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Relationship between autoimmune thyroid disease and nephropathy

A clinicopathological study

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Abstract

The association of nephropathy with autoimmune thyroid disease (AITD) has been reported previously. However, there is limited information on the relationship between thyroid autoantibodies and nephropathy. A retrospective study was conducted using the medical records of 246 patients with nephropathy, 82 of whom had concurrent AITD. General characteristics, thyroid function, autoantibodies, and the pathological types of nephropathy were analyzed. Immunohistochemistry was used to detect the thyroglobulin antibody (TG-Ab) and thyroid peroxidase antibody (TPO-Ab) in the kidneys. We found nephropathy patients with AITD exhibited higher serum levels of TPO-Ab, TG-Ab, thyroid-stimulating hormone receptor antibody (TR-Ab), and immunoglobulin G (IgG) ($P < .05$). Compared with the nephropathy without AITD group, the nephropathy with AITD group exhibited higher proportions of membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS), and relatively lower proportions of mesangial proliferative glomerulonephritis (MsPGN) and minimal change nephropathy (MCN) ($P = .005$). TPO-Ab and TG-Ab levels in the kidney were more prevalent in nephropathy patients with AITD than those without AITD ($P = .015$ and $P = .026$, respectively). Subgroup analysis demonstrated that serum levels of thyroid stimulating hormone (TSH), TG-Ab, TPO-Ab, immunoglobulin M (IgM), and IgG in the MN group were significantly higher, whereas the levels of free thyroxine (FT4) and estimated glomerular filtration rate (eGFR) were lower, as compared with MN with Hashimoto thyroiditis (HT) group ($P < .05$). TPO-Ab and TG-Ab expression levels in the kidneys were more prevalent in the MN group than in the MN with HT group ($P = .034$). The expression levels of FT4, TG-Ab, TPO-Ab, and thyroid-stimulating hormone receptor antibody (TSHR-Ab) in the serum were significantly higher in the MN group than in the MN with Graves disease (GD) group ($P < .05$). The expression of TPO-Ab in the kidneys was more prevalent in the MN group than in the MN with GD group ($P = .011$). In sum, the expressions of TPO-Ab and TG-Ab were more prevalent in the kidneys of patients with nephropathy and AITD. Our findings indicate that TPO-Ab and TG-Ab may play a role in the development of AITD-related nephropathy.

Abbreviations: AITD = autoimmune thyroid disease, eGFR = estimated glomerular filtration rate, FSGS = focal segmental glomerulosclerosis, FT3 = free triiodothyronine, FT4 = free thyroxine, GD = Graves disease, HT = Hashimoto thyroiditis, IgA-N = IgA nephropathy, IgG = immunoglobulin G, MCN = minimal change nephropathy, MN = membranous nephropathy, MsPGN = mesangial proliferative glomerulonephritis, TG-Ab = thyroglobulin antibody, TPO-Ab = thyroid peroxidase antibody, TR-Ab = thyroid-stimulating hormone receptor antibody, TSH = thyroid stimulating hormone, TSHR-Ab = thyroid-stimulating hormone receptor antibody.

Keywords: antithyroglobulin antibody, antithyroid peroxidase antibody, autoimmune thyroid disease, nephropathy

1. Introduction

Autoimmune thyroid disease (AITD) is the most common cause of both hyperthyroidism and hypothyroidism, including Hashimoto thyroiditis (HT), Graves disease (GD), and self-atrophic thyroiditis.[1] Among them, HT and GD are more common in clinical settings. AITD, a systemic immune disease, is often accompanied by the damage and lesions of other organs. Studies have found that adults with HT have a higher prevalence and a higher risk of concomitant non-thyroidal autoimmune diseases.[2] Thyroid function abnormalities are also common in systemic autoimmune disorders, including rheumatoid arthritis,[3] systemic sclerosis,[4] systemic lupus erythematosus,[5] and psoriatic arthritis.[6]

Nephropathy caused by immune mechanisms can be divided into 2 groups—one caused by anti-glomerular basement membrane antibodies and the other caused by the deposition of circulating immunocomplexes from the blood to the glomeruli.[7] Circulating immunocomplexes are common in patients with AITD, and studies have reported that immunocomplexes are present in up to 50% of patients with AITD. These complexes are mainly responsible for altering renal function by

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depositing on the basement membrane of the glomeruli.[8] AITD has a morbidity rate of approximately 2%, and when accompanied by kidney disease, it is known as AITD-associated nephropathy. Some patients with thyroid disease experience proteinuria for several months or years after confirmation of the disease.[9,10] A recent study has reported that subjects positive for thyroid autoantibodies had a significantly higher urinary albumin excretion rate compared with that of subjects without autoantibodies.[11] The clinical diagnosis of AITD-related renal damage is not uncommon.

