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REVIEW ARTICLE

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Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review

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Abstract

Patients with chronic spontaneous urticaria (CSU) are widely held to often have other autoimmune disorders, including autoimmune thyroid disease. Here, we systematically evaluated the literature on the prevalence of thyroid autoimmunity in CSU and vice versa. There is a strong link between CSU and elevated levels of IgG antithyroid autoantibodies (AAbs), with most of a large number of studies reporting rates of ≥10%. Levels of IgG against thyroid peroxidase (TPO) are more often elevated in CSU than those of other IgG antithyroid AAbs (strong evidence). Levels of IgG antithyroid AAbs are more often elevated in adult patients with CSU than in children (strong evidence). Patients with CSU exhibit significantly higher levels of IgG antithyroid AAbs (strong evidence) and IgE-anti-TPO (weak evidence) than controls. Elevated IgG antithyroid AAbs in CSU are linked to the use of glucocorticoids (weak evidence) but not to disease duration or severity/activity, gender, age, or ASST response (inconsistent evidence). Thyroid dysfunction rates are increased in patients with CSU (strong evidence). Hypothyroidism and Hashimoto's thyroiditis are more common than hyperthyroidism and Graves' disease (strong evidence). Thyroid dysfunction is more common in adult patients with CSU than in children (strong evidence) and in female than in male patients with CSU (weak evidence). Urticaria including CSU is more prevalent in patients with thyroid autoimmunity than in controls (weak evidence). CSU can improve in response to treatment with levothyroxine or other thyroid drugs (strong evidence). Pathogenic mechanisms in CSU patients with thyroid autoimmunity may include IgE against autoantigens, immune complexes, and complement.

KEYWORDS

chronic spontaneous urticaria, Graves' disease, Hashimoto's thyroiditis, prevalence, autoimmune thyroid disease

1 | INTRODUCTION

Chronic spontaneous urticaria (CSU) is a mast cell-driven disease characterized by the development of wheals, angioedema, or both for >6 weeks.[1] The point prevalence for CSU is estimated to be 0.5%-1%.[2] Autoimmunity due to IgE or IgG autoantibodies (AAbs) is thought to play a significant role in the etiology and pathogenesis of CSU in a subpopulation of patients.[3] These patients with autoimmune CSU are widely held to often have other autoimmune disorders, including autoimmune thyroid disease (AITD).[3,4]

Autoimmune thyroid disease encompasses a spectrum of disorders that affect 0.4%-9.1% of the population.[5-9] Susceptibility to develop AITD is attributed to genetic and environmental (eg, iodine, infection, drugs) factors.[10] The clinical presentation of AITD varies

Abbreviations: AAbs, autoantibodies; AITD, autoimmune thyroid disease; CSU, chronic spontaneous urticaria; GD, Graves' disease; HCs, healthy controls; HT, Hashimoto's thyroiditis; MC, mast cell; TG, thyroglobulin; TPO, thyroid peroxidase; TSHr, TSH receptor; TSH, thyroid-stimulating hormone

from hypothyroidism or euthyroidism in Hashimoto's thyroiditis (HT, also known as chronic autoimmune thyroiditis and autoimmune hypothyroidism) to hyperthyroidism in Graves' disease (GD). Both conditions are characterized by infiltration of the thyroid by T and B cells reactive to thyroid antigens and formation of autoantibodies against thyroid peroxidase (TPO), thyroglobulin (TG), and/or thyroid-stimulating hormone (TSH) receptor (anti-TSHr).[9,11] Recently, some studies have reported on the prevalence of urticaria including CSU in AITD patients.[12-15]

In 1907, at the VI International Dermatological Congress in New York, Ravitch suggested for the first time an association between CSU and thyroid disease and discussed the effects of thyrotherapy on urticaria symptoms.[16] The notion that both diseases are linked was further supported in 1968 by Rothfeld, who reported urticaria in three of 108 patients with hyperthyroidism. In two of them, "urticaria and pruritus seemed to vary with thyroid status".[17] Later, Juhlin and Thune and Granholt found thyroid disease in 6% and 4% of patients with recurrent urticaria, respectively.[18,19]

That chronic urticaria and thyroid disease in the same patient may be related to a common autoimmune phenomenon was originally postulated in 1971 by Isaacs. He described the clinical course of four patients with hyperthyroidism and chronic urticaria, in which controlling the hyperthyroid state cleared their urticaria.[20] Since then, a large number of studies on the comorbidity of CSU and thyroid autoimmunity have been conducted worldwide. Here, we systematically evaluated the literature on the prevalence of thyroid autoimmunity in CSU and vice versa, and we provide a structured review of the evidence for a causal and pathogenetic association of CSU with AITD.

2 | METHODS

2.1 | Search strategy

A PubMed search was performed to identify reports published from 1960 to December 2016 with the keywords "urticaria" in combination with the terms "thyroid," "TG," "TPO," "thyroglobulin," and "peroxidase" in individual searches. No language filter was applied.

The aim of our systematic review of the literature was to identify studies that provide information relevant for addressing one or more of the following questions: (i) What is the prevalence of elevated levels of IgG and IgE thyroid autoantibodies in patients with CSU? (ii) Do patients with CSU exhibit higher levels of IgG and IgE thyroid autoantibodies and higher rates of elevated levels as compared to controls? (iii) What is the association between levels of antithyroid AAbs and clinical and laboratory parameters of CSU? (iv) What is the prevalence of thyroid dysfunction or disease in patients with CSU (and controls)? (v) What is the prevalence CSU in patients with thyroid diseases? (vi) Do patients with CSU benefit from treatment with thyroid medication? (vii) What is the possible pathogenetic relationship between CSU and AITD?

2.2 | Selection and assessment of relevant studies

Using a hierarchical approach, we first screened titles and then abstracts of the publications identified by our search strategy for potentially relevant studies, after which full texts were assessed. This approach identified 240 studies, of which 138 were excluded from further analysis after review of the title and the abstract: irrelevant publications (n=111), reviews (n=8), case reports (n=13), reports on the same results from the same team (n=3), and publications where the data were not clearly described (n=3). The remaining 102 studies were included in the systematic review. We also examined the reference lists of the retrieved articles to identify additional studies (n=67). Reported data on cases of acute urticaria were excluded. Similarly, reports on patients with chronic inducible urticaria were excluded whenever possible. Some studies, however, did not differentiate clearly between CSU and chronic inducible urticaria. These studies are included in Tables 1-8, but are marked to be easily identified.

The following information was extracted from each study report when possible: the first author, published year, region of study population, design of study, age of patients and controls, number of patients and controls, frequency of antithyroid AAbs, Graves' disease (GD), Hashimoto's thyroiditis (HT), hypothyroidism and hyperthyroidism, and efficacy of antithyroid drugs or replacement treatment with levothyroxine in regard to CSU symptoms.

Hypothyroidism is defined as a serum TSH level above the upper limit of normal values and normal (subclinical hypothyroidism) or decreased (overt or clinical hypothyroidism) levels of serum free thyroxine (T4). Hyperthyroidism is defined as a serum TSH level below the lower limit of normal values and normal (subclinical hyperthyroidism) or elevated (overt or clinical hyperthyroidism) levels of serum free T4.[21]

2.3 | Assessment of quality of evidence and strength of associations

The links between CSU and AITD were assessed using a rating system as previously described.[22] Based on the outcome and number of studies, we categorized the levels of scientific evidence for "association" as follows:

- strong: three studies available that find an association in the same direction or ≥4 studies available, of which more than two-thirds find an association in the same direction and no more than 25% find an opposite association;
- weak: two studies available that find an association in the same direction or three studies available, of which two find an association in the same direction and the third study finds no association;
- no/too little evidence: ≤1 study available;
- inconsistent: remaining cases.

Evidence for "no association":

- strong: >4 studies are available, of which >85% find no association;
- weak: >4 studies are available, of which >75% find no association.

