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THE ASSOCIATION BETWEEN ALOPECIA AREATA AND THYROID DISORDERS: A SYSTEMATIC REVIEW

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Abstract:

Objectives: *To investigate the association between alopecia areata (AA) and thyroid disorders through a systematic review of the existing literature.* ***Methods:*** *PubMed, MEDLINE, and Embase were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process.* ***Results:*** *Our results included twelve studies with a total of 101,757 patients diagnosed with AA and 67,824 (66.7%) were females. We reported multiple thyroid dysfunctions associated with AA, including autoimmune hypothyroidism and Hashimoto thyroiditis. All of the included studies demonstrated a bidirectional relationship between AA and thyroid dysfunctions. Five studies reported that thyroid dysfunctions were the most associated comorbidity among AA patients. Two studies demonstrated that patients with thyroid autoimmunity (thyrotoxicosis, Graves disorders, and thyroiditis) have a higher risk of developing AA. Other two studies found that thyroid dysfunction was associated with increased AA severity and low response to treatments.* ***Conclusion:*** *Our review's findings are consistent with the theory that individuals with AA have a higher frequency of thyroid disease, indicating that AA patients ought to undergo thyroid disease screening. Thyroid function and thyroid autoantibodies should be more frequently evaluated in AA patients, even though there is no evidence of a causative relationship or interaction between AA and thyroid disease. It is necessary to conduct more research on potential pathways and interactions.*

Keywords*: alopecia areata; thyroid disorders; hypothyroidism; hyperthyroidism; hair loss; Systematic review.*

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BACKGROUND:

Alopecia areata (AA) is a common condition that affects millions of people worldwide. It can have a significant impact on a person's self-esteem and quality of life [1]. In 2019, the pooled prevalence of AA was 2.11% throughout the world [2]. Thyroid disorders, on the other hand, are a group of conditions that affect the thyroid gland. The thyroid gland plays a crucial role in regulating metabolism, growth, and energy levels in the body [3].

There has been a growing interest in the association between AA and thyroid disorders, as both conditions can have overlapping etiology and may share common underlying mechanisms. This systematic review aims to explore the relationship between AA and thyroid disorders, focusing on the existing evidence from scientific studies and clinical observations [4].

Several studies have reported a higher prevalence of thyroid disorders, particularly hypothyroidism and autoimmune thyroid diseases, in patients with AA compared to the general population [5]. Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormones, leading to symptoms such as fatigue, weight gain, and hair loss. Autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease resulting in thyroid inflammation and dysfunction [6].

The exact mechanisms underlying the association between AA and thyroid disorders are not fully understood, but several hypotheses have been proposed. One theory suggests that thyroid hormones play a crucial role in the hair growth cycle, and disruptions in thyroid function can lead to hair loss. Another theory suggests that autoimmune processes involved in thyroid disorders may also target hair follicles, leading to AA [7].

In addition to the potential biological mechanisms linking AA and thyroid disorders, there may also be genetic and environmental factors that contribute to the association. Family history of thyroid disorders and autoimmune diseases, as well as certain medications and stressors, have been identified as potential risk factors for both conditions [4].

The diagnosis and management of AA and thyroid disorders can be complex, as both conditions require thorough evaluation and individualized treatment plans. Patients with AA should be screened for thyroid disorders, and vice versa, to ensure timely diagnosis and appropriate management. Treatment options for thyroid disorders may include thyroid hormone replacement therapy, anti-thyroid medications, or surgery, depending on the specific condition and severity [8].

The association between AA and thyroid disorders is a complex and multifaceted relationship that warrants further research and clinical attention [4]. Understanding the links between these two conditions can help improve the diagnosis and management of patients with hair loss and thyroid dysfunction. Healthcare providers should be aware of the potential association between AA and thyroid disorders and consider screening for both conditions in patients presenting with hair loss or thyroid symptoms. By addressing both conditions simultaneously, we can better support the overall health and well-being of individuals affected by AA and thyroid disorders [1].

