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Evaluation of Modified Melasma Area and Severity Index in Hyperthyroid Patients Receiving Anti-thyroid Drugs

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Abstract

BACKGROUND: Melasma is a common hyperpigmentation disorder, which causes brownish discoloration of the face. Despite unclear mechanisms, thyroid hormones were thought to play a role in melasma.

AIM: This study aims to determine and compare the clinical improvement of melasma in hyperthyroid patients receiving anti-thyroid drugs.

METHODS: An interventional study with a quasi-experimental design (pre-post-intervention study) was conducted at the Internal Medicine Outpatient Clinic and Dermatology and Venereology Outpatient Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from July 2019 to March 2020. A comparative analysis was done to compare the modified melasma area and severity index (mMASI) in hyperthyroid patients before and after 12 weeks of anti-thyroid drugs. All subjects did not receive any additional topical therapies for their melasma. The clinical features were evaluated objectively at baseline and 12th-week visit, by mMASI score on different areas of the face (forehead, left-right malar, and chin) and Wood's lamp examination.

RESULTS: All areas showed a decline in mMASI score components (e.g., involvement areas and darkness degree) after 12 weeks of treatment. However, only the malar area showed a significant decline ($p < 0.05$). Wood's lamp examination at baseline revealed dermal type melasma on 17 subjects, mixed type on six subjects, and epidermal type on one subject. All types remained unchanged after 12 weeks of treatment.

CONCLUSIONS: Our study demonstrated that mMASI score in malar area improved significantly, this might be because malar area included this study were comprised of epidermal, dermal, and mixed type. On the other hand, based on Wood's lamp examination, all types of melasma remained unchanged after 12 weeks of treatment.

Introduction

Melasma is a common hyperpigmentation disorder of the skin due to the overproduction of melanin pigment on sun-exposed areas. It typically manifests as symmetrical hyperpigmented patches on the forehead, cheeks, and chin [1], [2], [3]. Melasma can be found in all races, particularly women aged 20–50 years with darker skin types and those who live in areas with high ultraviolet light exposure [4], [5], [6], [7], [8]. Several factors, such as pregnancy, photosensitizing cosmetics and drugs, oral contraceptive pills, hormones, inflammatory skin processes, and emotional stress, were known as contributing factors in the etiology and pathogenesis of melasma [8], [9], [10], [11]. The modified melasma area and severity index (mMASI) is a scoring system to determine the degree of severity [4]. Using clinical measures such as Wood's lamp do determine types of melasma, it can be classified into epidermal, dermal, and mixed [5], [6]. It can distinguish skin discoloration associated with pigmentation and changes [7]. Wood's lamp examination was performed because it is cheaper and easily used than dermoscope.

Thyroid hormone was thought to play a role in the pathogenesis of melasma. Although the exact mechanism remains unknown, melasma has been suspected to be associated with hyperthyroid condition [12], [13]. Three previous epidemiological studies found that thyroid disorders were found higher in melasma patients compared to control group [12], [14], [15], [16]. In contrast, Perez *et al*. [17] and Ameneh and Banafsheh [13] reported no significant correlation between thyroid hormone levels and melasma.

Thyroid hormones are not routinely checked in melasma patients; therefore, anti-thyroid drugs are not routinely administered to treat melasma. Therapeutic modalities of melasma are hydroquinone, tranexamic acid, 4-n-Butylresorcinol, oligopeptides, chemical peels, lasers, etc. [18], [19], which none of those modalities were given in this study, but only anti-thyroid drugs.

This study aims to determine and compare the clinical improvement of melasma in hyperthyroid

patients before and after 3 months of anti-thyroid drugs, using the mMASI score and Wood's lamp.

Methods

Study design

This study is an interventional study with a quasi-experimental design (pre-post intervention study) using comparative analysis to compare mMASI in hyperthyroid patients before and after 12 weeks of anti-thyroid drugs. The change of MASI to mMASI is more simple and reliable in assessing melasma, both for initial assessment and improvement evaluation [18], [19]. A Wood's lamp examination was performed to determine the types of melasma. Based on a sample size calculation for a paired t-test, at least 20 subjects were required to be included. This study was conducted at the Internal Medicine Outpatient Clinic and Dermatology and Venereology Outpatient Clinic, Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from July 2019 to March 2020.