TABLE 1 Prevalence of elevated IgG antithyroid autoantibodies in CSU

First author of the study (reference)	Year	Age (y)	n, CSU	CSU patients with elevated levels of IgG antithyroid AAbs, % (n)				Design	Country
				Anti-TPO, anti-TG, and both AAbs	Anti-TG	Anti-TPO	Both AAbs in the same patients		
Curto-Barredo et al.[110]	2016	≥18	101	22.8 (23)	–	–	–	–	Spain
Eser et al.[111]	2016	<18	52	–	3.8 (2)	7.7 (4)	–	P	Turkey
Magen et al.[39]	2016	≥18	41	–	17.2 (7)	31.7 (13)	–	P	Israel
Pedulla et al.[43]	2016	<18	40	17.5 (7)	–	–	–	–	Italy
Diaz-Angulo et al.[50]	2016	≥18	343	26.8 (92)	15.2 (52)	20.4 (70)	8.7 (30)	CC	Spain
Ye et al.[112]	2016	≥19	63	23.8 (15)	–	–	–	P	Korea
Kim et al.[56]	2016	≥12	184	23.4 (43)	20.6 (38)	13.6 (25)	10.9 (20)	R	Korea
Dionigi et al.[113]	2016	≥18	100	8 (8)	–	–	–	P	Brazil
Chuamanochan et al.[114]	2016	≥15	184[a]	–	15.8 (29)	15.8 (29)	–	R	Thailand
Oguz Topal et al.[115]	2016	≥14	58	–	17.2 (10)	22.4 (13)	–	P, CC	Turkey
Chaykivska et al.[40]	2015	–	100	–	–	17.4 (17)	–	–	Poland
Akarsu et al.[37]	2015	≥0	146	–	4.8 (7)	9.6 (14)	–	R	Turkey
Okba et al.[57]	2015	≥18	80[a]	–	17.5 (14)	25 (20)[b]	16.2 (13)	CC	Egypt
Shin et al.[36]	2015	≥18	96[c]	–	–	7.7 (7)	–	–	Korea
Magen et al.[116]	2015	≥18	569	–	12.1 (69)	14.6 (83)	–	R	Israel
Colgecen et al.[117]	2015	≥0	369[a]	–	3.2 (12)	8.9 (33)[b]	10.5 (39)	–	Turkey
Amin et al.[118]	2015	≥18	120[a]	28.2 (34)	–	–	–	R	USA
Sugiyama et al.[68]	2015	≥17	40	27.5 (11)	12.5 (5)	7.5 (3)	7.5 (3)	–	Japan
Karagol et al.[119]	2015	<17	80[d]	13.7 (11)	1.2 (1)	12.5 (10)	13.7 (11)	P, CC	Turkey
Lunge et al.[120]	2015	≥18	50	–	–	10 (5)[b]	–	CS	India
Rojo-Gutierrez et al.[121]	2015	≥18	35	11.4 (4)	–	–	–	CS	Spain
Arshi et al.[122]	2014	≥17	41	–	19.6 (8)	29.3 (12)	–	CC	Iran
Boonpiyathad et al.[123]	2014	≥18	60	10 (6)	–	–	–	P, CC	Thailand
Ban et al.[42]	2014	≥18	837	–	13.5 (113)	10 (84)[b]	–	R	Korea
Chansakulporn et al.[124]	2014	<16	92	0	0	0[b]	0	P	Thailand
Vikramkumar et al.[125]	2014	≥18	48	4.2 (2)	–	–	–	CS	India
Işik et al.[126]	2014	<17	58[a]	13.7 (8)	–	–	–	R	Turkey
Sun et al.[35]	2014	≥15	100	–	18 (18)	–	–	–	China
Ye et al.[127]	2014	≥18	82	18.3 (15)	–	–	–	CS	Korea
Asero[128]	2013	≥11	91	20 (18)	–	–	–	P	Italy
Calamita et al.[129]	2013	≥18	67	–	–	22.4 (15)	–	CS	Brazil
Ghaffari et al.[52]	2013	≥0	78[a]	17.9 (14)	12 (9)	6 (5)	–	D	Iran
Alpay et al.[48]	2013	≥18	50	–	14 (7)	12 (6)	–	P	Turkey
Wan et al.[33]	2013	≥12	60	27.3 (16)	16.6 (10)	8.3 (5)	–	P, CC	Taiwan
Yadav et al.[130]	2013	≥15	80	–	–	17.5 (14)	–	CC	India
Calamita et al.[131]	2013	≥18	49	–	–	24.5 (12)	–	–	Brazil
Misirlioglu et al.[132]	2013	<17	36[a]	5.5 (2)	–	–	–	R	Turkey
Cho et al.[38]	2013	≥18	27[a]	–	0	11 (3)	–	P	USA
Lee et al.[133]	2013	≥18	194	37.1 (72)	33 (64)	17.5 (34)	12.4 (24)	R	Korea
Kessel et al.[134]	2012	≥18	45	15.5 (7)	–	–	–	P	Israel
Magen et al.[81]	2012	≥18	749	–	4.1 (31)	5.2 (39)	–	R	Israel
Confino-Cohen et al.[27]	2012	≥18	12,778	–	1.1 (138)	4.7 (598)	–	R	Israel
Viswanathan et al.[135]	2012	≥18	195	–	6 (7/118)	26 (29/112)	–	R	USA
Iqbal et al.[136]	2012	–	46	21.7 (10)	–	–	–	R	UK

(Continues)

TABLE 1 (Continued)

First author of the study (reference)	Year	Age (y)	n, CSU	CSU patients with elevated levels of IgG antithyroid AAbs, % (n)				Design	Country
				Anti-TPO, anti-TG, and both AAbs	Anti-TG	Anti-TPO	Both AAbs in the same patients		
Tudose et al.[137]	2012	≥18	238	–	–	28.6 (68)	–	–	Romania
Irani et al.[138]	2012	≥18	90[a]	–	–	17.7 (16)	–	R	Lebanon
Missaka et al.[139]	2012	≥18	115	19.1 (22)	–	–	–	–	Brazil
Chomiciene et al.[140]	2012	≥20	128[a]	–	–	25 (32)	–	–	Lithuania
Sahiner et al.[28]	2011	<18	82	–	–	3.7 (3)	–	R	Turkey
Nuzzo et al.[51]	2011	≥15	54	22.2 (12)	11.1 (6)	22.2 (12)	22.2 (12)	P, CC	Italy
Tarbox et al.[70]	2011	≥21	356[a]	21.6 (77)	23.5 (32/136)	25.4 (45[b]/177)	–	R	USA
Sajedi et al.[141]	2011	≥18	58	17.2 (10)	–	–	–	–	Iran
El Gayyar et al.[58]	2011	≥0	35	–	20 (7)	14.2 (5)	–	–	Egypt
Abd El-Azim et al.[142]	2011	≥18	134	–	–	8.9 (12)	–	–	Egypt
Al-Balbeesi[54]	2011	≥18	68[a]	–	26.5 (18)	26.5 (18)[b]	–	P	Saudi Arabia
Karki et al.[143]	2011	≥18	102	–	6.9 (7)	–	–	–	Nepal
Kim et al.[144]	2011	–	45	28.9 (13)	13.3 (6)	24.4 (11)	8.9 (4)	–	Korea
Lee et al.[145]	2011	≥18	60	8.3 (5)	3.3 (2)	6.7 (4)[b]	–	–	Taiwan
Krupa Shankar et al.[146]	2010	≥0	127	6.2 (8)	–	–	–	P	India
Lai et al.[147]	2010	≥15	63	20.6 (13)	14.3 (9)	11.1 (7)[b]	–	–	Taiwan
Kilic et al.[91]	2010	<17	27	14.8 (4)	–	–	–	–	Turkey
Kessel et al.[148]	2010	≥18	189	14.8 (28)	–	–	–	P	Israel
Aamir et al.[149]	2010	≥21	47[a]	–	42.6 (20)	57.4 (27)[b]	–	D	Pakistan
Nebiolo et al.[150]	2009	≥16	228	34.2 (78)	–	–	–	P	Italy
Najib et al.[151]	2009	≥16	188	30.3 (57)	–	–	–	R	USA
Gregoriou et al.[152]	2009	≥18	2092	8.8 (184)	–	–	–	P	Greece
Gangemi et al.[23]	2009	≥18	95	32.6 (31)	13.7 (13)	26.3 (25)	7.4 (7)	–	Italy
Kulthanan et al.[153]	2007	≥15	407	3.7 (15)	16 (54/337)	12 (40[b]/337)	–	R	Thailand
Feibelmann et al.[49]	2007	≥18	49	12.2 (6)	4 (2)	12.2 (6)	4.1 (2)	CC	Brazil
Irinyi et al.[154]	2007	≥13	82	–	3.6 (3)	11 (9)	–	–	Hungary
Cebeci et al.[155]	2006	–	140	29.3 (41)	19.3 (27)	16.4 (23)	6.4 (9)	–	Turkey
Fernandez Romero et al.[156]	2005	–	61[a]	–	–	36 (22)	–	–	Argentina
Palma-Carlos et al.[157]	2005	–	56	28.5 (16)	23.2 (13)	26.8 (15)	21.4 (12)	–	Portugal
Caminiti et al.[158]	2005	<18	95	9.5 (9)	–	–	–	CC, CS	Italy
O'Donnell et al.[159]	2005	≥12	182	–	1.1 (2)	12.1 (22)[b]	–	–	UK
Farid et al.[71]	2005	≥14	60	36.6 (22)	15 (9)	5 (3)	16.7 (10)	–	Iran
Caproni et al.[160]	2005	≥18	28	53.6 (15)	25 (7)	35.7 (10)	–	–	Italy
Fusari et al.[90]	2005	≥18	82	29.3 (24)	–	–	–	P	Italy
Brunetti et al.[161]	2004	<16	52	0	0	0	–	–	Italy
Atta et al.[162]	2004	≥15	46	15.2 (7)	6.5 (3)	10.9 (5)	–	–	Brazil
Mete et al.[163]	2004	≥18	33	33.3 (11)	–	–	–	CC	Turkey
Sackesen et al.[29]	2004	<19	17[a]	0	0	0[b]	–	P	Turkey
Verneuil et al.[66]	2004	≥18	45[a]	27 (12)	17.8 (8)	17.8 (8)	8.9 (4)	P, CC	France
Caproni et al.[164]	2004	≥19	68	13 (9)	–	–	–	R	Italy
Toubi et al.[62]	2004	≥17	139	12 (17)	–	–	–	P	Israel
Gimenez-Arnau et al.[165]	2004	≥18	166	–	1.8 (3)	8.4 (14)	–	P	Spain
Pongpreuksa et al.[166]	2004	<15	38[a]	0	0	0[b]	0	–	Thailand

(Continues)

TABLE 1 (Continued)

First author of the study (reference)	Year	Age (y)	n, CSU	CSU patients with elevated levels of IgG antithyroid AAbs, % (n)				Design	Country
				Anti-TPO, anti-TG, and both AAbs	Anti-TG	Anti-TPO	Both AAbs in the same patients		
Hidvégi et al.[167]	2003	≥18	50	–	–	14 (7)[b]	–	–	Hungary
Levy et al.[168]	2003	<18	187	4.3 (8)	1.1 (2)	2.1 (4)	1.1 (2)	–	Israel
Asero et al.[169]	2003	≥13	257[a]	26 (66)	–	–	–	–	Italy
Bakos et al.[100]	2003	≥14	48	–	–	29.2 (14)	–	–	Hungary
Kikuchi et al.[87]	2003	–	282	19.5 (55)	8.5 (24)	16.6 (47)[b]	5.7 (16)	P	USA
Vermeulen et al.[170]	2003	–	57	21 (12)	–	–	–	–	France
Nettis et al.[171]	2002	–	102	12.7 (13)	–	–	–	–	Italy
Karaayvaz et al.[72]	2002	≥19	580	12 (70)	–	–	–	P	Turkey
Kullavanijaya et al.[172]	2002	–	100	21 (21)	–	–	–	–	Thailand
Tedeschi et al.[173]	2001	–	38	–	–	60.5 (23)	–	–	Italy
Kandeel et al.[73]	2001	≥12	610	9.8 (60)	–	–	–	–	USA
Zauli et al.[41]	2001	≥9	122	28.7 (35)	6.5 (8)	8.2 (10)	13.9 (17)	–	Italy
Ryhal et al.[174]	2001	≥15	25	–	–	20 (5)	–	–	USA
Gaig et al.[74]	2000	–	170	14.7 (25)	–	–	–	–	Spain
Wedi et al.[175]	1998	≥17	100	5 (5)	–	–	–	–	Germany
Turktas et al.[75]	1997	≥16	94	11.7 (11)	11.7 (11)	9.6 (9)[b]	9.6 (9)	–	Turkey
Zuberbier et al.[176]	1995	≥16	47[a]	6.3 (3)	–	–	–	P	Germany
Collet et al.[177]	1995	≥18	45[a]	18 (8)	–	–	–	–	France
Sibbald et al.[178]	1991	≥18	254[a]	–	2 (5)	11 (28)[b]	–	P	Canada
Leznoff et al.[76]	1989	≥8	624	14.4 (90)	–	–	–	–	Canada
Lanigan et al.[179]	1984	≥18	25	–	12 (3)	32 (8)[b]	–	–	UK
Leznoff et al.[53]	1983	≥10	140	–	–	12.1 (17)[b]	–	–	Canada