This study aimed to investigate the clinical features and pathological characteristics of patients with nephropathy, who were positive for thyroid autoantibodies. We used thyroglobulin antibody (TG-Ab) and thyroid peroxidase antibody (TPO-Ab) to identify possible immunopathological mechanisms during the progression of renal damage and attempted to clarify the relationship between nephropathy and AITD. In addition, with the findings that membranous nephropathy (MN) is the main pathological type in patients with AITD-related nephropathy, we further analyzed the relationship between MN and AITD (including HT and GD), hoping to provide more evidence about the immunological mechanisms underlying AITD-related nephropathy.

2. Materials and methods

2.1. Ethical statement

The study was approved by the local ethics committee and was conducted in accordance with the ethical principles described in the Declaration of Helsinki. Written informed consent was obtained from each patient, and the procedure was approved by the Ethics Committee of Shanxi Provincial People's Hospital.

2.2. Patients and sample collection

We retrospectively recruited 246 patients with glomerulonephritis in the Department of Hepatology, Shanxi Provincial People's Hospital, between June 2017 and October 2019. All patients underwent renal biopsy due to high 24-hour urine protein levels (>0.5 g/24 h). The complete clinical information of patients (including age, sex, family history, renal function, and thyroid function) and the pathological results of renal biopsy were systematically reviewed and recorded. All patient information was obtained before antithyroid therapy or immunotherapy.

As shown in Fig. 1, 82 patients were assigned to the nephropathy with AITD group, and age- and sex-matched (2:1) patients were included in the nephropathy without AITD

