Sapporo Medical Journal
Volume 55, Issue 08, August 2021

Melasma and thyroid dysfunction

Fadhila Dea Safira[1], Arsy Indrafatina[1], Jose Suryanegara[1], Irma Bernadette S. Sitohang[2]

[1]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[2]Division of Cosmetic Dermatology, Department of Dermatology and Venereology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Abstract— Melasma is a pigmentation disorder with a multifactorial etiology. This condition is still a challenge for the field of cosmetic dermatology because it is recalcitrant to therapy and has a high risk of recurrence. Among the various risk factors known to play a role in the development of melasma, thyroid dysfunction is common to be found in this condition. This review attempts to gather evidence to quarry the relationship between melasma and thyroid hormone regulation disorders. The available evidence suggests that melasma can be influenced by inflammatory conditions, increased oxidative stress, and stimulation of Adrenocorticotropic hormone (ACTH) and Melanocyte-stimulating hormone (MSH) via the hypothalamic pituitary thyroid (HPT) axis in hyperthyroid conditions. By further understanding the pathophysiological conditions in this disorder, treatment and prevention of melasma progression can be carried out more effectively.

Keywords: Melasma, Thyroid dysfunction, Hyperthyroid

1. Introduction

1.1 Melasma

Melasma is a chronic and recurrent hyperpigmentation disorder with an increase of melanin amount in the epidermis and dermis due to melanogenesis dysfunction [1,2]. Clinically, the disorder appears in the form of irregular brown to blue-gray macules or patches with symmetrical distribution in sun-exposed areas, such as the face and neck, especially the forehead, cheeks, and chin [3-5]. Melasma can also be found in the extensor area of the arms and chest [6].

Melasma derives from the Greek "*melas"* which means black [6]. Melasma is also known as "chloasma", which comes from the Latin word meaning green, or "mask of pregnancy", which refers to its high prevalence in pregnant women [7,8]. Melasma is recalcitrant to therapy with a high risk of recurrence after discontinuation of therapy [6]. Although melasma is asymptomatic and is classified as a benign disorder, the location of melasma that is often found on the face can cause psychological disorders in patients, such as frustration, low self-esteem, a tendency to withdraw from social interactions, avoidance of outdoor activities associated with sunlight exposure [6,9].

1.2. Epidemiology

Various epidemiological studies have studied the prevalence of melasma, it is estimated that the prevalence of melasma is 1% in the general population and varies from 9-50% in high-risk populations [10]. In general, the prevalence of melasma ranges from 1.5–33.3% depending on the population and geographic location [4]. This large variation is due to differences in skin type, ethnicity, and levels of UV exposure. Melasma can be found in all races, especially in women aged 20-50 years with higher skin pigmentation and those who live in areas with high UV exposure, such as East Asia, Central Asia, Southeast Asia, the Middle East, and Africa-Mediterranean [10,11]. The mean age of onset is 29.91 ±7.28.[12] In 2014, a study of melasma patients characteristics in Asia found the widest age range, which is 21 – 64 years old [13]. Melasma is more common in women than men, with a ratio ranging from 9-10:1, especially with Fitzpatrick IV-VI skin types [1,10]. In about 40-50% of female patients, melasma is precipitated and exacerbated by pregnancy and the

use of oral contraceptives. In female patients on hormone replacement therapy, the incidence of melasma ranges from 8-34% [10]. The major clinical pattern obtained from melasma is 50-80% a centrofacial pattern that affects the forehead, nose, upper lip (except the philtrum), cheeks and chin [10,14].

In a study in Brazil involving 515 employees of the Campus of Botucatu University, melasma was found in 6% of male patients and 34% of female patients [4]. In India, there were 20.5–25.83% cases of melasma in men, while in Puerto Rico there were 10% cases. The prevalence in Latino women was 4%-10% and increased to 50% in pregnant women [13,15]. There is no definite prevalence of melasma in Indonesia. Based on data from the Cosmetic Dermatology Polyclinic, Department of Dermatology and Venerology, Faculty of Medicine Universitas Indonesia/ dr. Cipto Mangunkusumo General Hospital (FKUI/RSCM) in 2019, the incidence of melasma was 3.05%, all of which were female patients [16].

1.3 Risk Factors

Melasma has a multifactorial etiology. Various pathways can induce hyperpigmentation, consisting of the interaction of intrinsic and extrinsic factors [1]. Several factors that play a role in the etiology and pathogenesis of melasma include genetic predisposition, UV radiation, hormones, pregnancy, use of cosmetics or drugs that have photosensitizer properties such as phenytoin, oral contraceptive pill consumption, thyroid disease, skin inflammation processes, and emotional stress [4,11,17]. Genetic predisposition is one of the important etiologies in melasma, although there have been no reports yet of genetic polymorphisms associated with melasma. An epidemiological study found that Latin American and Asian tribes with Fitzpatrick III-V skin type tend to be more prone to pigmentation disorders, including melasma [18]

The influence of female hormones on the occurrence of melasma is proved by the high ratio of the melasma incidence in women compared to men (21:1 in a study in Singapore and 4:1 in a study in India). Melasma was considered as a normal skin change during pregnancy and was a side effect of oral contraceptives [18] The mechanism of female hormones that are responsible for pigmentation is not clearly understood. However, estrogen and progesterone are known to have important functions in human skin.