–, no data, not defined in the paper or in the abstract; AAbs, autoantibodies; CC, case-control study; P, prospective study; R, retrospective study; CS, cross-sectional study; D, descriptive study; TPO, thyroid peroxidase; TG, thyroglobulin; CSU, chronic spontaneous urticaria.
[a]It is not clear from the paper whether patients with inducible urticaria were excluded.
[b]Antimicrosomal antibodies.
[c]Patients with aspirin intolerant chronic urticaria.
[d]Patients with idiopathic histaminergic acquired angioedema.

Because of the heterogeneity of data reported by the publications analyzed, that is, the identified studies are variable in design, patient population, disease definition, and laboratory methods, we did not perform a formal meta-analysis and, instead, used a descriptive approach.

3 | RESULTS

3.1 | Is CSU linked to elevated levels of thyroid autoantibodies?

3.1.1 | What is the prevalence of IgG thyroid autoantibodies in CSU?

Total IgG thyroid autoantibodies

In 68 studies, the prevalence of elevated blood levels of IgG antithyroid AAbs (IgG-anti-TPO, IgG-anti-TG, and both) in patients with CSU ranged from 0% to 53.6% (Table 1). Almost all of these studies (64 of 68) reported increased levels of IgG antithyroid AAbs in one or more patients, three-fourths in ≥10% of patients (51 of 68 studies), and more than a half of them in ≥15% of patients (37 of 68 studies).

When we analyzed only studies where a definite diagnosis of CSU was made in all patients (ie, inducible urticaria was excluded) and ≥100 patients were included (24 studies), the frequency of elevated IgG antithyroid AAbs varied from 3.7% to 37.1%. Two-thirds of these studies reported rates of increased IgG antithyroid AAbs in ≥10% of patients (17 of 24 studies).

IgG-anti-TPO vs IgG-anti-TG

Increased levels of IgG-anti-TG were reported in 0%-42.6% (54 studies), of IgG-anti-TPO in 0%-60.5% (69 studies), and of both AAbs in the same patient in 0%-22.2% (21 studies). Almost two-thirds of the studies analyzed (61.5%, 32 of 52 studies) found a higher prevalence of elevated levels of IgG-anti-TPO as compared to IgG-anti-TG (Figure 1). Higher rates of IgG-anti-TG than IgG-anti-TPO were reported in 25% (13 of 52) of studies, and 13.5% of studies (7 of 52) found no difference between the prevalence of both AAbs. Gangemi et al.[23] showed that in CSU, IgG-anti-TPO testing only would detect twice as many IgG antithyroid AAb-positive patients compared to IgG-anti-TG testing only. IgG-anti-TG alone in the absence of IgG-

TABLE 2 Prevalence of elevated TSH receptor antibodies in patients with CSU

			CSU patients			
First author of the study (reference)	Year	Age (y)	Total, n	With elevated anti-TSHr, % (n)	Design	Country
Wan et al.[33]	2013	>18	60	83.3 (50)	P, CC	Taiwan
Lee et al.[133]	2013	>18	194	7.2 (14)	R	Korea
Irani et al.[138]	2012	>18	90[a]	1.1 (1)	R	Lebanon
Verneuil et al.[66]	2004	>18	45[a]	0	P, CC	France
Caproni et al.[164]	2004	>18	68	7.4 (5)	R	Italy
Zauli et al.[41]	2001	>9	122	2.4 (3)	–	Italy

CC, case-control study; P, prospective study; R, retrospective study; D, descriptive study; –, no data, not defined in the paper or in the abstract; TSH, thyroid-stimulating hormone; TSHr, TSH receptor; CSU, chronic spontaneous urticaria.
[a]It is not clear from the paper whether patients with inducible urticaria were excluded.

anti-TPO is not significantly associated with thyroid disease in the general population.[21]

IgG-anti-TSHr

In six independent studies (Table 2), the prevalence of elevated IgG-anti-TSHr in patients with CSU was 0%-83.3%. Five of six studies reported rates of <10%.

Adult patients with CSU vs children with CSU

In adults with CSU (≥18 years, 29 studies), elevated IgG antithyroid AAbs were reported in 4.2%-53.6% of patients. Almost half of these studies reported rates of increased IgG antithyroid AAb levels in ≥20% of patients (12 of 29 studies). The prevalence of elevated levels of IgG antithyroid AAbs in children with CSU (<18 years, 11 studies) was lower: 0%-17.5%. More than a half of these studies reported rates of elevated IgG antithyroid AAbs in ≤10% of patients (7 of 11 studies), and one-third of the studies did not find increased IgG antithyroid AAbs in any young patients investigated (4 of 11 studies).

Thus, in most of the analyzed studies in patients with CSU, the prevalence of IgG antithyroid AAbs in children is lower than in adults. In several population-based studies, the prevalence of autoimmune thyroiditis in children was 0.35%-1.6%.[24-26] This low prevalence of thyroid autoimmunity in children compared to adults can be explained by data that the likelihood of having an autoimmune disease including AITD increases with age.[9,13,21,27] Thyroid pathology, including AITD, does not appear to be an important associated and/or etiological factor of CSU in children.[28-31] In this perspective, several environmental triggers and age-related mechanisms, such as prolonged inflammation and/or increased oxidative stress, may accumulate over the years, favoring the development of other autoimmune disorders in CSU and AITD.[13,32]

- There is a strong link between CSU and elevated levels of IgG antithyroid AAbs (strong evidence).
- Levels of IgG-anti-TPO are more often elevated in CSU than those of other thyroid AAbs (strong evidence).
- Levels of IgG antithyroid AAbs are more often elevated in adult patients with CSU than in children (strong evidence).

3.1.2 | As compared to controls, do patients with CSU exhibit higher levels of IgG antithyroid autoantibodies, and are elevated levels more common?

CSU vs controls

In 29 studies, the blood levels of IgG antithyroid AAbs and rates of elevated levels were compared in patients with CSU and healthy controls (HCs) or control subjects without urticaria (Table 3). Twenty-three of these studies (79%) found patients with CSU to exhibit higher levels of IgG antithyroid AAbs as compared to controls. Specifically, 15 of 17 (88%) and 11 of 15 (73%) studies found higher levels of IgG-anti-TPO and IgG-anti-TG, respectively, in patients with CSU vs controls. Only six of 29 (21%) studies did not report significantly higher rates of IgG antithyroid AAbs in patients with CSU as compared to controls.

In the analyzed comparative studies, in patients with CSU, the rates of elevated IgG antithyroid AAbs (IgG-anti-TPO, IgG-anti-TG, and both) ranged from 12% to 36.6% (14 studies), of elevated IgG-anti-TG varied from 0% to 30% (21 studies), of elevated IgG-anti-TPO from 4.7% to 43.3% (24 studies), and of both AAbs in the same patient from 4.1% to 22.2% (10 studies). In controls including HCs, the prevalence of elevated IgG antithyroid AAbs ranged from 0% to 14.8% (14 studies), with rates for IgG-anti-TG from 0% to 11% (16 studies), for IgG-anti-TPO from 0% to 20% (22 studies), and for both AAbs in the same patient from 0.4% to 3.3% (three studies).

Wan and Wu[33] found a significantly higher prevalence of elevated IgG-anti-TSHr in patients with CSU in comparison with controls (83.3% vs 0%, $P<.05$).