Study Objectives:

1. To assess the prevalence of thyroid disorders in individuals with AA.
2. To determine the strength of the association between AA and thyroid disorders.
3. To identify potential underlying mechanisms linking AA and thyroid disorders.
4. To provide recommendations for future research and clinical practice in managing individuals with both AA and thyroid disorders.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. A thorough search of electronic databases, including PubMed, MEDLINE, and Embase, was carried out to locate pertinent studies published in the English language. The search strategy incorporated keywords associated with alopecia areata and thyroid disorders. Two reviewers independently evaluated the search outcomes, chose suitable studies, extracted data, and evaluated the quality of the included studies using relevant assessment tools.

Eligibility Criteria

Inclusion criteria:

1. Studies investigate the association between AA and thyroid disorders.
2. Studies published in the English language.
3. Studies that include human participants of any age.
4. Studies that provide clear diagnostic criteria for AA and thyroid disorders.

5. Studies report quantitative data on the relationship between AA and thyroid disorders.
6. Studies conducted within the last 5 years (2019-2024).

Exclusion criteria:

1. Studies that do not focus on the association between AA and thyroid disorders.
2. Studies published in languages other than English.
3. Animal studies, case reports, reviews, and editorials.
4. Studies that do not report diagnostic criteria for AA and thyroid disorders.
5. Studies with insufficient data or unclear methodology.

Data Extraction

Rayyan (QCRI) [10] was used to validate the search results in order to guarantee correctness. The search results were subjected to inclusion and exclusion criteria in order to evaluate the relevancy of abstracts and titles. Reviewers carefully examined the papers that have been chosen and meet the inclusion requirements. Discussions were used to settle any disputes. Relevant study information, including titles, authors, study year, location, participants, gender, follow-up duration, disorder reported, and key outcomes, were entered into a pre-prepared data extraction form. We drafted a different paper just to evaluate bias risk.

Data Synthesis Strategy

A qualitative assessment of the research findings and components was provided through the creation of summary tables derived from pertinent studies. The best strategy for making use of the data from the included studies was decided upon after data for the systematic review was gathered.

Risk of Bias Assessment

The quality of the research was assessed using the Joanna Briggs Institute (JBI) [11] critical assessment criteria for studies reporting prevalence data. This tool consisted of nine questions. Positive answers receive a score of 1, while negative, unclear, or irrelevant answers receive a score of 0. Ratings of less than 4, five to seven, and more than eight will be categorized as low, moderate, and outstanding quality, in that order. Researchers evaluated the quality of the study on their own, and any disagreements were discussed and resolved.

RESULTS:

Search results

The systematic search yielded 502 study articles in total, of which 205 duplicates were eliminated. 297 studies were eliminated after 215 studies had their titles and abstracts screened. Of the 82 reports that were requested to be retrieved, only 4 items were found. After screening 78 papers for full-text assessment, 45 were rejected due to incorrect study results, 19 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review had twelve study papers that met the eligibility criteria. **Figure 1** presents an overview of the process used to select the studies.