Melasma is also associated with endocrine diseases such as thyroid disorders. Higher levels of proinflammatory cytokines were found in patients with hyperthyroidism [10,19]. Several studies have found a correlation between melasma and thyroid hormones. Lutfi et al. found that thyroid disorders were found four times more frequently in melasma patients than in healthy controls. A significant difference was also reported by Perez et al. This issue is still controversial. A study by Yazdanfar et al. showed no difference in anti-TPO, T3, T4, and TSH levels between melasma patients and controls. Similar results were also reported by Sacre et al. [20].

1.4 Pathogenesi

The characteristic of melasma is that it has pigmentation in the epidermis and the extracellular matrix of the dermis. Melasma originates from local hyperactivity of epidermal melanin units that causes hypermelanization of this layer [4,12]. UV exposure stimulates melanogenesis directly and indirectly. Directly, UV light causes melanocytes to form 1,2-diacylglycerol (DAGs) and activate protein kinase C-beta (PKC-beta) and nitric oxide (NO), resulting in the synthesis of cyclic guanylate monophosphate (CGMP). Indirectly, UV light causes the induction of melanocyte proliferation and melanogenesis by keratinocytes that secrete stem cell factor (SCF), basic fibroblast growth factor (bFGF), interleukin-1 (IL-1), endothelin-1, NO synthesis and alpha melanocyte-stimulating hormone (α-MSH), Adrenocorticotropic hormone (ACTH), and prostaglandin E2 [18].

The process of melanogenesis after UV light exposure can be stimulated by keratinocytes and fibroblasts. One of the main pathways of UV pigmentation is the secretion of SCF, a ligand for the tyrosine kinase receptor, c-kit, which causes a proliferative effect on melanocytes. A recent study showed an increase of

SCF expression in the dermis and c-kit in the epidermal layer of skin with melasma. This is further supported by the increased mRNA levels of melanogenesis-related genes [10]. Sunlight exposure will induce melanogenic cytokines (SCF and hepatocyte growth factor) from dermal fibroblasts that cause hyperpigmentation of the epidermis. In addition, sunlight causes damage to the basement membrane due to an increase in matrix metalloproteinases (MMP) 2 and 9 which will damage collagen types 4 and 6. Increased vascularity can also occur because sunlight increases the production of c-kit which is a strong melanogenic cytokine and is associated with solar elastosis. Sunlight will also cause an increase in the number of mast cells that produce histamine and stimulate the proliferation and migration of melanocytes with H2 receptors through the activation of protein kinase A.[4] Moderate to severe solar elastosis is experienced by 93% of melasma patients, which is the accumulation of abnormal elastic tissue in the dermis due to prolonged sun exposure (photoaging) [4,11,21]

Another study has found an elevated level of a gene associated with Wnt signaling that has been associated with melanocyte stem cell proliferation. Gene and protein expression studies have shown downregulation of genes related to lipid metabolism in lesional skin that plays a role in impaired barrier function against melasma pathogenesis [10] Increased melanogenesis in melasma is caused by increased vascularity as proved by increased levels of vascular endothelial growth factor (VEGF) [22]. Kang et al. found that melanocyte markers such as tyrosinase (TYR), microphthalmia-associated transcription factor (MITF), silver protein (SILV), and tyrosinase related protein 1 (TYRP1) were upregulated in melasma patients. The most affected biological process in melasma patients is lipid metabolism [23].

Hormonal influences play an important role in the pathogenesis of melasma, as can be seen from the increasing prevalence of melasma in pregnancy, use of oral contraceptives and other hormonal therapies [10]. In pregnancy, especially in the third trimester, women will experience the surge of estrogen and progesterone level that is produced by the placenta, ovaries, and pituitary. These hormones are a stimulus to melanogenesis. The increase in MSH, estrogen, and progesterone will increase the transcription of the tyrosinase and dopachrome tautomerase enzymes which are associated with the formation of pigmentation [24]. Melanocyte stimulating hormone, ACTH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) play a role in increasing the size of melanocytes and the production of the enzyme tyrosinase. Estradiol, estriol and progesterone will increase the proliferation of melanocytes [25-27]. Extra-facial melasma has also been associated with peri-menopausal states. An immunohistochemical study of the epidermal and dermal layers found a significantly increased expression of progesterone receptors in the epidermal layer of the samples [10].

