

Risk factors of thyroid dysfunction in patients with rheumatoid arthritis

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Abstract

Introduction: The study aimed to investigate the complicating thyroid dysfunction situation in patients with rheumatoid arthritis (RA) and to analyze the related risk factors of thyroid dysfunction in RA patients.

Material and methods: The retrospective analysis of the clinical data and laboratory examinations of 290 cases of RA and 200 healthy individuals undergoing the physical examination was carried out. The thyroid function, anti-thyroid antibodies, and routine laboratory test items were measured. The RA disease activity score (DAS28) was determined in RA patients. Logistic analysis was used to identify risk factors associated with thyroid dysfunction in RA patients.

Results: The detection rate of RA combined with thyroid dysfunction was 30.0%, which was higher than in the control group (7%, 14 cases). In the thyroid function test, levels of total triiodothyronine (T3) and free triiodothyronine (FT3) were lower, while thyrotropin (TSH), antithyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TgAb) were higher in the RA group. There was a difference in hemoglobin (HGB) and total cholesterol (TC) in RA patients with and without abnormal thyroid function.

Conclusions: Rheumatoid arthritis patients are more prone to develop thyroid dysfunction than healthy individuals, especially hypothyroidism. HGB and TC were correlated with thyroid hormones and antibodies and were risk factors correlated with thyroid dysfunction in RA patients. Clinical work should pay full attention to changes in thyroid function in patients with RA.

Key words: rheumatoid arthritis, thyroid function, risk, clinical.

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Introduction

Rheumatoid arthritis (RA) is a common clinical disease with a complex pathogenesis. It is a systemic immune disorder with erosive symmetric polyarthritis as its main clinical manifestation [1]. If it is not cured, RA will eventually lead to joint tissue degradation and loss of function [2]. The long term of RA seriously affects the quality of life of patients, leading to high disability and mortality rates and poor prognosis [3]. Autoimmune diseases often accompany each other, such as systemic lupus erythematosus, and Sjogren's syndrome [4]. Cardiovascular disease is one of the dominant causes of death in RA patients, and disease of cardiac origin accounts for nearly half of the causes of death in RA patients [5]. It has been reported that the occurrence of thyroid dysfunction is related to a variety of rheumatic diseases [6]. Hyperthyroidism and hypothyroidism play a vital role in cardiovascular disease, which can directly lead to arrhythmia,

heart enlargement, heart failure, and even other adverse outcomes [7].

Currently, thyroid function abnormalities have become a common disease worldwide. Autoimmune thyroid disease (AITD), including autoimmune thyroiditis and goiter, is one of the most important causes of thyroid dysfunction [8]. AITD is a common organ-immune disease with characteristic antibodies, but the pathogenesis is also unclear. As both thyroid dysfunction and RA are immune diseases, the association between them is interesting to explore. The association between RA and thyroid function has been extensively studied in recent years [9, 10]. However, a clear conclusion is still lacking [11].

In this study, thyroid function tests were performed on 290 RA patients to understand the status of thyroid function in RA patients. Meanwhile, the correlation between laboratory-related indexes and thyroid function indexes in RA patients and the related risk factors of thyroid dysfunction in RA patients were evaluated.

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Material and methods

Study population and general information

From October 2019 to December 2021, 290 RA patients who attended the Qinhuangdao Hospital of Integrated Traditional Chinese and Western Medicine were selected for the study, and all patients underwent relevant examinations. The participants met the 2010 classification criteria of the American College of Rheumatology/European League for the Control of Prevention of Rheumatic Diseases (ACR/EULAR) classification criteria [12]. According to the thyroid function, the RA patients were divided into the abnormal thyroid function RA group ($n = 87$) and the normal thyroid function RA group ($n = 203$). The clinical data of the patients were collected, including age and sex. The 87 RA patients with abnormal thyroid function were divided into four groups: (1) RA patients without thyroid dysfunction as group A, (2) RA patients with hypothyroidism as group B, (3) RA patients with hyperthyroidism as group C, (4) RA patients with low T3/T4 syndrome as group D.

Inclusion criteria: (a) all enrolled patients met the diagnostic criteria for RA; (b) all patients had undergone thyroid function tests (TT3, FT3, TT4, FT4, TSH) and thyroid antibody determination (TPO-Ab and TgAb); (c) RA patients had not taken any drugs that had significant effects on thyroid function within 1 year. Exclusion criteria: (a) patients diagnosed with thyroid diseases prior to RA diagnosis, including diffuse thyroid lesions (hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis) and focal thyroid lesions; (b) patients who had undergone thyroid surgery before; (c) relevant medication or radiotherapy for thyroid diseases; (d) patients with a history of malignant tumors; (e) patients with other autoimmune diseases.

