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A comparative study of melasma severity after hyperthyroid therapy in hyperthyroid subjects with melasma

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Abstract

Introduction: Melasma, and its variant chloasma, is an acquired and chronic disorder of hyperpigmentation, characterized by symmetrical hypermelanoses of the face. The exact pathogenesis of melasma remains unclear. Several hormones are thought to play a role, including thyroid hormones. The study's objectives are to determine the proportion of melasma cases in hyperthyroid patients and to compare the severity of melasma before and after medications of hyperthyroid therapy.
Methods: A quasi-experimental (pre-post intervention) study was conducted in Jakarta from August 2019 to February 2020. Twenty-three patients either newly diagnosed with hyperthyroidism or that had undergone hyperthyroid therapy for a maximum of 3 months and also had melasma were recruited. The severity of melasma was scored with the modified Melasma Area and Severity Index (mMASI), and dermoscopy of the lesions was performed. The evaluation was performed after 3 months of hyperthyroid therapy.
Results: Among the 69 hyperthyroid patients, 45 (65%) had melasma. The mean difference in the mMASI score was 0.49 ($p > 0.05$). Dermoscopy features did not show any differences between the start and end of the study.
Conclusions: There is no significant improvement of melasma severity in hyperthyroid patients after 3 months of hyperthyroid therapy.

Keywords: melasma, hyperthyroid, chloasma, mMASI

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Introduction

Melasma is a hyperpigmentation disorder that is common among most of the world's population. The location of melasma predilection is usually spread symmetrically across the forehead, cheeks, upper lip, and chin. The etiopathogenesis of melasma is unclear and is still debated. The risk factors for melasma are skin color type, genetics, ultraviolet (UV) exposure, pregnancy, cosmetics, anticonvulsant medications, and hormones (1–3). Thyroid hormones are hypothesized to play a role in melasma formation. The exact mechanism of how thyroid hormones could cause melasma is still unclear, but it is thought to be related to hyperthyroidism. The role of thyroid hormones in melasma is believed to be through the induction of inflammatory cytokine production, which causes melanogenesis. Hyperthyroidism is a pathological condition caused by excessive thyroid hormone production. This condition is characterized by low thyroid-stimulating hormone (TSH) followed by increased triiodothyronine (T3) and free thyroxine (FT4) levels (4).

Correlations between melasma and thyroid hormones have been reported (5–9). Lutfi et al. conducted a study and found a four-fold increase in the number of thyroid abnormalities in melasma patients, or 58.3% compared to the control group with the same age range (6, 10). Perez et al. and Yazdanfar et al. reported no significant correlation between thyroid levels and melasma (7, 11). There are no previous studies that have assessed the incidence of melasma in hyperthyroid patients.

The severity of melasma can be evaluated clinically or by using the Melasma Area and Severity Index (MASI) score. The MASI score has been adjusted into the modified MASI (mMASI) by eliminating the melasma lesions' homogeneity component, and its reliability and validity were established in 2010 (1).

This study was conducted to assess improvement in the severity of melasma in hyperthyroid patients treated with an anti-hyperthyroid drug (thiamazole) for 3 months.

Methods

The researchers traced data on female hyperthyroid patients seeking treatment at the Department of Internal Medicine's polyclinic unit. Patients that had their FT4 and TSH examined and met this study's criteria were brought to the polyclinic unit of the Cosmetic Dermatology Division, Department of Dermatology and Venereology, Dr. Cipto Mangunkusumo Hospital to assess the severity of their melasma. The subjects were then asked to continue the hyperthyroidism treatment as advised. All subjects were asked to return 3 months later to have their thyroid hormone levels (TSH and FT4) examined and the severity of their melasma reassessed. The subjects' thyroid level examinations were performed entirely at the clinical pathology laboratory at Dr. Cipto Mangunkusumo Hospital on a lower reading limit of < 0.003 µIU/ml and upper reading limit of > 5 ng/dl. For the statistical analysis, researchers input a value of 0.003 if the result was < 0.003 µIU/ml and a value of 5 if the result was > 5 ng/dl so that the TSH and FT4 components could be analyzed.

Female patients recently diagnosed with hyperthyroidism or that had been receiving therapy for hyperthyroidism for a maximum of 3 months, between the ages 18 and 60, and that had also been diagnosed with melasma, were consecutively recruited in this study.

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The exclusion criteria for this study were women that were pregnant or breastfeeding, women using hormonal contraception or that had used hormonal contraception during the past year, women currently receiving anticonvulsive therapy and/or hormone replacement therapy, women with a history of drug use that may affect thyroid function, women that had been using topical hydroquinone for the past 3 months and/or had been using topical steroids and/or vitamin A analogs and/or had been through chemical peeling treatment in the previous month, and those with a history of laser therapy and/or mechanical abrasion therapy during the past 9 months.

