The clinical significance of thyroid antibodies in non-thyroid diseases

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Abstract

Background: Epidemiological studies showed that the population has a high immune disease prevalence, and thyroid immune diseases are among the top autoimmune disorders seen in clinical practice. Investigators noticed an association between some non-thyroidal conditions with thyroid autoantibodies, and some of the outcomes of these non–thyroid diseases may be affected by the presence of these thyroid antibodies.

Objective: To investigate the association of thyroid autoantibodies with non-thyroidal diseases and their clinical significance, such as the positive or negative impact on the disease outcome.

Methods: A systematic literature review was done using selection criteria with the help of search questions. Multiple search engines were searched for eligible articles. Articles were filtered based on the inclusion and exclusion criteria. Data were extracted and analysed for clinical or statistical significance between case and control groups in selected studies.

Results: Eighteen (18) articles fulfilled the inclusion and exclusion criteria; 44.4% were analytical cross-section studies, 5% were prospective studies, 5.5% were meta-analysis studies, 5.5% were case-control studies, and 16.7% were retrospective studies. The included studies aimed to find an association between TPO-Ab, TG-Ab, and some non-thyroidal diseases such as Vitamin D deficiency, Allergic diseases, mood disorders, women's reproductive system diseases, abortion, systemic lupus erythematosus, rheumatoid disease, Celiac disease, Type 1 diabetes, and breast cancer. The ORs in the included studies were > 1, and the confidence intervals did not cross 1, which means both clinical (favour positivity in case groups) and statistical (existing difference between case and control groups) significance. The "I^2 value", which is an indicator for heterogeneity of the studies included in the meta-analysis, was high in the included research (>50%), which indicates heterogeneity of the included study. TPO-Ab was a favourable prognostic indicator in cases of breast cancer. Relative risk (RR) was used to assess the disease-free survival rate in subjects with breast carcinoma. The survival rate between patients with TPO-Ab > 0.3u/ml and <0.3u/ml was statistically significant (P value 0.016), and relative risk = 3.46.

Conclusion: Thyroid autoantibodies are not exclusively markers of thyroid autoimmune diseases but can also be markers and indicators of non-thyroidal illnesses. Their presence could be either a favourable prognostic indicator, as with breast carcinoma cases or unfavourable prognostic indicator, as with abortion. Further studies are recommended to explore more associations.

Key words: Thyroid, thyroid autoantibodies, thyroid diseases, non-thyroidal diseases.

Introduction

Thyroid hormones are the end products of the thyroid gland, which are transferred to the different parts of the body where different enzymes known as deiodinase enzymes work to form the active or inactive form of the thyroid hormones needed to regulate different human metabolic actions (1). The thyroid gland contains different antigens, which could be the site of autoimmune reactions and form specific antibodies (2). These antibodies may act within the thyroid gland and affect its function either as hypo or hyper-function or be found in the blood associated with other non-autoimmune thyroid diseases (2).

Three essential thyroid antigens are involved in thyroid autoimmunity: thyroglobulin, thyroid stimulating hormone receptor, and thyroid peroxidase (TPO).

Thyroglobulin is a protein of 670KDa composed of two polypeptide chains from which the thyroid hormones (T3 and T4) are produced. Scientists discovered about 40 antigenic epitopes on human thyroglobulin; 4-6 epitopes are believed to be recognized by B cells and involved in antibody response to thyroglobulin (3). There is evidence that the iodination of thyroglobulin results in the reconfiguration of the molecule and change in antigenic epitopes. The presence of these multi-configuration, iodine, TPO, and hydrogen peroxide is thought to be the thyroid autoimmune response trigger (4).

Thyroid Peroxidase is the second antigen (5). It was known as the thyroid microsomal antigen. It was identified as TPO in 1985. It is composed of 107KDa; 933 amino acid residue glycoprotein presents as a dimer on the apical surface of thyroid follicular cells and cytoplasm. Multiple B cell reactive epitopes are present in human TPO, and they are genetically determined and remain staple within each patient.

The third antigen is the Thyroid Stimulating Hormone – receptor protein. It is a 74 amino acids glycoprotein. It has two subunits, the extracellular ‘’A’’ subunit and the transmembrane ‘’B’’ subunit. There is controversy about whether specific epitopes exist for these antibodies (6). However, the majority believe there are no specific epitopes for the interaction of these antibodies on the protein. This antigen is exclusively associated with thyroid diseases. There are other antigens, but fewer will be described, like the sodium–iodide symporter. The aim of this review is to find the clinical significance of these antibodies’ presence in conditions unrelated to thyroid diseases.

