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Dermatology

Association of Melasma with Thyroid Disorders

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Abstract **Original Research Article**

Melasma, a common hyperpigmentation disorder, has been a subject of increasing interest due to its potential association with thyroid disorders. This systematic review and meta-analysis aimed to assess the relationship between melasma and thyroid function indicators, including thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), and thyroid antibodies, particularly anti-thyroid peroxidase (anti-TPO) and antithyroglobulin antibody. A comprehensive search across multiple databases identified 39 relevant studies for analysis. The systematic review and meta-analysis were ultimately conducted based on the data extracted from these 39 selected studies. The meta-analysis revealed significant differences in thyroid function indicators between individuals with melasma and control groups. Melasma patients exhibited higher TSH levels (SMD = 0.33, 95% CI: 0.18, 0.47) and lower T4 levels (SMD = -1.50, 95% CI: -2.96, -0.04). However, no significant difference in T3 levels was observed (SMD = -0.01, 95% CI: -0.20, 0.19). Notably, the presence of anti-TPO antibodies was significantly associated with melasma (Fisher = 26.80, P = 0.020). Gender-specific analyses revealed more pronounced thyroid function differences among women with melasma, suggesting potential hormonal influences. Melasma predominantly affects women and often exhibits exacerbations during pregnancy, indicating a complex interplay between sex hormones and thyroid function in pigmentation regulation. These findings have clinical implications for dermatologists and endocrinologists. Dermatologists should consider thyroid evaluation in melasma patients, especially in cases with treatment resistance. For endocrinologists, melasma could serve as a cutaneous marker for underlying thyroid dysfunction, particularly in women. Further research is needed to elucidate the mechanisms underlying this association and its temporal aspects. Longitudinal studies could provide insights into whether thyroid dysfunction precedes or follows the development of melasma. Understanding these relationships will contribute to improved patient care and may lead to novel therapeutic approaches.

Keywords: Melasma, thyroid disorders, thyroid function indicators, thyroid antibodies, hyperpigmentation.

INTRODUCTION

Melasma, characterized by the development of hyperpigmented patches on sun-exposed areas of the skin, particularly the face, poses a significant challenge in dermatology. It affects individuals of various ethnic backgrounds, with a predilection for those with Fitzpatrick skin types III to VI, and predominantly impacts women in their reproductive years [1]. While melasma is generally considered a benign condition, its psychological and emotional impact on those affected can be substantial, often leading to a decreased quality of life and self-esteem [2].

The pathogenesis of melasma is complex and multifactorial, involving genetic predisposition, ultraviolet (UV) radiation exposure, hormonal fluctuations, and inflammation [3]. Among these factors, the role of hormones, particularly thyroid hormones, has emerged as a topic of interest and debate in recent years. The thyroid gland produces essential hormones, thyroxine (T4) and triiodothyronine (T3), which play a pivotal role in regulating various metabolic processes, including those involved in skin pigmentation [4].

The connection between melasma and thyroid disorders, such as hypothyroidism and autoimmune thyroiditis, has been explored in clinical studies and epidemiological investigations. These studies have sought to elucidate whether aberrations in thyroid function could influence the development or exacerbation of melasma. However, the findings have been inconsistent, with some studies reporting a significant association while others failing to establish a

clear link [5]. Understanding the intricacies of this relationship is essential for several reasons.

Firstly, thyroid hormones influence skin pigmentation through various mechanisms. T3 and T4 have been shown to modulate the activity of melanocytes, the cells responsible for melanin production, which, in turn, plays a central role in determining skin color [4]. An imbalance in thyroid hormone levels may disrupt the delicate regulatory processes governing melanin production, potentially leading to hyperpigmentation or exacerbating existing melasma lesions.

Secondly, the recognition of an association between melasma and thyroid disorders can have clinical implications. Dermatologists and endocrinologists alike need to consider the possibility of thyroid dysfunction when evaluating patients with melasma. Accurate diagnosis and management of concurrent thyroid disorders could be crucial for achieving optimal outcomes in melasma treatment [6].

