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Evaluation of GPER1 Level in Patients with Melasma

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Abstract

Objective: Melasma, which is especially characterized by hyperpigmented patches on the face, has been associated with sun exposure, dark skin, genetic predisposition and sex hormones. GPER 1 is a transmembrane estrogen receptor and its importance in many diseases has been investigated in recent years.

Materials and Methods: Forty patients with melasma and 40 healthy controls were included in the study. All participants' age, gender, BMI, Fitzpatrick skin type, drug history, previous melasma treatment, smoking, MASI, presence of additional disease, number of pregnancies were recorded. GPER 1 serum levels were measured by the sandwich ELISA method using a commercial kit (MBS1603528, MyBioSource, Southern California, San Diego, USA).

Results: There was no difference in gender between the groups. Patients had higher BMI and darker skin type. The mean number of pregnancies in the patient group was higher. Hormone levels did not differ between groups. The GPER 1 level was significantly lower in the group with melasma.

Conclusion: The significantly lower serum GPER 1 level in the patient group was associated with the fact that GPER 1 was synthesized by many tissues and organs and was not evaluated at the tissue level. While serum GPER 1 level was not associated with smoking, gender and hormone levels, it was negatively correlated with BMI, age, number of pregnancies and MASI.

Keywords: Age, body mass index, GPER 1, melasma, melasma surface severity index, skin type.

Introduction

Melasma is a chronic acquired hyperpigmentation characterized by symmetrically distributed irregular brown macules in sun-exposed areas, especially on the face (1). Sex hormones such as estrogen and progestin are associated with the emergence of melasma. Pregnancy, combined oral contraceptive and hormone replacement therapy are the most common triggering factors that are held responsible for melasma to occur (2).

Estrogen is an important hormone that regulates many biological processes in human physiology. It is an important target in many diseases such as cancer, skeletal system diseases, neurological and immunological conditions (3). Estrogen shows its effects on the cell through two different classes of receptors. In the first class there are estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) both known as nuclear receptors. In the second class, there is membrane-bound Estrogen Receptor 1 (GPER 1), which was defined in the 1990s (4).

GPER 1, also known as G-Protein Coupled Receptor 30 (GPR 30), is a transmembrane receptor that promotes the specific binding of G-Protein Coupled endogenous and exogenous estrogens. GPER 1 has been associated with physiological and pathological events regulated by estrogen action, including the central nervous, immune, renal, reproductive, and cardiovascular systems (5). Estrogen receptors are found in the female reproductive tract and breast tissues as expected, as well as in various tissues such as bone, brain, liver, colon, salivary gland and skin (6). It has been reported that GPER 1 is highly expressed in melanocytes and triggers melanin synthesis (7).

In this study, it was aimed to investigate the GPER 1 receptor serum level in patients with melasma and healthy controls and to reveal its relationship with the disease.

Materials and Methods

The local ethics committee approval was obtained prior to the study (Date: 04.07.2018 Session: 2018/11 Decision no: 18). 40 patients between the ages of 18-50 who were diagnosed with melasma after dermatological examination in the Department of Dermatology, Faculty of Medicine, Kahramanmaras SutcuImam University and 40 healthy controls were included in the study. The subjects who participated in the study were informed about the study and the informed consent form was filled in. Pregnant or postmenopausal women, those with irregular menstrual cycles, those receiving hormone replacement therapy (e.g. oral contraceptives), those with endocrine disorders (diabetes mellitus, impaired thyroid functions), and those with known systemic and other dermatological diseases were not included in the study and control groups. It was preferred that the women included in the study were not in the menstrual period. The questionnaire form created by the researchers was filled out for each participant. All participants' name, surname, age, gender, height, weight, occupation, Fitzpatrick skin type, drug history, duration of illness, previous melasma treatment, smoking, melasma surface severity index, presence of additional disease, number of pregnancies resulted in birth or pregnancies that didn't result in birth were recorded. Body mass index (BMI) was calculated by dividing the weight of the patients in kilograms by the square of their height in meters. According to BMI, those below 18.5 kg/m^2 are grouped as underweight, those between 18.5-24.9 kg/m^2 are normal, those between 25-29.9 kg/m^2 are overweight, those between 30-34.9 kg/m^2 are first degree obese, 35-Those between 39.9 kg/m^2 are 2nd degree obese, and those over 40 kg/m^2 are grouped as morbidly obese.