Methodology

A systematic literature review was conducted. This review discussed thyroid autoantibodies’ presence and clinical significance in non-thyroidal diseases. A personal computer was used to search using the search question to select studies based on the inclusion criteria. A constructed search strategy using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model was followed. PRISMA flow diagram (Figure 1) delineates the number of studies found in the search, included and excluded, and the reasons for exclusions (7). PubMed, Google scholar and Cochrane Library were used as search engines. PubMed was the leading search engine used. The second step was to list the detected articles to remove duplicated titles and filter them based on selection criteria. In articles with titles irrelevant to the search question, abstracts were screened for any relation to the question; if not, the articles were excluded. Articles were then downloaded to review the full text. The third step was to review the full text to determine if the inclusion and exclusion criteria were satisfied. A double review was conducted if there was any doubt about the inclusion or exclusion criteria in any article. The following were the inclusion criteria; studies published in English without limited publication date, studies that involved human participants, studies that included only patients with euthyroid function not in current treatment for thyroid dysfunction, studies with free access to full text, studies with Systematic reviews, meta-analysis, case-control, cohort, and cross-section study designs. The following were the exclusion criteria; studies not showing details such as conference abstracts, studies included patients with thyroid diseases or receiving medicine for thyroid dysfunction, review articles, case studies, or case series studies, as these types of studies do not investigate association or correlation (8). Data from the included studies were extracted and discussed in studies’ summaries.

Results

Eighteen (n=18) studies were included after they met the selection criteria. Eight (n=8) were analytical cross-section studies, one (n=1) was a case-control study, one (n=1) was a meta-analysis study, five (n=5) were prospective, three (n=3) were retrospective, and one (n=1) was a case-control study (Table 1). All studies included patients with euthyroid function assessed by triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) or known to be euthyroid by researchers. The studies included 7063 patients (case groups) and 3966 healthy participants (control groups) (P <0.001) (Table 1). Five studies (n=5) included children only, and thirteen (n=13) included adults > 12 years (Table 1). Six (n=6) studies included only females, and twelve (n=12) included males and females (Table 1). No studies included only males (Table 1). One study compared populations from different geographical zones (Table 1). All studies used Thyroid peroxidase antibodies (TPO-ab) and thyroglobulin antibodies (TG-Ab) as thyroid autoimmunity markers. All studies included only patients with euthyroid

