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Serum Resolvin E1 Levels and Its Relationship with Thyroid Autoimmunity in Hashimoto's Thyroiditis

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Research article

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Abstract

Objective: Omega-3 polyunsaturated fatty acids (PUFAs) can produce lipid mediators with both antiinflammatory and pro-resolution properties, including resolvins. Resolvins have been associated with autoimmune disorders. This study aimed to measure the level of resolvin E1 (RVE1) in the serum of Hashimoto's thyroiditis (HT) patients and healthy controls (HCs) and to further analyze its correlation with thyroid autoantibodies and other clinical indicators.

Design, patients and measurements: Fifty-seven participants were recruited—30 untreated HT patients and 27 sex- and age-matched HCs. Levels of serum RVE1 were measured by ELISA according to the manufacturer's protocol. Serum total T3 (TT3), TT4, free T3 (FT3), FT4, thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb) and thyroid-stimulating hormone (TSH) levels were measured using an electrochemiluminescence immunoassay. Routine biochemical and hemogram tests were performed on each sample.

Results: Serum RVE1 levels in HT patients (24.09, 15.76-34.38 pg/mL) were significantly lower than those in HCs (28.51, 20.76-51.23 pg/mL) (P=0.027). As the TgAb level increased, the RVE1 content showed a decreasing trend (P for trend=0.001). Multivariable ordinal logistic regression analysis showed that RVE1 was negatively correlated with increasing TgAb in both the unadjusted (OR=0.9446, 95% CI=0.9111-0.9782, P=0.002) and adjusted models (OR=0.9380, 95% CI=0.8967-0.9811, P=0.005).

Conclusions: Decreased RVE1 levels indicate impaired resolution of inflammation in HT patients. RVE1 may be a protective factor for elevated TgAb levels.

Introduction

Hashimoto's thyroiditis (HT) is a common type of autoimmune thyroid disease and the leading cause of primary hypothyroidism. HT is characterized by inflammatory cells infiltrating the thyroid and producing autoantibodies against thyroglobulin (Tg) and thyroid peroxidase (TPO) [1]. A cross-sectional study of 31 provinces in mainland China showed that the positive rate of anti-TPO antibodies (TPOAb) in Chinese adults was 10.19%, and the positive rate of anti-Tg antibodies (TgAb) was 9.70% [2]. Recent studies have confirmed that TgAb and TPOAb can increase the risk of thyroid cancer and thyroid nodules [3, 4]. High levels of thyroid antibodies not only cause hypothyroidism but are also an essential factor in the progression of HT disease. Studying euthyroid HT patients revealed that high levels of thyroid antibodies can lead to a lower quality of life score and vestibular dysfunction [5, 6]. In view of the fact that euthyroid HT patients already bear the above burden, early diagnosis and early intervention are particularly important. Genetic and environmental factors can lead to the occurrence and development of HT. Among these factors, nutritional factors play an important role in the pathogenesis of HT. Studies have confirmed that high iodine intake, selenium deficiency, and vitamin D deficiency are closely related to the incidence of HT [7, 8]. Selenium supplementation can significantly reduce thyroid autoantibody levels in patients

with HT [9]; however, the clinical efficacy of selenium supplementation is controversial. Therefore, it is necessary to further study nutritional factors that have a protective effect on HT.

Chronic inflammation is the underlying mechanism of disease progression in many autoimmune diseases. Recent research suggests that the progression of chronic inflammatory diseases may be due to the presence of impaired resolution and has revealed the protective effect of endogenous lipid mediators [10]. Acute inflammation, once thought to be a passive process, has now been shown to involve an active inflammatory resolution process and promote the restoration of inflamed tissue to a steady state [11]. The resolution process involves the following steps: first, remove the harmful substances that trigger the inflammatory response, stop the synthesis of proinflammatory mediators and promote their decomposition and metabolism, and then terminate leukocyte recruitment. Neutrophils and lymphocytes undergo apoptosis or necrosis and are finally cleared by macrophages [12]. In addition, the resolution of inflammation is an active process induced by endogenous specialized pro-resolving mediators (SPMs). SPMs are produced by the catabolism of polyunsaturated fatty acids (PUFAs), mainly including lipoxins, resolvins, protectins, and maresins [13].