Morning blood samples were taken from the participants after 8-12 hours of fasting. Estrogen, prolactin, progesterone and TSH levels were studied in Chemwell fully automated micro-ELIZA device using commercial kits. For the GPER 1 analysis, fasting venous blood samples (10 mL) from each participant were drawn into anticoagulant-free tubes. Blood samples were centrifuged in a centrifuge device (Hettich MICRO 220 R; Andreas Hettich GmbH and Co. KG, Tuttlingen, Germany) at 3000g for 10 minutes at 4 ° C. Serum samples were stored in eppendorf tubes at -80°C until the analysis day. GPER 1 serum levels were measured by the sandwich ELISA method using a commercial kit (MBS1603528, MyBioSource, Southern California, San Diego, USA) according to the manufacturer's instructions.

Results

Demographic data of the participants are given in Table 1 and laboratory values are given in Table 2. The relationship between GPER 1 value and BMI, number of pregnancies, age, MASI and Fitzpatrick skin type is given in Table 3, and the relationship between GPER 1 value and laboratory parameters is given in Table 4.

Table 1. Demographic data of the participants

	Melasma group (n = 40)	Control group (n = 40)	P
Gender% (n) **Female** **Male**	 97,5 (39) 2,5 (1)	 82,5(33) 17,5 (7)	0,057*
Average age (years)	33,18±7,33	27,1±8,42	0,001**
Average BMI ratio	26,26±5,07	22,03±3,52	0,000**
Fitzpatrick skin type% (n)	17,5 (7) Type 2 52,5 (21) Type 3 30 (12) Type 4	47,5 (19) Type 2 50 (20) Type 3 2,5(1) Type 4	0,001*
Smoking% (n)	12,5(5)	15(6)	0,745*
Average number of pregnancies (n)	2,78 ±1,76	0,75 ±1,85	0,000**
* Chi squared test was performed. ** Student's T test was performed.			

Table 2. Laboratory parameters of the participants

	Melasma group (n = 40)	Control group (n = 40)	P
GPER 1 (ng/ml)	8,76 ± 2,5	12,67 ± 2,27	0,000*
Estrogen (pg / ml)	91,89 ± 74,63	98,97 ± 77,48	0,678*
Progesterone (ng / ml)	3,38 ± 5,04	3,08 ± 4,62	0,781*
Prolactin (ng / ml)	11,54 ± 9,77	12,32 ± 10,2	0,777*
TSH(mIU/L)	2,24 ± 1,66	1,98 ± 1,27	0,442*
*Student's T test was performed.			

Table 3. The relationship between GPER 1 value and BMI, number of pregnancies, age, MASI and Fitzpatrick skin type

	BMI	Number of pregnancies	Age	MASI	Skin Type
GPER 1	p*= 0,018 r= -0,265	p*= 0,006 r= -0,305	p*= 0,018 r= -0,265	p*= 0,000 r= -0,635	p*= 0,058 r= -0,213
* Pearson correlation analysis was performed. BMI: Body mass index MASİ:Melasma Area and Severity Index					

Table 4. Relationship between GPER 1 value and laboratory parameters

	Estrogen	**Progesterone**	**Prolactin**
GPER 1	p*= 0,198 r= +0,146	p*= 0,349 r= +0,106	p*= 0,892 r= -0,015
* Pearson correlation analysis was performed.			

Discussion

Melasma, which is the most common cause of facial hyperpigmentation, often affects women, but can rarely be seen in men. Only 10% of the reported cases are men (8). Therefore, the majority of the cases in this study were women. When the study and control groups were compared in terms of gender, they were similar. Melasma is common, especially in the third and fourth decades (9). In this study, the mean age of the group with melasma was 33, in line with the literature.

Free androgens are converted into free estrogens in the skin and adipose tissue. The location of adipose cells affects their activities. Women with central obesity have more androgens. A study in postmenopausal women showed that enough estrogen can be provided from circulating androgens to cause bleeding (10). In this study, the mean BMI of the melasma group was significantly higher than the healthy group. High BMI of women with melasma may be related to the high number of pregnancies and the weight gained during pregnancy.

It has been reported that melasma does not occur in people with skin type 1, and it is more common in individuals with dark skin and skin type IV-VI (9). In this study, there was no case with skin type 1 among the individuals included in the patient and control groups, and it was found that the patients with melasma had a statistically significantly darker skin type than the control group.