Figure 1: PRISMA Flow Diagram

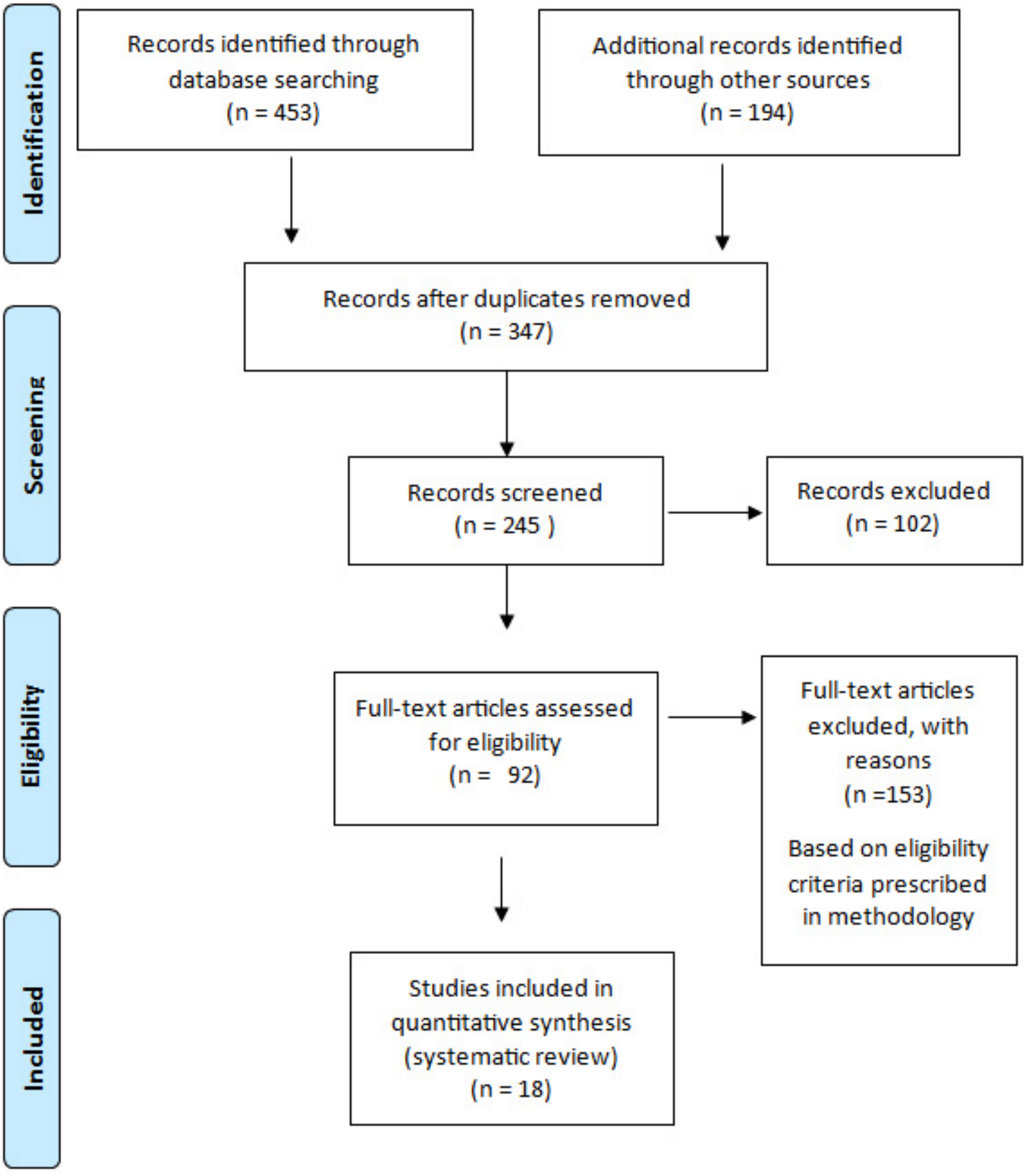

Table 1: Studies included in the review

Study	type	Date of publication	Population	Disease investigated	Statistical tool(s)
Carta et al (9)	Analytic Cross-sectional study	2004	222 adults	Mood disorders	Prevalence , OR,CI95%, P value, MVLR
Snijders et al (19)	Analytic Cross-sectional study	2020	1021 case group ,373 control group. Adults	Bipolar disorders	OR, P value
Shin et al (11)	Retrospective study	2014	304 participants. adults	Vit D deficiency	P value, correlation (r)
Darban et al (12)	Analytic cross section study	2022	35 case group, 35 control group. Adults	Vit D deficiency	OR, CI 95%, P value
Zhang et al (13)	Analytic cross sectional study	2022	217 case group, 217 control group. Adults	Allergic diseases	P value, CI 95%
Ismaeil et al (14)	Case control study	2020	25 case group, 25 control group. Children	Bronchial asthma	P value, correlation (r).
Levy et al (15)	Cohort prospective study	2003	187. Children	Chronic urticaria	Incidence rate
Zhang et el (16)	Analytic cross sectional study	2022	1100 case group, 1100 control group	Chronic spontaneous urticaria	OR, P value, correlation (r)
Singh et al (17)	Cohort retrosepctive study	1995	487 participants. Adult women	Reproductive failure	P value
Janssen et al (18)	Cohort prospective study	2004	175 case group, 168 control group.	Polycystic ovary	Incidence rate, P value
Wang et al (19)	Cohort retrospective study	2018	121 case group, 408 control group. Adult women	Female infertility	Incidence rate, P value
Stagnaro et al (20)	Cohort Retrospective study	1990	552 adult women	Miscarriage in at risk pregnancy	Prevalence, P value
Smyth et al (23)	Analytic cross sectional study	1998	478 case group, 222 control group	Breast cancer	P value, RR
Sharifi,Ghasemi and Mousavinasab (24)	Analytic cross sectional study	2008	91 case ,163 controls	Type 1 diabetes	P value, r, 95% CI
Kalyoncu and Urganci (25)	Cohort prospective study	2015	67 cases. children	Celiac disease	P value
Roldan et al (26)	Analytical cross sectional study	2012	800 cases. Adult	Rheumatoid disease	OR, P value, 95% CI

function, not in treatment for thyroid dysfunction. All studies used the correlation coefficient (r) had positive r values > 0, which means a positive correlation. Some studies used logistic regression to test the association between multiple factors and an outcome, such as age and sex, with thyroid autoantibodies. In the meta-analysis study included, the I^2 index assesses the heterogeneity. In this study, the I^2 for studies looks for the TG-Ab and TPO-Ab with patients with SLE; the higher the I^2, the more heterogenic the study will affect the study's strength. In the study, I^2 > 50% (50.4% and 62.5%, respectively). All studies were hospital-based studies except one study, which was a community-based study.

