# Oxidative Stress in Patients With Melasma: An Evaluation of the Correlation of the Thiol/Disulfide Homeostasis Parameters and Modified MASI Score

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## PRACTICE **POINTS**

- Melasma is a common pigmentation disorder that causes brown or grayish patches on the skin.
- Disulfide/native thiol and disulfide/total thiol ratios were higher in patients with melasma compared with controls, which indicated the presence of oxidative stress in melasma.
- The evaluation of modified melasma area and severity index score with disulfide/native thiol and disulfide/total thiol values suggests that oxidative stress is correlated with melasma disease severity.

Melasma is a common acquired hyperpigmentation disorder that affects mostly women and individuals with darker skin types. Oxidative stress may play a role in the pathogenesis of melasma. Dynamic thiol/disulfide homeostasis is one of the most important indicators of oxidative stress. This study aimed to investigate the presence of oxidative stress in patients with melasma by evaluating thiol/disulfide homeostasis. Sixty-seven patients with melasma and 41 healthy age- and sex-matched controls were included in the study. Disease severity was evaluated using the modified melasma area and severity index (mMASI). Thiol/disulfide homeostasis parameters of the melasma and control groups were measured using a novel, fully automated spectrophotometric method. Our data indicated the presence of oxidative stress in melasma, which may be correlated with disease severity. Because research on the presence of oxidative stress in melasma is limited, further studies are needed to support these conclusions.

Melasma is an acquired hyperpigmentation disorder characterized by irregular brown macules and patches that usually appear on sun-exposed areas of the skin. The term *melasma* originates from the Greek word *melas* meaning black.[1] Facial melasma is divided into 2 groups according to its clinical distribution: centrofacial lesions are located in the center of the face (eg, the glabellar, frontal, nasal, zygomatic, upper lip, chin areas), and peripheral lesions manifest on the frontotemporal, preauricular, and mandibular regions.[1,2] There is debate on the categorization of zygomatic (or malar) melasma; some researchers argue it should be categorized independent of other areas, while others include malar melasma in the centrofacial group because of its frequent association with the centrofacial type, especially with glabellar lesions.[2] Mandibular melasma is rare and occurs mostly in postmenopausal women after intense sun exposure.[1,2] Although the etiopathogenesis of the disease is not clearly known, increased melanogenesis, extracellular matrix alterations, inflammation, and angiogenesis are assumed

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The eTables are available in the Appendix online at www.mdedge.com/dermatology.

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to play a role.[3] Various risk factors such as genetic predisposition, UV radiation (UVR) exposure, pregnancy, thyroid dysfunction, and exogenous hormones (eg, oral contraceptives, hormone replacement therapy) have been identified; phototoxic drugs, anticonvulsants, and some cosmetics also have been implicated.[4,5] Exposure to UVR is thought to be the main triggering environmental factor by inducing both melanin production and oxidative stress.[5] However, it also has been shown that visible light can induce hyperpigmentation in darker skin types.[6]

The presence of oxidative stress in melasma recently has become an intriguing topic of interest. First, the presence of oxidative stress in the etiopathogenesis of melasma was thought to be based on the effectiveness of antioxidants in treatment. A few studies also have confirmed the presence of oxidative stress in melasma.[7-10] Classically, oxidative stress can be described as a disturbance in the balance between oxidants and antioxidants. Reactive oxygen species (ROS) are highly reactive molecules due to the unpaired electrons in their structure. Although ROS are present at low levels in physiologic conditions and are involved in critical physiologic events, they damage cellular components such as fat, protein, and nucleic acid at high concentrations.[5]

Dynamic thiol/disulfide homeostasis is one of the most important markers of oxidative stress in biological systems. Thiols are organic compounds containing a sulfhydryl (-SH) group. Thiols are considered highly potent antioxidants because they reduce unstable free radicals by donating electrons. They are the first antioxidants to be depleted in an oxidative environment.[11,12] In case of oxidative stress, they transform into reversible forms called disulfide bridges between 2 thiol groups. Disulfide bridges can be reduced back to thiol groups, which is how dynamic thiol/disulfide homeostasis is maintained. Dynamic thiol/disulfide homeostasis is responsible for cellular events such as antioxidant defense, signal transduction, regulation of enzyme function, and apoptosis.[11,12]

The aim of this study was to evaluate the presence of oxidative stress in melasma by comparing dynamic thiol/disulfide homeostasis in patients with melasma compared with age- and sex-matched healthy controls.