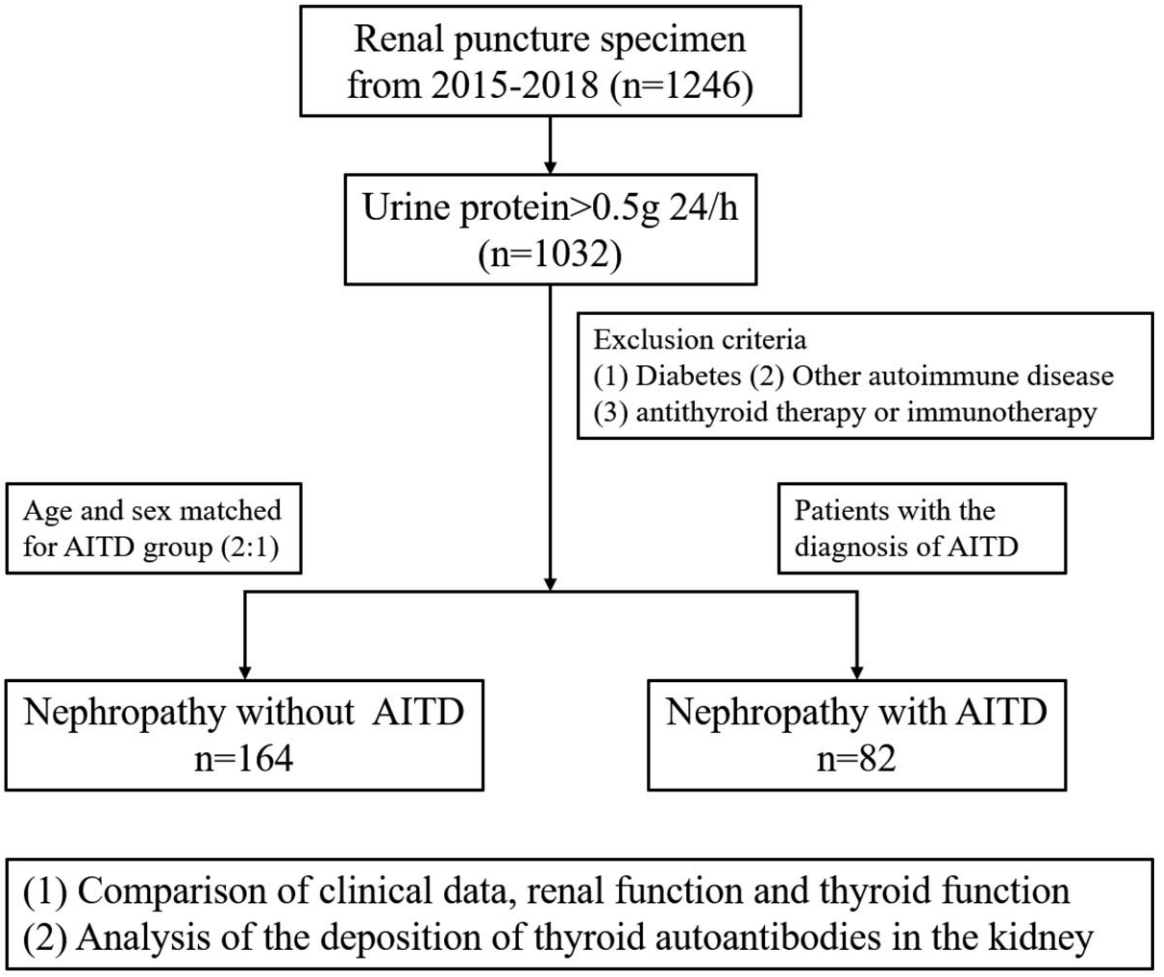

Figure 1. Flow chart of this study.

group. The phenotype of nephropathy was determined according to histological methods, as previously described.[12] The types of nephropathy diagnosed in this study included MN, focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgA-N), mesangial proliferative glomerulonephritis (MsPGN), and minimal change nephropathy (MCN). In our study, a diagnosis of AITD, which involved HT and GD, was made based on clinical examination, thyroid ultrasound, and titration of TG-Ab, TPO-Ab, and thyroid-stimulating hormone (TSH) receptor antibody (TSHR-Ab), as previously described.[13,14] Only 4 patients were diagnosed with specific thyroiditis; thus, they were excluded to analyze the relationship between different types of AITD and nephropathy.

2.3. Laboratory analysis

Thyroid function including serum free triiodothyronine (FT3), free thyroxine (FT4), and TSH levels were measured by electrochemiluminescence immunoassay using commercial Roche Elecsys reagent kits (Roche Diagnostica, Rotkreuz, Switzerland). Biochemical parameters including serum immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), albumin, creatinine, and estimated glomerular filtration rate (eGFR) were analyzed by turbidimetric inhibition immunoassay using an automatic biochemical analyzer (ADVIA 2400; Siemens, Newark, DE).

2.4. Immunohistochemical analysis

Renal sections were analyzed independently by 2 trained observers who were blinded to the clinicopathological characteristics of the patients. The specimens were preserved in 10% buffered formalin, and 4 μm-thick slices were obtained. After deparaffinization, the slides were pretreated with proteinase (P-8038; Sigma, St. Louis, MO) at 37 °C for 15 minutes, followed by incubation with normal serum (S2000; Vector Laboratories, Burlingame, CA) for 10 minutes. Primary antibodies for thyroid peroxidase (TPO-Ab, 1:500, rabbit polyclonal antibody, PA5-82323; Invitrogen, Carlsbad, CA) and thyroglobulin (TG-Ab, 1:2000, mouse monoclonal antibody, CL0164; Invitrogen, Carlsbad, CA) were added for 30 minutes at 37 °C. Negative control sections were treated with distilled phosphate-buffered saline. After incubation at room temperature for 1 hour and washing, secondary antibodies, diluted at 1:200, were added to the sections. The staining results for TG-Ab and TPO-Ab were evaluated using Image-Pro Plus (version 6.0; Media Cybernetics, Dallas, TX). Immunohistochemical results were examined by an investigator and confirmed by a pathologist blinded to the identity of each patient. The expression of TPO-Ab or TG-Ab in the kidney was scored by the pathologist, as shown in Fig. 2. Negative or weak staining for TPO-Ab or TG-Ab was scored 0, moderate staining was scored 1, while strong staining was scored 2.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL). Data for continuous variables are presented as means and standard deviations ($x \pm SD$), and Student t test was used to compare the differences in variables between the 2 groups. Non-normal continuous variables are expressed as medians and interquartile ranges (M [P25, P75]), and the Mann–Whitney U test was used. Categorical variables are expressed as actual numbers and percentages. Group comparisons of variables were performed with v2 test or Fisher exact test if the expected cell frequency was <5. Differences were considered statistically significant at $P < .05$.