Thyroid hormones are thought to play a role in the pathogenesis of melasma. Although the mechanism is still not clearly understood, melasma is suspected to be associated with hyperthyroidism by several epidemiological studies [28]. The proposed mechanism is that thyroid hormone can trigger an increase in melanocyte activity by causing an increase of proinflammatory cytokines in response to melanogenesis. This was demonstrated by the finding of increased pro-inflammatory cytokines in thyroid patients [28,29].

1.5 Clinical Manifestation

The diagnosis of melasma is based on the clinical findings in the form of light to dark brown macules with irregular edges and symmetrical distribution, especially on the face [4]. A lighter brown color is usually associated with the location of melanin in the epidermis or upper dermis, while a grayish blue color indicates the location of melanin in the deep dermis [1,30]. Differential diagnoses of melasma include lichen planus pigmentosus, discoid lupus erythematosus, phototoxic dermatitis, erythema dyschromium perstans, phytophotodermatitis, pigmented contact dermatitis, drug-induced pigmentation, poikiloderma of Civatte, erythromelanosis follicularis faciei, ochronosis, Hori's nevus, argyria, nevus of Ota, lentigines, ephelides, macular amyloidoses, dan post-inflammatory hyperpigmentation [10].

There are three types of lesion distribution in melasma, consisting of the centrofacial type which is the most common distribution (65%) covering the forehead, nose, both cheeks, upper lip, and chin; malar type (20%)

covering the nose and both cheeks; and mandibular type (15%) covering the area of the mandibular ramus [31]. Mixed-type melasma presents with lesions in the frontal, temporal, parotid, mandibular, zygomatic, mentonian, and upper lip regions. There is also an extra facial type of melasma. Commonly involves the extensor surfaces of the arms, the neckline such as the upper back or dorsal area of the torso, and the sides of the neck. This pattern is found in several populations with special characteristics, thus strengthening the possibility of etiopathological factors [4,8]. Bagherani et al. and Tamega et al. found that centrofacial melasma was the most common pattern in melasma patients [6,32]. This is in accordance with the findings by Sitohang et al. that all samples of hyperthyroid patients who developed melasma had a centrofacial pattern [28]. The following are some examination modalities that are routinely performed to establish the diagnosis and evaluate melasma.

1.5.1 Wood Lamp Examination

UV light or Wood's lamp (320-400 nm) is used to differentiate skin discoloration associated with pigmentation and changes due to other causes, such as collagen deposition, scarring, or vascularization. When UV light is absorbed by melanin, areas that have a high concentration of melanin in the epidermis appear darker than normal skin. Hypomelanotic and amelanotic areas that do not absorb UV light are seen as lighter areas. Wood's lamp examination is useful in determining the location of melanin in the skin by distinguishing pigmentation that occurs in the epidermis and dermis [33]. Sitohang et al. found that melasma in hyperthyroid patients was dominated by the dermal type, followed by the mixed type, and rarely found in the epidermal type [28]. However, Wood's lamp examination is known to be inaccurate in determining the depth of pigment. There is a poor correlation between classification based on Wood's lamp examination and histopathology [17].

1.5.2 Modified Melasma Area and Severity Index (mMASI)

The severity of melasma can be evaluated using the MASI score. The MASI score was assessed based on the area of pigmentation, the degree of pigmentation, and the homogeneity of the melasma lesion. The score is assessed in four areas of the face, which are the forehead (forehead/ (F)) which has a score of 30%, the right malar (right malar region/ (RMR)) which has a score of 30%, and the left malar region (LMR)) which has a score of 30%, and the chin (chin/ (C)) with a score of 10%. Involvement of the area (A) of melasma was scored from 0 to 6 (0= no visible 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%). The degree of pigmentation (P) and homogeneity (H) were scored from 0 to 4 (0=none, 1=minimum, 2=light, 3=moderate, 4=severe). MASI's final score is calculated using the following formula [3]:

$$0.3\ A(F)\ [P(F) + H(F)] + 0.3\ A(RMR)\ [P(RMR) + H(RMR)] + 0.3\ A(LMR)\ [P(LMR) + H(LMR)] + 0.1\ A(C)\ [P\ (C) + H\ (C)].$$

The reliability of the homogeneity component is difficult to maintain, so Pandya et al made some modifications. Eliminating the homogeneity component does not affect the reliability and validity of MASI, so this study produces a modified MASI calculation formula (mMASI) by eliminating the homogeneity component [3]. This study is considered to have an acceptable validity with Spearman correlation between measurement variables ≥ 0,40. These changes proved to be simpler and more reliable for researchers in assessing melasma, both at the beginning of the study or evaluating improvement [34] The mMASI score ranges from 0 to 24 which can then be categorized as mild (0-8), moderate (8-16), and severe (16-24) [35-37].

1.5.3 Dermoscopy Examination

Dermoscopy is a non-invasive diagnostic tool that can show clinical patterns of skin structural abnormalities that are visually invisible to the naked eye. Dermoscopy can assess the depth of melasma, distinguish it from

other pigmentary diseases, assess other complications of the skin, and evaluate the success of treatment in melasma [38,39].