Resolvins are produced from omega-3 PUFAs (EPA and DHA), including the E series (RVE1-RVE3) and D series (RVD1-RVD6). Among them, RVE1 triggers all aspects of the pro-resolution cascade, from inhibiting the aggregation of lymphocytes at the inflammation site to the efferocytosis or removal of inflammatory fragments [14]. Notably, RVE1 has a protective effect in many chronic inflammatory disease models. RVE1 can induce the expression of its specific receptor chemR23 on the surface of dendritic cells and inhibit the release of IL-12, thus hindering the progression of inflammation [15]. RVE1 can inhibit bone resorption in the inflammatory environment by controlling the ratio of RANKL/OPG and downstream genetic factors [16]. Additionally, omega-3 PUFAs are upstream substances of RVE1 and have a therapeutic effect on some autoimmune diseases. Eicosapentaenoic acid (EPA) can significantly alleviate the disease progression of experimental autoimmune encephalomyelitis (EAE) [17]. The application of omega-3 PUFAs and fish oil has a beneficial effect on reducing the recurrence rate and inflammatory indicators and improving quality of life in patients with multiple sclerosis [18]. Supplementing omega-3 fatty acids (EPA and DHA) can improve type 1 diabetes by regulating autoimmunity and suppressing inflammation [19, 20]. Similarly, omega-3 PUFAs have shown a protective effect in thyroid disease; a case report described a female HT patient who refused thyroid replacement therapy but was eventually cured clinically through dietary management (including omega-3 PUFAs) [21]. Therefore, we infer that the omega-3 PUFA downstream derivative RVE1 may also be related to HT.

To date, no studies have investigated the changes in RVE1 in HT patients and HCs. Therefore, this study mainly measured the serum RVE1 levels of HT patients and HCs and further analyzed the correlations between RVE1 and thyroid antibodies and other clinical indicators.

Materials And Methods

Study groups

We recruited 57 participants from the endocrinology clinic of Beijing Luhe Hospital, namely, 30 untreated HT patients and 27 age- and sex-matched HCs. The HT patients were positive for anti-TPO antibodies (TPOAbs) and/or anti-Tg antibodies (TgAbs) and were euthyroid. All participants were fasted, and blood samples were gathered between 8 and 10 AM. The following exclusion criteria were applied: smoking and alcohol intake; any acute or chronic illness, such as a rheumatic disease, diabetes or a family history of diabetes, haematopathy, stroke, other autoimmune disease, heart disease, hepatic or renal damage, or cancer; an age below 18 or above 70 years; current use of medications, such as immunosuppressive or immunomodulatory treatments, levothyroxine or antithyroid drugs, or corticosteroids; and pregnancy.

Serum total T4 (TT4), TT3, free T4 (FT4), FT3, TgAb, TPOAb and TSH levels were measured using an electrochemiluminescence immunoassay. The standard reference range for thyroid parameters and thyroid autoantibodies is: TgAb, 0-115 U/mL; TPOAb, 0-34 U/mL; TT3, 0.61-1.77 ng/mL; TT4, 5.13-14.06 ug/dL; FT3, 3.10-6.80 pg/mL; FT4, 12.00-22.0 ng/dL; TSH, 0.027-4.20 ulU/mL. In addition, routine biochemical tests and complete blood count were performed on each sample.

The study was approved by the Ethics Committee of the Beijing Luhe Hospital. After fully explaining the nature and purpose of all procedures utilized, consent was obtained from each participant.

Quantification of serum RVE1

Serum RVE1 levels were measured using a Resolvin E1 ELISA kit (Signalway antibody, USA) according to the manufacturer's instructions. All serum samples were measured on the same day. The interassay and intra-assay CVs for RVE1 were < 10%.

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 software (SPSS, Chicago, IL, USA). Means ± SDs and the medians with interquartile ranges (IQRs) were used to express normally and non-normally distributed data, respectively. Mann-Whitney U tests or independent samples t tests were used to compare the differences in variables between patients with HT and HCs.

According to the interquartile range, TPOAb was divided into Q1:<13.6 U/mL, Q2: 13.6–10.6 U/mL, Q3: 10.6–431 U/mL, and Q4: >431 U/mL; TgAb was divided into Q1:<12.9 U/mL, Q2: 12.9–79.1 U/mL, Q3: 79.1–361 U/mL, Q4: >361 U/mL. Multivariable ordinal logistic regression models were used to evaluate relationships between RVE1 and thyroid antibodies. The Jonckheere-Terpstra test was used to evaluate trends. The Spearman correlation coefficient (r) was used to evaluate correlations between variables. P < 0.05 indicated a statistical difference, and all P values were two-sided.