Participants

Eligible participants were adults aged 18–60 years old, diagnosed with the hyperthyroid condition by an endocrinologist, confirmed with the increased level of thyroid hormones by a laboratory examination, and melasma by a dermatologist. All participants had received adequate information regarding this study. Before included in this study, they were asked to sign a written informed consent. The exclusion criteria were pregnant or breastfeeding women; any use of anti-thyroid drugs more than 12 weeks; a history of hormonal contraception or hormone replacement therapy, anticonvulsant drugs, and drugs which could cause thyroid dysfunction (glucocorticoids, lithium, amiodarone, iodide, and octreotide) administration within the past month; topical steroid or Vitamin A analog use within the past month; topical hydroquinone use within the past 3 months; and laser or mechanical ablation therapy within the past 9 months.

Study protocols and objectives

All subjects were screened and enrolled consecutively. Those who had fulfilled the study's criteria were asked to sign a written informed consent. The data of preliminary thyroid stimulating hormone (TSH) and free T4 (FT4) were collected. We collected data on hyperthyroid patients with melasma who had available preliminary TSH and FT4 levels, were on anti-thyroid (thiamazole) medication for <12 weeks. Afterward, all subjects were assessed by a dermatologist at Cosmetic Dermatology Outpatient Clinic, Department of Dermatology and Venereology, Cipto Mangunkusumo Hospital. A thorough history taking was done before the clinical observation. The melasma severity was assessed on four different areas (forehead, left malar, right malar, and chin) using mMASI score and Wood's lamp examination. Facial photographs from three different angles (front, left, and right views) were obtained using a Canon Digital Inc., Kyoto, Japan (EOS 550D with EFS 18–135 mm lens). Two visits in this study took place at the baseline and 12th week after treatment. The standardized clinical photography, mMASI assessment, and Wood's lamp examination were repeated at each visit.

The subjects were asked to continue thiamazole regimen as hyperthyroidism treatment for 12 weeks. Thyroid function tests (TSH and FT4) were reexamined after each subject finished the 12th-week course of anti-thyroid drugs. All medications were prescribed in accordance with the dosage determined by the endocrinologist. All subjects were asked to return to the Cosmetic Dermatology Outpatient Clinic, Cipto Mangunkusumo Hospital after 12 weeks of therapy for the reassessment of their melasma. Data were recorded, collected, and further analyzed.

Objectives

The first objective was to evaluate the severity of melasma clinically or using a MASI score. This score assessed the area of pigmentation, degree of pigmentation, and homogeneity. In mMASI score (Table 1), the homogeneity component was removed. The mMASI score had been proven to be a valid and reliable tool to assess the severity of melasma [4].

Table 1: mMASI [4], [18]

Area	Score[a]
Forehead (F)	(0.3) (A) (D)
Left malar (LM)	(0.3) (A) (D)
Right malar (RM)	(0.3) (A) (D)
Chin (C)	(0.1) (A) (D)
Total score[b]	F+LM+RM+C mMASI scores

[a]Scoring system: A: Area of involvement, rated 0–6 (0 = no lesion, 1 = lesion area<10%, 2 = lesion area 10–29%, 3 = lesion area 30–49%, 4 = lesion area 50–69%, 5 = lesion area 70–89%, 6=lesion area 90–100%). D: Pigmentation severity, rated 0–4 (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe), [b]The total score ranges from 0 to 24 and is calculated by adding each mMASI score for four different areas of the face, mMASI: Modified melasma area and severity index.

The secondary objective was to evaluate all areas of the face (forehead, left and right malar, and chin) using the Wood's lamp. Each area was evaluated with Wood's lamp to determine the type of melasma (Table 2). This was determined to know which type responded after 12 week-course of anti-thyroid drugs.