The control group comprised 200 participants who underwent physical examination in our hospital during the same period. The control group included 52 males and 148 females with a mean age of 45.37 ± 12.01 years. The basic clinical data of the control group showed no statistically significant difference from the RA patient group.

This study was approved by the Ethical Committee of Qinhuangdao Hospital of Integrated Traditional Chinese and Western Medicine and written informed content was provided by all the participants.

Clinical observation indexes

Patients were advised to fast for more than 8 hours in one day before blood collection, and 5 ml of elbow vein blood was withdrawn early in the morning at about 8:00 a.m. The serum was centrifuged and set aside at -80°C for use. Blood routine indexes were detected by a SYS-MEX-XE2100 fully automatic hematology analyzer (Sysmex, Japan). The fully automated chemiluminescence analyzer (Roche Elecsys, Basel, Switzerland) was used to measure the total triiodothyronine (T3), free triiodothy-

ronine (FT3), total thyroxine (T4), free thyroxine (FT4), thyrotropin (TSH), antithyroglobulin antibody (TgAb), and antithyroid peroxidase antibody (TPOAb). The chemiluminescence immunoassay analyzer (Roche Diagnostics, Mannheim, Germany) was used to measure the erythrocyte sedimentation rate (ESR, measured by Westergren assay), C-reactive protein (CRP, determined by the latex agglutination method), and rheumatoid factor (RF, determined by the latex agglutination method).

Diagnostic criteria for thyroid function

Thyroid dysfunction was diagnosed based on the Guidelines for the Diagnosis and Treatment of Hypothyroidism in Adults issued by the Chinese Society of Endocrinology in 2017 and the Guidelines for the Primary Diagnosis and Treatment of Hyperthyroidism issued by the Chinese Society of General Medicine in 2019.

The abnormal thyroid function group included hyperthyroidism (clinical features and symptoms of hypermetabolism; goiter and/or thyroid nodules; serum T3, T4, FT3, FT4 increased, TSH decreased), subclinical hyperthyroidism (serum TSH level below the lower limit of normal value, while T3 and T4 are within the normal range, without or with mild hyperthyroidism symptoms), hypothyroidism (serum TSH increased, T4 and FT4 decreased, T3 and FT3 were normal in the early stage but decreased in the late stage), subclinical hypothyroidism (serum TSH increased while T4 and FT4 are normal), and low T3/T4 syndrome. The reference normal range of each item in our laboratory is as follows: TSH, 0.27-4.20 mIU/l; TT3, 1.30-3.10 nmol/l; FT3, 3.10-6.80 pmol/l; TT4, 66.0-181.0 nmol/l; FT4, 12.0-22.00 pmol/l; TPOAb < 34 IU/ml; TgAb < 115 IU/ml.

Disease activity assessment

The RA disease activity was assessed and expressed as the Disease Activity Score in 28 joints (DAS28). The formula was as follows:

$$\text{DAS28-ESR} = (0.56 \cdot \sqrt{\text{TJC}}) + (0.28 \cdot \sqrt{\text{SJC}}) + (0.7 \cdot \ln(\text{ESR})) + (0.014 \cdot \text{GH})$$

$$\text{DAS28-CRP} = (0.56 \cdot \sqrt{\text{TJC}}) + (0.28 \cdot \sqrt{\text{SJC}}) + (0.36 \cdot \ln(\text{CRP}+1)) + (0.014 \cdot \text{PtGA}) + 0.96$$

TJC = tender joint count and SJC = swollen joint count. Disease activity classification: disease remission: $\text{DAS28} < 2.6$; low disease activity: $2.6 \leq \text{DAS28} < 3.2$; moderate disease activity: $3.2 < \text{DAS28} \leq 5.1$; high disease activity: $\text{DAS28} > 5.1$.