Results

A total of 57 participants were included in our study—30 HT patients and 27 HCs. As shown in Table 1, there was no significant difference in sex or age between the HT and HCs. The levels of thyroid-specific antibodies (TPOAb and TgAb) in the HT group were significantly higher than those in the control group (P

< 0.001 for all). The thyroid parameters (TSH, TT3, TT4, FT3, FT4) in the two groups did not differ significantly (P > 0.05 for all). In addition, the levels of other clinical indicators, such as blood cells (neutrophils, leukocytes, hemoglobin, platelets), albumin, liver function markers (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), electrolytes (potassium and sodium), blood glucose, creatinine, blood urea nitrogen (BUN), uric acid, blood lipids (triglycerides (TGs), TC, high-density lipoprotein (HDL), low-density lipoprotein (LDL)) and C-reactive protein (CRP), did not differ between the HT group and the control group (P > 0.05 for all).

Table 1 Demographic and clinical characteristics of the HT patients and HCs

HT (n = 30)	HCs (n = 27)	P value
40.27 ± 14.43	50.22 ± 18.71	0.096
28/2	26/1	0.997
0.98 (0.86-1.12)	1.02 (0.89–1.15)	0.497
6.65 (5.78-7.94)	6.91 (5.82-7.58)	0.767
2.95 (2.74-3.10)	3.08 (2.81-3.35)	0.096
1.17 (1.02–1.32)	1.22 (1.16-1.33)	0.240
2.62 (1.95-3.05)	2.38 (1.54–2.94)	0.178
360.00 (151.75-400.00)	12.80 (10.80-14.10)	< 0.001
417.00 (132.00-522.75)	13.60 (9.00-16.69)	< 0.001
6.33 (5.46-6.95)	6.31 (5.36-7.90)	0.653
138.50 (132.00-152.00)	141.00 (134.00-146.00)	0.872
249.50 (185.00-266.50)	239.00 (219.00-287.00)	0.602
46.30 (44.50-47.75)	45.40 (44.30-47.20)	0.506
19.00 (15.75-34.00)	19.00 (9.00-28.00)	0.627
18.50 (14.75-24.00)	16.00 (15.00-24.00)	0.602
4.32 (3.95-4.73)	4.17 (3.90-4.41)	0.448
139.00 (138.00-140.00)	140.00 (139.00-141.00)	0.068
5.69 (5.26-6.08)	5.39 (5.21-5.98)	0.650
63.00 (54.50-76.50)	65.00 (63.00-80.00)	0.472
4.30 (3.82-5.34)	4.28 (3.32-5.47)	0.545
331.00 (252.50-374.50)	297.00 (259.00-323.00)	0.238
1.67 (1.14–2.10)	1.31 (0.80-1.72)	0.208
	HT (n = 30)40.27 ± 14.4328/20.98 (0.86 - 1.12)6.65 (5.78 - 7.94)2.95 (2.74 - 3.10)1.17 (1.02 - 1.32)2.62 (1.95 - 3.05)360.00 (151.75 - 400.00)417.00 (132.00 - 522.75)6.33 (5.46 - 6.95)138.50 (132.00 - 152.00)249.50 (185.00 - 266.50)46.30 (44.50 - 47.75)19.00 (15.75 - 34.00)18.50 (14.75 - 24.00)139.00 (138.00 - 140.00)5.69 (5.26 - 6.08)63.00 (54.50 - 76.50)4.30 (3.82 - 5.34)331.00 (252.50 - 374.50)1.67 (1.14 - 2.10)	HT (n=30)HCs (n=27)40.27±14.4350.22±18.7128/226/10.98 (0.86-1.12)1.02 (0.89-1.15)6.65 (5.78-7.94)6.91 (5.82-7.58)2.95 (2.74-3.10)3.08 (2.81-3.35)1.17 (1.02-1.32)1.22 (1.16-1.33)2.62 (1.95-3.05)2.38 (1.54-2.94)360.00 (151.75-400.00)12.80 (10.80-14.10)6.33 (5.46-6.95)6.31 (5.36-7.90)6.33 (5.46-6.95)6.31 (5.36-7.90)138.50 (132.00-152.07)141.00 (134.00-146.00)44.30 (14.50-47.75)19.00 (219.00-28.00)19.00 (15.75-34.00)19.00 (219.00-28.00)18.50 (14.75-24.00)19.00 (13.00-141.00)139.00 (138.00-140.00)140.00 (139.00-141.00)139.00 (138.00-140.00)140.00 (139.00-141.00)5.69 (5.26-6.08)5.39 (5.21-5.98)63.00 (54.50-76.50)65.00 (63.00-80.00)14.30 (3.82-5.34)4.28 (3.32-5.47)31.00 (252.50-374.50)297.00 (259.00-323.00)1.67 (1.14-2.10)1.31 (0.80-1.72)