Melasma severity assessment

The subjects were examined clinically and assessed by the main researcher and one cosmetic dermatology consultant from the Dermatology and Venereology Department using the mMASI. The formula for the mMASI score is: 0.3 *AD* (*f*) + 0.3 *AD* (*lm*) + 0.3 *AD* (*rm*) + 0.1 *AD*(*c*). *A* = area of involvement, *D* = lesion darkness, *f* = forehead region, *lm* = left malar region, *rm* = right malar region, and *c* = chin region. The range of the total score is 0 to 24. For the area of the lesion: 0 = no lesion. 1 ≤ 10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, and 6 = 90–100%. For lesion darkness: 0 = absent, 1 = slight, 2 = mild, 3 = marked, and 4 = severe.

Baseline clinical and dermoscopy photographs were taken for every patient and also at the end of the study. These clinical images were taken using a CANON EOS 550D camera with an EFS 18-135 mm lens. The dermoscopy instrument used was a Heine Optotechnik GmbH & Co.KG type Delta 20 plus.

Study design

This study was a quasi-experimental (pre-post intervention study) design, using comparative analysis to compare the mMASI on hyperthyroid patients before and after hyperthyroid therapy for 3 months. The length of this experiment was chosen for two reasons. First, improvements in melasma are evident after 5 to 8 weeks of treatment (12, 13). Second, euthyroidism can also be achieved in 12 weeks of hyperthyroidism treatment (14, 15). This study has been registered on Clinical.govt under no. NCT04346901.

Research ethics

The study received ethical approval and passed an ethical review from the Research Ethics Committee at the Faculty of Medicine, Universitas Indonesia (clearance number: KET-886/UN2.F1/ETIK/PPM.00.02/2019). The prospective study subjects and their family/relatives were given an oral and written explanation of the study's aims, benefits, and procedures as well as the advantages and disadvantages of being the subjects of this study.

Statistical analysis

The data were processed according to the purpose of the study using the statistics program Stata version 15.0 (Stata Corp.™). Bivariate analysis calculations were performed using Pearson or Spearman correlation tests. The significant test was done on a *p*-value of < 0.05.

Results

Out of 69 hyperthyroid patients that went to the Metabolic Endocrine Division's polyclinic at the Department of Internal Medicine of Dr. Cipto Mangunkusumo Hospital, 45 of them (65%) were found to have melasma. Based on the study's criteria, 23 subjects were selected. The inclusion for the age range of 18–60 was based on literature by Pandya et al., Noh et al., and Nanjundaswamy et al., which describes the age of melasma patients in Asia (16–18). Three subjects did not return for the final assessment, and they were therefore placed in the dropout category. Two subjects were unable to attend because they were out of town, and one subject refused to be re-examined. A summary of the subjects' characteristics is provided in Table 1.

A comparison of the clinical characteristics of melasma and thyroid abnormalities at the beginning and end of the study is shown in Table 2. The assessment of melasma severity using the mMASI score at the beginning and end of the study was carried out by two people. At the beginning of the study, the mean of the mMASI score was analyzed using a rater agreement statistics test and showed a kappa value of 0.902 with a *p*-value of < 0.0001. At the end of the study, the mean of the mMASI score was analyzed using a rater agreement statistics test and showed a kappa value of 0.913 with a *p*-value of < 0.0001. This shows that there was similarity between the two examiners in assessing mMASI. The initial mean value of the subjects' TSH level median was 0.003 (0.003–

Table 1 | Distribution of sociodemographic characteristics of hyperthyroid patients with melasma (*n* = 23).

Characteristics		*n* (%)
Educational level:	Elementary school	1 (4)
	Middle school	12 (52)
	College/university	9 (39)
	No school attendance	1 (4)
Working status:	Working	14 (61)
	Not working	9 (39)
Contraception history:	Hormonal	3 (13)
	Tubectomy	1 (4)
	Intrauterine device (IUD)	3 (13)
	None	16 (70)
Pregnancy history:	Yes	17 (74)
	No	6 (26)
Sun protection:	Umbrella	2 (9)
	Sunscreen	7 (30)
	None	14 (61)
Skin type (Fitzpatrick):	Type III	8 (35)
	Type IV	14 (61)
	Type V	1 (4)
Family history of melasma:	Yes	4 (17)
	None	19 (83)
Facial cosmetics usage:	Frequent	12 (52)
	Occasional	10 (43)
	None	1 (4)

Table 2 | Subjects' clinical characteristics at the study beginning and end.