## Materials and Methods

*Participants and Eligibility Criteria*—We conducted a prospective study in a tertiary-care hospital (Ankara Bilkent City Hospital [Ankara, Turkey]) of patients with melasma who were followed from October 2021 to October 2022 compared with age- and sex-matched healthy volunteers. Ethics committee approval was obtained from Ankara Bilkent City Hospital before the study (E2-21-881)(13.10.2021). Written informed consent was obtained from all participants, and all were older than 18 years. Patients were excluded if there was the presence of any systemic disease or dermatologic disease other than melasma; smoking or alcohol use; any use of vitamins, food supplements, or any medication in the last 3 months; or pregnancy.

*Melasma Severity*—The modified melasma area and severity index (mMASI) score was used to determine the severity of melasma. The score is calculated from assessments of the darkness of the pigmentation and the percentage of affected area on the face. The mMASI score is the sum of the darkness score (D); area score (A); and separate fixed coefficients for the forehead, as well as the right malar, left malar, and chin regions.[13] The mMASI score, with a range of 0 to 24, is a reliable and objective marker in the calculation of melasma severity.[4]

*Biochemical Analysis of Samples*—The 6-cc peripheral fasting venous blood samples obtained from the study participants were centrifuged at 1500 g for 10 minutes, and the separated sera were stored in a freezer at −80 °C until the time of analysis. When the study was completed, the disulfide and thiol values were analyzed. Serum native and total thiol concentrations indicating thiol/disulfide homeostasis were calculated by a new fully automatic colorimetric method developed by Erel and Neselioglu.[14] Using this method, short disulfide bonds are first reduced with sodium borohydride solution to form free-functional thiol groups, and then the unused sodium borohydride is removed using formaldehyde. Finally, all thiol groups are reacted with 5,5′-dithiobis-(2-nitrobenzoic) acid (Ellman reagent), and all thiol groups are detected after reaction with 5,5′-dithiobis-(2-nitrobenzoic) acid. When a disulfide bond (−S−S−) is reduced, 2 thiol groups are formed. For this reason, half of the difference between total thiol (-SH + the amount of thiol formed by the reduction of disulfides) and native thiol (-SH) corresponds to the dynamic disulfide amount (total thiol – native thiol/2).[14]

*Statistical Analysis*—Statistical analysis was performed using SPSS software (version 24.0). Descriptive statistics were presented as numbers and percentages for categorical variables, and numerical variables were presented as mean, SD, median, minimum, maximum, 25th quartile, and 75th quartile. The conformity of the variables to normal distribution was examined using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). In pairwise group comparisons for numerical variables, a Mann-Whitney *U* test was used when normal distribution was not met, and a *t* test was used when normal distribution was met. The statistical significance level was accepted as $P<.05$.

## Results

Our study included 67 patients with melasma and 41 healthy age- and sex-matched controls. Of the participants with melasma, 60 (89.5%) were female and 7 (10.5%) were male. The control group was similar to the melasma group in terms of sex (87.8% female vs 12.2% male [$P=.59$]). The mean age (SD) was 33.1 (6.7) years in the melasma group and 31.9 (6.7) years in the control group. Age was similar across both groups ($P=.41$). All participants were of Asian race, and Fitzpatrick skin types (types II–IV) were similar across both groups.

Fifty-four (80.6%) participants had centrofacial melasma and 13 (19.4%) had mixed-type melasma. The mMASI score ranged from 3 to 20; the mean (SD) mMASI score was 11.28 (3.2). Disease duration ranged from 2 to 72 months; the mean (SD) disease duration was 12.26 (6.3) months. The demographics and clinical characteristics of the study group are shown in eTable 1.

eTable 2 provides a summary of disulfide, native thiol, and total thiol levels, as well as disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios in the study population. Disulfide/native thiol and disulfide/total thiol ratios were higher in melasma patients (Figure 1), whereas the native thiol/total thiol ratio was higher in the control group ($P$=.025, $P$=.025, and $P$=.026, respectively).

