, 9, 10]. The reason for this association is that SLE is considered to have a pathological base of small vessel vasculitis. Extensive and severe vasculitis can affect other organs, including the thyroid, leading to damaged thyroid function and immune dysfunction in SLE patients. In addition, humoral immune hyperactivity can

produce large amounts of antibodies against different organs, resulting in the damage to organ function [11, 12]. Meanwhile SLE can cause multiple organ damage, including a decrease in 5-deiodinase activity when the liver is damaged, a decreased conversion of T4 into T3 when the kidney is damaged, an increased amount of T3, T4 discharge in the urine, and decreased T4 deiodinase activity decreased, causing significant T3 decreases.

In our study, ESR, CRP, and C3 levels displayed no significant differences in patients in the SLE-SH group and the SLE-ES group, indicating that there is no clear correlation in immune activity indicators in subclinical hypothyroidism and SLE patients. Thus, these factors may not play a major role in the in the occurrence of the disease, which matches the results of Rojas-Villarraga and Nakamura [13, 14]. However, these results suggest that TC and TG among the three groups were statistically different. The reason for this observation is that subclinical hypothyroidism is associated with dyslipidemia [15, 16], indicating that we should be concerned about patients with lipid disorders. Early intervention may prevent damage to endothelial function and stop subclinical hypothyroidism caused by elevated blood lipids and atherosclerosis in SLE, which can be followed by the emergence of concurrent ischemic heart disease. Meanwhile, SLEDAI, PGA, and SLICC were not significantly different between the three groups, indicating that subclinical hypothyroidism, SLE disease activity, and organ damage were not clearly related. In addition, our study did not find a direct correlation between 24-hour urine protein and LN in subclinical hypothyroidism. It cannot be demonstrated whether 24-hour urine protein and LN are independent risk factors for subclinical hypothyroidism, which is different from the result of Gao's study. These differences may be related to economic differences between regions or the rapidity with which patients in these studies received treatment. LN had a higher incidence of related cases which can be observed from our data, in which the three groups' 24-hour urine protein levels were significantly higher than in Gao's study.

These results indicate that for our SLE patients, regardless of their activity and organ damage, we should routinely test FT3, FT4, and TSH to confirm whether SLE is combined with subclinical hypothyroidism. However, we should also determine whether subclinical hypothyroidism affects the SLE disease process, which is an interesting clinical problem. Based on our data, we found that after 6 months of treatment without supplementary treatment, patients with SLE and subclinical hypothyroidism displayed immune activity indicators, SLE disease activity, and organ damage that were higher than in the SLE with euthyroid state group and even higher than the SLE and clinical hypothyroidism group who received supplementary treatment. The remission rate of the subclinical hypothyroidism group was lower than the other two groups of patients. This finding indicates that subclinical hypothyroidism can delay SLE remission. Future studies could determine whether the reason for this observation is that subclinical hypothyroidism affects the hypothalamus-pituitary-adrenal-related axis, thus affecting the adrenal cortex hormone receptors such that the group of patients on the drugs, whose glucocorticoid responsiveness is weakened, was associated with a decrease in remission rates.

It is still unclear whether we should start thyroid treatment for SLE combined with subclinical hypothyroidism. For primary subclinical hypothyroidism, the United States Association of Clinical Endocrinologists and the American Thyroid Association and the Endocrine Society proposed the following guidelines for subclinical hypothyroidism in 2012 [17]: patients should be treated when TSH > 10 mIU/L. This criterion is particularly applicable when patients have the following status: clinical symptoms of thyroid dysfunction, anti-microsomal/anti-thyroid peroxidase antibody (TPOAb) positive, atherosclerotic cardiovascular disease, evidence of heart failure, or risk factors for these diseases. However, when the TSH levels are 4.5-10.0 mIU/L, it is controversial whether treatment is necessary. Several researchers believe that little benefit is derived from this treatment and that the treatment increases the incidence of atrial fibrillation and osteoporosis. Therefore, the guidelines suggest that patients should be observed. It is not clear whether this recommendation is suitable for patients with SLE.

Our study found that the immune activity indicators, SLE activity, and organ damage remission rate were improved after 3 months' supplementary treatment in 14 subclinical

hypothyroidism cases after 6 months without remission, which was not significantly different from the group of SLE with patients with a euthyroid state.

These data show that subclinical hypothyroidism can slow the clinical remission rate of SLE. SLE patients remission rates can increase after hypothyroidism is corrected, but the statistical analysis indicated that the remission rate was still lower for the subclinical hypothyroidism patients than the SLE-ES group at 6th month. Therefore, SLE patients should routinely have FT3, FT4, and TSH tests and should take early supplemental treatments if they are found to have subclinical hypothyroidism, even in patients with TSH 4.5-10.0 mIU/L. Our advice is that in SLE patients with hypothyroidism, replacement therapy should be taken early to improve remission rates, but these recommendations differ from the AACE/ATA recommendations for stratified replacement therapy.

Our findings contribute to the growing body of evidence regarding adverse effects resulting from SLE subclinical hyperthyroidism. Although we observed statistically significant data for both end points of our study, our findings require confirmation with additional cohorts.

Acknowledgements

This study was supported by grants from the Chinese National Natural Science Foundation (No. 81160376, No. 81360462) Guangxi Natural Science Foundation (No. 2013GXNSFAA019111, No. 2013GXNSFBA019181), The Guangxi Department of education Natural Science Foundation (No. 201106LX363), Guilin Natural Science Foundation (No. 20120121-1-7).

Disclosure of conflict of interest

None.

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