Table 2: Classification of melasma based on the depth of melanin pigment [19]

Type	Normal light	Wood's lamp	Histology
Epidermal	Bright brown	Enhancement of contrast	Melanin deposition in basal and suprabasal layers of epidermis
Dermal	Bluish gray	No enhancement	Melanin deposition and macrophage seen in superficial to mid-dermis
Mixed	Dark brown	Some areas show contrast enhancement	Melanin deposition in epidermis and dermis

Additional data, consisted of FT4 and TSH levels, were taken at the initial recruitment and subsequently at the 12th week of therapy from medical record.

Ethical approval

The Ethics Committee of Faculty of Medicine Universitas Indonesia had reviewed and approved this study (registration number: KET-886/UN2.F1/ETIK/PPM.00.02/2019). This study was also registered at ClinicalTrials.gov with registration ID number: NCT04346901.

Statistical analysis

Comparative mMASI score was analyzed using statistical program Stata version 15.0 0 (Stata Corp.™, Texas, USA). The analysis of mMASI score before and after treatment was carried out using paired t-test. The statistical significance was set at $p < 0.05$.

Results

Out of 69 hyperthyroid patients treated at the Internal Medicine Outpatient Clinic during the study period, 45 (65.22%) patients had melasma. A number of 23 patients were eligible and enrolled in the study (Figure 1). There were three subjects who did not attend the final assessment; hence, they were dropped out from the study. Two subjects were unable to attend because they were out of town and one subject refused to be reexamined.

All subjects were women with a mean age of 40.17 ± 11.25 years and a median duration of experiencing melasma of 6.13 (range 1–24) months. Research subjects were diagnosed with hyperthyroidism for a mean score of 5.44 ± 3.342 weeks (confirmed with a low level of TSH and a high level of FT4 at the baseline), while the median duration of hyperthyroid medication consumption before enrollment was 4.57 (range 0–8) weeks. The subjects had skin type IV (60.87%), skin type III (34.78%), and only one person had skin type V. Family history of melasma were found in 19 (82.61%) subjects.

Participant's clinical characteristics

All subjects had centrofacial melasma with mean mMASI scores of 7.08 ± 3.88 and 5.59 ± 3.11, at baseline and week 12, respectively. The mean difference in the mMASI before and after medication was 0.49 ($p > 0.05$), thus showing no significant difference.

A further analysis was performed to compare each mMASI component before and after treatment

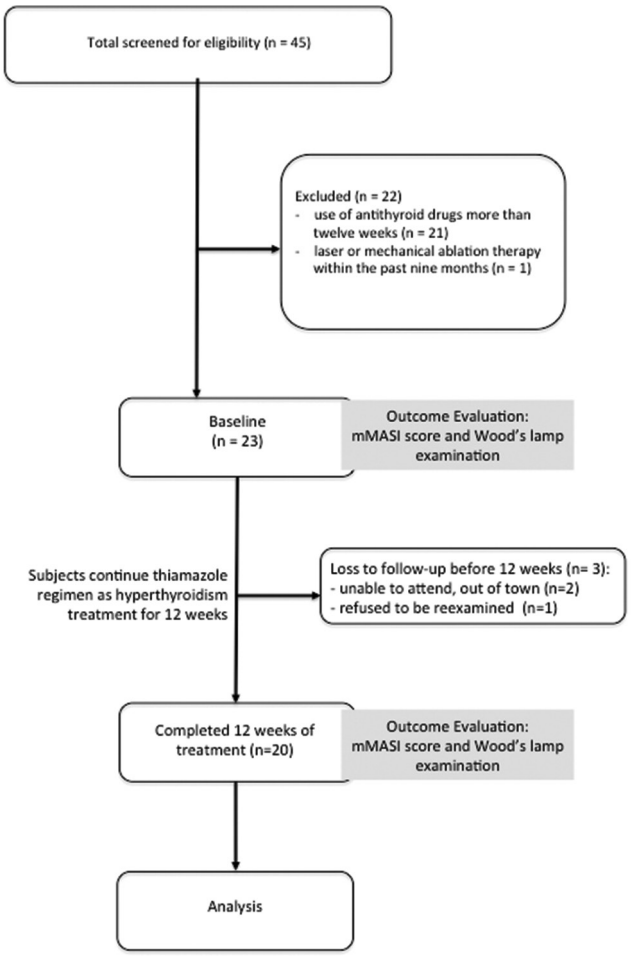

Figure 1: Participant flowchart showing patient journey over the 12-week study evaluating melasma in hyperthyroid patients receiving anti-thyroid drugs