Thus, patients with CSU exhibit significantly higher levels of IgG antithyroid AAbs than controls. This is in support of the results of a recent meta-analysis and a study with data on 12,778 patients and 10,714 controls.[27,34]

CSU vs other diseases

No significant difference in the prevalence of elevated IgG-anti-TG and/or IgG-anti-TPO was observed between patients with CSU and patients with acute urticaria,[35,36] urticarial vasculitis,[37] rheumatoid arthritis, or systemic lupus erythematosus.[38] In contrast, some studies showed that patients with CSU had

TABLE 3 Prevalence of elevated thyroid autoantibodies in patients with CSU and controls

First author of the study (reference)	Year	Age (y)	CSU (n)	Controls (n)	CSU patients/controls with elevated thyroid AAbs, % (n)				Design	Country
					Anti-TPO, anti-TG, and both AAbs	Anti-TG	Anti-TPO[a]	Both in the same patients		
Magen et al.[39]	2016	≥18	41	44[b]	–	17.2 (7)/2.3 (1)[‡]	31.7 (13)/6.8 (3)[‡]	–	P	Israel
Diaz-Angulo et al.[50]	2016	≥18	343	282[b]	26.8 (92)/2.5 (7)[†]	15.2 (52)/1.1 (3)[†]	20.4 (70)/1.8 (5)[†]	8.7 (30)/0.4 (1)[†]	CC	Spain
Okba et al.[57]	2015	≥18	80[c]	40[b]	–	17.5 (14)/2.5 (1)[d,†]	25 (20)/10 (4)[d,‡]	16.2 (13)/–	CC	Egypt
Karagol et al.[119]	2015	<17	80[e]	80[b]	13.7 (11)/2.5 (2)[‡]	1.2 (1)/2.5 (2)	12.5 (10)/0	13.7 (11)/–	P, CC	Turkey
Sun et al.[35]	2014	≥15	100	100[b]	–	18 (18)/11 (11)*	–	–	–	China
Ghaffari et al.[52]	2013	≥0	78[c]	67[b]	17.9 (14)/9 (6)	12 (9)/6 (4)[‡]	6 (5)/3 (2)[‡]	–	D	Iran
Cho et al.[38]	2013	≥18	27[c]	20[b]	–	0/10 (2)*	11 (3)/20 (4)*	–	P	USA
Hatada et al.[59]	2013	≥18	85[c]	67[b]	–	–/–*		–	–	Japan
Alpay et al.[48]	2013	≥18	50	50[b]	–	14 (7)/6 (3)*	12 (6)/4 (2)*	–	P	Turkey
Wan and Wu[33]	2013	≥12	60	40[b]	27.3 (16)/0[‡]	16.6 (10)/0[‡]	8.3 (5)/0[‡]	–	P, CC	Taiwan
Yadav et al.[130]	2013	≥15	80	40[b]	–	–	17.5 (14)/5 (2)[‡]	–	CC	India
Confino-Cohen et al.[27]	2012	≥18	12,778	10,714[f]	–	1.1 (138)/0.05 (5)[†]	4.7 (598)/0.5 (54)[†]	–	R	Israel
Irani et al.[138]	2012	>18	90[c]	684[b]	–	–	17.7 (16)/8.8 (60)[‡]	–	R	Lebanon
El Gayyar et al.[58]	2011	≥0	35	30[b]	–	20 (7)/–[‡]	14.2 (5)/6.7 (2)[†]	–	–	Egypt
Al-Balbeesi[54]	2011	≥18	68[c]	22[b]	–	26.5 (18)/0[†]	26.5 (18)/4.5 (1)[†]	–	P	Saudi Arabia
Nuzzo et al.[51]	2011	>15	54	108[b]	22.2 (12)/6.5 (7)[‡]	11.1 (6)/1.8 (2)	22.2 (12)/1.8 (2)	22.2 (12)/2.8 (3)	P, CC	Italy
Gangemi et al.[23]	2009	≥18	95	100[b]	32.6 (31)/13 (13)[†]	13.7 (13)/–	26.3 (25)/–	7.4 (7)/–	–	Italy
Aamir et al.[180]	2008	≥25	30[c]	30[b]	–	30 (9)/0[†]	43.3 (13)/0[†]	–	CC	Pakistan
Feibelmann et al.[49]	2007	≥18	49	112[g]	12.2 (6)/9.8 (11)*	4.1 (2)/–	12.2 (6)/–	4.1 (2)/–	CC	Brazil
Cebeci et al.[155]	2006	–	140	181[b]	29.3 (41)/5.6 (10)[†]	19.3 (27)/–	16.4 (23)/–	6.4 (9)/–	–	Turkey
Farid et al.[71]	2005	≥14	60	30[b]	36.6 (22)/10 (3)[h]	15 (9)/–	5 (3)/–	16.7 (10)/–	–	Iran
Palma-Carlos et al.[157]	2005	–	56	56[f]	28.5 (16)/0[†]	23.2 (13)/0[†]	26.8 (15)/0[†]	21.4 (12)/–	–	Portugal
Mete et al.[163]	2004	≥18	33	27[b]	33.3 (11)/14.8 (4)*	–	–	–	–	Turkey
Verneuil et al.[66]	2004	≥18	45[c]	30[b]	27 (12)/3.3 (1)[‡]	17.8 (8)/0	17.8 (8)/3.3 (1)	8.9 (4)/3.3 (1)	P, CC	France
Toubi et al.[62]	2004	≥17	139	60[b]	12 (17)/0[‡]	–	–	–	P	Israel
Kullavanijaya et al.[172]	2002	–	100	100[b]	21 (21)/9 (9)[‡]	–	–	–	–	Thailand

(Continues)

TABLE 3 (Continued)

First author of the study (reference)	Year	Age (y)	CSU (n)	Controls (n)	CSU patients/controls with elevated thyroid AAbs, % (n)				Design	Country
					Anti-TPO, anti-TG, and both AAbs	Anti-TG	Anti-TPO[a]	Both in the same patients		
Ryhal et al.[174]	2001	≥15	25	75[g]	–	–	20 (5)/0[‡]	–	–	USA
Turktas et al.[75]	1997	≥16	94	80[b]	–	11.7 (11)/3.7 (3)[‡]	9.6 (9), 3.7 (3)[‡]	–	–	Turkey
Leznoff et al.[53]	1983	≥10	140	477[g]	–		12.1 (17)/5.6 (27)[‡]	–	–	Canada

–, no data, not defined in the paper or in the abstract; CC, case-control study; P, prospective study; R, retrospective study; D, descriptive study; CSU, chronic spontaneous urticaria.
[a]Designated as antimicrosomal antibodies in some studies.
[b]Healthy controls.
[c]It is not clear from the paper whether patients with inducible urticaria were excluded.
[d]Statistically significant association is only between ASST+ CSU patients and controls.
[e]Patients with idiopathic histaminergic acquired angioedema.
[f]Subjects without CSU.
[g]Patients without urticaria but with other diseases.
[h]Farid et al. reported that CSU is significantly associated with thyroid autoimmunity. However, p-value was not mentioned in the paper.
[†]$P \leq .001$; [‡]$P < .05$; *$P \geq .05$ (statistically nonsignificant).

significantly higher levels of IgG antithyroid AAbs compared to patients with acute[23,39] and chronic inducible[40] urticaria. The difference in IgG antithyroid AAb levels was not statistically significant when CSU patients with atopic diseases were compared to nonatopic CSU patients.[41,42] However, another study showed higher rates of elevated IgG antithyroid AAbs in children with CSU and atopy.[43]

- Patients with CSU exhibit significantly higher levels of IgG antithyroid AAbs than controls (strong evidence).

3.1.3 | What is the prevalence of elevated IgE thyroid autoantibodies in CSU?

The rates of elevated IgE-anti-TPO and IgE-anti-TG in patients with CSU were investigated by five and two studies, respectively, and ranged from 0% to 54.2% (Table 4). In HCs, the prevalence of IgE-anti-TPO and IgE-anti-TG was 0% as reported by three studies. Two of six studies showed that serum levels of IgE-anti-TPO are significantly higher in patients with CSU than in normal subjects. Two studies failed to reproduce an association between IgE antithyroid AAbs and CSU.

The prevalence of these AAbs in the general population has not yet been evaluated in detail. Guo et al.[44] provided evidence for the presence of low-titer IgE-anti-TPO in patients with AITD using a very sensitive IgE capture assay.

There was no significant association between the prevalence of IgE-anti-TPO and IgG-anti-TPO in one study,[36] but such an association was demonstrated in another.[45]

- Patients with CSU exhibit significantly higher levels of IgE-anti-TPO than controls (weak evidence).

3.1.4 | Association between the presence of thyroid autoantibodies and CSU parameters

A total of 60 studies evaluated the association of IgG antithyroid AAbs and various clinical and laboratory features of CSU (Table 5). Our review of these studies identified weak evidence in support of an association of elevated IgG antithyroid AAbs and more frequent glucocorticosteroid use. The evidence for other parameters, for example, CSU duration, severity/activity, and ASST response, is inconsistent or nonexistent.

We found inconsistent evidence for an association of IgG antithyroid AAbs with the gender and age of patients with CSU. However, many large population-based studies and reviews reported that the prevalence of IgG antithyroid AAbs, AITD, and/or thyroid dysfunction increases with age and is higher in healthy women and in women without CSU compared to men.[9,13,21,46,47]

TABLE 4 Serum IgE thyroid AAb reactivity in patients with CSU and controls measured by immunoassays

First author of the study (reference)	Year	IgE antithyroid AAbs	Method	CSU patients with high levels of IgE AAbs, % (n/total)	HCs with high levels of IgE AAbs, % (n/total)	IgE AAbs are higher in CSU patients vs HCs
Shin et al.[36]	2015	anti-TPO	dELISA	8.3 (8/96[a])	0 (0/69)	Yes
Hatada et al.[59]	2013	anti-TG	dELISA	–[e] (–[e]/85)	–[e] (–[e]/67)	No
Altrichter et al.[45]	2011	anti-TPO	sELISA	54.2 (259/478)	–[e] (–[e]/127)	Yes
Concha et al.[60]	2004	anti-TPO, anti-TG	dELISA	10 (2[b]/20)	0 (0/12)[d]	–
Tedeschi et al.[173]	2001	anti-TPO	RIA	0 (0/38)	0 (0/11[c])	No
Gimenez-Arnau et al.[165]	2004	anti-TPO	ELISA	16.7 (2/12)	–	–

IgE AAbs, IgE autoantibodies; TPO, thyroid peroxidase; TG, thyroglobulin; ELISA, enzyme-linked immunosorbent assay; HCs, healthy controls; RIA, radioimmunoassay; dELISA, direct ELISA; sELISA, site-directed human IgE capture ELISA; –, no data; CSU, chronic spontaneous urticaria.
[a]Patients with aspirin intolerant chronic urticaria were included; it was not defined whether patients with inducible urticaria were excluded.
[b]One patient had antithyroid peroxidase IgE antibody and one patient had antithyroglobulin IgE.
[c]One of the control subjects had autoimmune thyroiditis and two others had allergic rhinitis.
[d]Patients with known Hashimoto's thyroiditis but with no history of urticaria.
[e]Data were not shown in the paper.