Statistical analysis

Measurement data are presented as mean \pm SD or median and interquartile range (M(P25, P75)), and count data are expressed as percentages. IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, New York, NY, USA) was used for statistical analysis and differences were tested using the *t*-test for measurement data and the χ^2 test for count data. Compar-

Table 1. Baseline data and blood test comparison of subjects

Parameters	Control	RA patients	P-value
	n = 200	n = 290	
Sex (male/female)	52/148	69/221	0.578
Age (years)	45.37 ±12.01	46.62 ±10.06	0.212
Thyroid function (abnormal/normal)	14/186	87/203	< 0.001
hyperthyroidism	2	9	0.122
subclinical hyperthyroidism	2	6	0.359
hypothyroidism	2	29	< 0.001
subclinical hypothyroidism	4	17	0.038
low T3/T4 syndrome	4	26	0.002
TC (mmol/l)	4.19 ±1.29	4.28 ±1.02	0.235
TG (mmol/l)	1.56 ±0.21	1.42 ±0.16	0.663

TC – total cholesterol, TG – triglyceride

Table 2. Thyroid function data comparison of the subjects

Parameters	Control	RA patients	P-value
	n = 200	n = 290	
T3 (nmol/l)	2.03 ±0.48	1.82 ±0.36	< 0.001
T4 (nmol/l)	104.24 ±19.38	101.24 ±22.84	0.119
FT3 (pmol/l)	4.28 ±0.84	4.11 ±0.76	0.018
FT4 (pmol/l)	15.96 ±2.91	14.90 ±2.98	< 0.001
TSH (mIU/l)	2.15 ±0.94	3.22 ±1.46	< 0.001
TPOAb (IU/ml)	20.30 (14.41, 25.36)	25.23 (18.39, 37.17)	< 0.001
TgAb (ng/ml)	17.66 (12.8, 22.92)	19.02 (14.03, 27.45)	< 0.001

T3 – triiodothyronine, T4 – total thyroxine, FT3 – free triiodothyronine, FT4 – free thyroxine, TSH – thyroid-stimulating hormone, TPOAb – thyroid peroxidase antibody, TgAb – thyroglobulin antibodies

isons between groups of non-normally distributed data were made using the Kruskal-Wallis H (K) test. The screened factors were included in the multivariate logistic regression analysis with a test level of $\alpha = 0.05$. The results with $p < 0.05$ were considered statistically significant.

Results

General data and detection rate of thyroid dysfunction in RA patients

The RA group included 69 males and 221 females with a mean age of 46.62 ±10.06 years (range, 29-65 years). Among the RA patients, 87 had thyroid function abnormalities, accounting for 30% of the total, of whom 15 had hyperthyroidism, including 9 cases of hyperthyroidism and 6 cases of subclinical hyperthyroidism, and 46 had hypothyroidism, including 29 cases of hypothyroidism and 17 of subclinical hypothyroidism, as well as 26 cases of low T3/T4 syndrome. The control group included 52 males and 148 females with a mean age of 45.37 ±12.01

years (range, 25-65 years). Among the control group, only 14 cases had abnormal thyroid function, including 2 hyperthyroidism cases, 2 subclinical hyperthyroidism cases, 2 hypothyroidism cases, 4 subclinical hypothyroidism cases, and 4 low T3/T4 syndrome cases. The number of patients with hypothyroidism and low T3/T4 syndrome were significantly different between controls and RA patients. The age and sex between control and RA groups were not significantly different, while the rate of thyroid dysfunction was significantly different (Table 1).

Comparison of thyroid gland function test results between groups

The results of T3, T4, FT3, and FT4 in the RA group were lower and the level of TSH in the RA group was higher than those in the control group, but only T3, FT3, FT4, and TSH had a significant difference (Table 2). The thyroid-related antibodies in both groups were compared. TPOAb and TgAb in the RA group were higher than those in the control group and the difference was statistically significant (Table 2).

Table 3. Comparison of laboratory indicators and DAS28 scores among rheumatoid arthritis patients with different thyroid function