(e.g., area of involvement and degree of darkness). Despite showing a decline, only malar area showed a significant improvement ($p = 0.025$). In contrast, degree of darkness on all areas, except the forehead, increased at 12th week after treatment (Table 3).

Table 3: mMASI component at baseline and 12th week after treatment

Component	Initial value (mean ± SD)	End value (mean±SD)	Delta	p-value
Forehead area	3.6 ± 1.14	3.4 ± 1.35	0.2	0.428
Malar area	3.375 ± 0.86	2.8 ± 0.99	0.575	0.025*
Chin area	2.65 ± 1.56	2.3 ± 1.3	0.35	0.406
Darkness of forehead	1.8 ± 0.69	1.55 ± 0.69	0.25	0.171
Darkness of malar	1.725 ± 0.66	1.95 ± 0.63	–0.225	0.154
Darkness of chin	1.3 ± 0.8	1.6 ± 0.82	–0.3	0.163

(*): *P*<0.05, mMASI: Modified melasma area and severity index.

Wood's lamp examination revealed dermal type melasma on 17 subjects, mixed type on 6 subjects, and epidermal type on 1 subject. The melasma types on all subjects remained unchanged at 12th week follow-up (Table 4).

Table 4: Wood's lamp examination results (number of samples)

Area	Epidermal	Dermal	Mixed type
Forehead	0	23	0
Malar	1	16	6
Chin	0	23	0

Mean value of initial TSH level was 0.003 (0.003–0.009) μIU/mL and mean value of FT4 level was 3.68 (1.52–23.61) ng/dL. Mean TSH and FT4 levels after 12 weeks' course of anti-thyroid drugs were 3.92 ± 7.55 μIU/mL and 1.43 ± 1.35 ng/dL, respectively. The mean differences in TSH and FT4 levels before and after 12 weeks were 3.92 ($p < 0.0001$) μIU/mL and 2.45 ($p < 0.05$) ng/dL, respectively. These findings indicate that the thyroid hormone levels were back to normal range after treatment with anti-thyroid drugs.

Discussion

The subjects' age ranged from 21 to 59 years with a mean value of 40.17 years. This result was in accordance with previous studies by Sarkar *et al*. [20] and Lima *et al*. [21], which reported that the majority of melasma patients are in the third and fourth decades of life.

A total of 19 (82.61%) subjects had a family history of melasma. The incidence of melasma in families varies. The lowest rate of positive family history was reported in Singapore by Goh *et al*. [22] (10.2%). In contrast, Handel *et al*. [9] reported a quite striking number in Brazil (61%). Genetic may serve as a contributing factor of melasma, considering the highest prevalence was found in Hispanic and Asian races. However, these numbers may vary largely since the etiology is multifactorial [23], [24].

In this study, all subjects with melasma had centrofacial pattern. Based on the spread and clinical manifestations, melasma is classified into four clinical patterns, namely, centrofacial (affecting the forehead, cheeks, nose, and chin), malar (affecting the cheek and nose), mandibular (affecting the ramus of the mandible), and extrafacial. Bagherani *et al*. [25] and Tamega *et al*. [26] reported that centrofacial pattern is the most common type of melasma. Centrofacial pattern is the most common type (65%), followed by malar (20%) and mandibular pattern (15%) [25], [27], [28].

In this study, thyroid hormone levels returned to normal 12 weeks after treatment with anti-thyroid drugs. Several studies reported that adequate therapy with anti-thyroid drugs might reverse the thyroid hormone levels in hyperthyroid patients to normal (euthyroid condition) after 3–6 months [29], [30].