Patients with IgE-anti-TPO had significantly increased total IgE levels compared to patients without IgE-anti-TPO in one study,[36] but not in another.[45] No difference was found in patients with and without IgE-anti-TPO in terms of age, gender ratio, duration, or severity and ASST response.[45]

- Elevated IgG antithyroid AAbs in CSU are linked to the use of glucocorticoids (weak evidence) but not to disease duration or severity/activity, gender, age or ASST response (inconsistent evidence)

3.2 | Is CSU linked to thyroid dysfunction and disease?

3.2.1 | What is the prevalence of thyroid dysfunction and diseases in patients with CSU?

Thyroid dysfunction

In 41 independent studies, the prevalence of thyroid dysfunction (hypothyroidism and/or hyperthyroidism) in patients with CSU ranged from 0% to 54.5% (Table 6). Thirty-two of 41 studies (76%), 25 of 41 studies (61%), and 20 of 41 studies (49%) reported thyroid dysfunction rates of ≥2%, ≥5%, and ≥10%, respectively.

Hypothyroidism vs hyperthyroidism

Specifically, 0%-42.6% and 0%-31% of patients with CSU showed clinical and subclinical hypothyroidism, respectively, whereas clinical hyperthyroidism was reported in 0%-17.6% and subclinical hyperthyroidism in 0%-5.5% of patients. Almost half of these studies demonstrated clinical and subclinical hypothyroidism in ≥5% of patients (44%, 17/41 of studies; and 40%, 6/15 of studies, respectively). In contrast, only 16% (5/32) and 8% (1/13) of studies showed clinical and subclinical hyperthyroidism, respectively, in ≥5% of patients. The prevalence of hypothyroidism and hyperthyroidism in the general population is 3.05%-4.6% and 0.75%-1.3%, respectively.[21,47]

These findings indicate that in CSU, hypothyroidism is more common than hyperthyroidism. This is further supported by the fact that 58% of studies (18 of 31) found higher rates of hypothyroidism than hyperthyroidism, as compared to only 13% of studies (4 of 31) reporting higher rates of hyperthyroidism than hypothyroidism. Moreover, hypothyroidism or subclinical hypothyroidism was more frequent than hyperthyroidism in a large sample of 12,778 patients with CSU.[27] In most studies (three of five), but not all studies,[48,49] patients with CSU were found to have significantly higher rates of hypothyroidism[27,50,51] and hyperthyroidism[27,50] than HCs and patients without CSU.

Adult patients with CSU vs children with CSU

In adult patients with CSU (≥18 years old, 20 studies), clinical hypothyroidism and clinical hyperthyroidism were found in 0%-42.6% and 0%-13.8%, respectively. Eleven of 20 studies (55%) and only 3 of 15 studies (20%) reported rates of ≥5% for clinical hypothyroidism and clinical hyperthyroidism, respectively. The prevalence of clinical hypothyroidism and clinical hyperthyroidism in children with CSU (<18 years) was much lower: from 0% to 1.1% (five studies) and 0% (four studies), respectively.

Graves' disease vs Hashimoto's thyroiditis

The reported rates of CSU patients with GD ranged from 0% to 9.1% and for HT from 0.5% to 27.5%. These are higher than reported for the general population with 0.4%-1.5% (GD)[5-8] and 0.9%-9.1% (HT).[9] Rates of GD in CSU were ≥5% in one of eight studies, and rates of HT were ≥5% in 9 of 16 studies. In all six of six studies, rates of HT were higher than those of GD. This indicates that patients with CSU have a higher prevalence of HT than GD.

IgG antithyroid AAbs and thyroid dysfunction in CSU

Although both hyper- and hypothyroidism are associated with CSU, some patients with antithyroid AAbs are asymptomatic with normal or slightly abnormal thyroid function.[52,53] Hollowell et al.[21] reported that elevated levels of IgG-anti-TPO, but not IgG-anti-TG, are significantly associated with hypothyroidism and hyperthyroidism. Elevated

TABLE 5 Association between the presence of IgG antithyroid AAbs and CSU parameters

	↑ IgG-anti-TPO and/or IgG-anti-TG		↑ IgG-anti-TG		↑ IgG-anti-TPO		Total n of studies		Levels of evidence for "association"
	Association was shown, Refs*								
CSU parameters	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	
↑Duration	54,62	112,150	133	57	23,58	57	5	3	Inconsistent
↑Severity/activity	148	62,66,81		54,57	111,120	54,57	3	5	Inconsistent
Gender (f>m)	27,50,56,74,151	118,147,181				159	5	4	Inconsistent
Age (elderly>nonelderly adults)	182			42,114		42,114,159	1	3	Inconsistent
↑Frequency of thyroid dysfunction	56			54		54	1	1	Inconsistent
↑Presence of AE	139	51,66,147			138		2	3	Inconsistent
↑Frequency of the crises		51,66					0	2	Inconsistent
↑Duration of CSU before hospitalization/admission	23	147					1	1	Inconsistent
Parameters associated with CSU diagnosis									
Greater prevalence of HLA B* 14					131		1	0	No
↑Prevalence of infection with *Helicobacter pylori*					100		1	0	No
ASST+	133,146,181	28,81,85,91,112,117,121, 141,164,171,183,184	57,133	28,48,81,185	39,57,100, 120,137,142,159	28, 48, 81, 130, 133, 140, 185, 186	10	18	Inconsistent
↑Total IgE	148	49					1	1	Inconsistent
ANA+	116	147,151			129		2	2	Inconsistent
ESR		147					0	1	No
Vitamin D		115					0	1	No
Positive BHRA, BAT and/or basophil activation marker expression	87,136,154	127,151,164				140	3	4	Inconsistent
ELISA for detection of IgG-FcεRI/IgE		85					0	1	No
Parameters associated with CSU treatment									
More frequent steroid use			133		138		2	0	Weak
↑Duration of AH treatment		81,119					0	2	Inconsistent
↑Odds of achieving control with AH	118						1	0	No
↑Resistance to AH		51,66,118,135					0	4	Inconsistent

ASST, autologous serum skin test; AE, angioedema; ANA, antinuclear antibodies; BAT, basophil activation test; BHRA, basophil histamine release assay; AH, antihistamines; AAbs, autoantibodies; CSU, chronic spontaneous urticaria; +, positive; ↑, elevated or higher values.

*Statistically significant association with a *P*-value <.05.

TABLE 6 Prevalence of thyroid diseases in CSU

First author of the study (reference)	Year	Age (y)	n, CSU	% (n), Graves' disease	% (n), Hashimoto's thyroiditis	% (n) of CSU patients with thyroid dysfunction					Design	Country
						Hypothyroidism		Hyperthyroidism				
						Clinical	Subclinical	Clinical	Subclinical	Total		
Curto-Barredo et al.[110]	2016	≥18	19	–	–	36.8 (7)	–	5.3 (1)	–	8	–	Spain
Eser et al.[111]	2016	<18	52	–	–	0	0	0	0	0	P	Turkey
Diaz-Angulo et al.[50]	2016	≥18	343	–	–	3.8 (13)	4.4 (15)	1.2 (4)	5.5 (19)	14.9 (51)	CC	Spain
Kim et al.[56]	2016	≥12	184	2.7 (5)	5.4 (10)	5.4 (10)	4.3 (8)	4.3 (8)	–	14.1 (26)	R	Korea
Akarsu et al.[37]	2015	≥0	146	1.4 (2)	4.8 (7)	–	–	–	–	–	R	Turkey
Okba et al.[57]	2015	≥18	80[a]	–	–	18.7 (15)	–	13.8 (11)	–	32.5 (26)	CC	Egypt
Magen et al.[116]	2015	≥18	569	2.3 (13)	15.6 (89)	–	–	–	–	–	R	Israel
Colgecen et al.[117]	2015	≥0	369[a]	–	–	3.5 (13)	–	1.1 (4)	–	4.6 (17)	–	Turkey
Sugiyama et al.[68]	2015	≥17	40	–	27.5 (11)	2.5 (1)	–	2.5 (1)	–	5 (2)	–	Japan
Karagol et al.[119]	2015	<17	80[b]	–	3.7 (3)	0	0	0	0	0	P, CC	Turkey
Arshi et al.[122]	2014	≥17	41	–	–	0	5 (2)	0	0	5 (2)	CC	Iran
Chansakulporn et al.[124]	2014	<16	92	–	–	0	–	0	–	0	P	Thailand
Magen et al.[182]	2013	≥18	1051	–	3.2 (34)	–	–	–	–	–	R	Israel
Calamita et al.[129]	2013	≥18	67	–	–	10.4 (7)	–	–	–	20.8 (14)	CS	Brazil
Ghaffari et al.[52]	2013	≥0	78[a]	–	–	1.3 (1)	0	0	0	1.3 (1)	D	Iran
Alpay et al.[48]	2013	≥18	50	–	–	6 (3)	–	0	–	6 (3)	P	Turkey
Wan et al.[33]	2013	≥12	60	–	–	0	–	0	–	0	P, CC	Taiwan
Calamita et al.[131]	2013	≥18	49	–	–	12.2 (6)	–	–	–	12.2 (6)	–	Brazil
Misirlioglu et al.[132]	2013	<17	36[a]	–	–	0	0	0	0	0	R	Turkey
Krupashankar et al.[184]	2012	≥10	80	–	–	2.5 (2)	–	–	–	2	P	India
Magen et al.[81]	2012	≥18	749	–	–	5.9 (44)	–	–	–	5.9 (44)	R	Israel
Confino-Cohen et al.[27]	2012	≥18	12,778	–	–	9.8 (1257)	–	2.6 (336)	–	12.5 (1593)	R	Israel
Missaka et al.[139]	2012	≥18	115	4.3 (5)	14.8 (17)	2.6 (3)	13.9 (16)	3.5 (4)	4.3 (5)	24.3 (28)	CC	Brazil
Tudose et al.[137]	2012	≥18	238	–	14.3 (34)	3.8 (9)	8.8 (21)	0	0	12.6 (30)	–	Romania
Irani et al.[138]	2012	≥18	90[a]	–	–	7.7 (7)	–	1.1 (1)	–	8.9 (8)	R	Lebanon
Chomiciene et al.[140]	2012	≥20	128[a]	–	–	3.1 (4)	–	7 (9)	–	10.1 (13)	–	Lithuania
Sahiner et al.[28]	2011	<18	82	–	1.2 (1)	–	–	–	–	–	R	Turkey
Nuzzo et al.[51]	2011	≥15	54	–	18.5 (10)	18.5 (10)	–	–	–	18.5 (10)	P, CC	Italy
Tarbox et al.[70]	2011	≥21	262[a]	–	–	4.6 (12)	–	3.8 (10)	–	8.4 (22)	R	USA
El Gayyar et al.[58]	2011	≥0	35	–	–	8.5 (3)	31 (11)	2.8 (1)	0	42.8 (15)	–	Egypt
Aamir et al.[149]	2010	≥21	47[a]	–	–	42.6 (20)	–	0	–	42.6 (20)	D	Pakistan
Kulthanan et al.[153]	2007	≥15	407	–	–	0.7 (3)	–	2.9 (12)	–	3.7 (15)	R	Thailand
Feibelmann et al.[49]	2007	≥18	49	–	–	6.1 (3)	4 (2)	2 (1)	0	12.2 (6)	CC	Brazil
Cebeci et al.[155]	2006	–	41	–	–	2.4 (1)	17.1 (7)	4.9 (2)	0	24.3 (10)	–	Turkey
Caminiti et al.[158]	2005	<18	95	–	4.2 (4)	–	–	–	–	–	CC, CS	Italy
O'Donnell et al.[159]	2005	≥12	182	–	–	3.8 (7)	–	–	–	3.8 (7)	–	UK
Farid et al.[71]	2005	≥14	60	–	–	0	1.7 (1)	0	0	1.7 (1)	–	Iran
Verneuil et al.[66]	2004	≥18	45[a]	0	8.9 (4)	0	0	0	0	0	P, CC	France
Toubi et al.[62]	2004	≥17	139	–	–	2.2 (3)	–	–	–	–	P	Israel
Levy et al.[168]	2003	<18	187	–	0.5 (1)	1.1 (2)	–	–	–	1.1 (2)	–	Israel
Asero et al.[169]	2003	≥13	257[a]	–	–	6.2 (16)	–	1.6 (4)	–	7.8 (20)	–	Italy