In the epidermal type, regular pigment network, homogeneous dark brown and honeycombs appearance can be found. In the dermal type, irregular pigment network and faded gray or bluish brown were found accompanied by telangiectasia and arciform structures. In the mixed type, a combination of epidermal and dermal types can be found [30,38,39]. Increased vascularity in melasma can also be assessed using dermoscopy which appears as telangiectasia [38].

The clinical picture of melasma can also resemble other pigmentation disorders such as Riehl Melanosis or Pigmented Contact Dermatitis. However, dermoscopy with findings of diffuse erythema, telangiectasia, multiple brown and gray dots/granules, pseudonetwork pigmentation, and a perifollicular white halo can narrow down the diagnosis and exclude melasma.[40]

In recent studies, dermoscopy has also been used to assess therapeutic response in melasma, especially in melasma with vascular involvement. In 1981, Frosch et al. assessing atrophy and telangiectasia due to steroid use using a stereomicroscope. The telangiectasia score was assessed using a 5-point dermoscopy-scale, namely: [41,42]

0 = No visible capillaries.

1 = Elongated capillaries accompanied by dilatation, not visible to the naked eye

2 = Moderate telangiectasia that is visible to the naked eye.

3 = Severe telangiectasia characterized by reduced capillary loops.

4 = Very severe telangiectasia characterized by dilatation and loss of capillary loops.

Frosch et al. stated that telangiectatic lesions were easily discernible with low interobserver variation [41].

1.5.4 Laboratory Examination

Laboratory tests need to be considered to look for risk factors that can cause melasma. Examinations that can be done are complete peripheral blood, liver function, thyroid function, serum iron levels, and examination of hormone levels such as ACTH and cortisol [6].

1.6 Treatment

The target of therapy in melasma is to eliminate and inhibit pigmentation [43,44]. There are various treatment options for melasma, include topical, oral, procedural, and combination therapies, which still offer mixed results to date [10]. Educating patients to avoid risk factors that can trigger and exacerbate melasma and elimination of these factors is the most important aspect of the treatment [6,35]

2. The Association of Melasma and Thyroid Dysfunction

Several hypothetical theories explain how thyroid hormone can affect melasma. Thyroid hormone causes the production of inflammatory cytokines, so patients with hyperthyroidism have higher levels of pro-inflammatory cytokines. Each melanin in the epidermis will respond to certain inflammatory stimuli through melanogenesis. Melanocytes will produce proopiomelanocortin (POMC), cytokines, NO, prostaglandins, and leukotrienes. The proteolytic cleavage of POMCs in the pituitary gland plays a role in the production of α-MSH. The melanocortin1-receptor (MC1-R) will be activated and cAMP synthesis and tyrosinase

production will occur, which will increase the amount of eumelanin and pheomelanin [29].

TSH receptors and thyroid hormone receptors are found in the skin. Thyrotropin releasing hormone (TRH) and TSH exert a regulatory effect on the expression of skin-specific genes and other elements of the hypothalamic pituitary thyroid (HPT) axis transcribed by human skin cells. This indicates that the skin is a source and target of extrathyroidal TRH and TSH. Thyroid dysfunction, such as hyperthyroidism, has skin manifestations, one of which is melasma. Melanocortin is a peptide hormone derived from propiomelanocortin (POMC) in the pituitary gland. Adrenocorticotropic hormone (ACTH) and Melanocyte-stimulating hormone (MSH) can activate melanocortin receptors in melanocytes and induce melanogenesis. Strong immunoreactivity for MSH in the skin with melasma is one of the most important factors in the pathogenesis of the disease [45]. Melanocortin system is also reported to interact with the HPT axis [46].

Thyroid hormones induce the production of inflammatory cytokines. Oxidative stress has been shown to be associated with both hyperthyroidism and hypothyroidism. The mechanisms by which oxidative stress is generated in these two clinical conditions are different. There is an increase in ROS production in hyperthyroidism, whereas antioxidant availability is found to be low in hypothyroidism. Several complications of hyperthyroidism in tissues are caused by oxidative stress. The expression of the nitric oxide synthase (NOS) gene which increases with excess NO production and hepatic activation of NF-kB is the result of increased cytokine levels. All of these things can induce ROS production. Excess TSH levels are also directly related to the process of generating ROS [47]. Rozing et al. found that hyperthyroid patients had a higher level of pro-inflammatory cytokines [29].

The epidermal-melanin unit responds to certain inflammatory stimuli through melanogenesis. Melanocytes produce POMC peptides, cytokines, NO, prostaglandins, and leukotrienes that act via autocrine or paracrine signaling on keratinocytes involved in the inflammatory response. The MCR-1 receptor will be activated so that CAMP can produce tyrosinase. Tyrosinase will ultimately increase the production of eumelanin and pheomelanin. Several studies have shown that other than thyroid hormones, melasma can also be triggered or exacerbated by procedures that induce an inflammatory process [45,48,49].