All correlations between age, disease duration, and mMASI scores and disulfide, native thiol, and total thiol levels, as well as disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios, are summarized in eTable 3. No significant correlation was observed between age and disease duration and disulfide, native thiol, and total thiol levels or disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios.

We independently assessed whether Fitzpatrick skin types II, III, and IV exhibited distinct levels of oxidative stress in clinical melasma. There were no significant correlations with Fitzpatrick skin type (disulfide/native thiol, $P$=.25; disulfide/total thiol, $P$=.19). We further evaluated if the thiol/disulfide parameters were correlated with duration of melasma by dividing the melasma patients into 3 groups (<6 months [n=12], 6–18 months [n=32], >18 months [n=23]), but there was not any significant correlation (disulfide/native thiol, $P$=.15; disulfide/total thiol, $P$=.15). We also divided our patients into 3 groups according to age (<27 years [n=14], 27–36 years [n=33], >36 years [n=20]). There was no correlation of the parameters with age (disulfide/native thiol, $P$=.15; disulfide/total thiol, $P$=.14).

There was a positive correlation between mMASI score and disulfide, native thiol, and total thiol levels and disulfide/native thiol and disulfide/total thiol ratios, as well as a negative correlation between mMASI score and native thiol/total thiol ratio. The correlations between mMASI scores and disulfide/native thiol and disulfide/total thiol ratios are shown in Figure 2 and eTable 3.

## Comment

Melasma is a common condition that may cause psychosocial problems in affected patients and negatively affect quality of life.[1] It occurs in all races but is more common in individuals with darker skin types (eg, Fitzpatrick skin types III and IV). Although melasma is more common in women during reproductive years (50%–70%), it also has been observed in 10% to 30% of men.[5]

Treatment options include topical bleaching agents, chemical peels, and laser therapy, as well as discontinuation of medications that may potentially trigger melasma; use of broad-spectrum sunscreens also is recommended.[4] Vitamins A, C, and E, as well as niacinamide, are used in the treatment of melasma, especially for their antioxidant properties. The key role of antioxidants in the treatment of melasma supports the importance of oxidative stress in the pathogenesis.[7] Melasma often is challenging to treat, particularly the mixed or dermal types, due to their stubborn nature. This condition poses a considerable therapeutic challenge for dermatologists.[4]