The results are expressed as the mean ± SD or median (interquartile range) values; HT, Hashimoto's thyroiditis; TT4, total T4; TT3, total T3; FT3, free T3; FT4, free T4; TSH, thyroid-stimulating hormone; TPOAb, anti-thyroperoxidase antibody; TgAb, anti-thyroglobulin antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TG, triglyceride, TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

The P values were obtained through statistical analyses using independent samples t-tests or Mann-Whitney U tests.

	HT (n = 30)	HCs (n = 27)	P value	
TC (mmol/L)	5.04 (4.73-5.55)	4.41 (4.12-5.35)	0.191	
HDL (mmol/L)	1.26 (1.02–1.63)	1.33 (1.14–1.77)	0.404	
LDL (mmol/L)	3.05 (2.86-3.55)	2.69 (2.19-3.07)	0.091	
CRP (mg/L)	0.91 (0.78-2.52)	1.73 (0.36–2.92)	0.997	
The results are expressed as the mean + SD or median (interquartile range) values. HT Hashimoto's				

The results are expressed as the mean ± SD or median (interquartile range) values; HT, Hashimoto's thyroiditis; TT4, total T4; TT3, total T3; FT3, free T3; FT4, free T4; TSH, thyroid-stimulating hormone; TPOAb, anti-thyroperoxidase antibody; TgAb, anti-thyroglobulin antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TG, triglyceride, TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.

The P values were obtained through statistical analyses using independent samples t-tests or Mann-Whitney U tests.

As shown in Fig. 1, we measured the serum RVE1 content in the HT and control groups and found that the serum RVE1 level in the HT group (24.09, 15.76-34.38 pg/mL) was significantly lower than that in the control group (28.51, 20.76–51.23 pg/mL) (P = 0.027). We used Spearman correlation analysis to assess the relationships between the levels of RVE1 and those of thyroid function parameters and other clinical indicators. As shown in Table 2, RVE1 was significantly negatively correlated with TgAb (r=-0.426, P = 0.001), TT3 (r=-0.348, P = 0.008) and FT3 (r=-0.339, P = 0.010).

Table 2 Spearman correlation analysis among serum RVE1 levels, clinical characteristics and inflammatory markers.

	Correlation coefficient	P value
TT3 (ng/mL)	-0.348	0.008*
TT4 (µg/dL)	0.011	0.934
FT3 (pg/mL)	-0.339	0.010*
FT4 (ng/dL)	0.146	0.278
TSH (ulU/mL)	-0.019	0.891
TgAb (U/mL)	-0.426	0.001*
TPOAb (U/mL)	-0.244	0.067
Leukocyte levels (× 10 ⁹ /L)	-0.083	0.645
Hemoglobin (g/L)	-0.101	0.574
Platelet count (× 10 ⁹ /L)	-0.133	0.461
Albumin (g/L)	0.059	0.743
ALT (U/L)	-0.001	0.996
AST (U/L)	-0.153	0.396
Serum potassium (mmol/L)	-0.157	0.391
Serum sodium (mmol/L)	0.273	0.130
Blood glucose (mmol/L)	0.249	0.169
Creatinine (µmol/L)	0.038	0.836
BUN (mmol/L)	-0.207	0.256
Uric acid (µmol/L)	-0.094	0.611
TG (mmol/L)	0.167	0.395
TC (mmol/L)	-0.161	0.413
HDL (mmol/L)	0.062	0.752
LDL (mmol/L)	-0.176	0.371

TT4, total T4; TT3, total T3; FT3, free T3; FT4, free T4; TSH, thyroid-stimulating hormone; TPOAb, antithyroperoxidase antibody; TgAb, anti-thyroglobulin antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TG, triglyceride, TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; *P < 0.05.