3. Results

3.1. General characteristics of patients at the time of renal biopsy

Table 1 showed the demographic and clinical features of the 246 patients with nephropathy, grouped into patients without AITD (n = 164) and patients with AITD (n = 82). Patient information was obtained at the time of renal biopsy before any treatment. There were no significant differences in age, sex, body mass index (BMI), and family history of complications, including hypertension and diabetes mellitus, between nephropathy patients with and without AITD. In terms of thyroid function and antibodies, nephropathy patients with concurrent AITD had higher levels of TG-Ab ($P = .021$) and TPO-Ab ($P < .001$) compared with the levels of those without AITD. However, no statistical significance was observed in the comparison of the levels of TSH, free triiodothyronine (FT3), FT4, and TSHR-Ab ($P > .05$ in each case). Laboratory results revealed that the levels of IgG were higher in nephropathy patients with AITD than in nephropathy patients without AITD ($P = .031$). Except for IgG, other biochemical parameters (including IgA, IgM, albumin, creatinine, and eGFR), at presentation, did not differ significantly between the 2 groups ($P > .05$).

3.2. Comparison of renal pathological types between nephropathy patients with and without AITD

As shown in Table 1, nephropathy patients without AITD exhibited various types of nephropathy, including MN (31.71%), FSGS (12.20%), IgA-N (14.63%), MsPGN (18.29%), and MCN (17.68%), and others (5.49%). However, the proportions of the types of nephropathy were different for patients with concurrent AITD, which included MN (37.80%), FSGS (28.05%), IgA-N (12.19%), MsPGN (6.10%), and MCN (9.76%). The nephropathy with AITD group exhibited higher proportions of MN and FSGS, and relatively lower proportions of MsPGN and MCN as compared with nephropathy group ($P = .005$ for each).

3.3. Correlation of renal thyroid autoantibodies between nephropathy patients with and without AITD

As AITD may be associated with glomerulonephritis due to a common autoimmune etiology, we investigated whether there was any difference in the common thyroid autoantibodies deposited in the kidneys between nephropathy patients with and without AITD. As shown in Table 2, immunohistochemical results revealed that TPO-Ab expression in the glomeruli was more prevalent in nephropathy patients with AITD than in those without AITD ($P = .015$). Similarly, TG-Ab expression in the glomeruli was more prevalent in nephropathy patients with AITD than in those without AITD ($P = .026$).

3.4. Comparison of renal thyroid autoantibodies between MN patients with and without HT

MN was the most common type of nephropathy among patients with AITD, we therefore further compared the clinical character-