Moreover, the presence of thyroid autoantibodies, such as anti-thyroid peroxidase (anti-TPO) and antithyroglobulin antibodies, has been investigated in the context of melasma. These autoantibodies are hallmarks of autoimmune thyroiditis, a condition that may be accompanied by thyroid dysfunction. Recent research has suggested a potential association between the presence of anti-TPO antibodies and the severity of melasma, further underscoring the intricate relationship between the skin and the thyroid gland [7].

Additionally, the gender-specific differences observed in the association between melasma and thyroid disorders warrant closer examination. Several studies have suggested that women with melasma may be more likely to exhibit abnormalities in thyroid function indicators compared to men with the same condition [8]. This gender disparity raises intriguing questions about hormonal influences and genetic predispositions in the pathogenesis of melasma. In light of these considerations, this systematic review and meta-analysis aim to comprehensively assess the existing body of evidence regarding the association between melasma and thyroid disorders. By critically reviewing and synthesizing the findings from relevant studies, we seek to provide a clearer understanding of the relationship between these two conditions. Additionally, we aim to explore potential gender disparities in this association and elucidate the role of thyroid autoantibodies, such as anti-TPO, in melasma [9].

The insights gained from this review have the potential to inform clinical practice by highlighting the importance of thyroid function assessment in melasma patients and advancing our understanding of the underlying mechanisms linking these two conditions. Furthermore, it may pave the way for more tailored approaches to diagnosis and treatment, ultimately improving the management of patients affected by melasma.

MATERIALS AND METHODS

Study Selection:

We conducted a comprehensive search of the literature to identify studies investigating the association between melasma and thyroid disorders. The search was performed across multiple electronic databases, including PubMed, Embase, Scopus, Web of Science, CINAHL, PsycINFO, and Google Scholar. The search strategy included a combination of MeSH terms and keywords related to melasma, thyroid function, and thyroid antibodies. The search was limited to articles published up to the date of our search cutoff in September 2022.

Inclusion Criteria:

- Studies directly investigating the relationship between melasma and thyroid disorders.
- Original research with observational designs (cross-sectional, case-control, cohort).
- Involving human participants.
- Containing data necessary for effect size calculations.

Exclusion Criteria:

- Review articles, case reports, abstracts, and non-primary data publications.
- Studies not in English.
- Inclusion of participants with a history of thyroid surgery or cancer.
- Irrelevant studies not addressing the research question.
- Lack of essential data for analysis.

These criteria guide the selection of relevant, high-quality studies for our systematic review and meta-analysis on melasma and thyroid disorders.

Search Strategy

The search strategy for this systematic review involves a comprehensive approach to identifying relevant studies that explore the association between melasma and thyroid disorders. We will search multiple electronic databases, including PubMed, Embase, Scopus, Web of Science and Google Scholar, using a combination of relevant terms and keywords. The initial focus is on capturing studies related to melasma, utilizing various terms associated with the condition. Then, we incorporate terms related to thyroid function, including thyroid hormones and antibodies, to identify studies examining this aspect. Finally, we employ terms related

to the association or relationship between melasma and thyroid disorders. This structured search strategy aims to ensure the systematic identification of all pertinent literature for our review and meta-analysis.

Study Selection

The process of study selection for this systematic review will follow a structured and rigorous approach. It involves several key steps:

- **Database Search:** We will execute the defined search strategy in selected electronic databases (e.g., PubMed, Embase, Scopus, Web of Science, Google Scholar) to identify relevant studies.
- **Initial Screening:** Two independent reviewers will initially screen the search results based on titles and abstracts to identify potentially relevant studies according to the predefined inclusion and exclusion criteria.
- **Full-Text Assessment:** The selected studies from the initial screening will undergo a thorough full-text assessment. Reviewers will examine the complete articles to ensure they meet all inclusion criteria and do not violate any exclusion criteria.
- **Data Extraction:** For studies meeting the inclusion criteria, relevant data will be extracted, including study characteristics, participant demographics, methodology, and outcome measures.
- **Quality Assessment:** The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of each included study, with particular attention to study design, participant selection, comparability, and outcome measurement.
- **Resolution of Discrepancies:** Any discrepancies or disagreements between the two independent reviewers during the study selection process will be resolved through discussion and, if necessary, consultation with a third reviewer to reach a consensus.
- **Data Management:** Data from selected studies will be systematically organized and managed to facilitate subsequent analysis.
- **Sensitivity Analysis:** Sensitivity analysis will be conducted to assess the robustness of the results by evaluating the impact of individual studies on the overall findings.
- **Study Flow Diagram:** A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be created to visually depict the study selection process, including the number of studies screened, assessed for eligibility, and included in the final analysis.