	Correlation coefficient	P value			
CRP (mg/L)	-0.999	0.645			
TT4, total T4; TT3, total T3; FT3, free T3; FT4, free T4; TSH, thyroid-stimulating hormone; TPOAb, anti thyroperoxidase antibody; TgAb, anti-thyroglobulin antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; TG, triglyceride, TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; *P < 0.05.					

To evaluate the relationship between RVE1 and thyroid antibodies, we divided the TPOAb and TgAb levels into four categories according to the interguartile range. As the TgAb level increased, the RVE1 content showed a decreasing trend (P for trend = 0.001). As shown in Table 3, the RVE1 content in the Q4 (TgAb > 361 IU/mL) group (19.21, 13.81-27.34 pg/mL) was significantly lower than that in the Q1 (TgAb < 34 IU/mL) group (37.70, 24.66–99.16 pg/mL) (P = 0.005). Multivariable ordinal logistic regression analysis showed that RVE1 was negatively correlated with TgAb in both the unadjusted (OR = 0.9446, 95% CI = 0.9111-0.9782, P = 0.002) and adjusted models (OR = 0.9475, 95% CI = 0.9166-0.9792, P = 0.001 and OR = 0.9380, 95% CI = 0.8967-0.9811, P = 0.005). We also assessed the relationship between RVE1 and TPOAb levels, and as TPOAb increased, the RVE1 levels showed an inverted U-shaped trend (P for trend = 0.036). The content of RVE1 reached the highest value in the Q2 group. Moreover, the RVE1 content in the Q4 group (19.21, 15.11–26.01 pg/mL) was significantly lower than that in the Q2 group (31.39, 23.79–62.31 pg/mL) (P = 0.019). Multivariable ordinal logistic regression analysis showed that RVE1 was negatively correlated with TPOAb in both the unadjusted (OR = 0.9762, 95% CI = 0.9559-0.9970, P = 0.028) and adjusted models (OR = 0.9772, 95% CI = 0.9567-0.9980, P = 0.011, adjusted for age and sex). However, when the model was adjusted for age, sex, TT3, TT4, TSH, FT3, FT4, and TgAb, RVE1 showed no significant correlation with increasing TPOAb (OR = 0.9860, 95% CI = 0.9627-1.010, P = 0.244).

Table 3

Multivariable ordinal logistic regression to investigate the association between RVE1 and TgAb.

Interquartile range of	Q1 (< 12.9 U/mL)	Q2 (12.9–79.1 U/mL)	Q3 (79.1–361 U/mL)	Q4 (> 361 U/mL)	
TgAb	(n = 14)	(n = 14)	(n = 15)	(n = 14)	
^b RVE1 Levels	37.70 (24.66- 99.16)	26.46 (18.91– 34.87)	28.51 (19.53- 37.61)	19.21 (13.81– 27.34) *	^a P for trend = 0.001
Multivariable or	dinal logistic regr	ession			
	β (95% CI)		OR (95% CI)		P value
Model 1	-0.057 (-0.093, -	0.022)	0.9446 (0.9111,	0.9782)	0.002
Model 2	-0.054 (-0.087, -	0.021)	0.9475 (0.9166,	0.9792)	0.001
Model 3	-0.064 (-0.109, -	0.019)	0.9380 (0.8967,	0.9811)	0.005
According to the interquartile range, TgAb was divided into four groups: Q1: the first TgAb quartile group (TgAb < 12.9 U/mL), Q2: the second TgAb quartile group (12.9–79.1 U/mL), Q3: the third TgAb quartile group (79.1–361 U/mL), Q4: the fourth TgAb quartile group (> 361 U/mL).					
^a The Jonckheere-Terpstra test was used to evaluate trends of RVE1 levels when the TgAb level increased.					

^b Results are expressed as medians (interquartile ranges). The Kruskal-Wallis test was used to detect differences in RVE1 levels among the four groups, and Bonferroni-adjusted P values were used, *P = 0.005 vs Q1 group.

Multivariable ordinal logistic regression models were used to evaluate relationships between RVE1 and increasing TgAb levels. **Model 1** was not adjusted for other variables; **Model 2** was adjusted for age and sex; **Model 3** was adjusted for age, sex, TT3, TT4, TSH, FT3, FT4 and TPOAB. RVE1, resolvin E1; OR, odds ratio; 95% CI, 95% confidence interval.