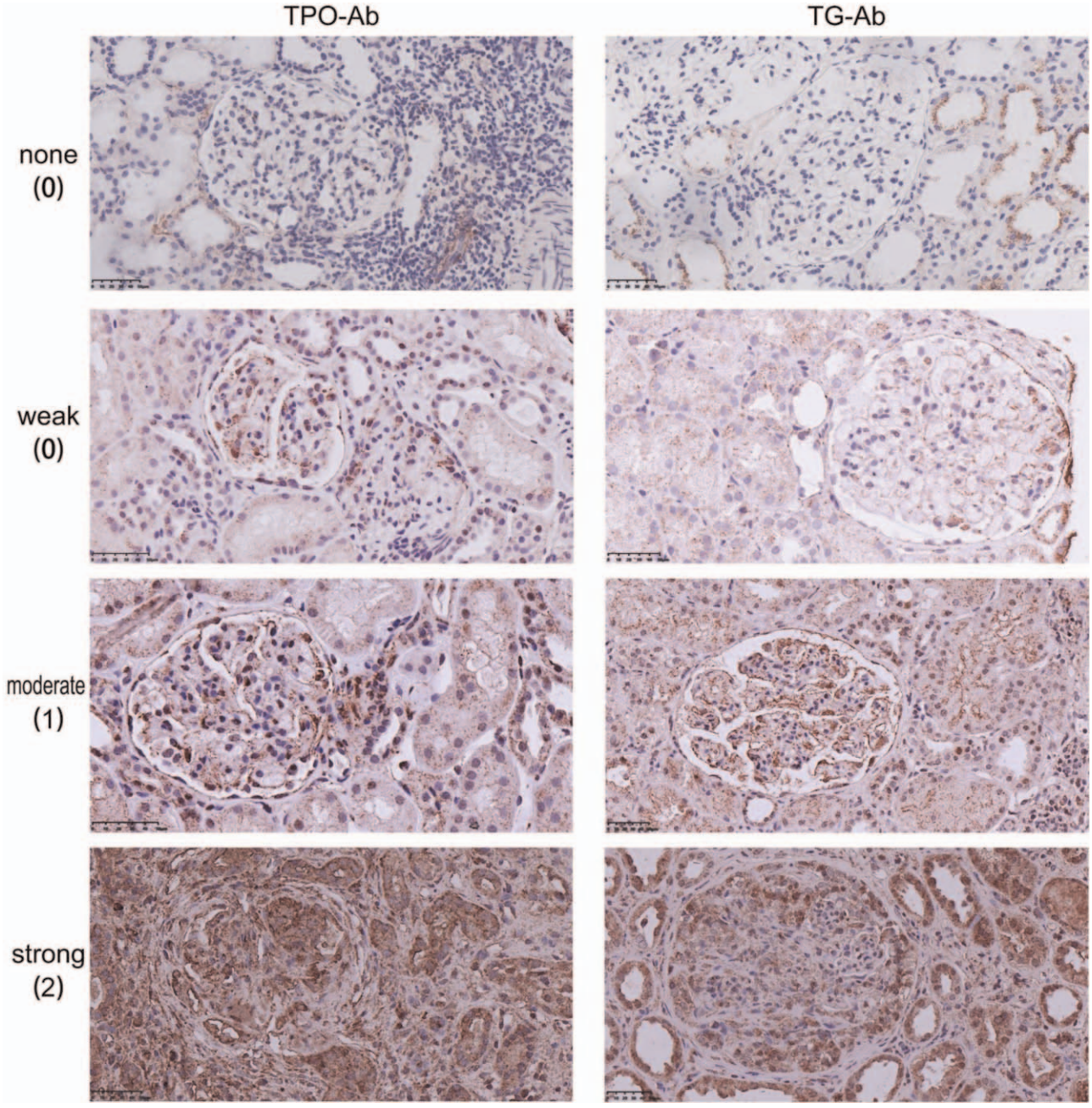

Figure 2. Immunohistochemistry for TPO-Ab or TG-Ab in renal tissue from patients with Hashimoto thyroiditis-related membranous nephropathy at 400× magnification. Negative or weak staining for TPO-Ab or TG-Ab was scored 0, moderate staining was scored 1, while strong staining was scored 2. TG-Ab = thyroglobulin antibody; TPO-Ab = thyroid peroxidase antibody.

istics and thyroid autoantibodies deposited in the kidneys between MN patients with and without AITD. Due to the difference in thyroid function and autoantibodies between HT and GD, we analyzed the relationship between MN and AITD by subgroup analysis. As shown in Table 3, there were 19 patients in the MN with HT group with a higher frequency of women (57.90% vs 38.46%, $P = .017$) compared with the corresponding frequency in the MN group. The expression levels of TSH, TG-Ab, and TPO-Ab in the serum were significantly higher in the MN group than in the MN with HT group; however, the level of FT4 was lower. In addition, plasma IgM and IgG levels were significantly higher in the MN group than in the MN with HT group (IgM: 1.15 ± 0.33 vs 1.43 ± 0.45 mg/dL, $P = .002$; IgG: 7.19 [3.65–13.05] vs 11.04 [4.93–36.06] mg/dL, $P = .021$). However, eGFR was lower in the MN group than in the MN with HT group (eGFR: 83.21 ± 10.55 vs 77.53 ± 9.81 mL/min/1.73 m^2, $P = .041$). The results further demonstrated that the expression levels of TPO-Ab and TG-Ab in the glomeruli were more prevalent in patients with MN than in those with MN and HT ($P = .034$).

Table 1

Comparison of the clinical characteristics of the nephropathy patients with or without AITD.

	Nephropathy (n = 164)	Nephropathy with AITD (n = 82)	*P* value
Clinical characteristics			
Age, y	52.49 ± 7.60	53.66 ± 6.47	.638
Gender (female, %)	116 (70.73%)	63 (76.83%)	.783
BMI, kg/m^2	24.21 ± 4.60	25.1 ± 5.41	.726
Hypertension	111 (67.68%)	46 (56.10%)	.211
Thyroid function and antibodies			
TSH, mU/L	3.61 ± 1.92	3.03 ± 1.45	.117
FT3, pmol/L	6.23 ± 2.72	7.53 ± 3.07	.181
FT4, pmol/L	13.26 ± 6.31	16.41 ± 6.93	.279
TG-Ab, IU/mL	18.67 (6.52–67.46)	94.58 (17.41–334.92)	<.001*
TPO-Ab, IU/mL	14.59 (8.13–29.52)	80.64 (9.60–423.97)	<.001*
TR-Ab, IU/L	3.99 (0.52–18.17)	9.84 (4.88–29.50)	<.001*
Laboratorial results			
IgA, mg/dL	2.12 ± 0.69	2.35 ± 0.76	.237
IgM, mg/dL	1.39 ± 0.44	1.53 ± 0.57	.184
IgG, mg/dL	6.95 (4.23–11.64)	9.51 (5.80–36.06)	.031*
Albumin, mg/dL	30.22 ± 7.54	28.90 ± 6.13	.183
Creatinine, μmol/L	90.72 (71.90–113.63)	93.5 (83.51–121.39)	.701
eGFR, mL/min/1.73 m^2	80.21 ± 7.94	79.77 ± 8.83	.872
Renal biopsy (%)			.005*
MN	52 (31.71%)	31 (37.80%)	
FSGS	20 (12.20%)	23 (28.05%)	
IgA-N	24 (14.63%)	10 (12.19%)	
MPGN	30 (18.29%)	5 (6.10%)	
MCN	29 (17.68%)	8 (9.76%)	
Others	9 (5.49%)	5 (6.10%)	

