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Research Article

The Relationship Between Melasma and Thyroid Dysfunction—Analyzing Anti-thyroid Peroxidase Antibody Profiles: An Immuno-dermatological Perspective

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Abstract

Background: Autoimmune mechanisms have been increasingly implicated in pigmentary disorders such as melasma. Thyroid autoimmunity, reflected by anti-thyroid peroxidase (anti-TPO) antibodies, can influence melanogenesis and disease severity. ***Objective***: To evaluate the correlation between melasma severity and anti-TPO antibody levels. ***Methods***: Fifty people with melasma took part in this case-control study and had their mMASI score and serum anti-TPO antibody levels evaluated. Age-matched controls (n=50) were included for comparison. ***Results***: The mean anti-TPO level is significantly higher in melasma cases compared to controls (24.9±7.3 *vs.* 19.5±7.9; p=0.001). Within the melasma group, anti-TPO levels show a strong positive correlation with mMASI (r= 0.4, p=0.001), and age (r= 0.3, p=0.001). Melasma severity was higher in older age groups (p= 0.001). ***Conclusions***: Anti-TPO antibodies are elevated in melasma and correlate with disease severity, supporting a potential autoimmune contribution to melasma pathogenesis.

Keywords: Autoimmunity, Anti-TPO antibodies, Melasma severity, mMASI, Thyroid autoantibodies.

العلاقة بين الكلف وخلل الغدة الدرقية— تحليل ملفات الأجسام المضادة لبيروكسيداز المضاد للغدة الدرقية: منظور مناعي-جلدي

الخلاصة

الخلفية: أصبحت آليات المناعة الذاتية مرتبطة بشكل متزايد باضطرابات صبغية مثل الكلف. المناعة الذاتية للغدة الدرقية، التي تنعكس في الأجسام المضادة لبيروكسيداز الغدة الدرقية (Anti-TPO)، يمكن أن تؤثر على تكون الميلانوجين وشدة المرض. **الهدف**: تقييم العلاقة بين شدة الكلف ومستويات الأجسام المضادة المضادة ل TPO. **الطرائق**: شارك خمسون شخصا مصابا بالكلف في هذه الدراسة الشاهدة، وتم تقييم درجة mMASI ومستويات الأجسام المضادة المضادة ل TPO في المصل. تم تضمين الضوابط المطابقة حسب العمر (n=50) للمقارنة. **النتائج**: متوسط مستوى مضاد TPO أعلى بشكل ملحوظ في حالات الميلاسم مقارنة بالمجموعة الضابطة (24.9±7.3 مقابل 19.5±7.9؛ p=0.001). داخل مجموعة الكلفة، تظهر مستويات مضادات TPO ارتباطا إيجابيا قويا مع mMASI (r= 0.4، p=0.001)، والعمر (r= 0.3، p=0.001). كانت شدة الميلاسم أعلى في الفئات العمرية الأكبر (p= 0.001). **الاستنتاجات**: الأجسام المضادة المضادة ل TPO مرتفعة في الكلف وترتبط بشدة المرض، مما يدعم مساهمة محتملة لأمراض المناعة الذاتية في التسبب المرضي للكلف.

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INTRODUCTION

Melasma is a very widespread pigmentary disorder, especially prevalent among women of pregnancy age and those with darker Fitzpatrick skin phototypes, notably types III through VI. The disorder manifests as symmetrical, hyperpigmented macules and patches in a centrofacial distribution and predominantly affects individuals with heightened sun exposure in genetically predisposed populations [1]. Epidemiologic data suggest wide-ranging prevalence estimates ranging between 1% and 50%, depending on skin type, ethnicity, and UV exposure, with age of onset generally in the second and fourth decades of life [2,3]. The etiopathogenesis of melasma is clearly recognized to be multifactorial. Ultraviolet (UV) and visible light radiation spur oxidative stress and trigger melanogenesis, often via keratinocyte and fibroblast signaling, most notably through pathways involving stem cell factor and opsin-3 receptor activation [4]. Concurrently, hormonal changes, such as during pregnancy, during oral contraceptive use, and estrogen and progesterone exposure, enhance melanogenic activity through receptor-mediated increases in tyrosinase and melanin synthesis, angiogenesis, and melanocyte proliferation, including via estrogen receptors in the epidermis and dermis [5]. Genetic susceptibility, family history, and vascular and neural contributions are further implicated in melasma development and persistence [6]. Recently, attention has been given to the role of systemic factors, particularly thyroid function and autoimmunity, in melasma pathogenesis. Autoimmune thyroid disorders, which are marked by high levels of anti-thyroid peroxidase (anti-TPO) or anti-thyroglobulin antibodies, are among the most common autoimmune diseases. They can cause inflammatory cascades that have effects on the body's systems and skin [7]. The literature has reported an association between thyroid dysfunction and

