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META-ANALYSIS

The prevalence of thyroid autoimmunity in patients with urticaria: a systematic review and meta-analysis

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Abstract Thyroid autoimmunity is the most common organ-specific autoimmune disorder, which is characterized by the production of thyroid autoantibodies and lymphocytic infiltration into the thyroid. The majority cases of chronic urticaria have unknown (idiopathic) causes, with about 30–40 % possibly having an autoimmune substrate. Considering that autoimmune factors may be the common features of both thyroid autoimmunity and urticaria, it is likely that both entities may coexist within the same patient. A number of studies have investigated the association between thyroid autoimmunity and urticaria. However, most of these studies are relatively small sample size, the power achieved in those studies was not sufficient to detect whether there is an association between urticaria and thyroid autoimmunity. The aim of this study is to combine primary data from all relevant studies to produce reliable estimates of the associations between thyroid autoantibodies and urticaria. Literature databases were searched including Medline, Embase, Web of Science, Chinese Wanfang, and CBM databases from January 1980 to December 2013. A total of 14,203 urticaria cases and 12,339 non-urticaria controls were included in this study. From these data, the odds ratio (OR) with 95 % confidence interval (95 % CI) was calculated. The meta-analysis results showed that the prevalence of positive thyroid autoantibodies in patients with urticaria was higher than non-urticaria controls (TgAb: OR 6.55, 95 % CI 3.19–13.42, $P < 0.00001$, $I^2 = 67$ %; TmAb: OR 4.51, 95 % CI 2.78–7.33, $P < 0.00001$, $I^2 = 47$ %; TPOAb: OR 8.71, 95 % CI 6.89–11.01, $P < 0.00001$, $I^2 = 20$ %, respectively). The results of this meta-analysis suggested that patients with urticaria were more likely to have thyroid autoimmunity than the control groups.

Keywords Thyroid autoimmunity · Urticaria · Meta-analysis

Introduction

Thyroid autoimmunity is the most prevalent autoimmune disorder affecting up to 5 % of the general population [1, 2]. The clinical presentation varies from hyperthyroidism in Graves' disease to hypothyroidism in Hashimoto's thyroiditis. Thyroid autoimmunity is characterized by the production of thyroid autoantibodies and lymphocytic infiltration into the thyroid. The laboratory diagnosis of thyroid autoimmunity by evaluating the titers of thyroid autoantibodies is necessary. While the exact etiology of thyroid autoimmunity is not known, the interaction between genetic susceptibility and environmental factors appears to be of fundamental importance to initiate the process of thyroid autoimmunity [3, 4].

Urticaria is a frequent disease, with complex etiopathogeny, raising important problems in clinical practice. In general population about 15–20 % of subjects have suffered from one episode of urticaria–angioedema syndrome in their life. Urticaria is frequently caused by allergic reactions, but there are also many non-allergic causes. The majority cases of chronic urticaria have unknown (idiopathic) causes, with about 30–40 % possibly having an autoimmune substrate [5, 6]. Since autoimmune factors play an important role in the pathogenesis of urticaria,

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there may be some association between thyroid autoimmunity and urticaria.

Until recently, a number of studies have investigated the association between thyroid autoimmunity and urticaria by detecting the thyroid autoantibodies in patients with urticaria, including thyroglobulin antibody (TgAb), thyroid microsome antibody (TmAb), and thyroid peroxidase antibody (TPOAb). However, most of these studies are relatively small sample size, the power achieved in those studies was not sufficient to detect whether there is an association between urticaria and thyroid autoimmunity. Using all available published data to increase statistical power, meta-analysis is an efficient way of analytically combining the results of individual studies together to detect and quantify an effect with a more precision. The main objective of this meta-analysis is to combine primary data from all relevant studies to produce reliable estimates of the association between thyroid autoimmunity and urticaria.

Materials and methods

Literature and search strategy

A systematic search was conducted for eligible studies on Medline, Embase, Web of Science, Chinese Wanfang, and CBM databases from January 1980 to December 2013 without language restriction, using the key words "autoimmune thyroid diseases" or "thyroid autoimmunity" in combination with the terms "urticaria" or "hives" or "nettle rash" and a filter for studies in human beings. In addition, the reference lists of the retrieved articles were reviewed to identify eligible studies. Study selection was conducted by two independent reviewers. The relevance of studies was assessed with a hierarchical approach on the basis of title, abstract, and the full manuscript. After the initial screening of titles and abstracts, the studies included by both reviewers were compared, disagreement was resolved by consensus.