Data Extraction

In this systematic review entails a structured process of gathering essential information from the chosen studies. Utilizing a standardized form, data encompassing study particulars (e.g., title, authorship, publication year), participant demographics (e.g., sample size, age, gender distribution), thyroid function indicators (e.g., mean TSH, T4, T3 levels), thyroid antibodies presence, outcome measures, quality assessment scores (e.g., NOS), and other pertinent data will be systematically collected. Two independent reviewers will perform the extraction, with discrepancies resolved through discussion or third-party consultation. The organized dataset will undergo validation to ensure accuracy and consistency, providing a robust foundation for meta-analysis and effectively addressing the research question while ensuring transparency and reliability in the data collection process.

Statistical Analysis

This systematic review and meta-analysis will employ rigorous methods to synthesize data from selected studies and derive meaningful insights. Using SPSS (Statistical Package for the Social Sciences) software, we will calculate effect sizes such as the standardized mean difference (SMD) for continuous outcomes (e.g., thyroid function indicators like TSH, T4, T3) and odds ratios (ORs) for binary outcomes (e.g., presence of thyroid antibodies) along with 95% confidence intervals (CIs). Heterogeneity among studies will be assessed through Cochrane's Q statistic and the I-squared (I^2) statistic. Subgroup analyses will explore potential sources of heterogeneity, including gender disparities, geographic variations, and study design. Sensitivity analyses will gauge result robustness, with consideration for study exclusion if necessary. Furthermore, we will examine publication bias using funnel plots and Egger's test, and if detected, potential adjustments will be made using the trim-and-fill method. The meta-analysis results will be presented through forest plots, visually illustrating individual study effects and overall summary effects. This thorough statistical analysis, implemented using SPSS, aims to provide robust, evidence-based conclusions regarding the association between melasma and thyroid disorders, with relevance for clinical practice and future research.

RESULTS

Search Results

The systematic literature search yielded a total of 1,235 potentially relevant articles across multiple electronic databases, including PubMed, Embase, Scopus, Web of Science and Google Scholar. The initial screening involved reviewing titles and abstracts to identify studies that potentially met the inclusion criteria. After this initial screening, 457 articles were considered for full-text assessment based on their relevance to the

research question. These articles underwent a thorough evaluation to determine their eligibility for inclusion in the systematic review and meta-analysis. Following the full-text assessment, 39 studies were identified as meeting the predefined inclusion criteria. These studies provided relevant data on the association between melasma and thyroid disorders, including thyroid function indicators (e.g., TSH, T4, T3) and the presence of thyroid antibodies (e.g., anti-TPO, antithyroglobulin antibody). The systematic review and meta-analysis were ultimately conducted based on the data extracted from these 39 selected studies. The results of the meta-analysis will be presented in subsequent sections, providing insights into the association between melasma and thyroid disorders, potential sources of heterogeneity, and the overall findings. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the study selection process will be included in the final report to enhance transparency and clarity in presenting the search results and study selection.

Quality Assessment Summary:

A total of 39 studies were included in the systematic review and meta-analysis.

- Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) for observational studies.
- The maximum possible score on the NOS is nine stars, distributed across three domains: selection of study groups, comparability of groups, and ascertainment of exposure/outcome.
- Studies with six or more stars were considered of high quality.

Quality Assessment Findings:

- Among the selected studies, 28 were rated as high quality, scoring six stars or more on the NOS.
- The high-quality studies demonstrated robust methodologies, including well-defined participant selection criteria, adequate control for potential confounders, and reliable ascertainment of exposure and outcome measures.
- The remaining 11 studies, while relevant, scored below six stars on the NOS, indicating potential limitations in study design or reporting.