(Continues)

TABLE 6 (Continued)

First author of the study (reference)	Year	Age (y)	n, CSU	% (n), Graves' disease	% (n), Hashimoto's thyroiditis	% (n) of CSU patients with thyroid dysfunction					Design	Country
						Hypothyroidism		Hyperthyroidism				
						Clinical	Subclinical	Clinical	Subclinical	Total		
Nettis et al.[187]	2003	≥5	485	–	–	1.4 (7)	–	0.6 (3)	–	2.1 (10)	P	Italy
Liutu et al.[188]	1998	≥13	107	–	–	1.9 (2)	–	–	–	1.9 (2)	–	Finland
Turktas et al.[75]	1997	≥16	11	9.1 (1)	18.2 (2)	27.3 (3)	18.2 (2)	9.1 (1)	–	54.5 (6)	–	Turkey
Zuberbier et al.[176]	1995	≥16	47[a]	4.2 (2)	–	–	–	–	–	–	P	Germany
Collet et al.[177]	1995	≥18	45[a]	2.2 (1)	–	–	–	–	–	–	–	France
Lanigan et al.[179]	1984	≥18	25	–	4 (1)	20 (5)	–	–	–	20 (5)	–	UK
Leznoff et al.[53]	1983	≥10	17	–	17.6 (3)	17.6 (3)	–	17.6 (3)	–	35.3 (6)	–	Canada
Small et al.[189]	1982	–	208	–	–	–	–	3.8 (8)	–	3.8 (8)	–	Canada

–, no data, not defined in the paper or in the abstract; CC, case-control study; P, prospective study; R, retrospective study; CS, cross-sectional study; D, descriptive study; CSU, chronic spontaneous urticaria.

[a]It is not clear from the paper whether patients with inducible urticaria were excluded.

[b]Patients with idiopathic histaminergic acquired angioedema.

levels of IgG-anti-TPO and TSH were shown to predict the future development of hypothyroidism in a euthyroid general population.[9,46] The prevalence of hypothyroidism in patients with CSU[27,54] as well as in the general population[9] increases with age. In >80% of patients with CSU, thyroid dysfunction was diagnosed within 10 years of the diagnosis of CSU.[27] Thus, annual reassessment of thyroid function in CSU patients with elevated IgG antithyroid AAb levels may be warranted and is recommended by some urticaria specialists.[55]

Women with CSU vs men with CSU

The frequency of thyroid dysfunction (hyperthyroidism and/or hypothyroidism) in women with CSU is significantly higher than in men.[27,56] Females in the general population were also shown to have a greater risk of having hypothyroidism and AITD (both Hashimoto's thyroiditis and Graves' disease) than men.[9,21,46]

Patients with CSU vs HCs

In two studies,[57,58] but not all studies,[38,49] patients with CSU had significantly higher rates of thyroid dysfunction compared to HCs.

Limitations

Inconsistent or conflicting results between the studies on the prevalence of IgG antithyroid AAbs, AITD, and/or thyroid dysfunction in CSU may be associated with various limitations. Some studies are of relatively small sample size and/or not well controlled and have low statistical power. In many papers, CSU and chronic inducible urticaria are not clearly differentiated. Different methods are used to detect antithyroid AAbs with no standardization of positive cut points. For example, in one study IgE-anti-TPO AAbs were measured by site-directed ELISA.[45] In other studies, a direct ELISA approach[36,59,60] was carried out, where IgG AAbs to the antigen can mask the presence of IgE AAbs due to competition.[61] IgG-anti-TPO and IgG antimicrosomal antibodies are the same type of autoantibody, and some papers referring to the latter may have used passive hemagglutination instead of immunometric methods.[23,34,62] Moreover, a small minority of patients with AITD may have no detectable IgG-anti-TPO/TG.[34]

In some older studies, antithyroid AAbs were not investigated, and patients with CSU were labeled as having "thyroid disease".[19] In other studies, the diagnosis of chronic urticaria was solely based on the patient history, and not confirmed by a medical specialist.[63]

There is substantial geographic variation in the diagnosis of AITD, both GD and HT, maybe because of environmental and/or genetic factors.[9] For example, iodine-sufficient populations appear to have higher incidences of hypothyroidism and more thyroiditis compared to those that are iodine-deficient.[9] In addition, the prevalence of IgG antithyroid AAbs is greater in Caucasian and Mexican Americans than in African Americans.[9,21] At last, preclinical and clinical thyroid disease definitions and terminology are nonstandardized.

- Thyroid dysfunction rates are increased in patients with CSU (strong evidence).
- Hypothyroidism and Hashimoto's thyroiditis are more common than hyperthyroidism and Graves' disease (strong evidence).
- Thyroid dysfunction is more common in adult patients with CSU than in children (strong evidence).
- Thyroid dysfunction is more common in female than in male patients with CSU (weak evidence).

3.2.2 | What is the prevalence of urticaria including CSU in patients with thyroid disease?

Little is known about the prevalence of CSU in thyroid diseases. Most studies fall short on differentiating CSU from acute urticaria, inducible urticaria, and/or urticarial vasculitis. In 19 independent

TABLE 7 Prevalence of urticaria including CSU in patients with thyroid diseases

First author of the study (reference)	Year	Age (y)	Patients with thyroid diseases		% (n/total) controls with urticaria including CSU	Design	Country
			n, total	% (n) with urticaria including CSU			
Ruggeri et al.[13]	2017	≥3	1,053[a]	0.6 (6)	–	CS	Italy
Kumar et al.[190]	2016	≥16	320[b]	17.2 (55)[c]	–	D	India
Philip et al.[14]	2016	≥18	63[a]	6.3 (4)[d]	–	CS	India
Brănişteanu et al.[191]	2014	≥14	38	13 (5)[d]	–	R	Romania
Jamwal et al.[192]	2013	≥8	100[b]	4 (4)[c]	–	P	India
Keen et al.[193]	2013	≥5	460[b]	13 (60)[c]	–	D	India
Haritha et al.[194]	2013	–	100[b]	9 (9)[d]	–	–	India
Nagaraj et al.[15]	2012	–	1,020[e]	11.2 (114)[c]	–	–	India
Puri[195]	2012	–	50[f]	6 (3)[c]	–	–	India
Saadia et al.[67]	2010	≥18	60[b]	16.7 (10)[c]	3.3 (3/90)[g]	CC	Saudi Arabia
Artantas et al.[64]	2009	≥3	220[h]	6.8 (15)[d]	– (–/90)[i]	–	Turkey
Singh et al.[196]	2009	≥16	51[j]	13.7 (7)[d]	–	D, CS	India
Aamir et al.[180]	2008	≥25	30[b]	56.7 (17)[d]	– (–/30)[i]	CC	Pakistan
Feibelmann et al.[49]	2007	≥18	60/29[k]	3.3 (2)/3.4 (1)[k]	–	CC	Brazil
Dogra et al.[197]	2006	≥6	32[b]	12.5 (4)[d]	–	–	India
Verneuil et al.[66]	2004	≥18	32/22[k]	12.5 (4)/9.1 (2)[k,l]	–	P, CC	France
Ramanathan et al.[198]	1989	–	236[m]	0.4 (1)[d]	–	R	Malaysia
Lanigan et al.[63]	1987	≥18	50/50[k]	28 (14)/4 (2)	6 (3/50)	–	UK
Moens et al.[65]	1984	≥18	100[n]	4 (4)[c]	6 (12/200)[o]	CC	Netherlands