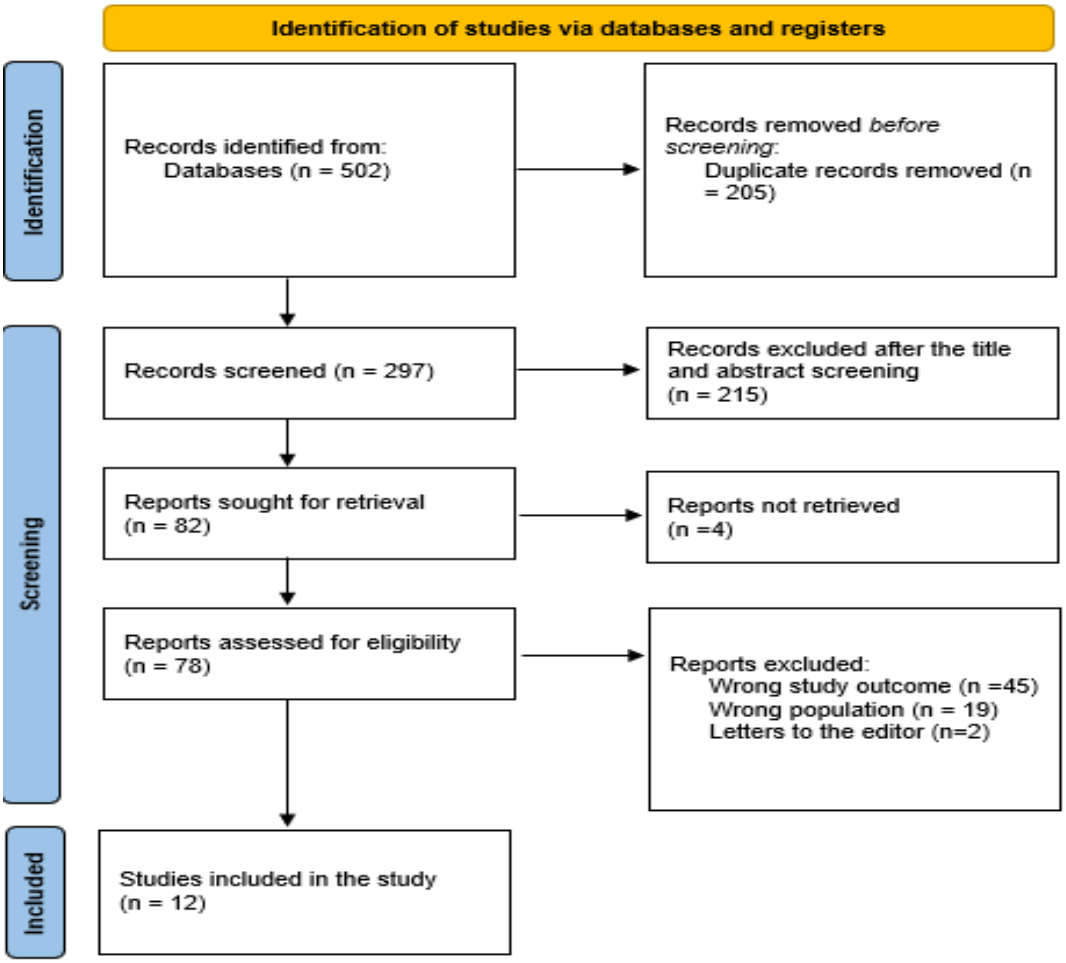

Figure (1): Study decision is summed up in a PRISMA diagram.

Characteristics of the included studies

The sociodemographic details of the research articles that are included are shown in **Table 1.** Our results included twelve studies with a total of 101,757 patients diagnosed with AA and 67,824 (66.7%) were females. Four studies were cross-sectional [16, 18, 21, 23], three were prospective in nature [14, 19, 20], three were case-control [12, 13, 22], and two were retrospective in nature [15, 17]. Two studies were conducted in the USA [15, 20], two in Saudi Arabia [16, 21], three in India [18, 19, 23], one in Pakistan [12], one in Tunisia [14], one in Taiwan [17], and one in Thailand [23].