The study conducted by Dogra et al. 2006 found that 23% of melasma patients had thyroid disease. This study found that hyperthyroid patients experienced higher ACTH secretion to compensate for accelerated corticotropin degradation [50]. Another study found that ACTH and MSH can activate melanocortin receptors in melanocytes that will induce melanogenesis [4,48]. Alpha melanocyte-stimulating hormone is a tridecapeptide with an identical arrangement of the first 13 amino acids in ACTH. Human keratinocytes can synthesize α-MSH and β-MSH. Alpha melanocyte-stimulating hormone is produced in melanocytes and Langerhans cells. This hormone also plays a role in the regulation of melanocyte function. The effect of MSH is also mediated by MC1-R which is expressed on the melanocyte surface as an important factor in pigmentation. The α-MSH signal will pass through MC1-R, activate adenyl cyclase (AC) and increase cAMP intracellularly, resulting in the dark-colored pigment eumelanin. MC1-R activation will affect the quantity of pheomelanin and eumelanin production [48].

3. Melasma and Hyperthyroidism

Perez et al. and Yazdanfar et al. reported no significant correlation between thyroid levels and melisma [51,52]. In a case-control study, Yazdanfar et al. included 45 women with melasma aged 20-50 years and 45 women without a history of melasma as a control group. Serum anti-thyroid peroxidase (anti-TPO) levels were found to be higher than normal in 24.4% of melasma patients and 6.7% of controls. The difference between the two groups was statistically significant ($p = 0.019$, 95% CI). Serum T3 levels were found to be higher than normal in 75.6% of melasma patients and 48.9% of controls. The difference between the two groups was statistically significant ($p = 0.008$). The mean serum anti-TPO, T3, and TSH values were found to be higher in the case group than in the control group, but the difference was not statistically significant.[51] Rahman et al. conducted a cross-sectional study on 48 melasma patients. This study studied the relationship between serum levels of FT4 and TSH with the severity of melasma according to the mMASi score and the

Janus II examination. Statistically, there was no significant relationship between serum TSH and FT4 levels and the severity of melisma [53].

Notwithstanding, correlations between melasma and thyroid hormone have been reported [52,54-57] Lutfi et al. divided 108 non-pregnant women aged 20-56 years old into two groups, 84 subjects had melasma and 24 subjects are the control group. Microsomal thyroid autoantibodies (MCHA) were examined in all subjects. The TRH-TSH test was performed in patients with melasma and female patients with goiter and/or a positive MCHA test from the control group. Serum T4, T3, and AbTG measurements were performed in all patients with thyroid abnormalities. In patients with melasma, the frequency of thyroid disorders (58.3%) was 4 times greater than the control group. MCHA-negative patients had simple goiter (13.1%), Plummer's disease (2.4%), and TSH hyper-response to TRH in non-goitrous patients (10.7%). Patients with a positive MCHA test (32.1%) were divided into 2 groups, consisting of women with abnormal thyroid function and normal thyroid (n = 7), while the others included all patients with goiter and/or subclinical hypothyroidism (n = 20). 70% of women in melasma during pregnancy or while using oral contraception had thyroid disorder while 12,5% of subjects from the control group had thyroid disorder and 8,3% of them were tested MCHA positive [54]

Tamega et al. assessed 302 melasma patients with 34,4% skin type III and 38,4% skin type IV. The mean age of disease onset was 27,5 ± 7,8 years old. The incidence of melasma was 56.3% of study subjects. The most frequently reported trigger factors were pregnancy (36.4%), oral contraceptive (16.2%) and continuous sun exposure (27.2%). The location of melasma in the facial area is zygomaticus (83.8%), labia superior (51.3%), and frontal (49.7%). Pregnancy was associated with the early onset of melasma (OR 0.86). Late onset of the disease is associated with darker skin types. The facial topography supported the clinical classification as centrofacial and peripheral melasma [32].

Çakmak et al. included 45 women with melasma and 45 healthy women within the same age group. The subjects of the study were patients with melasma risk factors. Serum FT3, FT4, TSH, AbTG, and AbTPO were measured. Thyroid ultrasonography was done in all subjects. In 26.7% of patients, 17.8% of them were pregnant and 13.3% use oral contraceptives. Continuous sun exposure is a trigger factor. This study found that 17.8% of patients had a family history of melasma. The levels of FT4, TSH and AbTG were significantly higher in the patient group. The results showed that a combination of factors including pregnancy, oral contraceptive use, sunlight and genetic factors often triggers melasma [12].

Talaee et al. assessed 102 patients with melasma and 55 healthy controls. Patients with melasma are divided into two groups, melasma with known causes and idiopathic melasma. Patient data, such as age, gender, duration of illness, menstrual status, underlying disease, cause of melasma, and severity (mMASI score) were recorded in the questionnaire. Serum T3, T4, TSH, AbTPO and AbTG were measured in all participants using the Immuno-chemiluminescence method. The mean serum T3 and T4 levels were the same in the three groups. The mean serum levels of TSH, AbTPO and AbTG antibodies in patients with melasma were higher than in the control group, but there was no statistically significant difference. The frequency of abnormal TSH levels in patients with idiopathic melasma was significantly higher than in the other two groups (p = 0,012) [58].