Parameters	Thyroid function				P-value
	A (n = 203)	B (n = 46)	C (n = 15)	D (n = 26)	
PLT (10 ⁹ /l)	221.60 (182.8, 269.8)	215.00 (175.5, 257.6)	260.4 (182.2, 268.2)	248.8 (182.2, 266.8)	0.51
HGB(g/l)	129.50 ±11.62	121.80 ±12.09*	121.9 ±11.65	117.2 ±10.25*	< 0.001
TC (mmol/l)	4.17 ±1.07	4.70 ±0.87*	4.44 ±0.73	4.47 ±0.61	0.007
TG (mmol/l)	1.41 ±0.15	1.46 ±0.10	1.44 ±0.07	1.42 ±0.09	0.21
CRP (mg/l)	32.65 ±11.49	30.61 ±10.88	33.64 ±9.15	33.39 ±11.72	0.65
ESR (mm/H)	28.60 (20.83, 40.10)	30.24 (21.30, 36.81)	32.94 (24.04, 41.30)	29.97 (22.22, 40.13)	0.80
C3 (g/l)	1.13 ±0.10	1.18 ±0.09*	1.20 ±0.15	1.17 ±0.12	0.01
C4 (g/l)	0.28 ±0.11	0.29 ±0.10	0.32 ±0.09	0.26 ±0.11	0.34
IgG (g/l)	18.31 ±7.79	17.32 ±7.53	16.07 ±7.55	18.81 ±7.83	0.60
IgA (g/l)	2.72 ±1.05	2.58 ±0.79	2.40 ±0.81	2.74 ±0.81	0.55
IgM (g/l)	2.05 ±0.77	2.21 ±0.74	1.82 ±0.76	2.16 ±0.84	0.32
RF (IU/ml)	129.1 ±69.76	123.3 ±64.69	122.9 ±62.56	128.9 ±67.46	0.95
DAS28 score	4.81 ±1.53	4.93 ±1.66	4.94 ±0.89	4.96 ±1.48	0.92

PLT – platelet, HGB – hemoglobin, TC – total cholesterol, TG – triglyceride, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, C3 – complement 3, C4 – complement 4, IgG – immunoglobulin G, IgA – immunoglobulin A, IgM – immunoglobulin M, RF – rheumatoid factor
*p < 0.05 vs. group A

Table 4. Correlation between thyroid function and laboratory parameters in patients with rheumatoid arthritis (r)

Indicators	T3	T4	FT3	FT4	TSH	TPOAb	TgAb
HGB	0.086	0.015	0.351*	0.031	-0.244*	-0.020	-0.028
TC	-0.090	-0.020	-0.298*	-0.033	0.181*	0.043	0.022

T3 – triiodothyronine, T4 – total thyroxine, FT3 – free triiodothyronine, FT4 – free thyroxine, TSH – thyroid-stimulating hormone, TPOAb – thyroid peroxidase antibody, TgAb – thyroglobulin antibodies, HGB – hemoglobin, TC – total cholesterol.
*indicates p < 0.05

Comparison of general laboratory results of RA patients with abnormal and ordinary thyroid function

Compared with the normal thyroid function RA group (group A), hemoglobin (HGB) was lower, and total cholesterol (TC) and complement 3 (C3) were higher in the RA patients with abnormal thyroid function (p < 0.05, Table 3). The HGB, TC, and C3 values in patients with hypothyroidism (group B) showed a significant difference from RA patients without thyroid dysfunction. In addition, patients with hypothyroidism (group B) showed higher TC values in contrast with hyperthyroidism (group C), but it was not a significant difference. The differences in platelet (PLT), triglyceride (TG), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complement 4 (C4), immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), and rheumatoid factor (RF) were not significant. The DAS28 score in the RA patients with abnormal thyroid function was higher than that in the RA patients

with normal thyroid function, but the difference was not statistically significant (Table 3).

Correlation between laboratory indicators and thyroid function indicators in RA patients

Furthermore, HGB and TC were included in the correlation analysis with thyroid function indicators in RA patients. The data in Table 4 indicate that HGB levels were correlated with FT3 (positively) and TSH (negatively). The TC levels were correlated with FT3 (negatively) and TSH (positively).

Analysis of risk factors of RA complicated with thyroid dysfunction

To further investigate the risk factors for RA combined with thyroid dysfunction, the laboratory indicators were included in the multivariate logistic regression analysis, and RA patients with normal thyroid function were used as the reference. The data indicated that HGB and TC were

risk factors for RA patients with abnormal thyroid dysfunction (Table 5).

Discussion

With the in-depth study of RA, it is increasingly recognized that RA is not just a disease confined to the joints but is an autoimmune disease that can involve multiple systems throughout the body, and damage to the endocrine system often occurs [13]. RA-complicated thyroid dysfunction is now receiving more attention, but its exact pathogenesis is unclear. The incidence of thyroid dysfunction in patients with RA ranges from 6.0% to 33.8% in the literature [14]. The prevalence of RA with thyroid dysfunction varies greatly [10, 11]. Nazary K and co-workers reported that 25.5% of RA patients had thyroid dysfunction compared to 11.5% of controls [10]. A study on 65 consecutive RA patients by Li Q and co-workers reported a high prevalence rate (32.3%) of abnormal thyroid function in contrast to controls (14.2%) and revealed that both hypothyroidism and hyperthyroidism were correlated with RA [9]. Herein, the detection rate of thyroid dysfunction in RA patients was 30%, of which hypothyroidism and subclinical hypothyroidism constituted 52.87%. In contrast, the prevalence of thyroid dysfunction was only 7% in the control group. Moreover, our case study indicated that hypothyroidism, subclinical hypothyroidism, and low T3/T4 syndrome in RA patients were different from the controls, which further confirmed the relationship between RA and hypothyroidism and provided evidence that RA patients may have a tendency for low T3/T4 syndrome. Regarding the discrepancy in studies reporting RA combined with abnormal thyroid function, a possible explanation is that the prevalence of abnormal thyroid function may be related to differences in iodine intake in some regions [15, 16].