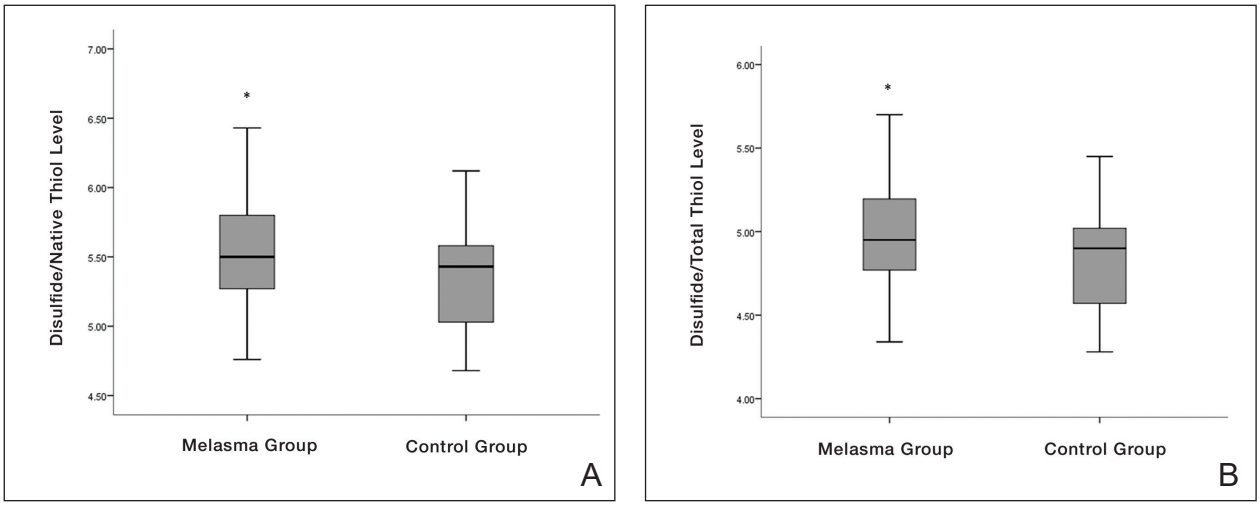


**FIGURE 1.** A, Disulfide/native thiol homeostasis parameters in participants with melasma and controls. B, Disulfide/total thiol homeostasis parameters in participants with melasma and controls. Higher scores indicate that in patients with melasma, oxidative stress shifts the thiol/disulfide balance to disulfide formation, causing thiols to oxidize into disulfide bonds. The horizontal bar inside the boxes indicates the mean, and the lower and upper ends of the boxes are the 25th and 75th quartiles. The whiskers indicate the range of the parameters of thiol/disulfide homeostasis. Asterisk indicates $P$=.025.

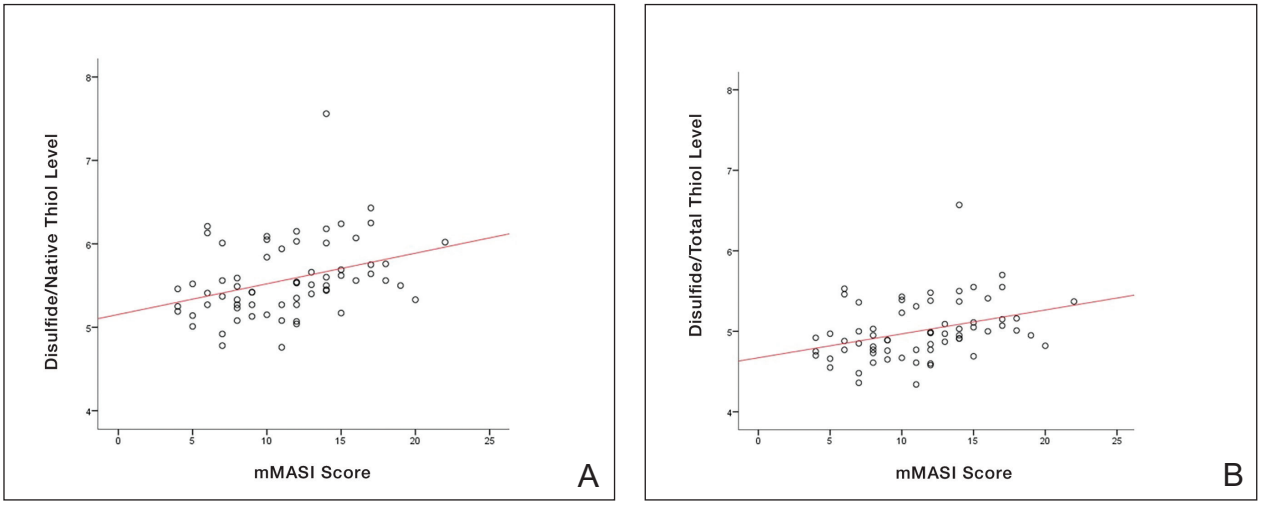


**FIGURE 2.** A, Correlations between modified melasma area and severity index (mMASI) scores and disulfide/native thiol ratios ($P<.001$; $r=0.42$). B, Correlations between mMASI scores and disulfide/total thiol ratios ($P<.001$; $r=0.42$). The correlation of mMASI scores with disulfide/native thiol and disulfide/total thiol values in the melasma group indicates that oxidative stress is linked to melasma severity. The red diagonal lines indicate correlation, showing that as one value increases, the other also increases.