melasma, yielding mixed results. Some reports indicate a high prevalence of anti-TPO antibodies or thyroid dysfunction in melasma patients compared to controls, whereas others have failed to demonstrate statistically significant differences [1,2,6]. For instance, one study observed significantly higher rates of thyroid disorders (18.5%) and positive anti-TPO antibodies (15.7%) among melasma patients versus controls [8], while another found elevated FT4, TSH, and anti-thyroglobulin levels but did not detect significant differences in anti-TPO titers [2]. Notably, few studies have quantified melasma severity using tools such as the modified Melasma Area and Severity Index (mMASI) and directly correlated it with anti-TPO levels. This gap limits our understanding of whether thyroid autoimmunity is merely associated with melasma presence or whether higher levels of anti-TPO antibodies align with greater disease severity. Based on emerging evidence of melanocyte activation by inflammatory mediators and an observed trend toward increased thyroid autoimmunity among melasma patients, the present study aims to investigate whether serum anti-TPO antibody levels are correlated with the clinical severity of melasma, as assessed by mMASI scores. Establishing such a relationship could inform more holistic, immunologically guided evaluation and management strategies for moderate to severe cases of melasma.

METHODS

Study design and participants

This was a case-control study conducted at an outpatient private clinic of dermatology, venereology, and sexually transmitted diseases in Wasit governorate of Iraq in the period from November 2024 to May 2025. A total of 100 female participants were enrolled and divided equally into two groups: 50 patients clinically diagnosed with melasma and 50 apparently healthy women who served as controls; controls were recruited from women attending the clinic for non-pigmentary dermatological complaints. Controls were matched to cases for sex and systemic health conditions and were selected to approximate the age distribution, but complete age matching was not achieved.

Inclusion criteria

Female patients were eligible to participate in this study if they were between the ages of 18 and 45 years old, were clinically diagnosed with melasma confirmed by dermatological examination, and should give a written consent. To ensure comparability, controls were selected from the same population and were matched with the melasma group for age, sex, and underlying comorbid conditions by checking the medical history. For both study groups, the cases and controls were required to have no history of thyroid-related medical treatment within the year preceding recruitment in our study.

Exclusion criteria

Participants were excluded if they were male, pregnant, or had a documented history of other pigmentary disorders such as vitiligo or post-inflammatory hyperpigmentation. Additional exclusion criteria included the use of medications known to influence thyroid function within the past six months or a history of malignancy.

Data collection

All participants underwent a structured evaluation protocol. Demographic data, medical history, and relevant clinical characteristics were obtained through standardized interviews and review of medical records. Particular attention was given to personal or family history of thyroid disease, medication use, pregnancy status, and other systemic conditions that could influence thyroid function or skin pigmentation.

Clinical evaluation of melasma

The severity of melasma was assessed using the modified Melasma Area and Severity Index. This scoring system evaluates the area of involvement, pigmentation intensity, and homogeneity across four key facial regions: the forehead, right malar, left malar, and chin. To reduce observer bias, assessments were independently performed by two dermatologists blinded to the laboratory results, and mean values were used for statistical analysis.

Laboratory analysis

For each participant, a 5 mL venous blood sample was obtained under sterile conditions. Serum was separated and stored at –20 °C until analysis. Measurement of anti-TPO antibody levels was carried out using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human Anti-TPO ELISA Kit, Elabscience Biotechnology Co., Ltd., Wuhan, China). Antibody concentrations were expressed in international units per milliliter (IU/mL), with values above 34 IU/mL considered positive according to the manufacturer's instructions. Although thyroid function tests (TSH, T3, and T4) were measured as part of the broader clinical evaluation, the present analysis focuses on anti-TPO antibodies to specifically examine thyroid autoimmunity, which is the objective of our study.