Implications:

- The majority of included studies were of high quality, enhancing the overall reliability of the evidence synthesized in the systematic review.
- High-quality studies are essential for drawing meaningful conclusions about the association between melasma and thyroid disorders.
- The potential limitations identified in lower-scoring studies will be considered when interpreting the results and discussing the overall quality of evidence in the final report.

The quality assessment results provide valuable insights into the reliability and methodological rigor of the selected studies, ensuring that the systematic review and meta-analysis are based on a solid foundation of evidence.

TSH and Melasma

Association between thyroid-stimulating hormone (TSH) and melasma has been a subject of interest in dermatological research. Several studies have explored the relationship between TSH levels and the development or exacerbation of melasma. One study investigated the TSH levels in individuals with melasma. They reported that TSH levels were significantly higher in patients with melasma compared to controls [10]. This finding suggests that thyroid function, as indicated by TSH levels, may play a role in the pathogenesis of melasma. However, it's important to note that the association between TSH and melasma remains a topic of ongoing research, and the mechanisms underlying this relationship are complex. Further studies are needed to elucidate the precise mechanisms and potential clinical implications of thyroid function in melasma development.

Table: Summary of Selected Studies on Melasma and Thyroid Disorders

Study	Sample Size	Thyroid Function Indicators	Thyroid Antibodies	Findings
Demirkan *et al.*, [11]	400 cases, 350 controls	- Increased TSH levels (SMD = 0.28, 95% CI: 0.10, 0.45)	- Elevated anti-TPO (Fisher = 18.12, P < 0.001)	- Significant association between melasma and higher TSH and anti-TPO levels among cases.
Rahman *et al.*, [12]	250 cases, 300 controls	- Lower T4 levels (SMD = -1.20, 95% CI: -1.98, -0.42)	- No significant association with anti-TPO	- Melasma patients exhibited reduced T4 levels compared to controls. No significant association with anti-TPO.
Zhang *et al.*, [13]	150 cases, 150 controls	- No significant differences in TSH, T4, and T3 levels	- Elevated anti-TPO (Fisher = 12.45, P = 0.003)	- Melasma cases did not show significant differences in thyroid

Study	Sample Size	Thyroid Function Indicators	Thyroid Antibodies	Findings
				function indicators, but anti-TPO antibodies were elevated.
Al-Shamma *et al.*, [14]	300 cases, 200 controls	- Increased TSH levels (SMD = 0.42, 95% CI: 0.18, 0.67)	- Elevated anti-TPO (Fisher = 22.78, P < 0.001)	- Significant association between melasma and higher TSH and anti-TPO levels among cases.
Yadav, *et al.*, [15]	180 cases, 180 controls	- Lower T4 levels (SMD = -1.35, 95% CI: -2.12, -0.57)	- No significant association with anti-TPO	- Melasma patients exhibited reduced T4 levels compared to controls. No significant association with anti-TPO.

This table provides a summary of selected studies, including sample sizes, findings related to thyroid function indicators (TSH, T4, T3), and the presence of thyroid antibodies (anti-TPO). It highlights variations in results across different studies, emphasizing the diversity in findings within the field of melasma and thyroid disorders research.

DISCUSSION

The association between melasma and thyroid disorders has been a subject of increasing interest and debate in recent years. This systematic review and meta-analysis aimed to provide a comprehensive evaluation of the existing evidence on this relationship. By synthesizing data from 39 selected studies, we sought to shed light on the potential association between melasma and thyroid dysfunction, including thyroid function indicators and the presence of thyroid antibodies. In this discussion, we will delve into the key findings, implications, potential mechanisms, gender disparities, and clinical relevance of this association.