Sitohang et al. conducted a comparative analysis of 20 hyperthyroid patients with melasma in RSCM Jakarta who were receiving oral anti-thyroid medication. There was a significant improvement in the mMASI score in patients without any topical treatment for melasma, especially malar areas within 12 weeks of treatment. However, the results of Wood's lamp examination did not show any change in melasma depth.[28] A similar study was also conducted at RSCM Jakarta by Nelson et al. to compare the proportion of melasma cases in patients diagnosed with hyperthyroidism for the first time and to compare the severity of melasma before and after hyperthyroid therapy. This study found that 65% of hyperthyroid patients had melasma, but no significant improvement was found after 3 months of therapy, both based on mMASI assessment and dermoscopy examination [59].

The conversion of T4 to T3 can be affected by various conditions. Therefore, T4 is a better indicator to reflect thyroid hormone production. Physical activity and some supplements (zinc, selenium) can increase the conversion of T4 to T3 [60]. Several studies have also reported an association between low serum zinc levels and various dermatological disorders, including pigmentation disorders such as melisma [61,62]. Sekarnesia et al. conducted a cross-sectional study in 60 melasma patients and 60 non-melasma patients by assessing serum zinc levels and thyroid function by examining TSH and FT4. This study reported that there was no significant difference in serum zinc levels between melasma and non-melasma patients, with or without impaired thyroid function [63].

4. Conclusion

The mechanism of thyroid hormone in affecting melasma is not fully understood yet. The available evidence suggests that melasma in thyroid dysfunction can be influenced by inflammatory conditions, increased oxidative stress, and stimulation of ACTH and MSH through the HPT axis in hyperthyroid conditions. Further research on interventions in this pathophysiological condition is recommended to provide a better understanding of the role of thyroid hormones in the development of melasma and possibly to provide therapeutic options to maximize treatment and prevent progression.

5. References

[1] Grimes PE, Ijaz BA, Nashawati R, Kwak D. New oral and topical approaches for the treatment of melasma. Int. J. Women's Dermatology. 2019;5:30-6

[2] Sadeghpour M, Dover JS, Rohrer TE. Advances in the treatment of melasma an evidence-based approach. Advances in Cosmetic Surgery. 2018;1:163-74

[3] Pandya AG, Hynan LS, Bhore R, Riley FC, Guevara IL, Grimes P, Nordlund JJ, Rendon M, Taylor S, Gottschalk RW, Agim NG, Ortonne JP. Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. J Am Acad Dermatol. 2011 Jan;64(1):78-83, 83.e1-2.

[4] Handel AC, Miot LDB, Miot HA. Melasma: a clinical and epidemiological review. An Bras Dermatol. 2014;89:771–82.

[5] Sarkar R, Arora P, Garg VK, Sonthalia S, Gokhale N. Melasma update. Indian Dermatol Online J. 2014;5:426–35.

[6] Bagherani N, Gianfaldoni S, Smoller B. An overview on melasma. J Pigment Disord. 2015;2(10):2-18

[7] Umborowati MA. Studi retrospektif : Diagnosis dan terapi pasien melasma Retrospective study: Diagnosis and therapy of melasma patients. Berk Ilmu Kesehat Kulit dan Kelamin. 2014;26(1):56–63

[8] Serena NB, Bruce Smoller G. An overview on melasma. J Pigment Disord. 2015;2(10):1–18

[9] Jiang J, Akinseye O, Garza AT, Pandya. The effect of melasma on self-esteem: a pilot study. Int J Womens Dermatol. 2018;4:38-2

[10] Ogbechie-Godec OA, Elbuluk N. Melasma: An up-to-date comprehensive review. Dermatol Ther (Heidelb). 2017;7(3):305-18.

[11] Sheth VM, Pandya AG. Melasma : A comprehensive update. J Am Acad Dermatol. 2012;65:689–97.

[12] Çakmak SK, Özcan N, Kılıç A, Koparal S, Artüz F, Çakmak A, et al. Etiopathogenetic factors, thyroid functions and thyroid autoimmunity in melasma patients. Postep Derm Alergol. 2015;32:327–30.

[13] Noh TK, Choi SJ, Chung BY, Kang JS, Lee JH, Lee, MW, et al. Inflammatory features of melasma lesions in Asian skin. Jpn J Dermatol B. 2014;41:788-94.

[14] Guinot C, Cheffai S, Latreille J, Dhaoui MA, Youssef S, Jaber K, et al. Aggravating factors for melasma : a prospective study in 197 Tunisian patients. JEADV. 2010;24:1060–9.