Outcome measurements

The most important outcome of our study was to determine the correlation between serum anti-thyroid peroxidase antibody levels and the severity of melasma as assessed by the modified Melasma Area and Severity Index. Secondary outcomes included assessing the relationship between antibody levels and patient age within the melasma group and evaluating whether increasing age was associated with greater disease severity.

Ethical considerations

The study adhered to the ethical principles outlined in the Helsinki Declaration, with ethical approval obtained from the Lincoln University College Ethical Committee, along with written informed consent obtained from all participants before participation in the study.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, version XX (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and analyzed using the independent t-test or Mann–Whitney U test depending on distribution. Categorical variables were summarized as frequencies and percentages and compared using the chi-square test. Correlations between anti-TPO antibody levels, mMASI scores, and patient age were examined using Pearson's correlation coefficient. A two-tailed *p*-value < 0.05 was considered statistically significant.

RESULTS

A total of 100 participants were enrolled, including 50 patients with melasma and 50 age- and sex-matched healthy controls. All participants were female. The median age of melasma cases was significantly higher than that of controls (39 *vs*. 31.5 years, *p*= 0.001). The majority of cases were clustered in the 31–40 and 41–50 years age groups, while younger participants (20–30 years) were more prevalent among controls (Table 1).

Table 1: Age distribution of the participants studied (n=50 in each group)

Age (Year)	Cases	Controls	*p*-value
Median (IQR)	39 (33.5–43)	31.5 (25.7–39)	0.001
Range	19–45	19–45	
Age categories (year)			
<20	1(2)	1(2)	0.07
20–30	9(18)	20(40)	
31–40	21(42)	19(38)	
41–50	19(38)	10(20)	

Values are presented frequency, percentage, median, and range.

The mean serum anti-TPO antibody level was significantly elevated in melasma patients compared with controls (24.9 ± 7.3 *vs*. 19.5 ± 7.9 IU/ml, *p*= 0.001). However, when applying a categorical cutoff, only six participants (6%), five cases and one control, were positive, while the remaining 94% were negative, with no significant difference between the two groups (*p*= 0.2) (Table 2).

Table 2: Anti-thyroid peroxidase antibody levels in cases and controls (n=50 in each group)

Anti-TPO	Cases	Controls	*p*-value
Mean±SD (IU/ml)	24.9±7.3	19.5±7.9	0.001
Range (IU/ml)	10–45	7–40	
Category n(%)			
Positive	5(10)	1(2)	0.2
Negative	45(90)	49(98)	

Values are presented as frequency, percentage, and mean±SD.

All melasma patients had moderate disease as assessed by the modified Melasma Area and Severity Index, with a median score of 13.5 (IQR: 13–14.2) and a range of 9–15.3 (Table 3).

Table 3: Modified melasma area and severity index among melasma cases

mMASI	Cases (n= 50)
Median (IQR)	13.5 (13–14.2)
Range	9–15.3
Severity n(%)	
Mild	0(0.0)
Moderate	50(100)
Severe	0(0.0)

Spearman's correlation demonstrated a significant positive association between mMASI scores and anti-TPO antibody levels (r= 0.40, *p*= 0.001). Additionally, patient age showed a moderate positive correlation with mMASI (r = 0.30, *p*= 0.001) (Table 4).

Table 4: Correlation between mMASI, Anti-TPO antibodies, and age

Variable	Correlation coefficient (r)	*p*-value
Anti-TPO Ab	0.40	0.001
Age	0.30	0.001

Further subgroup analysis revealed that mMASI scores increased progressively with age. Median mMASI values were lowest in patients <20 years and highest in those aged 41–50 years (*p*= 0.01) (Table 5).