Table 4

Multivariable ordinal logistic regression to investigate the association between RVE1 and TPOAb.

Interquartile range of	Q1 (< 13.6 U/mL)	Q2 (13.6-106 U/mL)	Q3 (106-431 U/mL)	Q4 (> 431 U/mL)	
TPOAb	(n = 14)	(n = 14)	(n = 15)	(n = 14)	
^b RVE1 Levels	26.16 (19.53– 38.64)	31.39 (23.79- 62.31)	28.51 (17.03- 40.38)	19.21 (15.11- 26.01) *	^a P for trend = 0.036
Multivariable or	dinal logistic regr	ession			
	β (95% Cl)		OR (95% CI)		P value
Model 1	-0.024 (-0.045, -(0.003)	0.9762 (0.9559,	0.9970)	0.028
Model 2	-0.023 (-0.044, -(0.002)	0.9772 (0.9569,	0.9980)	0.011
Model 3	-0.014 (-0.038, 0	0.010)	0.9860 (0.9627,	1.010)	0.244
According to the interquartile range, TPOAb was divided into four groups: Q1: the first TPOAb quartile group (TgAb < 13.6 U/mL), Q2: the second TPOAb quartile group (13.6–10.6 U/mL), Q3: the third TPOAb quartile group (> 431 U/mL).					
^a The Jonckheere-Terpstra test was used to evaluate trends in RVE1 levels when TPOAb levels increased.					
^b Results are expressed as medians (interquartile ranges). The Kruskal-Wallis test was used to detect differences in RVE1 levels among the four groups, and Bonferroni-adjusted P values were used, *p = 0.019 vs Q2 group.					

Multivariable ordinal logistic regression models were used to evaluate relationships between RVE1 and increasing TPOAb levels. **Model 1** was not adjusted for other variables; **Model 2** was adjusted for age and sex; **Model 3** was adjusted for age, sex, TT3, TT4, TSH, FT3, FT4 and TPOAB. RVE1, resolvin E1; OR, odds ratio; 95% CI, 95% confidence interval.

Discussion

To the best of our knowledge, this is the first study investigating serum RVE1 in HT patients. In the present study, we found that the serum RVE1 level in the HT group was significantly lower than that in the control group, which might indicate dysregulation of inflammation resolution in HT patients.

Omega-3 PUFAs can produce lipid mediators with both anti-inflammatory and pro-resolution properties, including resolvins [22]. The anti-inflammatory action indicates that proinflammatory mediators are suppressed, while pro-resolution represents the activation of the termination process of inflammation, such as the removal of apoptotic cells by macrophages [23]. Dysregulation of resolution has been shown to increase the risk of autoimmune diseases. Although anti-inflammatory drugs can improve the symptoms of autoimmune diseases, they cannot achieve the purpose of curing the disease and are even ineffective for most patients. Therefore, the combination of anti-inflammation and pro-resolution may

become a superior treatment method. Moreover, pro-resolution pathways themselves will not increase the body's susceptibility to infection [24]. Omega-3 PUFAs have shown therapeutic potential in some autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and type 1 diabetes mellitus (T1DM) [25]. After treatment with omega-3 PUFAs in patients with inflammatory arthritis, the RVE1 in the knee effusion and plasma was significantly higher than that in the healthy control group, suggesting that RVE1 may be the mediator of omega-3 PUFAs [26]. In the present study, the serum levels of RVE1 in HT patients were significantly lower than those in HCs. We inferred that this might be a sign that HT is associated with inflammatory resolution dysfunction. Similarly, RVE1 was also a marker of inflammatory resolution defects in other diseases, such as cardiovascular diseases [27], periodontitis [28], and type 2 diabetes mellitus [29].