Variables with non-normal distribution and demonstrated as median (range).

AITD = autoimmune thyroid disease, BMI = body mass index, eGFR = estimated glomerular filtration rate, FSGS = focal segmental glomerulosclerosis, FT3 = free triiodothyronine, FT4 = free thyroxine, IgA-N = IgA nephropathy, MCN = minimal change nephropathy, MN = membranous nephropathy, MPGN = mesangial proliferative glomerulonephritis, TG-Ab = antithyroglobulin antibody, TPO-Ab = anti-thyroid peroxidase antibody, TR-Ab = thyrotropin receptor antibody, TSH = thyrotropin.

* indicated statistical significant.

3.5. Comparison of renal thyroid autoantibodies between MN patients with and without GD

As shown in Table 4, there were 12 patients in the MN with GD group. The expression levels of FT4, TG-Ab, TPO-Ab, and TSHR-Ab in the serum were significantly higher in the MN group than in the MN with GD group ($P < .05$ for each). However, there was no statistical difference when comparing the levels of IgM, IgG, and eGFR between the MN group and the MN with GD group ($P > .05$ for each). Interestingly, although TG-Ab was detected more often in the MN with GD group than in the MN group, the difference was not statistically significant ($P = .120$). In contrast, the expression of TPO-Ab in the glomeruli was more prevalent in the MN group than in the MN with GD group ($P = .011$).

4. Discussion

The association of renal disease with AITD has been reported previously.[15] In addition to thyroid damage and thyroid functional hormonal changes, AITD may also cause other systemic damage.[16] For example, patients with AITD may have proteinuria (also known as AITD-related nephropathy).[17] Horvath et al[18] suggested that immune complex glomerulonephritis is associated with thyroid antigens in GD. However, most of these studies are case reports, and to date, limited cohort studies have been conducted to elucidate the relationship between AITD and nephropathy. In our study, we retrospectively analyzed 1032 nephropathy patients with and without AITD, and showed that the frequency of AITD among patients with nephropathy was 7.94% (82/1032). We also noticed that a

Table 2

Comparison of thyroid autoantibodies between nephropathy patients with or without AITD by using immunohistochemistry.

Antibodies	Intensity	Nephropathy (n = 164)	Nephropathy with AITD (n = 82)	*P*
TPO-Ab	0	111 (67.68%)	40 (48.78%)	.015
	1	32 (19.51%)	24 (29.27%)	
	2	21 (12.81%)	18 (21.95%)	
TG-Ab	0	96 (58.54%)	35 (42.68%)	.026
	1	56 (34.14%)	34 (41.46%)	
	2	12 (7.32%)	13 (15.86%)	

AITD = autoimmune thyroid disease, TG-Ab = antithyroglobulin antibody, TPO-Ab = anti-thyroid peroxidase antibody.

Table 3

Comparison of clinical characteristics of patients with MN and Hashimoto's thyroiditis (HT).

	MN (n = 52)	MN with HT (n = 19)	*P* values
Age, y	53.06 ± 6.37	52.47 ± 7.18	.739
Gender (female, %)	17 (38.46%)	11 (57.90%)	.017*
Thyroid function and antibodies			
TSH, mU/L	3.76 ± 1.01	4.29 ± 1.17	.002*
FT3, pmol/L	6.94 ± 1.71	6.13 ± 1.42	.069
FT4, pmol/L	14.18 ± 3.23	12.04 ± 3.69	.020*
TG-Ab, UI/mL	28.85 (6.18–75.73)	97.18 (12.08–266.42)	<.001*
TPO-Ab, UI/mL	19.32 (9.87–41.75)	55.17 (14.32–343.04)	.003*
TR-Ab, UI/mL	5.42 (1.75–14.09)	5.57 (1.96–20.95)	.138
Laboratorial results			
IgA, mg/dL	3.28 ± 0.65	3.06 ± 0.48	.104
IgM, mg/dL	1.15 ± 0.33	1.43 ± 0.45	.002*
IgG, mg/dL	7.19 (3.65–13.05)	11.04 (4.93–36.06)	.021*
Albumin, mg/dL	30.18 ± 7.46	28.55 ± 6.84	.408
Creatinine, μmol/L	85.72 (70.90–133.63)	93.5 (84.51–142.39)	.153
eGFR, mL/min/1.73 m^2	83.21 ± 9.55	77.53 ± 9.81	.041*
TPO-Ab			.024*
0	29 (55.77%)	4 (21.05%)	
1	18 (34.62%)	10 (52.63%)	
2	5 (9.61%)	5 (26.32%)	
TG-Ab			.000*
0	29 (55.77%)	2 (10.53%)	
1	20 (38.46%)	11 (57.90%)	
2	3 (5.77%)	6 (31.58%)	