Although the thyroid hormones returned to normal, the mMASI scores at baseline and 12th week after therapy with thiamazole produced a mean difference of 0.49 without statistical significance.

In this study, melasma generally did not improve due to several factors. In melasma, there is an increase in melanocyte activities, and this condition is more significant than an increase in the number of melanocytes itself [8], [31]. Increased activities of melanocytes, which could be influenced by thyroid hormone, cause an increase in pro-inflammatory cytokines as a response to melanogenesis. This was demonstrated by higher pro-inflammatory cytokines found in hyperthyroid patients [32]. On the contrary, FT4 and TSH levels that have returned to normal would cause pro-inflammatory cytokines to decline [33], but until now it remains unclear how long the thyroid hormone in melanocytes could affect the age and activities of melanocytes [34].

When Wood's light beam is absorbed by melanin, the area with a high epidermal concentration of melanin will be seen as darker than normal skin [7]. The Wood's lamp is not only beneficial to confirm the diagnosis, but it can also identify the hyperpigmentation as epidermal, dermal, or mixed, and determine the effectiveness of the therapy [5], [35]. In melasma, abnormal pigmentation in the epidermal layer can be treated more easily with tretinoin, hydroquinone, and superficial chemical peeling. However, the dermal pigmentation is more challenging since the abnormalities lie deeper histologically. Therefore, some authors had reported that some patients with mixed type melasma showed improvement and lost the epidermal melanin deposition, and finally categorized as having dermal type melasma after receiving adequate therapy. Considering there was no intervention with topical therapy in this study, all melasma types remained unchanged.

Melasma is treated with depigmenting cream products [5]. The gold standard treatment is a topical triple combination, which was not given to subjects in this study. With the Kligman formula, which is a form of triple combination, the severity of melasma would improve within 8–12 weeks, when the regimen is used regularly with appropriate dosage [19], [36], [37], or in conjunction with other methods such as laser and IPL therapy. In this treatment, response to therapy mainly occurred in the epidermal pigment [5].

Is the mechanism of anti-thyroid therapy in melasma similar to that of topical therapy? A topical therapy would elicit response at epidermal lesion first. In this study, the results of Wood's lamp examination showed significant improvement on malar area after 3 months of hormonal therapy, with statistically significant improvement of mMASI score on the malar area. The malar area consisted of epidermal, dermal, and mixed type melasma. Wood's lamp examination results, with 6 mixed types and 1 epidermal, might explain why the darkness component in malar became more apparent. This might be due to the possibility that hormonal therapy does not reach the epidermal layer. The hormone therapy is thought to reach the dermis first, thus leading a decline of pro-inflammatory cytokines in the dermis. It differs from topical therapies. In our study, the increase of pigmentation in dermis and eventually the overall appearance, might be because

we did not give the subjects any treatment or education (e.g., to use avoid sun exposure and use sunscreen) with tropical country setting.

Nevertheless, it is still unclear why the darkness in the chin also appeared to increase, considering that the chin is not an epidermal component. Further research with a larger sample size and better research methods are certainly required.

To the best of authors' knowledge, this is the first study in Indonesia, which correlates the severity of melasma, and changes in thyroid hormone levels (TSH and FT4).

Study limitation

First, subjects with hyperthyroid disorders in this study were not classified based on their etiology (adenomas, multinodular goiters, subacute thyroiditis, and others) and possible specific causes of melasma were not explored, such as sun exposure and others that might affect or response differently to the outcome. Moreover, to assess the improvement after therapy, this study did not have best study design. Because it is unethical to perform randomized controlled trial, since all hyperthyroid patients should receive drugs, not only placebo. Further research is needed.

Conclusions

Our study demonstrated that mMASI score in malar area improved significantly, in this might be because malar area included this study were comprised of epidermal, dermal, and mixed type. On the other hand, based on Wood's lamp examination, all types of melasma remained unchanged after 12 weeks of treatment.

Data Availability

This published article included all generated and analyzed data.

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