In this study, we also analyzed the correlation between RVE1 levels and thyroid antibodies. The HT patients recruited in our study were euthyroid, so the interference of thyroid hormones can be excluded. Spearman correlation analysis showed that RVE1 levels were negatively correlated with TgAb (r=-0.426, P = 0.001). As the TgAb level increased, the RVE1 content showed a decreasing trend (P for trend = 0.001). Moreover, multivariable ordinal logistic regression analysis showed that RVE1 was negatively correlated with TgAb in both the unadjusted (OR = 0.9446, 95% CI = 0.9111-0.9782, P = 0.002) and adjusted models (OR = 0.9380, 95% CI = 0.8967 - 0.9811, P = 0.005). We also assessed the relationship between RVE1 and TPOAb levels, and as TPOAb increased, the RVE1 levels showed an inverted U-shaped trend (P for trend = 0.036). However, when the logistic model was adjusted for age, sex, TT3, TT4, TSH, FT3, FT4, and TgAb, RVE1 showed no significant correlation with increasing TPOAb (OR = 0.9860, 95% CI = 0.9627-1.010, P = 0.244). Although it is currently believed that TgAb is not as specific and sensitive as TPOAb, some studies have confirmed that TgAb and TPOAb may represent two different aspects of thyroid autoimmunity. TgAb represents the initial or innate immune response, and TPOAb represents the later adaptive immune response [1]. Studies have confirmed a significant positive correlation between TgAb and clinical symptoms (fragile hair, face edema, edema of the eyes and harsh voice) in untreated HT patients [29]. Therefore, we speculate that RVE1 may be a protective factor for elevated TgAb levels. However, further research is needed to verify the relationship between RVE1 and TgAb.

A recent study confirmed that topical application of RVE1 can alleviate inflammation-induced tissue damage and reduce bone loss in an animal model of periodontitis [30]. Similarly, RVE1 could reverse experimental periodontitis and malnutrition [31]. RVE1 can inhibit the activation of dental pulp fibroblasts in a ChemR23-dependent manner and inhibit inflammation in the early stages of pulpitis [32]. The pathogeneses of autoimmune thyroid disease and periodontitis are different: the former is an autoimmune-driven disease, and the latter is an infection-driven disease. However, the two have many common pathological and immunological characteristics, such as autoimmune antibodies, apoptosis, inflammation, and oxidative stress. Therefore, we infer that RVE1 may also have a protective effect on HT [33]. Further longitudinal studies are needed to verify our speculation. In some other diseases, the application of RVE1 has also been shown to promote inflammation resolution. RVE1 can reduce airway responsiveness and inflammation in asthmatic mice [34]. Moreover, RVE1 can reduce neutrophil infiltration, reduce proinflammatory cytokine expression, and reduce inflammatory pain [35]. Oral or

topical application of RVE1 can prevent vascular inflammation and arteriosclerosis and reduce systemic CRP levels [36]. RVE1 can reduce lipopolysaccharide (LPS)-induced proinflammatory factors (IL-8, MCP-1) in isolated human pancreatic islets and exhibit antiapoptotic effects in a proinflammatory environment [37].

This study has many limitations. First, our study was a cross-sectional study, and whether RVE1 undergoes dynamic alterations related to changes in thyroid function and thyroid autoimmunity could not be determined. Second, our sample size was small; thus, a longitudinal study with a larger sample size is needed to explore the role of RVE1 in HT.

In conclusion, we found that the serum content of RVE1 in HT patients was significantly lower than that in HCs, and RVE1 may be a protective factor for elevated TgAb levels. A follow-up longitudinal study with a larger sample size is needed to verify the role of RVE1 in the development of HT.

Abbreviations

ΗT

Hashimoto's thyroiditis; Tg:thyroglobulin; TPO:thyroid peroxidase; TPOAb:anti-TPO antibodies; TgAb:anti-Tg antibodies; SPMs:specialized pro-resolving mediators; PUFAs:polyunsaturated fatty acids; EPA:Eicosapentaenoic acid

Declarations

Acknowledegments

Not applicable.

Consent for publication

Not applicable.

Authors' contributions

JS conceived and coordinated the study, designed, performed and analyzed the experiments, wrote the paper. JS, RXS, YYZ, JK and DZ carried out the data collection, data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Beijing Luhe Hospital. After fully explaining the nature and purpose of all procedures utilized, consent was obtained from each participant.

Competing interests

The author reports no conflicts of interest in this work.

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Figures



Figure 1

Levels of resolvin E1 (RVE1) in serum from HT patients (n=30) and matched controls (n=27). The levels are expressed in pg/ml as medians (horizontal bars) with 25th and 75th percentiles (boxes) and minimum and maximum values (bars). HT: Hashimoto's thyroiditis. HCs: Healthy controls.