Characteristics	Study beginning (*n* = 23)	Study end (*n* = 20)
mMASI score	7.08 (*SD* = 3.88)	5.59 (*SD* = 3.11)
Δ mMASI	0.49 (*SD* = 2.63)	
TSH level, median (range)*	0.003 (0.003–0.009)	3.92 (*SD* = 7.55)
FT4 level, median (range)**	3.68 (1.52–23.61)	1.43 (*SD* = 1.35)

*in μIU/ml, normal range (0.35–4.94); **in ng/dl, normal range (0.7–1.48), FT4 = free thyroxine, mMASI = modified Melasma Area and Severity Index, SD = standard deviation, TSH = thyroid-stimulating hormone.

0.009) µIU/ml and the initial mean value of the subjects' FT_4 level was 3.68 (1.52–23.61) ng/dl. Therefore all the subjects met the inclusion criteria of being in a hyperthyroid state.

The dermoscopy examination carried out upon the subjects' initial arrival showed 1) uniform dark brown hyperpigmented lesions with a reticuloglobular pattern on all subjects (Fig. 1); and 2) islands of a brown reticular network with dark fine granules on seven subjects (Fig. 2), as well as 3) telangiectasia on five subjects. The result of the dermoscopy examination of the melasma lesions of all the subjects after 3 months of hyperthyroid therapy did not show a distinct difference compared to the initial examination.

The correlation between mMASI and thyroid hormone level is shown in Table 3. The statistics test was deemed to show a correlation if the value of the correlation coefficient (r) was at least 0.3, and it was considered significant if the p-value was < 0.05.

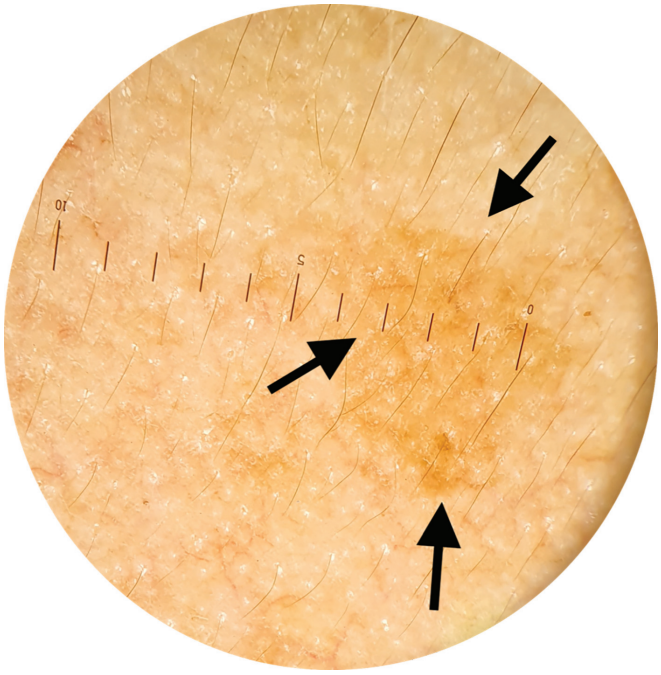

Figure 1 | Uniform dark brown hyperpigmented lesions with reticuloglobular pattern.

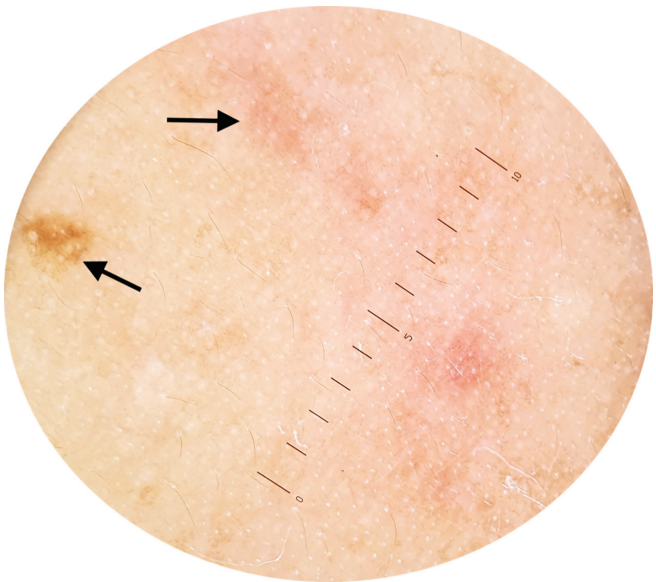

Figure 2 | Islands of brown reticular network with dark fine granules and telangiectasia.