Summaries of included studies

Carta et al (2004).
This is a cross-sectional community-based study. It found that 16.6% of the overall sample had a TPO-Ab value above the standard cut-off. Multivariate logistic regression for TPO- Ab on the risk of one mood diagnosis considering age and gender showed a positive relation to anti-TPO (OR 2.89, CI 95% years (38), and there was no relation with positive TPO-Ab, age and sex (gender F vs. M – OR 1.38, CI 95% 0.68 – 2.82), age (<44 vs.>44 years, OR 1.14 CI95% 0.57 – 2.30), for anxiety disorder, positive vs. negative TPO-Ab risk was 4.5, CI 95% 2.02 -10-04), while for gender F vs. M, OR 1.58, CI 95% 0.75 – 3.31 and for age (<44 vs.>44 years) OR 1.91, CI 95% 0.92 -3.96.

Limitation: the study included a small size, which increases the bias of including the actual number of rare psychiatric diagnoses less frequently observed in the general population, such as panic disorder (lifetime prevalence 2.7%).

Sneijders et al (2020).
This is a cross-sectional study which found that TPO-Ab significantly increased in bipolar patients versus controls and more in women than men (11% versus 5.3%, P<0.001). It was higher in subjects with ages above 45 than those below 45 (9.7% versus 6.8%) P= 0.07, which was not statistically significant. TPO-Ab did not differ between bipolar patients (8.4%) and controls (9.1%) P= 0.964, which confirms the absence of an association of BP with TPO-Ab. Even after adjusting for age and sex, no significant association was found (P=0.123). For the first-degree relatives' group, the TPO-Ab level did not differ compared to the bipolar control groups (P=0.538, P=0.402, respectively) even after adjustment for age and sex. Investigators combined meta-analysis with their study to support their findings. The meta-analysis results showed that the overall odds ratio was 1.3 (95% CI 0.7-2.3, P=0.3), which is mildly clinically significant but not statistically significant as the CI crosses the 1.

Limitation: cross-sectional design, hospital-based, measuring TPO-Ab years after disease onset and inclusion of controls from two different studies. The combined meta-analysis showed moderate heterogeneity (I^2 =63%).

Shin et al (2014).
This is a retrospective study which found that Patients with elevated TPO-Ab had lower Vit D than those who did not (12.6 +/- 5.5ng/ml vs. 14.5+/- 7.3 ng/ml respectively (P <0.001) after adjusting for age, sex, and BMI, a negative correlation was recognized between Vit D3 and TPO-Ab levels (r = - 0.252, P <0.001). This correlation did not exist in the non-AITD (r=0.117, P= 0.127); the P value > 0.05. Vit D level was a significant determinant for the presence of TPO-Ab (OR 0.917, 95% CI 0.858 – 0.953 , P=0.039).

Limitations: this is a retrospective study with a relatively small sample size and was hospital-based. The study did not measure Thyroglobulin and TG-Ab, so the association with Vit D was not tested.

Darban et al (2022).
This is a cross-sectional study. TPO-Ab was high (>40iu/ml) in 31.4% of patients with Vit D deficiency and 11.4% of the control group (P=0.041). Logistic regression analysis showed the chance of positive TPO-Ab in people with vitamin D (Vit D) deficiency was 3.55% in comparison with the subjects without Vit D deficiency (OR 3.55, CI 95% 1.01 -12.55, P = 0.049).

Limitation: the study neglects the effect of confounders such as season and gender on Vit D and thyroid function. The study had a small sample size, most participants were females, and it was hospital-based.

Zhang et al (2022).
This case-control study explored the relationship between allergies and autoimmune diseases; Allergic Rhinitis (AR), Atopic Dermatitis (AD), and Chronic Spontaneous Urticaria (CSU). TG-Ab positivity was identified as a risk factor for AR, CSU, and AD in Chinese children (OR 2.333, CI 95% 1.243 – 4.378). Multivariate regression analysis also confirmed that TG-Ab (P=0.004) rather than TPO-Ab (P=0.0468) significantly impacted the occurrence of allergic disease.

Limitations: it is a hospital-based study, retrospective, with a small sample size. The study did not correlate between the level of thyroid autoantibodies and allergic diseases. The study could not identify the roles of TG-Ab and TPO-Ab in the pathogenesis of atopic autoimmune reactions.

Ismaeil et al (2020).
This is a case-control study. The study found that there was no significant difference between case and control groups regarding levels of T3 (P=0.131), T4 (P=0.49), TSH (P=0.504), TPO-Ab (P=0.345), and TG-Ab (P 0.307). The correlation was not significant between asthma severity and TPO-Ab (r=0.139, P=0.394) and TG-Ab (r=0.164, P=0.311); the P value was > 0.05.

Limitations: hospital-based study, with a small sample size. Statistic methods needed to be explained clearly within the study.

Levy et al (2003).
This is a cohort study. The study found only 4.3% (8 participants) had increased antithyroid antibodies. All positive were females, 4 with increased TPO-Ab, 2 with increased TG-Ab, and 2 with both increased. The duration of urticaria was four months to 7 years. Five patients were euthyroid, and one was found to have increased antithyroid antibodies five years from the onset of urticaria.