The preliminary search using these terms yielded 787 potential articles. The author read the abstracts of these 787 publications and identified 170 publications appearing to contain relevant data. These 170 publications were read in full text and scrutinized for the presence of data. This process identified 20 studies appropriate for the analysis based on inclusion criteria.

Inclusion criteria

Eligible studies included in this meta-analysis must meet all of the following criteria: (1) evaluate the association between thyroid autoimmunity and urticaria by detecting thyroid autoantibodies. (2) case–control design. (3) provide sufficient data of cases and controls that could allow us to calculate the odds ratio (OR) with 95 % confidence interval (CI) and a P value.

Data extraction

The following information was extracted from each study: the first author, published year, region of study population, numbers of cases and controls, and numbers of cases and controls with different thyroid autoantibodies. Information was carefully extracted from all of the eligible publications, independently by two of the authors. Disagreement was resolved by discussion between the authors. If they could not reach a consensus, another investigator adjudicated over the disagreements.

Statistical analyses

The association between thyroid autoimmunity and urticaria was evaluated by OR with the corresponding 95 % CI. The significance of OR was determined by a z test ($P < 0.05$ was considered statistically significant), and Cochrane's Q test was performed to test the between-study heterogeneity using a cutoff of $P < 0.1$ as statistically significant. OR analyzed by random effects model or fixed effects model was in keep with the heterogeneity, which was tested with Cochran's Q-statistic. I^2 values of 25, 50, and 75 % were defined as low, moderate, and high estimates, respectively. When a significant Q test ($P < 0.10$) or $I^2 > 50$ % indicated heterogeneity across studies, the random effects model was used for meta-analysis. Otherwise, the fixed effects model was adopted. The publication bias was examined by Begg's test. All the statistical analysis was performed using *Stata Version 12.0* and *Review Manager Version 5.0.16* software.

Results

Characteristics of the studies

According to the study inclusion criteria, a total of 20 relevant studies with case–control design about the relationship between thyroid autoimmunity and urticaria by detecting thyroid autoantibodies were identified. The detailed procedure of inclusion or exclusion of studies is presented in Fig. 1. We chose these eligible studies to perform this meta-analysis, which included 14,203 urticaria cases and 12,339 non-urticaria controls. Characteristics of each study included in this meta-analysis are summarized in Table 1.

Meta-analysis result

A summary of the meta-analysis findings of the association between urticaria and thyroid autoimmunity with all eligible studies according to the types of thyroid autoantibodies is