The clinical features are displayed in **Table (2)**. We reported multiple thyroid dysfunctions associated with AA, including autoimmune hypothyroidism [13] and Hashimoto thyroiditis [19]. All of the included studies demonstrated a bidirectional relationship between AA and thyroid dysfunctions [12-23]. Five studies reported that thyroid dysfunctions were the most associated comorbidity among AA patients [14, 15, 16, 21, 22]. Two studies demonstrated that patients with thyroid autoimmunity (thyrotoxicosis, Graves disorders, and thyroiditis) have a higher risk of developing AA [17, 20]. Other two studies found that thyroid dysfunction was associated with increased AA severity [18] and bad response to treatments [19].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age	Females (%)
Habib et al., 2023 [12]	Case-Control	Pakistan	204	30.4±12.5	164 (80.4%)
Holmes et al., 2023 [13]	Case-Control	UK	8051	39.3 ± 14.3	4398 (54.6%)
Arousse et al., 2019 [14]	Prospective cohort	Tunisia	204	23	121 (59.3%)
Senna et al., 2021 [15]	Retrospective cohort	USA	68,121	40.3 ± 17.8	41,561 (61%)
Alamoudi et al., 2021 [16]	Cross-sectional	Saudi Arabia	177	28.4 ± 12.7	92 (52%)
Dai et al., 2021 [17]	Retrospective cohort	Taiwan	5929	32.6	2855 (48.2%)
Bhardwaj et al., 2021 [18]	Cross-sectional	India	50	10.8 ± 3.8	29 (58%)
Lalosevic et al., 2019 [19]	Prospective cohort	India	73	10.3 ± 5	36 (49.3%)
Moseley et al., 2023 [20]	Prospective cohort	USA	18,012	66.3 ± 6.6	18,012 (100%)
Alshahrani et al., 2020 [21]	Cross-sectional	Saudi Arabia	216	25.6 ± 12.9	91 (42.1%)
Chanprapaph et al., 2021 [22]	Case-Control	Thailand	615	36.8 ± 10.7	412 (66.9%)
Shrestha et al., 2023 [23]	Cross-sectional	India	105	18-59	53 (50.5%)

*NM=Not-mentioned

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Follow-up duration (Years)	Disorder	Main outcomes	JBI
Habib et al., 2023 [12]	NM	Thyroid autoimmunity	Five patients (4.90%) and none of the Controls had elevated Anti-TPO Ab titres, indicative of thyroid autoimmunity. The statistical significance was established by the p-value of 0.024.	Moderate
Holmes et al., 2023 [13]	1	Autoimmune hypothyroidism	When evaluating specific illnesses, those with AA had greater prevalence and incidence of vitiligo, autoimmune hypothyroidism, atopic dermatitis, allergic rhinitis, and SLE.	Moderate
Arousse et al., 2019 [14]	NM	Thyroid disorders	Thyroid problems (12.7%) were the most frequent autoimmune diseases that were associated with AA.	High
Senna et al., 2021 [15]	1	Thyroid disorders	Hyperlipidemia (22.4%), hypertension (21.8%), thyroid conditions (13.1%), eczema or contact dermatitis (10.8%), depression (9.5%), and anxiety (8.4%) were the most prevalent comorbidities.	Moderate
Alamoudi et al., 2021 [16]	NM	Hypothyroidism	The most common comorbidity was hypothyroidism (11.8%), which was followed by atopic diseases (10.7%), diabetes (6.2%), and mood disorders (6.2%).	Moderate
Dai et al., 2021 [17]	4.69–11.37	Thyroid disorders	Patients with thyrotoxicosis (aHR 9.29; 95% CI, 7.11–12.14), Graves disorders (aHR 8.66; 95% CI 6.03–12.42), and thyroiditis (aHR 6.42; 95% CI 3.15–13.11) had a markedly higher risk of developing AA, but not Hashimoto's thyroiditis patients. To sum up, there is a reciprocal relationship between AA and thyroid conditions.	Moderate
Bhardwaj et al., 2021 [18]	NM	Thyroid disorders	Although not statistically significant ($p > 0.05$), female gender, younger age, nail involvement, and the occurrence of concurrent vitiligo, atopy, and thyroid dysfunction were linked to severe illness.	High
Lalosevic et al., 2019 [19]	1	Hashimoto thyroiditis	Compared to people with Hashimoto's thyroiditis, those without the condition had a 9.8-fold increased risk of having a good response.	Moderate
Moseley et al., 2023 [20]	NM	Hypothyroidism	An elevated risk of AA was linked to a history of systemic lupus erythematosus (HR 5.43), multiple sclerosis (HR 4.10), vitiligo (HR 3.13), psoriasis (HR 2.01), hypothyroidism (HR 1.88), and rheumatoid arthritis (HR 1.66).	Moderate
Alshahrani et al., 2020 [21]	NM	Hypothyroidism	Atopic disorders, diabetes mellitus, and hypothyroidism are common comorbid illnesses.	Moderate
Chanprapaph et al., 2021 [22]	1	Autoimmune thyroiditis	The most common condition was autoimmune thyroid disease (n = 42, 6.8%) in AA patients.	Moderate
Shrestha et al., 2023 [23]	NM	Thyroid disorders	Even in the absence of clinical signs of thyroid dysfunction, patients with AA should be screened for thyroid functions and thyroid autoimmunity in order to detect thyroid abnormalities early on. This is true even though our study found a negligible correlation between thyroid function tests and AA patients.	Low