Oxidative stress and oxidant-antioxidant imbalance previously have been studied in various diseases, but research investigating the presence of oxidative stress in melasma are limited.[7-10] Exposure of the skin to polluted air and intense UVR, as well as some food by-products, cosmetics, and drugs (eg, oral contraceptives), can directly or indirectly cause ROS production in the skin. Reactive oxygen species are thought to be involved in the pathophysiology of melasma by affecting apoptotic pathways and causing cell proliferation. The intermediate heme pathway has pro-oxidant effects and produces ROS and metabolites such as redox-active quinines. Exposure to UVR leads to the generation of ROS, highlighting the role of oxidative stress in the onset of melasma.[5]

In any cutaneous disease in which oxidative stress plays a role, oxidant and antioxidant levels may be expected to vary both locally and systemically; however, measurement of oxidative stress markers in serum instead of skin is technically and economically more advantageous.[8] Firstly, serum collection is less invasive and technically simpler than skin biopsies. Drawing blood is a routine procedure that requires minimal specialized equipment and training compared to the extraction and processing of skin samples. Secondly, analyzing serum samples generally is less expensive than processing skin tissue.[8]

In our study, we evaluated dynamic thiol/disulfide homeostasis in serum to investigate the presence of oxidative stress in the setting of melasma. Functional sulfhydryl (-SH) groups in thiols act as substrates for antioxidant enzymes and as free-radical scavengers. They constitute one of the most powerful defense systems against the unwanted effects of ROS. Thiols, which become the main target of ROS under oxidative stress, oxidize with oxidant molecules and form disulfide bridges.[15]

Thiol/disulfide homeostasis has been studied many times in dermatologic diseases,[16-19] and the results obtained from these studies are heterogenous depending on the extent of oxidative damage. It has been shown that thiol/disulfide homeostasis plays a role in oxidative stress in conditions such as psoriasis,[17] seborrheic dermatitis,[11] atopic dermatitits,[18] and rosacea.[19] In our study, disulfide/native thiol and disulfide/total thiol levels were significantly higher (both $P=.025$) in the melasma group compared with the control group, which indicates that the thiol/disulfide balance in patients with melasma is shifted to disulfide formation and thiols are oxidized to disulfide bonds in the presence of oxidative stress.

Seçkin et al[7] evaluated the role of oxidative stress in the pathogenesis of melasma and found that the serum levels of the antioxidants superoxide dismutase and glutathione peroxidase were significantly higher in the patient group compared with the control group (both $P<.001$). They also found that the levels of nitric oxide (another antioxidant) were increased in the patient group and the levels of protein carbonyl (an oxidative metabolite) were significantly lower (both $P<.001$). These findings indicated that free-radical damage may be involved in the pathogenesis of melasma.[7]

In a study of 75 patients with melasma, serum levels of the antioxidants melatonin and catalase were significantly ($P<.001$ and $P=.001$, respectively) lower in the melasma group compared with the control group, while serum levels of the oxidants protein carbonyl and nitric oxide were significantly higher ($P=.002$ and $P=.001$, respectively). No significant correlation was found between oxidative stress parameters and melasma severity.[8]

Choubey et al[9] found that serum malondialdehyde (an end product of lipid peroxidation), superoxide dismutase, and glutathione peroxidase levels were significantly

higher in the melasma group (n=50) compared with the control group (n=50)(all $P<.001$). In addition, a significant positive correlation (correlation coefficient, +0.307; $P<.05$) was found between serum malondialdehyde levels and melasma severity. The mean age (SD) of the patients was 32.22 (6.377) years, and the female (n=41) to male (n=9) ratio was 4.55:1. The most common melasma pattern was centrofacial, followed by malar.[9]

In a study with 50 melasma patients and 50 controls, Rahimi et al[10] examined bilirubin and uric acid levels, which are major extracellular antioxidants. The mean age (SD) at disease onset was 32.6 (6.7) years, and the mean MASI score (SD) was 18.1 (9). Serum bilirubin levels were found to be higher in the melasma group than in the control group and were correlated with disease severity. No significant difference in uric acid levels was found between the groups, and no correlation was found between MASI score and bilirubin and uric acid levels.[10]

In our study, the melasma group was similar to those in other reports in the literature regarding gender distribution, mean age, and melasma pattern.[7-10] Additionally, the correlation of mMASI score with disulfide/native thiol and disulfide/total thiol values in the melasma group suggested that oxidative stress also is correlated with melasma severity.