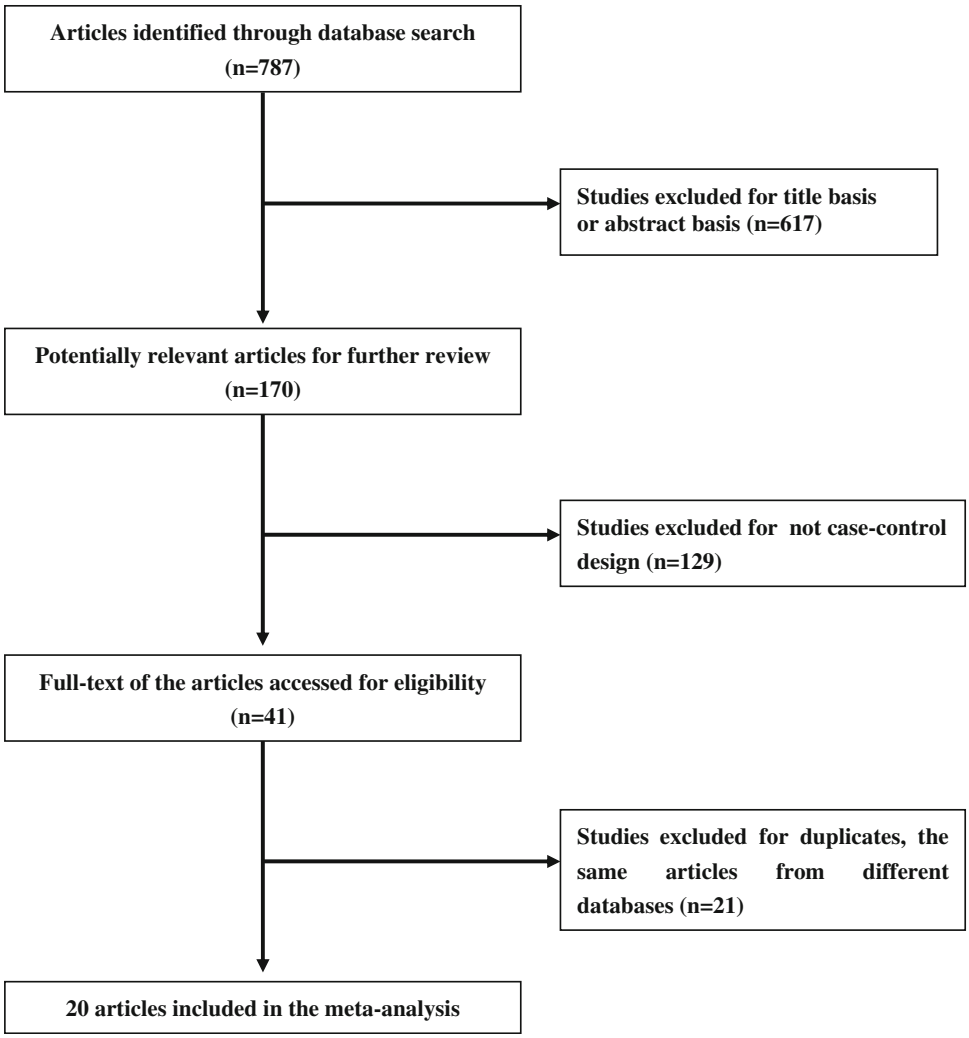

Fig. 1 Flow charts show the detailed procedure of inclusion or exclusion of studies. Twenty independent articles were included in the meta-analysis

provided in Table 2. The prevalence of positive antibodies in patients with urticaria and those without urticaria was compared (TgAb: OR 6.55, 95 % CI 3.19–13.42, $P < 0.00001$, $I^2 = 67$ %; TmAb: OR 4.51, 95 % CI 2.78–7.33, $P < 0.00001$, $I^2 = 47$ %; TPOAb: OR 8.71, 95 % CI 6.89–11.01, $P < 0.00001$, $I^2 = 20$ %, respectively). The meta-analysis results showed that patients with urticaria were more likely to have positive thyroid autoantibodies than the control groups.

In the subgroup analysis, based on different continents of study population, subjects of all included studies were divided into the Asian, American, and European populations due to the significant geographic variation. Results of subgroup analysis showed that there was a positive association between TgAb and urticaria in the Asian population (OR 8.02, 95 % CI 3.58–17.97, $P < 0.00001$), but not in the European population (OR 3.64, 95 % CI 0.67–19.83, $P = 0.14$). Positive associations between TmAb and urticaria were determined in both Asian and American populations (OR 8.82, 95 % CI 3.70–21.03, $P < 0.00001$; OR 2.30, 95 % CI 1.22–4.36, $P = 0.01$, respectively). Similarly, the positive association has been found between TPOAb and urticaria in all of the Asian, American, and European populations (OR 8.94, 95 % CI 6.96–11.48, $P < 0.00001$; OR 40.51, 95 % CI 2.15–763.20, $P = 0.01$; OR 5.81, 95 % CI 2.96–11.40, $P < 0.00001$, respectively). The forest plots for the prevalence of positive thyroid autoantibodies in patients with urticaria are shown in Fig. 2.

Sensitivity analysis

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of meta-analysis affected the final results. A single study involved in the meta-analysis was deleted each time to reflect the influence