Limitation: small-size study, hospital-based. Researchers ignore factors that may aggravate urticaria and thyroid function.

Zhang et al (2022).
This is a multicentre, analytic cross-sectional study that explored the relationship between allergies and autoimmune diseases; allergic rhinitis (AR), Chronic spontaneous urticaria (CSU), and/or atopic dermatitis (AD). They found that the prevalence rates of TPO-Ab IgE and IgG, TG-b IgE, or TG-Ab IgG in patients were significantly higher than in controls. Significant correlations were observed between prevalence rates of TPO-Ab IgE and TPO-Ab IgG (r=0.297, P<0.001) and between TG-Ab IgE and IgG in patients (r=0.137, P<0.001). Positive anti-TPO-Ab IgE, positive TPO-Ab IgG, and total IgE<40iu/ml were independent predictors of refractory antihistamine cases.

Limitation: Chinese health system differs from western health systems as it allows multiple visits within a hospital to the same specialty, reflecting bad patient compliance. It was challenging to encourage patients to stop antihistamine use seven days before; this created difficulty in assessing the number of wheals in a patient in the last week.

Singh et al (1995).
This is a cohort study. Researchers found that about 22% of patients were positive for TG-Ab, TPO-Ab, or both while 78% were negative. In the antibody-positive group, there was a 32% spontaneous abortion rate versus 16% in the antibody-negative group. In all antibody-positive groups, 26% miscarried versus 13% in the negative group (P=0.002). In biochemical abortion, the association was not significant. The distribution of aetiology of infertility in the positive antibody group was 33% tubal–pelvic factor, 24% male factor, 23% unexplained, and 20% ovulatory dysfunction. In the negative group, it was 34% tubal–pelvic, 27% male factor, 19% unexplained and 18% ovulatory dysfunction, and 2% uterine-cervical factor. Interestingly, researchers found that none of the thyroid antibody-positive groups had any clinical evidence of thyroid disease; only 18 patients had a history of thyroid disease on replacement therapy, and 50% had thyroid autoantibodies.

Limitation: This is a small-size study, hospital-based, and does not involve a control group.

Janssen et al (2004).
This is a prospective, multicentre case-control study. Researchers found Elevated TPO-Ab or TG-Ab in 8.3% of the control group and 26.9% in the PCOS group (P<0.001). The thyroid ultrasound in the PCOS (42.3%) group showed a picture of autoimmune thyroiditis more than the control group (6.5%) with P <0.001. TSH was normal in both groups. Researchers studied the influence of thyroid antibodies on the characteristics of PCOS patients, and they found that only the age, the pattern of ultrasound (hypoechoic), and the LH to FSH ratio were statistically significant (P value <0.05, <0.001, and <0.05, respectively).

Limitations: This is a hospital-based study with a small sample size.

Wang et al (2018).
This is an analytic cross-sectional study. Researchers found that among patients with positive TPO-Ab, the incidence rate of endometriosis was 28.1% and 18.6% in the negative group (P<0.005). The incidence rate of Polycystic ovary syndrome (PCOS) in the positive group was 37.1% and 19.4% in the controls (P<0.001). The difference was not statistically significant for primary ovarian failure and tubal obstruction (P>0.05). The difference in the percentage of positive simple TPO-Ab among age groups was statistically significant (P value = 0.035). The age group, 28-35 years with infertile PCOS, was noticed to be influenced by TPO-Ab positivity.

Limitations: small-size study, hospital-based.

Stagnaro-Green et al (1990).
This is a retrospective, multicentre study. The outcome was defined as:
1) elective abortion,
2) spontaneous abortion in either the first or second trimester
3) successful pregnancy. 80.4% of participants were negative for IgG thyroid antibodies, while 19.6% were positive for TG-Ab and/or TPO-Ab. The overall abortion incidence was 10.2%. Spontaneous abortion occurred in 17% of the thyroid autoantibodies positive group and 8.4% of the negative group (P=0.011). Second-trimester abortion occurred in 29% of the thyroid autoantibodies-positive group and 24% of the antibody-negative group. Miscarriage was not related to the presence of any specific IgG subclass of thyroid autoantibody.

Limitations: relatively small study, hospital-based, and retrospectively designed.