Association between Melasma and Thyroid Function Indicators:

Our meta-analysis revealed a significant association between melasma and alterations in thyroid function indicators, particularly thyroid-stimulating hormone (TSH) and thyroxine (T4) [16]. The standardized mean difference (SMD) in TSH levels was estimated to be 0.33 (95% CI: 0.18, 0.47), indicating that individuals with melasma tended to have higher TSH levels compared to controls. Similarly, T4 levels were significantly lower in melasma patients, with an SMD of -1.50 (95% CI: -2.96, -0.04). These findings underscore the potential influence of thyroid hormones on melanin production and skin pigmentation. TSH, as a key regulator of thyroid function, can indirectly impact melanocyte activity, potentially contributing to hyperpigmentation observed in melasma. The lower T4 levels in melasma patients may reflect a state of subclinical hypothyroidism, which could disrupt melanin synthesis and distribution, contributing to the development or exacerbation of melasma [17].

Presence of Thyroid Antibodies in Melasma:

Another notable result of our meta-analysis was the significant association between melasma and the presence of thyroid antibodies, particularly anti-thyroid peroxidase (anti-TPO). The analysis revealed a Fisher value of 26.80 (P = 0.020), indicating a substantial relationship between elevated anti-TPO levels and the presence of melasma [18]. This finding suggests a potential autoimmune component in the pathogenesis of melasma among certain individuals. Anti-TPO antibodies are characteristic markers of autoimmune thyroiditis, which can coexist with thyroid dysfunction. The presence of anti-TPO antibodies may signal autoimmune mechanisms that extend beyond thyroid tissue and impact skin pigmentation. However, further research is needed to elucidate the precise mechanisms by which these antibodies might contribute to melasma development.

Gender Disparities in the Association:

Gender-specific analyses revealed interesting disparities in the association between melasma and thyroid disorders. Among women with melasma, the differences in thyroid function indicators appeared more pronounced. For instance, the SMD for TSH levels among women with melasma was 0.35 (95% CI: 0.17, 0.52), while among men, it was 0.10 (95% CI: -0.17, 0.38). Similarly, the SMD for T4 levels among women was -2.75 (95% CI: -6.30, 0.81), compared to -0.99 (95% CI: -1.83, 0.14) among men [16]. These gender disparities raise intriguing questions about the potential hormonal and genetic influences in the pathogenesis of melasma. It is well-established that melasma predominantly affects women, often becoming more pronounced during pregnancy or with the use of oral contraceptives, suggesting a hormonal component. The influence of female sex hormones, such as estrogen and progesterone, on melanin production may interact with thyroid hormones, leading to gender-specific variations in the association [19].

Clinical Implications:

The findings of this systematic review and meta-analysis hold clinical significance for both dermatologists and endocrinologists. Dermatologists treating patients with melasma should be aware of the potential link with thyroid disorders. Routine assessment

of thyroid function, particularly TSH and T4 levels, may be considered in melasma patients, especially in cases where the pigmentation is resistant to conventional treatments. On the other hand, endocrinologists should recognize that melasma could serve as a cutaneous marker for underlying thyroid dysfunction, particularly in women [20]. The presence of melasma may prompt thyroid function testing and evaluation for autoimmune thyroiditis in clinical practice. Early detection and management of thyroid disorders in individuals with melasma may not only improve skin outcomes but also address potential systemic health concerns [21].

Potential Mechanisms and Future Research:

While this meta-analysis offers valuable insights, the precise mechanisms underlying the association between melasma and thyroid disorders remain incompletely understood. Future research should explore the molecular and cellular interactions between thyroid hormones, thyroid antibodies, and melanocytes. Investigating the role of autoimmune processes, including the impact of anti-TPO antibodies on skin pigmentation, is of particular interest. Additionally, longitudinal studies are warranted to assess whether thyroid dysfunction or the presence of thyroid antibodies can predict the development or exacerbation of melasma over time. Understanding the temporal relationship between these factors could provide further clarity on causality.

CONCLUSION

In our systematic review and meta-analysis provide evidence of a significant association between melasma and thyroid disorders, with alterations in thyroid function indicators and the presence of thyroid antibodies observed in melasma patients. Gender-specific disparities suggest hormonal and genetic influences that warrant further investigation. Clinically, these findings underscore the importance of considering thyroid evaluation in melasma patients and may guide more targeted approaches to diagnosis and treatment. Future research should delve deeper into the mechanisms underlying this association and its potential implications for both dermatology and endocrinology.

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