ORIGINAL ARTICLE

Relationship between brain-derived neurotrophic factor serum levels with the severity of melasma

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ABSTRACT

Aim To determine the relationship between brain-derived neurotrophic factor (BDNF) levels and the severity of melasma.

Methods This cross-sectional analytic study included consecutive patients from the Dermatology and Venereology Polyclinic at Prof. dr. Chairuddin Panusunan Lubis Universitas Sumatera Utara (Prof. dr. CPL USU) Hospital Medan from May to December 2022. Serum BDNF levels and the severity of melasma were analysed using the Kruskal-Wallis test.

Results Of the total of 30 patients enrolled in the study, the majority were in the age group of 36–45 (average of 44) years and work as housewives. The highest risk factor was sun exposure. The melasma pattern was dominated by centrofacial patterns, majority of melasma types were epidermal, and the most severe degree was moderate. A moderate negative correlation between BDNF levels and the duration of melasma was found (p=0.007; r= -0.485). There was no significant relationship between BDNF levels and the severity of melasma (p=0.387).

Conclusion No significant relationship between BDNF levels and the severity of melasma indicates that the causes of melasma are multifactorial, such as sun exposure, genetic, hormonal, and other factors (drugs, neural and psychological, and lipid metabolism).

Key words: melanosis, brain-derived neurotrophic factor, nerve growth factor

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INTRODUCTION

Melasma is one of the most common pigmentation problems that can affect people of any race, but it mostly affects people with Fitzpatrick IV-VI skin type who live in areas with high levels of ultraviolet (UV) radiation (1,2). Melasma is more common in middle-aged women. Latin women have prevalence of 4-10%, which increases to 50% in pregnant women, and Southeast Asian women have prevalence of 40% (3,4). In Indonesia, the prevalence of melasma is estimated at around 0.25-4% of all cases of skin disease (5).

Melasma usually appears as areas of light brown to dark brown pigmentation that spread over the midface (1,6). Various scoring systems can be used to evaluate the severity of melasma lesions. The Melasma Area and Severity Index (MASI) score is the most popular and the earliest-used score (5).

The pathogenesis of melasma is not fully understood. Melanocytes are biologically active, genetic and hormonal influences and exposure to UV light are known to be important in the pathogenesis of melasma (1). UVB exposure can stimulate keratinocytes to increase melanocytes and secrete various growth factors (GFs), cytokines, and hormones to produce melanin (5). In addition, stress has also been implicated in exacerbating the condition of this pigmentation disorder (1,7).

It has been reported that some patients develop lesions or worsen melasma lesions after experiencing stress which causes anxiety and depression (7). Stress and depression increase cortisol levels and pro-opiomelanocortin, such as melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH), with melanogenic potential (7).

Several studies have also implicated low levels of brain-derived neurotrophic factor (BDNF) in depression (8,9). The link between BDNF and depression is inseparable from the hypothalamic-pituitary-adrenal (HPA) axis (10). In addition, there is also a possible relationship between BDNF and melanocytes in humans. The tyrosine kinase B receptor (TrkB) is a high-affinity receptor for BDNF, and BDNF also interacts with the low-affinity p75 kDa NT receptor (p75NTR) (11). Human basal keratinocytes secrete the biologically active BDNF. BDNF exhibits its effects by stimulating keratinocyte apoptosis through p75NTR (12,13). Normal human melanocytes also express p75NTR and its level of expression is regulated by various stimuli including UV light (11).

It is suspected that BDNF may be involved in the pathogenesis of several skin disorders exacerbated by stress, such as psoriasis and vitiligo (11-13), but their relationship with melasma has not been studied. Melasma is thought to have a relationship with BDNF levels, where BDNF is one of the factors involved in the process of melanogenesis and BDNF plays a role in the pathogenesis of depression, where depression also plays a role in the pathogenesis of melasma (1,14).

The aim of this study was to investigate a correlation between BDNF serum levels and the severity of melasma.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study included all consecutive patients from the Dermatology and Venereology Polyclinic of Prof. dr. Chairuddin Panusunan Lubis University of North Sumatra (Prof dr. CPL USU) Hospital Medan from May to December 2022. The inclusion criteria were patients diagnosed with melasma aged ≥ 18 years and those who agreed to participate in the study by filling out and signing a research informed consent form. Breastfeeding and pregnant patients and patients taking drugs such as statins, antidepressants, corticosteroids, hormonal therapy, psychotropic drugs, and beta-blocking agents during the last 6 months were excluded from this study.

Selected patients underwent anamnesis, physical examination, examination of the severity of melasma, and blood sampling.

This research was conducted after obtaining an approval from the Ethics Committee of the Faculty of Medicine, University of North Sumatra, North Sumatra, Indonesia with the registration number 586/KEPK/USU/2022.

Methods

The severity of melasma was determined based on the melasma area and severity index (MASI) score, where the degree was mild (score 0–16.9), moderate (score 17–32.9), and severe (score 33–48).

Blood sampling was carried out by the Integrated Laboratory of the Faculty of Medicine, Uni-

versity of North Sumatra, Medan. BDNF levels were measured using the enzyme-linked immunosorbent assay (ELISA) method to obtain the concentration of serum in pg/mL units.

Statistical analysis

Univariate analysis was conducted to analyse characteristics of a variable by descriptive test. Bivariate analysis was conducted to analyse the relationship between research variables: to determine the relationship between serum BDNF levels and the severity of melasma by the Kruskal-Wallis test. A $p< 0.05$ was considered statistically significant.

RESULTS

This study consisted of 30 female melasma patients, with the majority age group of 36–45 years, 14 (46.7%), with the average age of 46.20 years; they were mostly housewives, 18 (60%) (Table 1).