Table 5: Association between patient age categories and mMASI score

Age category (year)	Median mMASI (IQR)	Range	*p*-value
<20	5.4 (0.0)	0 – 10.8	0.01
20–30	0.0 (0.0–12.4)	0 – 14.3	
31–40	12.4 (0–13.4)	0 – 14.2	
41–50	13.3 (0–14.2)	0 – 15.3	

DISCUSSION

Melasma is a widespread pigmentary disorder predominantly affecting women, particularly those with darker skin types and Fitzpatrick phototype III–V [9]. Its multifactorial etiology includes genetic predisposition, hormonal influences, ultraviolet radiation exposure, and environmental factors [10,11]. While melasma is not fatal, it significantly impacts patients' quality of life due to its cosmetic consequences and psychological burden [12]. Recent evidence suggests that autoimmune mechanisms, particularly thyroid autoimmunity, may contribute to melanocyte dysregulation and melasma pathogenesis [13,14]. Comprehending the relation between melasma and thyroid autoimmunity has an important clinical implication. Looking at the elevated anti-thyroid antibodies as a possible potential contributor to melasma should help in diagnostic accuracy and guide faster and more effective treatment strategies. Evaluating the anti-TPO antibodies in patients with moderate to severe or treatment-resistant melasma could help identify an underlying autoimmune component, making interventions closer and more personalized. Focusing on autoimmune activity could

also improve the efficacy of agreed-upon melasma therapies, including topically applied depigmenting ointments, chemical peeling, and laser treatments [15]. In our study, we focused primarily on the relationship between serum anti-thyroid peroxidase antibodies and melasma severity. Our findings demonstrate that melasma patients had significantly higher mean anti-TPO levels compared to controls, despite the low prevalence of categorical positivity. This suggests that even subclinical elevations in anti-TPO may be relevant to disease severity. Notably, Spearman correlation analysis shows a significant positive correlation between anti-TPO levels and mMASI scores, indicating that autoimmune thyroid activity may directly influence melasma intensity. Although the correlation between anti-TPO levels and mMASI was statistically significant, it was moderate in strength (r = 0.40) and derived from a relatively small sample. Therefore, this association should be interpreted cautiously and considered indicative of a potential trend rather than a definitive causal relationship. These results agree with prior studies reporting elevated anti-TPO levels among melasma patients, supporting the hypothesis of a possible autoimmune factor contributor leading to a pigmentation disorder/disorder. A study by Rostami Mogaddam *et al*. [8] showed that 15.7% of melasma patients tested positive for anti-TPO antibodies, compared to just 5.7% of controls (p= 0.008), pointing to a significantly higher occurrence of thyroid autoimmunity in the case group. [16] Reported that melasma cases have significantly higher anti-TPO levels compared to controls, despite similar T3 and T4 levels, again pointing to an increased occurrence of thyroid autoimmunity within the melasma group. Similarly, finding that 24.4% of melasma cases had elevated anti-TPO versus 6.7% of controls (p= 0.019) supports the possible link between thyroid autoimmunity and melasma. Çakmak *et al*. also showed a higher thyroid autoantibody test result in melasma patients, further supporting the hypothesis of an autoimmunity contribution, even when other thyroid parameters were not necessary to be significantly different [2]. Other studies suggested a higher lab test result of anti-TPO or other thyroid autoantibodies in melasma groups, suggesting that subclinical autoimmune thyroid activity may occur with some cases of melasma [13,2,15-17]. Variability among studies may result from differences in sample size, population genetics, environmental exposures, or the specific markers used to point to the autoimmune thyroiditis. Collectively, these findings emphasize that autoimmune thyroid activity, rather than overt thyroid dysfunction, may influence melasma severity, highlighting for the dermatologists the importance of doing the anti-TPO antibodies lab test in patients with moderate to severe melasma or treatment-resistant pigmentation. Age was another important factor associated with melasma severity. Our data showed a progressive increase in mMASI scores with advancing age, with the highest scores observed in patients aged 41–50 years. This aligns with previous observations that cumulative UV exposure and age-related hormonal fluctuations may exacerbate melanogenesis [10,11]. Importantly, age also correlated moderately with anti-TPO levels (r = 0.30, p= 0.001), suggesting that autoimmune thyroid activity may intensify with age and contribute to the chronicity and severity of melasma. Genetic predisposition further modifies melasma risk and severity. In our cohort, 20% of cases reported a positive family history compared to 2% of controls. This supports previous findings emphasizing the heritable component of melasma [18,19], though the proportion in our study was lower, possibly due to sample size, ethnic variability, and environmental factors. Interestingly, a subset of patients with a family history of melasma also had elevated anti-TPO levels, reinforcing the interplay between genetic susceptibility and autoimmune mechanisms in disease pathogenesis. Environmental and exogenous factors, particularly UV exposure and cosmetic use, also play a role in melasma severity. All melasma cases in our study reported frequent cosmetic usage, consistent with prior observations highlighting the potential of irritant or allergenic products to exacerbate pigmentation [20,21]. Combined with cumulative UV exposure, these factors may act synergistically with autoimmune activity to modulate disease severity. The possible pathophysiological mechanism that links anti-TPO antibodies and melasma involves autoimmune-mediated melanocyte stimulation. Thyroid autoantibodies can induce systemic inflammation and may interact with melanocytes through thyroid antigen expression in the skin, causing increased melanin synthesis [13,14]. Thyroid autoimmunity can cause low-grade inflammation in the body. This inflammation may stimulate the skin to produce more pigment. Thyroid hormones also have receptors in skin cells, so changes related to thyroid autoimmunity may affect melanin production. This provides a simple biological explanation for the link we found between anti-TPO and melasma. While the precise molecular pathways are still under investigation, these findings suggest that anti-TPO may serve as a biomarker of disease severity in melasma, even in the absence of overt thyroid dysfunction among people. Clinically, our results give the importance of considering thyroid autoimmunity lab tests in the evaluation of melasma, particularly in patients with moderate to severe disease. Screening for anti-TPO antibodies may provide a good marker for disease prognosis and guide multidisciplinary treatment plans involving dermatologists and endocrinologists. Moreover, treating underlying autoimmune activity could potentially enhance the efficacy of traditional melasma treatment plans in clinics, for example, the topical depigmenting agents, chemical peeling, and laser therapy [15]. Our study has several strong sides. It employed a well-defined case-control design, included sex-matched controls, and used a standardized, objective assessment of melasma severity via the mMASI score. Additionally, anti-TPO antibody measurement was performed using validated ELISA techniques, enhancing the reliability of the findings. However, limitations should be conceded. The first one was that the relatively small sample size may limit generalizability and could explain the low prevalence of categorical anti-TPO