eGFR = estimated glomerular filtration rate, FT3 = free triiodothyronine, FT4 = free thyroxine, MN = membranous nephropathy, TG-Ab = antithyroglobulin antibody, TPO-Ab = anti-thyroid peroxidase antibody, TR-Ab = thyrotropin receptor antibody, TSH = thyrotropin.

* indicated statistical significant.

Table 4

Comparison of clinical characteristics of patients with MN and Grave's disease (GD).

	MN (n = 52)	MN with GD (n = 12)	*P* values
Age, y	53.06 ± 6.37	54.19 ± 8.09	.600
Gender (female, %)	17 (38.46%)	7 (58.33%)	.113
Thyroid function and antibodies			
TSH, mU/L	3.76 ± 1.01	3.15 ± 0.83	.056
FT3, pmol/L	6.94 ± 1.71	7.96 ± 2.35	.082
FT4, pmol/L	14.18 ± 3.23	17.94 ± 6.16	.004*
TG-Ab, UI/mL	28.85 (6.18–75.73)	34.80 (8.72–158.22)	.018*
TPO-Ab, UI/mL	19.32 (9.87–41.75)	32.44 (15.06–185.51)	<.001*
TSHR-Ab, UI/mL	5.42 (1.75–14.09)	7.06 (2.11–38.27)	<.001
Laboratorial results			
IgA, mg/dL	3.28 ± 0.65	3.11 ± 0.72	.426
IgM, mg/dL	1.15 ± 0.33	1.36 ± 0.38	.058
IgG, mg/dL	7.19 (3.65–13.05)	8.93 (4.26–28.75)	.103
Albumin, mg/dL	30.18 ± 7.46	29.27 ± 8.16	.710
Creatinine, μmol/L	85.72 (70.90–133.63)	90.61 (82.69–141.97)	.569
eGFR, mL/min/1.73 m^2	83.21 ± 9.55	80.39 ± 7.60	.344
TPO-Ab			.011*
0	29 (55.77%)	1 (8.33%)	
1	18 (34.62%)	8 (66.67%)	
2	5 (9.61%)	3 (25.00%)	
TG-Ab			.120
0	29 (55.77%)	3 (25.00%)	
1	20 (38.46%)	7 (58.33%)	
2	3 (5.77%)	2 (16.67%)	

eGFR = estimated glomerular filtration rate, FT3 = free triiodothyronine, FT4 = free thyroxine, MN = membranous nephropathy, TG-Ab = antithyroglobulin antibody; TPO-Ab = anti-thyroid peroxidase antibody; TR-Ab = thyrotropin receptor antibody; TSH = thyrotropin.

* indicated statistical significant.

relative high proportion of TPO-ab or TG-ab in nephropathy patients without AITD in our study. Although the reason is unclear, we could still conclude that AITD may be one of the factors that contribute to renal impairment in proteinuria. Previous studies have indicated that changes in thyroid hormone levels (hyperthyroidism or hypothyroidism) could impair renal function.[19] Nevertheless, in the current study, there was no statistical difference between FT3, FT4, and TSH levels, indicating that there may be other mechanisms causing kidney damage in nephropathy with concomitant AITD.

We found that serum IgG levels were higher in cases of nephropathy patients with concomitant AITD than in cases of patients with nephropathy alone. A previous study reported that approximately 25.5% of patients with HT had elevated serum IgG levels.[20] Therefore, it is possible that the presence of AITD could increase the serum levels of IgG in patients with nephropathy. Moreover, circulating immunocomplexes are common in patients with AITD, including HT and GD.[21] As expected, we found that serum TG-Ab, TPO-Ab, and TSHR-Ab were significantly higher in patients with nephropathy and AITD than in those with nephropathy alone. The results indicated the potential relationship between circulating immunocomplexes and the pathogenesis of AITD-related nephropathy. Although both circulating and renal deposited TG-Ab and TPO-Ab were higher in patients with nephropathy and AITD than in patients with nephropathy alone, we were unable to determine if their deposition is secondary to circulating complexes or a result of "in situ" complex formation.