*NM=Not mentioned

DISCUSSION:

The evidence that AA patients are more likely to develop thyroid disease is compiled and assessed in this review. We demonstrated a bidirectional relationship between AA and thyroid dysfunctions in the included studies [12-23]. Five studies reported that thyroid dysfunctions were the most associated comorbidity among AA patients [14, 15, 16, 21, 22]. Two studies demonstrated that patients with thyroid autoimmunity (thyrotoxicosis, Graves disorders, and thyroiditis) have a higher risk of developing AA [17, 20]. Similarly, **Lee *et al.*** in a systematic review reported that individuals diagnosed with AA were more likely to have abnormal results on free triiodothyronine, free thyroxine, and thyrotropin levels, as well as increased probabilities of thyroid dysfunction. Furthermore, patients with AA had a significantly higher prevalence of autoimmune thyroid disorders [24]. Another meta-analysis by **Xin *et al.*** also found that AA patients had a considerably greater incidence of thyroid disease than did the control group [25].

T lymphocytes and associated cytokines that infiltrate the skin lesions' hair follicles are crucial to the pathophysiology of AA. Thus, thyroid illness and AA may potentially be influenced by regulatory T cells [26]. HLA antigens are another factor connecting thyroid illness with AA. HLA-DRB1*03 has been positively linked to Graves' disease and negatively linked to AA [27, 28]. HLA-DQB1*03 has positive relationships with both autoimmune hypothyroidism and AA. Furthermore, TRAb-positive patients with AA had a considerably higher haplotype frequency of DRB1*15: 01-DQB1*06:02 than control participants, according to a genetic association study of HLA genes [29].

There is currently disagreement over thyroid disease testing, and expert consensus maintains that autoimmune screening studies are not necessary for patients with AA. The majority of specialists on hair loss concur that autoimmune illnesses such as vitiligo, thyroid disease, and atopy/atopic dermatitis enhance the likelihood of developing AA. Therefore, adequate confirmation testing is necessary in patients whose symptoms are clearly consistent with autoimmune comorbidities [30].

In this review, other two studies found that thyroid dysfunction was associated with increased AA severity [18] and low response to treatments [19]. In context to our results, **Todorova & Petrov,** analyzed research and case studies attest to the link between AA and thyroid autoimmune and/or malfunction. If the thyroid gland is impacted, the research points to a relationship between the severity and duration of AA [31]. The illness has an unpredictable path. Roughly 80 percent of the individuals had abrupt relapses and spontaneous hair growth. Persistent hair loss is possible in certain people [32, 33]. Although the exact cause of AA is unknown, new research on the pathogenesis of the disorder points to a genetic, immunological, and environmental risk factor for the illness, as well as viral infections, traumatic experiences, and psychological stress. The immunological privilege of the anagen hair follicle is violated by CD4+ and CD8+ T-lymphocytes, which are associated with the loss of the developing hair shafts. Thus, AA frequently coexists with autoimmune concomitant illnesses [32-34].

Due to a lack of data in the literature, more subgroup analysis or meta-regression using patient variables, such as patient age and AA subtype, was not possible.

CONCLUSION:

Our review's findings are consistent with the theory that individuals with AA have a higher frequency of thyroid disease, indicating that AA patients ought to undergo thyroid disease evaluation. It is necessary to conduct more research on potential pathways and interactions.

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