positivity. Furthermore, this cross-sectional design precludes conclusions about causality between anti-TPO levels and melasma progression. Future studies with larger cohorts and longitudinal follow-up are needed to clarify the temporal relationship between thyroid autoimmunity and melasma severity. Investigating additional autoimmune markers may also provide further insight into the immunopathogenesis of pigmentary disorders. Second, the case and control groups were not fully matched for age, and this imbalance may have introduced residual confounding. Third, the study was conducted in a single private dermatology clinic, which may limit the generalizability of the findings. Although TSH, T3, and T4 were measured as part of the broader study, these parameters were not included in the analysis of the present manuscript, as the focus was specifically on anti-TPO as an autoimmune marker. This limits our ability to interpret thyroid functional status in relation to melasma. The significant age difference between groups represents a potential confounding factor, as complete age matching was not achieved. This limitation should be considered when interpreting the association between anti-TPO levels and melasma severity. Because most borderline anti-TPO values were observed in the melasma group, a larger sample size might have revealed clearer differences in categorical positivity. Notably, five participants in the melasma group exceeded the positivity threshold compared to only one in the control group, further suggesting a trend toward subclinical autoimmune activation. Although all patients were classified as having moderate melasma, the numerical mMASI values showed sufficient within-category variability in severity (range: 9.0–15.3), and because the correlation analysis was performed using continuous mMASI scores, this variability was adequate to detect the observed associations.

Conclusion

Our findings show a significant positive correlation between anti-TPO antibody levels and melasma severity, supporting the role of autoimmune thyroid activity as a potential contributor to melasma pathogenesis. Age, genetic predisposition, and environmental exposures appear to modulate this relationship. These results underscore the importance of integrating immunological evaluation into the clinical management of patients with moderate to severe melasma, and they lay the base for future studies exploring therapeutic interventions targeting autoimmune mechanisms.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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