Table 1. Characteristics of 30 female melasma patients

Characteristics	No (%) of patients
Age (years)	
18–25	0
26–35	2 (6.7)
36–45	14 (46.7)
46–55	9 (30)
56–65	5 (16.6)
> 65	0
Mean age (SD)	46.20 (9.45)
Occupation	
Housewives	18 (60)
Saleswoman	6 (20)
Retired	3 (10)
Cleaning Service	3 (10)

SD, standard of deviation

Table 2. Characteristics of 30 melasma patients

Variable	No (%) of patients
Risk Factor	
Contraception	5 (16.7)
Cosmetics	4 (13.3)
Sun radiation	13 (43.3)
Sun radiation and contraception	3 (10)
Sun radiation and cosmetics	3 (10)
Unknown	2 (6.7)
Melasma pattern	
Centrofasial	26 (86.7)
Malar	4 (13.3)
Mandibular	0
Melasma type	
Epidermal	22 (73.3)
Dermal	3 (10)
Mix	5 (16.7)
Severity of melasma	
Mild	13 (43.3)
Moderate	14 (46.7)
Severe	3 (10)

The most frequent risk factor was sun exposure, 13 (43.3%). Centrofacial pattern was dominated, 26 (86.7%); the majority of melasma types were epidermal, 22 (73.3%), and the most severe degree was moderate, 14 (46.7%) (Table 2).

There was a moderate negative correlation between BDNF levels and the duration of melasma ($p=0.007$; $r= -0.485$).

There was no significant relationship between BDNF levels and the severity of melasma ($p=0.387$) (Table 3).

Table 3. Relationship between brain-derived neurotropic factor (BDNF) serum levels with the severity of melasma

Severity of melasma	No (%) of patients	Median BDNF level (Min-Max) (pg/mL)	p
Mild	13 (43.3)	4.09 (1.88-99)	0.387
Moderate	14 (46,7)	3.26 (2,35-6.92)	
Severe	3 (10)	3.6 (2.8-4.17)	

DISCUSSION

Melasma is known as the most common pigmentation disorder in women. This disease is mainly found in premenopausal women (1). In this study it was found that the mean age of the women was 46.20 years with the most common age group being 36–45 years (46.7%). This is in accordance with research conducted by Zulfa et al. (15) in Medan who reported that the majority of female melasma patients were in the age range of 36–45 years (46%). This was also in line with research conducted by Pramedisca (16) in Jakarta. Although melasma is not an age-related disease, it is known to develop more frequently with age (17).

Occupation that is thought to play a role in causing melasma is work done outside the home or building that allows a person to be exposed to excessive sunlight (18). In this study, most women worked as housewives. This is in accordance with research conducted by Fajriah (19) in Jakarta. This is also in line with other authors (16,18, 20-22)

UV-induced hyperpigmentation soon resolves spontaneously. This is not the case with melasma. The main and important pathway in melanogenesis, cAMP activates protein kinase A (PKA), then it stimulates cAMP-response element binding protein (CREB), which is a transcription factor and increases the expression of microphthalmia-associated transcription factor (MITF) regulation. MITF and tyrosinase bonds increase melanin synthesis (21).

Based on the pattern of melasma, most of the patients in this study showed a centrofacial pattern, while the mandibular pattern was not found in this study. This result is also in line with a study conducted by Rambe et al. (18) in Medan, and no mandibular pattern was found. A similar finding was also found in the results of other studies (23).

In contrast to the study conducted by Salim et al. (24) in Padang showing mostly the melasma malar pattern (48.4%). Malar and mandibular region, forehead, chin, and upper lip were most frequently affected by melasma, with the most common patterns being centrofacial (63%), malar (21%), and mandibular (16%). Melasma does not involve the periorbital skin area as well as the lips, neck, and ears (1).

Based on the type of melasma, most women showed epidermal type followed by mixed type and dermal type. This is in line with other authors (23,25).

In this study, moderate degree of melasma was mostly found, followed by mild and severe degrees. This is consistent with research conducted by other authors (18,26).

A significant relationship was found between BDNF levels and the duration of melasma negative correlation between BDNF levels and the duration of melasma. The negative correlation indicates that the lower the BDNF level, the longer the duration of suffering from melasma. The level of correlation strength obtained was moderate.

The highest levels of BDNF were shown in patients with mild degrees of melasma without significant relationship between BDNF levels and the severity of melasma.

This study is the first study to link BDNF levels with melasma. Botchkarev et al. previously described the molecular mechanisms of normal skin and hair loss due to stress, psoriasis, and atopic dermatitis (11). In the skin, BDNF is produced by fibroblasts and T lymphocytes, while BDNF is expressed in skin nerve fibres and arrector pili muscle myocytes (27). Neurotrophins appear to play an important role in the development and maintenance of cutaneous innervation (11). There is also evidence of non-neurotropic functions of neurotrophins in the skin, including regulation of epidermal proliferation and apoptosis, control of hair follicle development and cycles, and melanogenesis (11).

BDNF shows its effect by stimulating keratinocyte apoptosis through p75NTR (13-15). Normal human melanocytes also express p75NTR and its expression level is regulated by various stimuli including UV light, so BDNF is thought to influence the process of melanogenesis in melasma (11).

One of the weaknesses of this study is the small number of patients (only three patients with a severe degree found).

There is no significant relationship between BDNF levels and the severity of melasma indicating that the causes of melasma are multifactorial, such as sun exposure, genetic, hormonal, and other factors (drugs, neural and psychological, and lipid metabolism). In future studies, it is recommended to pay attention to other extrinsic factors.

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TRANSPARENCY DECLARATION

Competing interests: none to declare.

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