Hypothyroidism was the most prevalent, followed by low T3/T4 syndrome and subclinical hypothyroidism, and hyperthyroidism was the least common. Corresponding to this, T3 and FT3 were lower, TSH was higher, and TPOAb and TgAb were higher in the RA group than in the control group. The lower FT3 and higher TSH were analyzed as a biofeedback effect of lower T3. Moreover, FT4, sensitive to hypothyroidism [17], was lower in RA patients than in the control group. Elevated TPOAb and TgAb, on the other hand, suggest the presence of an abnormal autoimmune response. It has been reported that in a Colombian cohort of 800 RA patients, the prevalence of TPOAb antibodies was 37.8%, that of TgAb antibodies was 20.8%, and 14.1% of patients had multiple autoimmune antibodies [18]. In a recent study, TPOAb antibodies were positive in 32.0% of cases in RA patients compared to 15.0% in controls [14].

In this study, a comparison between laboratory parameters and DAS28 scores in RA patients with abnormal and normal thyroid function was carried out and differences were found in HGB and TC. Consequently, the thyroid

Table 5. Risk factors of thyroid dysfunction in patients with rheumatoid arthritis

Parameters	Multivariate logistic analysis		P-value
	HR	95% CI for HR	
Age	0.839	0.492-1.431	0.519
Sex	0.933	0.498-1.751	0.830
PLT	0.811	0.477-1.379	0.439
HGB*	1.700	1.003-2.881	0.049
TC*	0.528	0.304-0.914	0.023
TG	0.606	0.353-1.041	0.069
CRP	1.261	0.740-2.150	0.394
ESR	0.800	0.465-1.379	0.423
C3	0.724	0.4261.232	0.234
C4	0.991	0.582-1.687	0.974
IgG	1.087	0.632-1.872	0.762
IgA	1.339	0.783-2.289	0.286
IgM	0.647	0.378-1.106	0.111
RF	1.145	0.675-1.943	0.615

PLT – platelets, HGB – hemoglobin, TC – total cholesterol, TG – triglyceride, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, C3 – complement 3, C4 – complement 4, IgG – immunoglobulin G, IgA – immunoglobulin A, IgM – immunoglobulin M, RF – rheumatoid factor
* $p < 0.05$

function of RA patients was correlated with HGB and TC. The levels of HGB and TC levels were correlated with FT3 and TSH. These data suggest that RA patients with abnormal thyroid function are prone to complicated anemia and hypercholesterolemia [19, 20]. RA itself is often associated with the pathogenesis of anemia in chronic disease, and the degree of anemia is related to inflammatory activity [21]. Hypothyroidism also inhibits bone marrow hematopoiesis and reduces erythropoietin, leading to anemia [22, 23]. Anemia due to RA inflammation and thyroid dysfunction are causally related and mutually reinforcing. Therefore, patients with RA should pay attention not only to the diagnosis of thyroid disease, but also to the results of laboratory tests such as routine blood tests and blood lipids, to observe whether there is a combination of hyperlipidemia, anemia, and other complications.

This study has certain limitations. Firstly, it is a retrospective study with a small sample size, which may have a certain selection bias. A large cohort is needed to reduce analysis bias in future research. Secondly, the data collected in this study have a long time span, which may lead to errors in the laboratory results. Finally, the potential harm of thyroid dysfunction in RA patients needs to be further explored.

Conclusions

This study indicated that RA patients are more likely to have thyroid function abnormalities than the healthy population, with hypothyroidism being the most common.

HGB and TC were risk factors associated with thyroid dysfunction in RA patients. Therefore, it is suggested that clinicians should pay attention to the detection of thyroid function in patients with RA, especially in patients with concomitant hypothyroidism.

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Disclosures

The study was approved by the Bioethics Committee of the Qinhuangdao Hospital of Integrated Traditional Chinese and Western Medicine (Approval No. 2019-053).

The authors declare no conflict of interest.

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