A retrospective study by Kocak et al[22] pointed out that the pathological types of HT-related nephropathy are diverse with the highest prevalence for MN, followed by FSGS, IgA-N, chronic glomerulonephritis, and MCN. Consistently, our biopsy results also showed that MN (37.80%) and FSGS (28.05%) were the most common renal lesions in cases of nephropathy with AITD. Similarly, Mubarak[23] found that MN and FSGS are the most common causes of nephrotic syndrome in nondiabetic adults. The proportions of the types of nephropathy were different among the patients in this study. The proportions of MsPGN and MCN were higher in cases of nephropathy but lower in cases of nephropathy with concomitant AITD; the proportion of FSGS was increased in the latter. These findings suggest that different circulating immunocomplexes may cause different types of nephropathy. Further studies, however, are needed to investigate this possible association.

MN was the most common type of nephropathy in both groups in our study. MN is characterized by the deposition of antibodies that recognize specific glomerular epitopes. These antibodies may develop in autoimmune diseases after exposure to new antigens or after passive maternal transfer, for example, in cases of neonatal MN secondary to the in utero transfer of anti-neutral endopeptidase protein IGs.[24] To further investigate the relationship between thyroid autoantibodies and MN, we compared demographic and clinical parameters as well as the deposition of thyroid autoantibodies in the kidneys of MN patients with and without AITD. We analyzed HT and GD patients in this study. We found no statistically significant correlation between albumin, creatinine, and eGFR in the nephropathy with AITD group. However, subgroup analysis demonstrated that eGFR was lower in cases of MN with concomitant HT than in cases of MN alone. A recent study indicated that thyroid hormones could cause renal impairment.[25] Hyperthyroidism or hypothyroidism may affect mature kidney function directly by disrupting glomerular filtration and the structure of the kidneys.[26] The reason for the absence of eGFR reduction in cases of nephropathy with concomitant GD (but not in cases of nephropathy with concomitant HT) remains unknown. We hypothesized that hypothyroidism may result in greater damage to kidney function.

As an autoimmune disease, the diagnosis of AITD-related nephropathy requires 3 conditions: the diagnosis of AITD and nephropathy, the exclusion of other factors related to secondary nephropathy, and the presence of antithyroid antibodies in renal tissues.[27] Several studies have established that thyroglobulin and thyroid microsomal antigens are deposited in the glomeruli; however, their deposition sites are unclear as they can be deposited outside the basement membrane or in the damaged mesangial area.[28] In MN, the target antigen may be TPO-Ab or TG-Ab in the glomeruli.[29] With immunohistochemistry, we found that both TOP-Ab and TG-Ab were deposited in the glomeruli and tubules. TG-Ab is considered to be the dominant antigen or early antigen in AITD, and TPO-Ab is the most sensitive biomarker for AITD.[30] It has also been reported that the positive rate of TG-Ab in patients with HT is 25% to 50%, whereas that of TPO-Ab is 90%.[31] In this study, we found that TG-Ab and TPO-Ab were both higher in patients with MN and HT or GD than in those with MN alone. Furthermore, we found that the expression of TPO-Ab in renal tissues was more prevalent in patients with MN and AITD than in those with MN alone. However, there was no statistical difference between patients with MN and those with MN and GD in terms of TG-Ab deposition in the kidneys. TG-Ab is known to cause no direct damage to the thyroid. After TG-Ab binds to thyroglobulin via interaction with Fc receptors, natural killer cell receptors can be activated; thus, the target cells are attacked, causing the destruction of thyroid cells.[32] However, TPO-Ab directly destroys thyroid follicular cells through the activation of helper T lymphocytes (CD4+), antibodies, complement-dependent cytotoxicity, and the inhibition of TPO enzyme activity.[33] Therefore, the differential expression of TG-Ab and TPO-Ab in the kidneys of MN patients may be attributed to their different functions.

5. Conclusion

In conclusion, based on the present results, we demonstrated that the levels of both TG-Ab and TPO-Ab in the serum and kidneys were higher in patients with AITD-related nephropathy. TPO-Ab and TG-Ab could be regarded as the immunocomplexes involved in the pathogenesis of MN in patients with AITD. These findings further clarify the immunological mechanisms of AITD-related nephropathy.

Author contributions

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