Thiol-based treatments such as n-acetyl cysteine, which contains a thiol compound, may be helpful in melasma.[20] In a double-blind, placebo-controlled study, topical n-acetyl cysteine combined with hydroquinone 2% was used in 10 female patients with melasma. Mild to strong bleaching of the skin was observed in 90% (9/10) of the patients.[21] Systemic use of n-acetyl cysteine in melasma also may be a potential research topic.

Major limitations of our study were the small sample size and lack of measurement of oxidative stress parameters in the skin concurrently with serum.

## Conclusion

In our study, the presence of oxidative stress in melasma was demonstrated by evaluating thiol/disulfide homeostasis—one of the strongest markers of oxidative stress. Oxidative stress also correlated with melasma disease severity in our analysis. The data obtained in this study may contribute to understanding the etiopathogenesis of melasma and may open new horizons in treatment; however, more comprehensive studies should be conducted to support our findings.

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## APPENDIX

### eTABLE 1. Demographics and Clinical Characteristics of Melasma Group vs Control Group

| Characteristic | Melasma group (n=67) | Control group (n=41) | *P* value |
|---|---|---|---|
| Mean age (SD), y | 33.1 (6.7) | 31.9 (6.7) | .41 |
| Age range, y | 22–48 | 22–46 | .41 |
| Gender, n | | | |
| Female | 60 | 36 | .59 |
| Male | 7 | 5 | |
| Fitzpatrick skin type, n | | | |
| II | 4 | 3 | |
| III | 51 | 32 | |
| IV | 12 | 6 | |
| Melasma type, n (%) | | | |
| Centrofacial | 54 (80.6) | N/A | |
| Mixed | 13 (19.4) | N/A | |
| mMASI | | | |
| Mean score (SD) | 11.28 (3.2) | N/A | |
| Score range | 3–20 | N/A | |
| Disease duration, mo | | | |
| Mean (SD) | 12.26 (6.3) | N/A | |
| Range | 2–72 | N/A | |

Abbreviations: mMASI, modified melasma area and severity index; N/A, not applicable.

### eTABLE 2. Parameters of Thiol/Disulfide Homeostasis in Melasma Group vs Control Group

| | Melasma group, mean (SD) | Control group, mean (SD) | *P* value |
|---|---|---|---|
| Native thiol | 394.4 (40.5) | 397.2 (48.4) | .43 |
| Total thiol | 438.2 (44.2) | 439.5 (52.6) | .54 |
| Disulfide | 21.9 (2.5) | 21.2 (2.5) | .31 |
| Disulfide/native thiol | 5.6 (0.5) | 5.3 (0.4) | .025[a] |
| Disulfide/total thiol | 4.95 (0.4) | 4.8 (0.3) | .025[a] |
| Native thiol/total thiol | 89.9 (0.7) | 90.3 (0.6) | .026[a] |

[a]Statistically significant.

**eTABLE 3. Correlations Between Age, Disease Duration, and mMASI Scores and Thiol/Disulfide Homeostasis Parameters**

| | Age | | Disease duration | | mMASI score | |
|---|---|---|---|---|---|---|
| **Homeostasis parameter** | ***P*** | ***r***[a] | ***P*** | ***r***[a] | ***P*** | ***r***[a] |
| Native thiol | .14 | −0.14 | .41 | 0.1 | <.001[b] | 0.53 |
| Total thiol | .15 | −0.14 | .33 | 0.1 | <.001[b] | 0.59 |
| Disulfide | .47 | −0.07 | .17 | 0.17 | <.001[b] | 0.78 |
| Disulfide/native thiol | .33 | 0.09 | .17 | 0.17 | <.001[b] | 0.42 |
| Disulfide/total thiol | .32 | 0.09 | .17 | 0.16 | <.001[b] | 0.42 |
| Native thiol/total thiol | .32 | −0.09 | .16 | −0.17 | <.001[b] | −0.42 |

Abbreviation: mMASI, modified melasma area and severity index.

[a]Pearson correlation coefficient.

[b]Statistically significant.