Table 3 | Correlation of melasma severity (mMASI) and thyroid hormone level.

Parameter	r	p-value
Initial mMASI to initial TSH	0.101	0.646
Initial mMASI to initial FT_4	0.222	0.308
Final mMASI to final TSH	0.187	0.430
Final mMASI to final FT_4	0.110	0.644
ΔmMASI to ΔTSH	0.059	0.802
ΔmMASI to ΔFT_4	0.344	0.138

FT4 = free thyroxine, mMASI = modified Melasma Area and Severity Index, TSH = thyroid-stimulating hormone, r = correlation coefficient.

Discussion

Modified Melasma Area and Severity Index score

The mMASI assessment conducted by both examiners was deemed valid if the Spearman correlation between both results was ≥ 0.40 (1.15). A total of 17 subjects (74%) had mild melasma, and six subjects (26%) had moderate to severe melasma. The subjects' mMASI score on the 3-month control showed an average value of 5.59. The mean difference in the mMASI score before and after therapy was 0.49 with a p-value of > 0.05, which means that there was no significant difference between the two mMASI scores. The severity of the non-improving melasma might be caused by melasma, which is more likely a result of increasing melanocyte biological activity rather than an increase in their number (10). The thyroid hormones increased melanocyte activity by producing pro-inflammatory cytokines, which cause melanogenesis (16).

Dermoscopy

Dermoscopy is able to assess the depth of melasma and hence distinguish it from other skin pigmentation disorders, assess other skin complications, and evaluate the treatment for melasma (14, 23, 24). The dermoscopy examination on all the subjects showed uniform dark brown hyperpigmented lesions with a reticuloglobular pattern, which indicates melasma of dermal depth. Seven of the subjects also had an additional dermoscopy feature of islands of a brown reticular network with dark fine granules, indicating melasma of epidermal depth, and five of the subjects had an additional feature of telangiectasia, a permanent dilation of small blood vessels (14, 23, 25, 26). On human skin, melanocytes are located in the basal layer of the epidermis and hair follicles. The melanocytes' activities in the basal layer of the epidermis are regulated by keratinocytes, which produce pro-inflammatory factors and cytokines (22). On the melasma of dermal depth, there was basal membrane damage accompanied by pendulous melanocytes under the dermo-epidermal junction and an increase in matrix metalloproteinase (27, 28). Telangiectasia found in several subjects is consistent with the results of a study conducted by Kim et al., which found that increasing melanogenesis on melasma was caused by increasing vascularization, proven by an increasing vascular endothelial growth factor (VEGF) level (29). A study by Li et al. found a significant correlation between TSH and VEGF level in patients with papillary thyroid carcinoma (30). Meanwhile, a study by Rendon et al. found that telangiectasia in melasma could also be caused by photodamage, hormonal factors, and prolonged steroid use (26). Dermoscopy features that do not improve after 3 months of hyperthyroid therapy are in accordance with the severity of melasma, which also has not improved.

Relationship between melasma severity (mMASI) and thyroid hormone level

A positive correlation was found between the difference of the mMASI score results and the FT4 results ($r = 0.344$), and it was not statistically significant ($p > 0.05$). The exact mechanism by which thyroid hormones are able to influence melasma is yet to be established, although the correlation between melasma and thyroid hormones has been widely reported (6, 7, 11). Previous studies had sought to determine the correlation between melasma and thyroid hormones by examining the thyroid in melasma patients. A study by Kiani et al. found a significant correlation between melasma and thyroid disorders (31). Kumre et al. reported that the TSH level was normal in 65.8% of melasma patients, increased in 27.3% patients, and even decreased in 7.6% patients (32). Another study conducted by Talaee et al. found an abnormal TSH level in mild and severe melasma patients (33). This study was carried out on hyperthyroid patients with melasma to assess the role of thyroid hormones and hyperthyroid therapy on melasma.

Study limitations

The sensitivity of the subjects' thyroid level examinations was measured on a lower reading limit of < 0.003 μIU/ml and upper reading limit of > 5 ng/dl. Out of 23 subjects, 21 of them had a TSH level < 0.003 μIU/ml at the beginning of the study and seven of them had the same level at the end of the study. The researchers had to input a value of 0.003 so that the components could be analyzed.

Conclusions

Although thyroid hormones are often related to melasma, there are still only a few studies on this issue, making it a debatable topic. To date, no study has evaluated melasma in relation to hyperthyroid improvement. There is no decrease in mMASI in hyperthyroid patients with melasma after 3 months of hyperthyroid therapy. We suggest that larger and longer studies be performed on the potential improvement of melasma in hyperthyroid patients with melasma.

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