Pan et al (2015).
This is a meta-analysis study. The study found TG-Ab OR=2.99,95% CI=1.83- 4.89. TPO-Ab OR =2.20, 95% CI= 1.27 – 3.82. The study went further and analysed the demographical association with thyroid autoimmunity. The association was positive between TG-Ab and SLE in both

American and European populations (OR 4.03, 95% CI 2.08 – 7.8, OR 1.81, 95% CI= 1.23 -2.65) but not in Asian or African populations (OR=5.43,95% CI = 0.76 – 39.1, OR 2.44, 95% CI0.36 – 10.7). The association was positive between TPO-Ab and SLE in African and European populations (OR=4.55,95% 1.33 -15.49; OR=2.32,95% CI 1.62 -3.32) but not observed in either Asian or American populations (OR=0.66,95% CI=0.16-2.76, OR=1.10,95% CI=0.55-2.24).

Limitations: studies included were relatively small. A study was done in different parts of the world, so time and methodology were different, carrying risk heterogeneity (I^2 for studies targeted TG-Ab was 50.4% and TPO-Ab 62.5%).

Sieiro Netto et al (2004).
This is a prospective study. A total of 5.4% were TPO-Ab positive (95% CI 3.7 -707). TSH was found high in TPO-Ab positive group compared with TPO-Ab negative group (13.8% vs. 2.4%, P value 0.017). The overall risk of abortion was 2.4% (95% CI 1.3 -4.1). The risk of abortion was higher among women >= 35 years (7.7%, CI 95% 1.6 -20.9), TPO-Ab positive (10.3%, CI 95% 2.1 -27.3), and presenting a high level of TSH (12.5%, CI 95% 1.5 -38.3). These factors remain independently associated with the risk of abortion in a complete multivariate analysis.

Limitations: this is a hospital-based study with a risk of selection bias. The sample size is relatively small. Investigators use self-filled questionnaires to collect the history of participants with the risk of information bias.

Smyth et al (1998).
This is a case-control study. TPO-Ab was detected in 34% of carcinoma patients compared to 18.5% in their control group (P <0.001) and 28.7% in the benign breast disease group compared to their control group 13.6% (P<0.05). In survival group analysis, patients with high TPO-Ab titre (>=0.3 U/ml) were associated with a significantly better disease–free period (Relative risk RR 3.46, P<0.02) compared with those who were negative. The positive effect of TPO-Ab was noticed when the thyroid volume was within the intermediate range (10.1 -18.8ml).

Limitations: the study had a relatively small sample size and was hospital-based.4.2.10.

Roldan et al (2012).
This is a cross-sectional, analytical study. The prevalence of AITD was 9.8%. The presence of autoantibodies was 37.8% for TPO-Ab and 20.8% for TG-Ab. Type 2 diabetes (OR 13.61; 95% CI 1.61 – 111.96; P= 0.016), thrombosis (OR 24.4; 95%CI 2.72- 218.42; P=0.004), abnormal BMI (OR 4.22;95% CI 1.19-14.93; P=0.025) were positively associated with patients with RA and AITD (P value <0.05).

Limitation: hospital-based study, risk of information bias as only patients with thyroid dysfunction tested for thyroid antibodies while others were not tested.

Sharifi, Ghasemi and Mousaviasab (2008).
This is an analytic cross-sectional study. TPO-Ab was detected in 39.6% of patients and 6.7% of controls (P=0.001). 38.2% of male diabetics had positive TPO-Ab, and 40.4% of female diabetics had positive TPO-Ab (P=0 .8). 39.3% of female diabetics had positive TG-Ab, and 14.7% of males had positive TG-Ab (P=0.14). The correlation was positive between age and TPO-Ab but not for TG-Ab among people with diabetes (r=0.29, P=0.006) as well as the duration of diabetes and the level of TPO-Ab (r=0.33, P 0.004), but there was no correlation with TG-Ab. Approximately 22.4 % of diabetic patients were positive for both TPO-Ab and TG-Ab. There was no difference between males and females regarding TSH level and the frequency of abnormal thyroid function (P =0.5).

Limitations: small-size study, hospital-based, regional (conducted in a city in the northwest of Iran).

Kalyoncu and Urganci (2015).
This is a descriptive cross sectional study. About 16.4% of patients had antithyroid antibodies, which became positive after 2-3 years from celiac disease diagnosis. No other immune diseases among patients except two patients with type 1 diabetes were diagnosed before the celiac disease. Age was significantly different between the positive antithyroid group and the negative group (P=0.004), with no difference with gender, weight, height, clinical presentation, and compliance to a gluten-free diet (P value >0.05). In patients with positive antibodies, 72.7% remained euthyroid during the follow-up time (8.05 +/- 3.6 years).

Limitations: Small size study, hospital-based, cross-sectional design did not allow researchers to assess the correlation. All patients had a severe histopathological degree which did not allow researchers to assess the association of different classes to thyroid antibodies.