Table 1 General characteristics of the studies included in this meta-analysis

Author	Year	Region	Continent	Thyroid antibodies	Urticaria cases (n/N)	Non-urticaria controls (n/N)
Leznoff et al. [7]	1983	Canada	American	TmAb	17/140	27/477
Turktas et al. [8]	1997	Turkey	Asian	TgAb, TmAb	11/94, 9/94	3/80, 3/80
Ryhal et al. [9]	2001	USA	American	TPOAb	5/25	0/75
Yang et al. [10]	2002	China	Asian	TgAb, TmAb	8/58, 7/58	0/30, 0/30
Su et al. [11]	2003	China	Asian	TgAb, TPOAb	10/61, 5/61	0/64, 0/64
Yang et al. [12]	2003	China	Asian	TPOAb	13/60	2/60
Yang et al. [13]	2003	China	Asian	TgAb, TmAb	12/86, 11/86	0/30, 0/30
Verneuil et al. [14]	2004	France	European	TgAb, TPOAb	8/45, 8/45	0/30, 1/30
Cebeci et al. [15]	2004	Turkey	Asian	TgAb, TPOAb	22/52, 16/52	1/40, 1/40
Palma-Carlos and Palma-Carlos [16]	2005	Portugal	European	TgAb, TPOAb	13/56, 15/56	0/56, 0/56
Cebeci et al. [17]	2006	Turkey	Asian	TgAb, TPOAb	27/140, 23/140	8/181, 8/181
Feibelmann et al. [18]	2007	Portugal	European	TgAb, TPOAb	2/49, 6/49	8/112, 7/112
Aamir et al. [19]	2008	Pakistan	Asian	TgAb, TmAb	20/47, 27/47	0/30, 0/30
Nuzzo et al. [20]	2011	Italy	European	TgAb, TPOAb	6/54, 12/54	5/108, 5/108
Al-Balbeesi [21]	2011	Saudi Arabia	Asian	TgAb, TmAb	18/68, 18/68	0/22, 1/22
Confino-Cohen et al. [22]	2012	Israel	Asian	TgAb, TPOAb	138/12,778, 598/12,778	5/10,714, 54/10,714
Wan and Wu [23]	2013	Taiwan	Asian	TgAb, TPOAb	10/60, 5/60	0/40, 0/40
Yadav et al. [24]	2013	India	Asian	TPOAb	14/80	2/40
Alpay et al. [25]	2013	Turkey	Asian	TgAb, TPOAb	7/50, 6/50	3/50, 2/50
Sun et al. [26]	2013	China	Asian	TgAb	33/200	11/100

TgAb thyroglobulin antibody, *TmAb* thyroid microsome antibody, *TPOAb* thyroid peroxidase antibody, *n* number of people with positive antibodies, *N* total number of people with urticaria disease or non-urticaria controls

Table 2 Meta-analysis of the association between urticaria and thyroid autoimmunity

Type of antibody	Eligible studies	OR (95 % CI)	*P* value	Heterogeneity test	Effect model
Anti-TG	16	6.55 (3.19–13.42)	<0.00001	pH < 0.0001, I^2 = 67 %	Random
Asian	12	8.02 (3.58–17.97)	<0.00001	pH = 0.0003, I^2 = 68 %	Random
European	4	3.64 (0.67–19.83)	0.14	pH = 0.03, I^2 = 66 %	Random
Anti-TM	6	4.51 (2.78–7.33)	<0.00001	pH = 0.09, I^2 = 47 %	Fixed
Asian	5	8.82 (3.70–21.03)	<0.00001	pH = 0.26, I^2 = 25 %	Fixed
American	1	2.30 (1.22–4.36)	0.01	–	Fixed
Anti-TPO	13	8.71 (6.89–11.01)	<0.00001	pH = 0.24, I^2 = 20 %	Fixed
Asian	8	8.94 (6.96–11.48)	<0.00001	pH = 0.51, I^2 = 0 %	Fixed
American	1	40.51 (2.15–763.20)	0.01	–	Fixed
European	4	5.81 (2.96–11.40)	<0.00001	pH = 0.18, I^2 = 39 %	Fixed

of the individual date set on the pooled OR, and the corresponding pooled OR was not materially altered, indicating that our results were relatively stable and credible.

Publication bias

A funnel plot and Begg's test were performed to assess publication bias. The funnel plot is relatively straightforward in observing whether the publication bias is present, and Begg's test was used to provide statistical evidence of symmetries of the plots. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Fig. 3). Similarly, the results of Begg's test still did not suggest any evidence of publication bias (TgAb: $Pr > |z| = 0.392$; TmAb: $Pr > |z| = 0.452$; TPOAb: $Pr > |z| = 0.127$, respectively), all $Pr > 0.05$.