–, no data; CC, case-control study; R, retrospective study; P, prospective study; CS, cross-sectional study; D, descriptive study; CSU, chronic spontaneous urticaria.
[a]Patients with Hashimoto's thyroiditis.
[b]Patients with hypothyroidism.
[c]it is not clear from the paper whether patients with acute urticaria, inducible urticaria, and urticarial vasculitis were excluded.
[d]It is not clear from the paper whether patients with inducible urticaria and urticarial vasculitis were excluded.
[e]Patients with autoimmune thyroid disease.
[f]72% patients had hypothyroidism and 28% patients had hyperthyroidism.
[g]Euthyroid patients presenting for gynecological consultation.
[h]Patients with thyroid diseases.
[i]Healthy controls.
[j]31 patients were hypothyroid, 13 hyperthyroid, and 7 euthyroid.
[k]Patients with thyroid diseases and thyroid autoantibody positivity/negativity.
[l]It is not clear from the paper whether patients with urticarial vasculitis were excluded.
[m]Patients with thyrotoxicosis.
[n]73 patients with Graves' disease and 27 with primary hypothyroidism.
[o]100 eye clinic patients and 100 nonpatients.

studies (Table 7), the prevalence of urticaria including CSU in patients with thyroid disease including AITD ranged from 0.4% to 56.7%. In all but two studies, the prevalence of urticaria including CSU was found to be >1% (1% is believed to be the prevalence of CSU in the general population).[2]

Two of three studies that directly compared AITD patients and controls including HCs showed a higher prevalence of urticaria including CSU in AITD patients;[63,64] one study did not.[65] Only one of four studies showed a higher rate of urticaria including CSU in patients with AITD as compared to patients with nonautoimmune thyroid diseases;[63] the other three did not.[49,64,66]

No difference in the prevalence of urticaria including CSU in hypothyroid and hyperthyroid patients was demonstrated compared to HCs.[64] However, Saadia et al.[67] found that hypothyroid women, as compared to euthyroid women, showed significantly higher rates of urticaria and puffiness of hands and feet.

- Urticaria including CSU is more prevalent in patients with AITD than in controls (weak evidence).

3.3 | Efficacy of treatment with thyroid drugs on CSU symptoms

A total of 22 studies assessed the effects of thyroid medication including levothyroxine (n=16), methimazole (n=2), propylthiouracil (n=2), and triiodothyronine (n=1) on CSU (Table 8). For seven

TABLE 8 Efficacy of thyroid treatment on CSU symptoms

First author of the study (reference)	Year	Age (y)	n, CSU	n (%), IgG thyroid AAbs	% (n/total), efficacy of thyroid treatment on CSU symptoms				Design	Country
					Hypothyroidism	Hyperthyroidism	Euthyroidism	Total treated		
Kim et al.[56]	2016	≥12	184	43 (23.4)	20 (2/10)[L]	0 (0/5)[M,P]	–	15	R	Korea
Sugiyama et al.[68]	2015	≥17	40	11 (27.5)	–	–	80 (4/5)[T]	5	–	Japan
Magen et al.[81]	2012	≥18	749	–	0 (0/44)[L,a]	–	–	44	R	Israel
Kirkpatrick[69]	2012	≥18	6	5 (83.3)	100 (2/2)[L]	–	100 (4/4)[L]	6	–	USA
Nuzzo et al.[51]	2011	≥15	54	12 (22.2)	0 (0/10)[L]	–	–	10	P, CC	Italy
Sahiner et al.[28]	2011	<18	82	–	100 (1/1)	–	–	1	R	Turkey
Tarbox et al.[70]	2011	≥21	356[b]	77 (21.6)	100 (1/1)[L]	–	0 (0/1)[L]	2	R	USA
Farid et al.[71]	2005	≥14	60	22 (36.7)	–	–	69.2 (9/13)[L]	13	–	Iran
Aversano et al.[77]	2005	≥18	20	20 (100)	100 (8/8)[L]	–	66.7 (8/12)[L]	20	–	Italy
Concha et al.[60]	2004	–	32	32 (100)	25 (2/8)[L]	–	75 (3/4)[L]	12	–	USA
Toubi et al.[62]	2004	≥17	139	17 (12)	0 (0/3)	–	–	3	P	Israel
Levy et al.[168]	2003	<18	187	8 (4.3)	0 (0/3)[L]	–	–	3	–	Israel
Vermeulen et al.[170]	2003	–	57	12 (21)	–	0 (0/1)[L]	–	1	–	France
Karaayvaz et al.[72]	2002	≥19	580	70 (12.1)	100 (4/4)[L]	–	65.4 (17/26)[L]	30	P	Turkey
Zauli et al.[41]	2001	≥9	122	35 (28.7)	0 (0/4)	–	–	4	–	Italy
Kandeel et al.[73]	2001	≥12	610	60 (9.8)	21.4 (3/14)	–	0 (0/3)	17	–	USA
Gaig et al.[74]	2000	–	170	25 (14.7)	94.4 (17/18)[L,c]	100 (2/2)[M]	–	20	–	Spain
Turktas et al.[75]	1997	≥16	94	11 (11.7)	33.3 (1/3)[L]	100 (1/1)	–	4	–	Turkey
Rumbyrt et al.[32]	1995	≥18	10	7 (70)	–	–	70 (7/10)[L]	10	P	USA
Leznoff et al.[76]	1989	≥8	624	90 (14.4)	17.4 (8/46)[L]	–	–	46	–	Canada
Leznoff et al.[53]	1983	≥10	140	–	66.7 (2/3)[L,d]	100 (1/1)[P]	71.4 (5/7)[d]	11	–	Canada
Small et al.[189]	1982	–	208	–	–	100 (8/8)	–	8	–	Canada
Total					28 (51/182)	66.7 (12/18)	67 (57/85)	285		

M, treated with methimazole; P, treated with propylthiouracil; L, treated with levothyroxine; T, treated with triiodothyronine; –, no data, not defined in the paper or in the abstract; CC, case-control study; P, prospective study; R, retrospective study; CSU, chronic spontaneous urticaria.

[a]During the treatment, a significant reduction in UAS was observed in hypothyroid CSU subjects. However, the mean UAS after 3 and 6 months of L-thyroxine treatment remained not significantly different from that in control euthyroid subjects with CSU

[b]It is not clear from the paper whether patients with inducible urticaria were excluded.

[c]Some patients were euthyroid.

[d]Hypothyroidism developed in three of seven euthyroid patients.

studies, the drug that was used for the treatment was not specified in the publication.

Of 285 patients treated with thyroid medication, CSU was improved in 120 (42%) patients. Fourteen studies reported complete remission of CSU in 68 patients (24%) and partial improvement in 28 patients (10%).[28,32,53,56,60,68-76] Beneficial effects were not specified in 24 (8%) of 285 patients in two studies and were not seen in six studies in all patients. In total, 182, 85, and 18 patients were hypothyroid, euthyroid, and hyperthyroid, respectively. Treatment of hypothyroidism (n=182 patients, 17 studies), euthyroid CSU patients (n=85 patients, 10 studies), and hyperthyroidism (n=18 patients, six studies) led to improvement or remission of CSU in 28% (n=51 patients, 12 studies), 67% (n=57 patients, eight studies), and 67% (n=12 patients, four studies) of patients, respectively. In five of 17, two of 10, and two of six studies, treatment of hypothyroidism, euthyroid CSU patients, and hyperthyroidism, respectively, had no effect on CSU in any of 64, 4, and 6 patients.

Patients with CSU in four studies were treated for HT or GD. Urticaria improved in 24 of 34 (70.6%) CSU patients with HT and in five of 10 (50%) CSU patients with GD.[56,69,74,75]

First effects of levothyroxine treatment on CSU were seen after 3-12 weeks.[68,69,77] According to one study, CSU symptoms decreased within 2 months after the start of treatment of hyperthyroidism with thiourea drugs.[53]

The data on the efficacy of treatment with thyroid drugs including levothyroxine in CSU are not consistent. Conflicting evidence may be explained by the various confounding factors and limitations such as the small numbers of patients included in some studies and the absence of appropriate controls. A correlation between IgG antithyroid AAbs and clinical improvement of CSU was seen only in two of five studies[72,77] and was not seen in the three others.[32,74,78] Different antithyroid drugs and levothyroxine were administered in different doses with various durations of treatment. In some studies, drugs, doses, duration of treatment, measurement of treatment

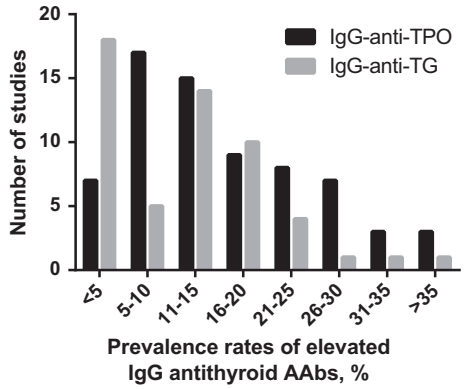

FIGURE 1 Prevalence rates of elevated IgG antithyroid AAbs in CSU

efficacy, the speed of effect, and numbers of patients with partial improvement and remission of CSU were not described. In some cases, levothyroxine was used in combination with other drugs such as antihistamines.[68] Moreover, no randomized double-blind, placebo-controlled studies are available.[79] Of importance may be the fact that spontaneous remission may occur in up to 50% of patients with CSU.[80,81] For instance, in one study, the mean Urticaria Activity Score after 3 and 6 months of levothyroxine treatment was not significantly different in hypothyroid CSU patients than in control untreated euthyroid subjects with CSU and without antithyroid AAbs.[81] In addition, hyperthyroidism per se[82] and antithyroid drugs themselves may be a cause of itch or urticaria.

The results of our analysis do not indicate that the use of thyroxine treatment is beneficial in euthyroid CSU patients, at least until data from well-controlled studies provide evidence for this. Selected CSU patients with hypo- or hyperthyroidism, however, may benefit from treatment with levothyroxine or other thyroid drugs, respectively.

- CSU can improve in response to treatment with levothyroxine or other thyroid drugs (strong evidence).
- CSU in hyperthyroid and euthyroid patients is more likely to respond to such treatment than in hypothyroid patients (strong evidence).

3.4 | Possible pathogenetic relationship between chronic spontaneous urticaria and autoimmune thyroid diseases

Our systematic review of the literature supports the widely held view that CSU is linked to elevated IgG antithyroid AAb levels. For example, 11% (89/828) of allergists, members of the American Academy of Allergy, Asthma and Immunology, strongly believe that there is a pathogenic link between CSU and AITD, and 65% (531/823) test for IgG antithyroid AAbs at least 50% of the time.[83] However, the mechanism whereby thyroid autoimmunity is associated with CSU is poorly understood.