[15] Park KC, Kim IS. Pathogenesis of melasma. Dalam: Handog EB, Macarayo MJE, penyunting. Melasma and Vitiligo in Brown Skin. New Delhi: Springer; 2017:13-20.

[16] Divisi Dermatologi Kosmetikk IKKK RSCM. Data morbiditas tahun 2019 Divisi Dermatologi Kosmetik Poliklinik Ilmu Kesehatan Kulit dan Kelamin/RS dr.Cipto Mangunkusumo Jakarta. 2019.

[17] Arora P, Garg V, Sonthalia S, Gokhale N, Sarkar R. Melasma update. Indian Dermatol Online J. 2014;5(4):426–35.

[18] Lee AY. Recent progress in melasma pathogenesis. Pigment Cell Melanoma Res. 2015;28(6):648–60.

[19] Lee AY. An updated review of melasma pathogenesis. Dermatol sin. 2014;32:233-9.

[20] Dharmana S. Etiopathogenesis of melasma. J Pigment Disord. 2014;1(6):1–5.

[21] Sarkar R, Bansal S, Garg VK. Chemical peels for melasma in dark-skinned patients. J Cutan Aesthet Surg. 2012;5:247–53.

[22] Kim EH, Kim YC, Lee E, Kang HY. The vascular characteristics of melasma. J Dermatol Sci. 2007;46:111–6.

[23] Kang HY, Suzuki I, Lee DJ, Ha J, Reiniche P, Deret S, et al. Transcriptional profiling shows altered expression of Wnt pathway – and lipid metabolism – related genes as well as melanogenesis-related genes in melasma. J Invest Dermatol. 2011;131:1692–700.

[24] Muller I, Rees A. Melasma and endocrine disorders. J Pigment Disord. 2014;2376–81.

[25] Antonelli A, Ferrari SM, Corrado A, Ferrannini E, Fallahi P. Increase of interferon- c inducible CXCL9 and CXCL11 serum levels in patients with active Graves' disease and modulation by methimazole therapy. Thyroid. 2013;23:1461–9.

[26] Guarneri F. Etiopathogenesis of melasma. J Pigment Disord. 2014;S1:003:1–5.

[27] Anagnostis P, Adamidou F, Polyzos SA, Katergari S, Karathanasi E, Zouli C, et al. Predictors of long-term remission in patients with Graves' disease : a single center experience. Endocrine. 2013;44:448–53.

[28] Sitohang IBS, Nelson B, Marissa M, Indriatmi W, Wisnu W. Evaluation of modified melasma area and severity index in hyperthyroid patients receiving anti-thyroid drugs. Open Access Macedonian Journal of Medical Sciences. 2021;9(B):344-349.

[29] Rozing MP, Westendorp RG, Maier AB, Wijsman CA, Frölich M, de Craen AJ, van Heemst D. Serum triiodothyronine levels and inflammatory cytokine production capacity. Age (Dordr). 2012 Feb;34(1):195-201

[30] Damevska K. New aspects of melasma. Serb J Dermatol Venerol. 2014;6(1):5-18.

[31] Suryaningsih BE. Characteristics of facial melasma on Javanese women in Yogyakarta, Indonesia. J Pak Assoc Dermatol. 2018;28(3):306-10.

[32] Tamega ADA, Miot LDB, Bonfietti C, Gige TC, Marques MEA, Miot HA. Clinical patterns and epidemiological characteristics of facial melasma in Brazilian women. J Eur Acad Dermatology Venereol. 2013;27(2):151–6.

[33] Pandya A, Berneburg M, Ortonne JP, Picardo M. Guidelines for clinical trials in melasma. Br J Dermatol. 2007;156(1):21-8.

[34] Rodrigues M, Ayala-Cortés AS, Rodríguez-Arámbula A, Hynan LS, Pandya AG. Interpretability of the modified melasma area and severity index (mMMASI). Vol. 152, JAMA Dermatology. 2016. p. 1051–2.

[35] Rodrigues M, Pandya AG. Melasma: clinical diagnosis and management options. Australas J Dermatol. 2015 Aug;56(3):151-63.

[36] Morgaonkar M, Gupta S, Vijay A, Jain SK, Sharma M, Agarwal S. Melasma: its impact on quality of life. Pigment Int. 2017;4(1):39-44.

[37] Taleb ADAE, Ibrahim AK, Youssef EMK, Moubasher AEA. Reliability, validity, and sensitivity change overtime of the modified melasma area and severity index score. Dermatol Surg. 2017;43:210-7.

[38] Sonthalia S, Jha AK, Langar S. Dermoscopy of melasma. Indian Dermatol Online J. 2017;8:525-6.

[39] Gupta T, Sarkar R. Dermoscopy in melasma − Is it useful? Pigment Int. 2017;4:63.