It is known that smoking causes aging of the skin, an increase in skin lines and mucosal pigmentation (11). It has been shown that smoking increases cornification in the skin, suppresses inflammation and causes vasoconstriction (12). However, no study investigating the relationship between smoking and melasma has been found in the literature review. In this study, there was no significant difference between the groups in terms of smoking. Pregnancy, menstruation process and the use of birth control pills trigger melasma formation. In this study, the mean number of pregnancies in the patient group was statistically significantly higher than the control group. Those with irregular menstrual cycles and those using birth control pills were not included in the study.

Melasma occurs due to the sensitivity of melanocytes to UV as a result of hormonal interactions (13). Estrogen levels were found to be high in patients with melasma in some studies, and normal or low in some others. As a result, it has been accepted that the effect of estrogen in melasma varies at the receptor level (14-16). In individuals with melasma; It has been reported that ACTH, prolactin and MSH functions may also be impaired (17). In a study conducted on patients with melasma, no difference was found in progesterone and prolactin levels (14). Similar to the literature, in this study, estrogen, progesterone, prolactin and TSH values did not make a significant difference between the groups.

The expression of estrogen receptors varies depending on the location and tissue type. Facial skin has been shown to express higher concentrations of estrogen receptors than skin of breast or thigh (18). It has been reported that the expression of GPER 1 and TYR in skin with cloasma is increased compared to normal skin (7). In this study, the mean GPER 1 value of the patient group was statistically significantly lower than healthy controls. This situation may be associated with the evaluation of GPER 1 levels in serum.

We think that the detection of GPER 1 at the tissue level will be more useful in revealing the relationship between the GPER 1 receptor and the disease as GPER 1 is produced by many tissues.

The relationship between the various factors in our study and the GPER1 receptor, whose importance has been studied and whose importance has been tried to be understood, was investigated. When the relationship between GPER1 level and smoking status was examined, no significant relationship was found. There is no study examining the relationship between smoking and GPER1 in the literature.

Recently, the synthesis of GPER 1 from neural, endocrine, cardiovascular, kidney, liver, colon, skin, brain, salivary gland and adipose tissue, especially reproductive tissues, has been detected (19). In this study, when the relationship between GPER 1 and gender was examined, no significant relationship was found. There were conflicting results in the literature regarding this situation. While GPER 1 was higher in female mice in a study conducted in mice, GPER 1 levels were found similar in another study (20,21). In a study conducted in humans, no significant relationship was found between GPER 1 levels and gender (22). In a study, it has been shown that GPER 1 has a protective effect against obesity (23). In support of the literature, there was a significant negative relationship between GPER 1 and BMI in this study.

It is known that the density of receptors in a tissue can vary depending on the level of hormones. There may be a decrease in the number of receptors in response to an increase in hormone levels. It can happen the other way around (24). In this study, when the relationship between GPER 1 and estrogen and other hormones was examined, no significant relationship was found. This was related to the fact that GPER 1 is not the only estrogen receptor and that the detected estrogen is not the free estrogen fraction but the total estrogen level. In studies examining the relationship between GPER 1 and estrogen, the results did not support each other (22,25,26). There is no study investigating the relationship between GPER 1 and progesterone and prolactin in the literature.

In this study, there was a statistically negative significant relationship between GPER 1 and age and number of pregnancies. It is known that GPER 1 is especially synthesized from reproductive tissues and these tissues regress with increasing age (27). Similarly, low GPER 1 levels in those with a high number of pregnancies may be associated with increasing age.

GPER 1 is a membrane receptor that enables the synthesis of estrogen-dependent melanin. In a study, 95% pure GPER 1 was applied topically to the ears of mice for three weeks, and significant hyperpigmentation was observed in the ear skin (28). In another study, it was reported that GPER 1 and TYR expression was higher in skin with chloasma compared to normal skin (7). In this study, there was a negative relationship between GPER 1 and MASI. This surprising result between GPER 1 level and melasma severity can be associated with the fact that GPER 1 is not synthesized only from the skin and the GPER 1 level in the skin has not been evaluated.

In conclusion, melasma, whose etiopathogenesis is still under investigation, was common in female and dark-skinned people in this study. BMI and number of pregnancies of the patient group were higher than the control group. Hormone levels did not differ between groups. Significantly lower serum GPER 1 level in the patient group was associated with the fact that GPER 1 was synthesized by many tissues and organs and it was not evaluated at the tissue level. Also the blood samples were not taken during the menstrual cycle, pregnancy and the use of hormone-containing drugs, when hormones were active and melasma developed. While GPER 1 level was not associated with smoking, gender and hormone levels, it was negatively correlated with BMI, age, number of pregnancies and MASI.

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