Discussion

Autoimmune thyroid diseases are common endocrine diseases associated with detecting thyroid autoantibodies. These autoantibodies are frequently found in patients with autoimmune thyroid diseases and individuals without thyroid dysfunction manifestations. Circulating thyroid autoimmune antibodies are not restricted to autoimmune thyroid diseases but can also be detected in other common autoimmune diseases.

Vitamin D deficiency is one of the non-thyroidal diseases found to be associated with thyroid autoantibodies. Shin et al. (11) showed the association between Vit D deficiency and thyroid autoantibodies, particularly with TPO-Ab. Tamer et al. (27) argued that Vit D deficiency could be a sign of autoimmune thyroid disease. Darban et al. (12) found that there was no significant correlation between Vit d deficiency and thyroid function in both case and control groups. However, there was a significant statistical association between TPO-ab and level of Vit D. The odds ratio in this study to have Vit D deficiency in subjects with

TPO-ab >= 40iu was 3.55, (95% CI 1.12 -1.55, P=049), which indicates clinical and statistical significance. Kivity et al. (28) studied the presence of antithyroid antibodies and abnormal thyroid function and Vit D. They found a statistically significant correlation between the presence of antithyroid antibodies and Vit d deficiency (P= 0.01) but not with thyroid function (P=0.059).

Many researchers studied the association between mood disorders and symptomless Autoimmune thyroid diseases (AITDs). Carta et al. (9) showed an association between mood disorders and positive TPO-Ab in a community-based study. They found that age and gender were independent risk factors for this association. Major depressive episodes (OR 2.7, 95%CI 1,1 -6.7, P = 0.033), depressive disorder not otherwise specified (OR 4.4, 95% CI 1.1-9.3, P = 0.049), and anxiety disorders not otherwise specified (OR 4, 95% CI 1.1 -15.5, P = 0.045) were the most associated disorders to positive TPO-Ab. Snijders et al. (10) investigated the association between TPO-Ab and bipolar disorder; interestingly, this study found no association of TPO-Ab with bipolar disorder even after adjusting to age and gender (P= 0.709, after adjusting 0.123).

Zhang et al. (13) compared thyroid autoantibodies levels among Chinese patients with allergic diseases and their age and sex-matched controls. The study found a significant association between the presence of TG-Ab rather than TPO-Ab on the occurrence of allergic disease. This phenomenon can be explained by forming immune complexes in AITD patients; these complexes can further bind to the Fc receptor on mast cells (29). El Shabrawy et al. (30) showed that TPO-Ab was more related to allergic diseases than TG-Ab (30). Ismaeil et al. (14) studied the association between some allergic diseases and bronchial asthma with thyroid antibodies; interestingly, they did not find any association between TPO-Ab and TG-Ab and bronchial asthma. The relationship between chronic urticaria and autoimmune thyroid disease has recently been frequently reported in the literature. The prevalence in adult series ranges from 14 -33% (31). Levy et al. (15) studied this association in children (6-18 years). They found a prevalence of about 4.8%, lower than the adult prevalence but higher than that found by Marwaha et al. (32) and Rallison et al. (33). Although the study included 187 participants, 90 were males. However, participants with chronic urticaria and thyroid autoimmunity were females. This is comparable with other researchers who noticed a more predominant association among females (34). The deposition of thyroid immune complexes on the skin could trigger an allergic reaction, but the exact mechanism is not yet precise.

Women's reproductive system is another target for thyroid autoimmune. Singh et al. (17) studied the association of thyroid antibodies to pregnancy loss in a particular population (women who conceived with assisted reproductive techniques) who were euthyroid. The study found a high prevalence of miscarriage in patients with positive thyroid antibodies (32%) compared to those with negative thyroid antibodies (P =0.002). Stagnaro-Green et al. (20) and Glinoer et al. (35) found a significant correlation between thyroid antibodies and the risk of abortion; in both studies; >98% of participants were euthyroid. The mechanism involved the thyroid autoimmunity and pregnancy loss could be related to the interaction between thyroid antibodies and the several thyrotropin-like hormones produced by the placenta (36).

Wang et al. (19) studied the association between thyroid antibodies and pregnancy loss. They found that the association was more positive in patients with endometriosis and polycystic ovary syndrome. The positive rate of TPO-Ab in infertile females with PCOS ages 28-35 years was increased significantly (P=0.035); these findings made the authors recommend screening females with PCOS aged 28-35 years for thyroid antibodies. Janssen et al. (18) found the exact relation of thyroid antibodies in patients with PCOS, but they did further thyroid ultrasound assessment. They found that in patients with PCOS, their thyroid ultrasound showed a picture of autoimmune thyroiditis in 42.3% compared to the control group (6.5%); P<0.001. Thyroid autoimmune antibodies could affect the outcome of pregnancy as well. Stagnaro -Green et al. (20) observed that the abortion rate was higher among women with positive thyroid antibodies. 92.7% of participants in this study were <35 years, and autoimmunity was associated with higher abortion risk; it is significant because this population has a low risk of abortion that becomes higher when associated with thyroid autoantibodies (37). The presence of thyroid autoantibodies may reflect minimal thyroid dysfunction. Some studies postulated that the association of abortion with thyroid autoantibodies could be related to this minimal dysfunction, not to the antibodies themself (38). Geva et al. (39) postulated that the absence of TPO-Ab could strongly predict success in women submitted to assisted reproduction.