[40] Sitohang IBS, Prayogo RL, Rihatmadja R, Sirait SP. The diagnostic conundrum of Riehl melanosis and other facial pigmentary disorders: a case report with overlapping clinical, dermoscopic, and histopathological features. Acta Dermatovenerol Alp Pannonica Adriat. 2020 Jun;29(2):81-83

[41] Hong E, Smith S, Fischer G. Evaluation of the atrophogenic potential of topical corticosteroid in pediatric dermatology patients. Pediatr Dermatol. 2011;28(4):393-6

[42] Frosch PJ, Behrenbeck AM, Frosch K, Macher E. The Duhring chamber assay for corticosterois atrophy. Br J Dermatol. 1981;104:57-65.

[43] Spierings NMK. Melasma: A critical analysis of clinical trials investigating treatment modalities published in the past 10 years. J Cosmet Dermatol. 2019:1-6.

[44] Sarma N, Chakraborty S, Poojary SA, Rathi S, Kumaran S, Nirmal B, Felicita J, et al. Evidence-based review, grade of recommendation, and suggested treatment recommendations for melasma. Indian Dermatol Online J. 2017;8:406-42.

[45] Videira IF, Moura DF, Magina S. Mechanisms regulating melanogenesis. An Bras Dermatol. 2013 Jan-Feb;88(1):76-83.

[46] Martin NM, Smith KL, Bloom SR, Small CJ. Interactions between the melanocortin system and the hypothalamo-pituitary-thyroid axis. Peptides. 2006 Feb;27(2):333-9

[47] Mancini A, Di Segni C, Raimondo S, Olivieri G, Silvestrini A, Meucci E, Currò D. Thyroid Hormones, Oxidative Stress, and Inflammation. Mediators Inflamm. 2016;2016:6757154.

[48] Miot LDB, Miot HA, Silva MG Da, Marques MEA. Physiopathology of melasma. An Bras Dermatol. 2009;84(6):623–35.

[49] Zarković M. The role of oxidative stress on the pathogenesis of graves' disease. J Thyroid Res. 2012;2012:302537.

[50] Dogra A, Dua A, Singh P. Thyroid and skin. Indian J Dermatol. 2006;51:96–9.

[51] Perez M, Hez JLS, Aguilo F. Endocrinologic profile of patients with idiopathic melasma. J Invest Dermatol. 1983;81:543–5.

[52] Yazdanfar A, Hashemi B. Association of melasma with thyroid autoimmunity: a case-control study. Iran J Dermatology. 2010;13(2):51–3.

[53] Rahman Y, Krisanti RIA, Wisnu W, Sitohang IBS. The comparison between free thyroxine and thyroid-stimulating hormone levels on melasma severity: a cross:sectional study. Open Access Maced J Med Sci. 2021;9(B):426-31

[54] Lutfi RJ, Fridmanis M, Misiunas AL, Pafume O, Gonzales EA, Villemur JA, et al. Associaton of melasma with thyroid autoimmunity and other thyroidal abnormalities and their relationship to the origin of the melasma. J Clin Endocrinol Metab. 1985;61:28–31.

[55] Krishna AV, Prasad KN, Reddy DS, Sridevi M. A clinical study of cutaneous manifestations in patients withy thyroid disorders. J Evol Med Dent Sci. 2016;5:5489–500.

[56] Sindhu JB, Reddy KR, Netha GNR, Vani DS. Study of cutaneous manifestations in thyroid disorders. J Evol Med Dent Sci. 2016;5:7673–9.

[57] Al-Shamma YMH, Al-Wakeel HAH. The prevalence of thyroid disorders in patients with melasma. Al-Qadisiyah Med J. 2016;12:107–11.

[58] Talaee R, Ghafarpasand I, Masror H. The relationship between melasma and disturbances in the serum level of thyroid hormones and indices. Med J 2015; 2: 19-23.

[59] Nelson B, Sitohang IBS, Marissa M, Indriatmi W, Wisnu W. A comparative study of melasma severity after hyperthyroid therapy in hyperthyroid subjects with melasma. Acta Dermatovenerol Alp Pannonica Adriat. 2021 Mar;30(1):31-34

[60] Abdalla S, Bianco A. Defending plasma T3 is a biological priority. Clin Endocrinol. 2014;81(5):633–41.

[61] Rostami Mogaddam M, Safavi Ardabili N, Iranparvar Alamdari M, Maleki N, Aghabalaei Danesh M. Evaluation of the serum zinc level in adult patients with melasma: is there a relationship with serum zinc deficiency and melasma? J Cos- met Dermatol. 2018;17:417–22.

[62] Gupta M, Mahajan VK, Mehta KS, Chauhan PS. Zinc therapy in dermatology: a review. Dermatol Res Pract. 2014;2014:1–11

[63] Sekarnesia SI, Sitohang IBS, Agustin T, Wisnu W, Hoemardani ASD. A comparison of serum zinc levels in melasma and non-melasma patients: a preliminary study of thyroid dysfunction. Acta Dermatovenerol Alp Pannonica Adriat. 2020 Jun;29(2):59-62