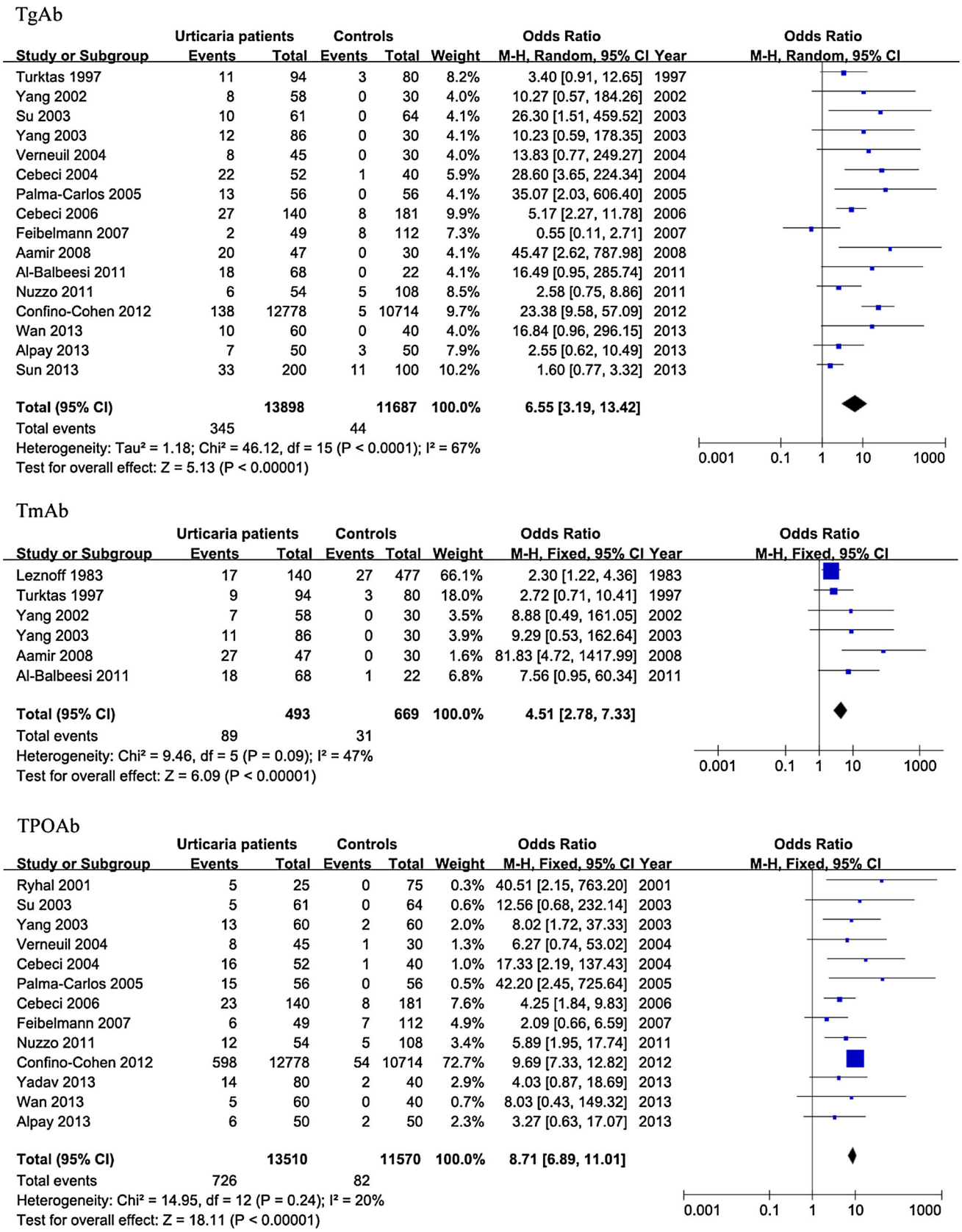

Fig. 2 The forest plots for the prevalence of positive thyroid autoantibodies in patients with urticaria compared with non-urticaria controls

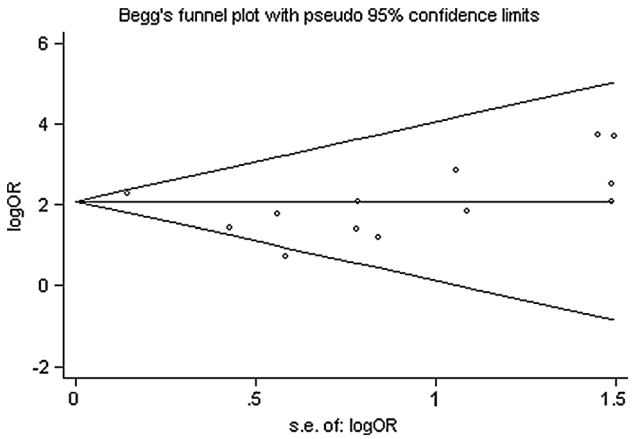

Fig. 3 Begg's funnel plot for publication bias test of the association between urticaria and the risk of thyroid autoimmunity by detecting TPOAb. Each point represents a seperate study for the indicated association. Log OR, natural logarithm of OR. Horizontal line means effect size