The meta-analysis by Pan et al. (21) tried to find an association between SLE and thyroid antibodies. Researchers found an association between thyroid antibodies (TPO-Ab and TG-Ab) and SLE. The study dug deep and analysed the occurrence of association based on demographical distribution. They compare the American, European, Asian, and African populations for the presence of TPO-Ab among SLE patients. TG-Ab was associated with SLE in the American and European populations but not in Africans and Asians. TPO-Ab was positively associated with SLE in the African and European populations but not in the American and Asian populations.

A lengthy debate about thyroid and breast diseases was running between researchers. A higher prevalence of TPO-Ab in breast carcinoma patients than in controls was reported (40). Smyth et al. (23) demonstrated a high TPO-Ab positivity (34%) in patients with breast carcinoma compared with 18.5% inappropriate female control, even in patients with benign breast diseases was higher than their control (28.7% vs. 13,6%). The association suggested

the presence of subclinical autoimmune thyroid disease. Higher TSH, even within the normal range, may indicate the tendency to hypothyroid function in such patients (41). The TPO-Ab positivity was associated with better disease outcomes. Also, the size of the thyroid gland (=<10ml, >=18ml) is associated with a better outcome. Fukutomi, Nanasawa, and Yamamoto (42) shared the same finding regarding the positive prognostic of TPO-Ab in a patient with breast carcinoma. The mechanism that high TPO-Ab can positively affect the outcome of breast carcinoma is not yet precise; it could be through an effect on mammary receptors affecting the cytotoxicity of the cancer cell; still, it is a matter of research.

Rheumatoid Disease was another autoimmune disease that underwent investigation for the possibility of the occurrence of thyroid antibodies within its pathophysiology. Roldan et al. (26) worked to determine the prevalence and impact of autoimmune thyroid disease in patients with rheumatoid arthritis. The worldwide prevalence of Autoimmune Thyroid Disease (AITD) in rheumatoid arthritis varies considerably, ranging from 0.5% in Morocco to 27% in Slovakia (43). Type 1 diabetes was another disease brought under focus. Sharifi, Ghasemi, and Mousavinasab (24) investigated the prevalence of TPO-Ab, and TG-Ab in patients with type 1 and compared the effect of age and sex on patients with AITD with type 1 diabetes. Type 1 diabetes was considered an autoimmune disease (44) associated strongly with other organ-specific diseases such as AITDs. Also, thyroid antibodies are more prevalent with type 1 diabetes and AITD (45). Chang et al. (46) reported that 10-24% of type 1 diabetic patients who were clinically euthyroid had been reported to be positive for TPO-Ab. Sharifi, Ghasemi, and Mousavinasab (24) reported a 39.6% prevalence of positive TPO-Ab among type 1 diabetics. Researchers found a tendency for TPO-Ab to occur with increasing age; this finding comes with what Verge et al. (47) reported. Kalyoncu and Urganci (25) investigated the association of Celiac disease with thyroid autoimmune antibodies. The association between celiac disease and other autoimmune disorders, such as type 1 diabetes, is well established (48). The prevalence of antithyroid antibodies has been reported to be high in patients with celiac disease (25), and some reported low prevalence (49). Researchers only observed a significant difference between the observed antithyroid antibodies and younger age in patients with celiac disease. The frequency of antithyroid antibodies did not correlate with the duration of gluten intake and compliance with a gluten-free diet.

Conclusion

Thyroid autoantibodies are frequently found in patients with AITDs and subjects without manifest thyroid dysfunction. Thyroid antibodies can be detected in a group of non-thyroidal illnesses and participate in the pathogenesis of these diseases. These antibodies could be a trigger for inflammatory or allergic reactions. The association of these antibodies with the illness could be a positive or negative correlation. These antibodies could be a prognostic indicator to increase disease-free survival, as in the case of breast carcinoma. Thyroid autoantibodies were not an exclusive indicator for thyroid diseases. However, they became clinical indicators of other non-thyroidal diseases, and their clinical significance must be assessed and followed.

Conflict of interest:
I had declared that I have no conflict of interest. Also, I had no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work and any other relationships or activities that could appear to have influenced the submitted work.

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