Many studies and reviews have suggested that IgG antithyroid AAbs do not play a direct causative and pathogenic role in CSU, but rather represent a parallel autoimmune event.[79,84-88] Current hypotheses for the role and relevance of IgG antithyroid AAbs in CSU are shown in Figure 2:

IgG antithyroid AAbs do not seem to be directly involved in the degranulation of mast cells (MCs),[85,89] but may enhance MC susceptibility to other activating signals.[90] Rumbyrt and co-workers hypothesized that an inflammatory response in the thyroid gland leads to a generalized inflammatory state and lowers the threshold of MCs to other stimuli.[32] TSH might drive the production of proinflammatory cytokines that induce the synthesis of IgG antithyroid AAbs.[27,77,85,91-93] Chronic inflammation, caused by IgG antithyroid AAbs, disrupts the normal architecture of the gland and leads to the release of sequestered autoantigens, which induce a low-grade autoimmune response.[91] Products of this autoimmune response such as thyroid protein immune complexes activate classical complement pathway, leading to the generation of C3a and C5a, which cause degranulation of mast cells.[94] It has been speculated that different autoantibodies (eg, anti-FcεRI, anti-TPO) synergize in the activation of the complement system, the generation of C5a, and triggering MCs and basophils in patients with CSU.[69,79,95,96] Hence, levothyroxine treatment may reduce cytokine production and IgG-anti-TPO/TG-mediated complement activation by decreasing serum TSH and thus reducing thyroid stimulation and symptoms of CSU.[77,79]

Several potential mechanisms whereby infectious agents may trigger both AITD and CSU have been hypothesized.[79] *Helicobacter pylori* infection has been linked to CSU and AITD in some studies but not in others.[97-99] For example, Bakos and Hillander[100] found a high prevalence of IgG and IgA antibodies to 19-kDa *H. pylori*-associated lipoprotein in CSU. An association between *H. pylori* infection and IgG antithyroid AAbs in CSU has been proposed based on the reactivity and molecular similarity of antibodies against *H. pylori* and TPO.[79,99] *Staphylococcus aureus* superantigens were shown to activate MCs and basophils to release proinflammatory mediators and cytokines.[101,102] Moreover, Wan et al.[103] described the adoptive transfer of experimental autoimmune thyroiditis in mice based on staphylococcal enterotoxin A superantigen stimulation of thyroglobulin-primed cells. A role of hepatitis C virus infection in the etiology and pathogenesis of both urticaria and AITD has been suggested.[79,104]

Recently, some studies have shown high levels of IgE AAbs such as IgE-anti-TPO and IgE-anti-dsDNA in the blood of patients with CSU.[36,45,59] These IgE autoantibodies are held to be relevant for the pathogenesis of CSU in a subpopulation of patients.[3] IgE-anti-TPO autoantibodies, when bound on the surface of mast cells and basophils, could cause "autoallergic" activation and degranulation of cells,[36] after exposure to the specific circulating antigen, which is released as a result of autoimmune thyroid damage.[105]

The hypothesis that IgE AAbs including IgE-anti-TPO can induce CSU symptoms is further supported by the analogy with acute urticaria due to IgE-mediated hypersensitivity,[106] efficacy of omalizumab in IgE-anti-TPO-positive patients,[107] evidence of MC activation in other chronic inflammatory skin and autoimmune diseases such as

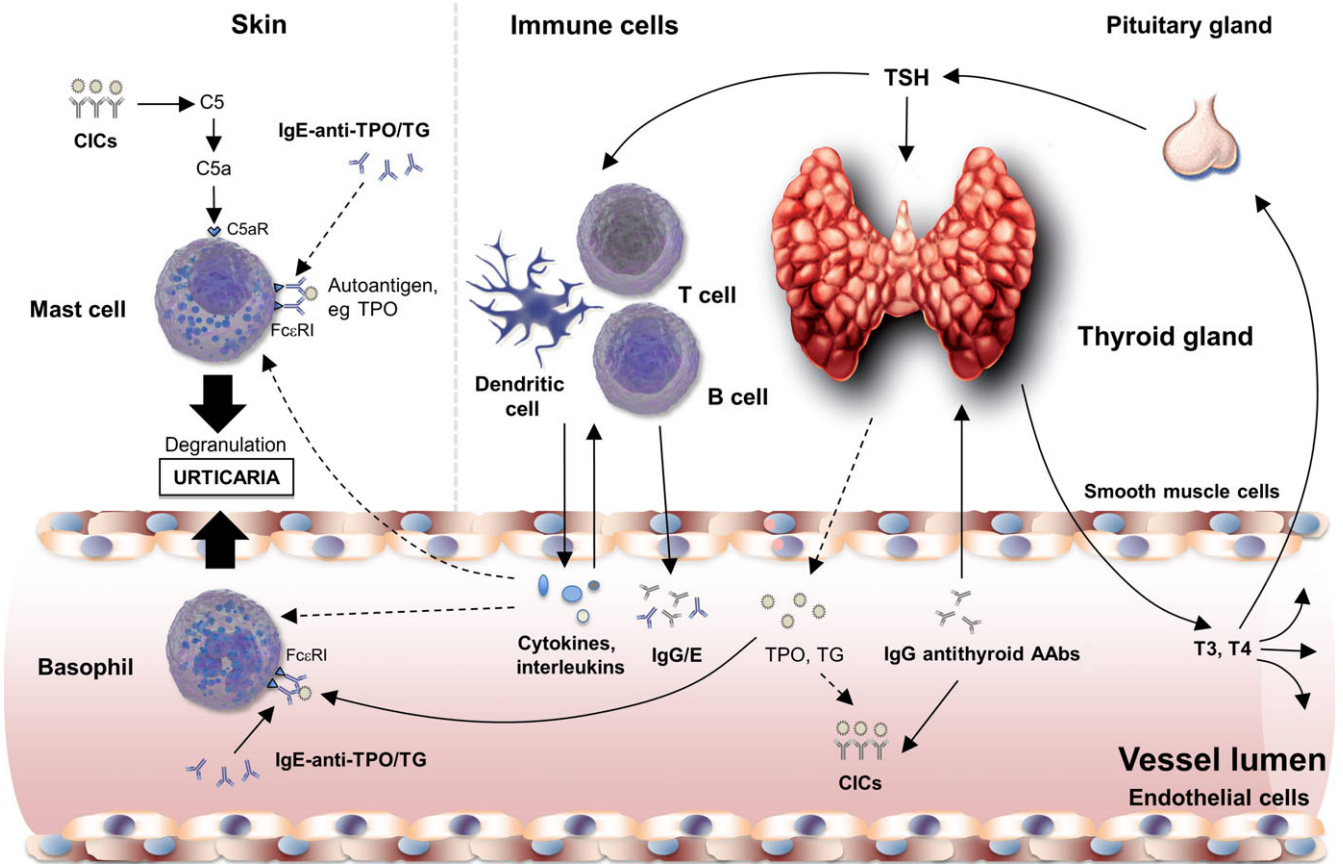

FIGURE 2 Possible pathogenetic relationship between chronic spontaneous urticaria and autoimmune thyroid diseases. IgE-anti-TPO/TG autoantibodies, when bound on the surface of basophils, could cause "autoallergic" activation and degranulation of cells probably after exposure to the specific extracutaneous thyroid autoallergens such as TPO and/or TG, which are released into the circulation as a result of autoimmune thyroid damage. IgG antithyroid AAbs do not seem directly involved in the MCs degranulation but may be enhancing factor of MCs sensitivity. TSH might drive the production of proinflammatory cytokines by lymphocytes and monocytes that induce the synthesis of IgG antithyroid AAbs. The inflammation, caused by the presence of IgG antithyroid AAbs, disrupts the normal architecture of the gland and leads to release of sequestered autoantigens, which induce a low-grade autoimmune response. Products of this autoimmune response such as thyroid protein immune complexes activate classical complement pathway, leading to generation of C3a and C5a, which cause degranulation of mast cells. Inflammatory response in the thyroid gland might lead to a generalized inflammatory state and lowers the threshold of MCs to other stimuli. TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TG, thyroglobulin; CICs, circulating immune complexes

bullous pemphigoid,[108] and possible antigen mimicry between aeroallergens and thyroid antigen.[109]

- Pathogenic mechanisms in CSU patients with thyroid autoimmunity may include IgE against autoantigens (eg, TPO), formation of immune complexes, and activation of the complement.

4 | CONCLUSIONS AND NEED FOR FURTHER RESEARCH

Taken together, our systematic review indicates that CSU and autoimmune thyroid diseases are closely linked in many ways. Why patients with CSU have higher rates of thyroid autoimmunity than those in the general population[9,21,46] remains unclear.

Further research is needed to address this, ideally guided by the following questions:

- What is the role of IgG or IgE antithyroid AAbs in the pathogenesis of CSU, and how does their presence affect the course, clinical characteristics of disease, and response to treatment?
- How many CSU patients with antithyroid AAbs develop a clinically significant AITD (HD and GD), and how much time does this clinical conversion take? What is the risk of developing hypo/hyperthyroidism in CSU patients with antithyroid AAbs?[23]
- What is the mechanism of the effects of levothyroxine treatment on CSU, and how does the efficacy of this treatment compare to that of other CSU therapies?
- Are chronic inducible urticaria and urticarial vasculitis also linked to thyroid autoimmunity?

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Pavel Kolkhir conceived and designed the study, drafted the article, analyzed and interpreted the data, and approved the final version to be submitted; *Martin Metz* analyzed and interpreted the data, drafted the article, and approved the final version to be submitted; *Sabine Altrichter* analyzed and interpreted the data, revised the article critically for important intellectual content, and approved the final version to be submitted; and *Marcus Maurer* conceived and designed the study, revised the article critically for important intellectual content, and approved the final version to be submitted.

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