Discussion

Thyroid autoimmunity is the archetypal organ-specific autoimmune disorder and is characterized by the production of thyroid autoantibodies [27]. The laboratory diagnosis of thyroid autoimmunity by evaluating the titers of thyroid autoantibodies is necessary. The persistent presence of thyroid autoantibodies in the serum in titers greater than or equal to the upper level of normal interval represents the minimum criterion for the diagnosis of thyroid autoimmunity. The cause of chronic spontaneous urticaria has been an enigma for decades, but the recognition of functional autoantibodies in some patients with the spontaneous chronic urticaria has opened up a new concept of autoimmune urticaria [28]. Considering that autoimmune factors may be the common features of both thyroid autoimmunity and urticaria, it is likely that both entities may coexist within the same patient. As reported, patients with chronic idiopathic urticaria have an increased frequency of Hashimoto thyroiditis with the presence of TgAb or TPOAb, even in euthyroid patients [29]. This is an important issue, which may have clinical implications in planning preventive and therapeutic strategies, such as L-thyroxine in ameliorating the skin manifestations of urticaria [30, 31]. The possible association of thyroid autoimmunity with urticaria deserves particular attention in view of the implications for screening/surveillance strategies of the growing number of autoimmune thyroid patients.

Although there were some studies evaluating the association between urticaria and thyroid autoimmunity, most of these studies are relatively small sample size, the power achieved in those studies was not sufficient to detect whether there was an association between urticaria and thyroid autoimmunity. Our meta-analysis quantitatively assessed the association between thyroid autoimmunity and urticaria. Finally, 20 independently relative studies with case–control design were included and assessed. The results of this meta-analysis showed that prevalence of positive thyroid autoantibodies in patients with urticaria was significantly higher than the control groups. In the subgroup analysis by geographic distribution, results showed that patients with urticaria were more likely to have positive TmAb and TPOAb regardless of continent. TPOAb and TmAb are the same autoantibody. Probably the papers referring to TmAb use passive hemagglutination instead of immunometric method: This is the possible reason of the (minor) differences between TPOAb and TmAb results. As for TgAb, which as a marker of thyroid autoimmunity nowadays plays a minor role with respect to TPOAb, there was a positive association between TgAb and urticaria in the Asian population, but not in the European population, which suggested a possible role of geographic differences in genetic backgrounds and the environment they lived in.

Our meta-analysis of relevant studies showed that the prevalence of thyroid autoimmunity was higher in patients with urticaria than the control groups. Although with between-study heterogeneity, sensitivity analysis indicated that no single study influenced the pooled OR qualitatively of each thyroid autoantibody. Stratified analysis according to the different study characteristics including types of antibodies and continents did not differ substantially. Taken together, these data further confirm the reliability and stability of the meta-analysis results.

The main purpose of performing this meta-analysis was to shed light on the relationship between thyroid autoimmunity and urticaria by statistical methods. However, there were some limitations in our meta-analysis. First, several relevant studies failed to be included in this meta-analysis, because of incomplete raw data or publication limitations. Second, in the subgroup analyses, the number of studies about American population was relatively small, not having enough statistical power to explore the real association. Additionally, no data were available about African population. Third, due to the lack of thyroid function criteria in different countries, this meta-analysis merely deals with the relationship between urticarial and thyroid autoantibodies. Fourth, although thyroid autoantibodies are a sensitive marker of autoimmune thyroid diseases, their positivity does not imply the patient has actually thyroid disease, that is, structural thyroid damage or thyroid dysfunction. In addition, a small minority of patients with autoimmune thyroid disease have no detectable TPOAb or TgAb. Finally, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the

adjustment of other co-variants including age, environmental factors, and lifestyle. Consequently, the meta-analysis results should be explained cautiously.

In conclusion, the results of our meta-analysis support that the prevalence of positive thyroid autoantibodies in patients with urticaria is higher than non-urticaria population, which suggest that urticaria may be associated with increased thyroid autoimmunity risk.

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Conflict of interest None.

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