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Evaluation of Salivary Malondialdehyde Levels to Assess Oxidative Stress in Postmenopausal Women

ABSTRACT

Objective: Malondialdehyde (MDA), a by-product of lipid peroxidation, is considered one of the biological markers for oxidative stress. Oxidative stress increases with age, especially after menopause. The aim is to evaluate the oxidative stress levels in pre-, peri-, and postmenopausal women by measuring salivary malondialdehyde levels.

Methods: The study included 45 participants, who were categorized into premenopausal, perimenopausal, and postmenopausal groups. Salivary MDA levels were measured biochemically using the thiobarbituric acid method.

Results: A statistically significant rise ($P < .001$) in the mean salivary MDA level was observed in postmenopausal women (0.94 ± 0.18 nmol/mL) when compared to perimenopausal (0.78 ± 0.08 nmol/mL) and premenopausal women (0.48 ± 0.09 nmol/mL). Salivary MDA levels were also positively correlated with the age of the participants ($r = 0.79$; $P < .00$) and the duration of menopause ($r = 0.609$; $P = .015$).

Conclusion: Salivary MDA levels were highest in postmenopausal women, followed by perimenopausal and premenopausal women. The changes observed in salivary MDA levels could be probably due to the oxidative stress during menopause.

Keywords: Saliva, malondialdehyde levels, oxidative stress, menopause

Introduction

One-third of a woman's lifetime is likely to be spent in the postmenopausal phase.[1] The spontaneous cessation of menstruation due to decreased ovarian follicular activity is known as menopause. The physiological change associated with menopause either occurs or begins before the last menstrual cycle, called the perimenopausal period. The estrogen decline occurs during this menopausal transition, which influences the development of many symptoms associated with middle age and chronic illnesses, including postmenopausal osteoporosis and cardiovascular disease (CVD).[2]

Estrogen is a potent antioxidant that reduces reactive oxygen species (ROS) generation.[3] Oxidative stress is caused by abnormal synthesis of ROS, which frequently occurs along with a decrease in the antioxidants that can neutralize these reactive species. Oxidative stress typically increases with age, especially after menopause. It is speculated that the low levels of estrogen in postmenopausal women contribute to cellular stress and the generation of ROS, which are the underlying cause of many diseases. Reactive oxygen species, which includes peroxide and superoxide anions, can damage the cells when accumulated in large quantities. As a result, metabolizing and scavenging systems consisting of superoxide dismutase, catalase, and glutathione peroxidase (GPX) protect the cell from ROS damage.[4] Postmenopausal women have been found to have low levels of GPX, superoxide dismutase, and antioxidants like ascorbic acid, tocopherol, total thiols,[5] and higher levels of lipo peroxide and pro-oxidant markers such as malondialdehyde (MDA), 4-hydroxynenal, and oxidized low-density lipoprotein.[6] Malondialdehyde is a highly reactive aldehyde formed as a product of polyunsaturated fatty acid peroxidation and arachidonic acid metabolism. Malondialdehyde is considered one of the biological indicators of oxidative stress, which is usually found in the enol form.[7]

Soydinç S et al[8] demonstrated an increase in serum MDA levels in coronary artery disease, which indicates a relation between oxidative stress and atherosclerosis. Saliva, a non-invasive tool, can help diagnose oxidative stress levels, which in turn plays a vital role in the etiopathogenesis of CVD. Increased salivary MDA levels can serve as an early marker of oxidative stress

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in perimenopausal and postmenopausal women, indicating the necessity to initiate antioxidant therapy to prevent further complications. The current study aimed to study and compare salivary MDA levels in pre-, peri-, and postmenopausal women.

Materials and Methods

Study design: The present cross-sectional study was approved by the Institutional Review of SRM Dental College (approval number: SRMU/M&HS/SRMDC/2021/PG/0 06B; date: 21/08/2021). After obtaining written informed consent from the participants, all procedures were performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki, as revised in 2013.

Study setting: 45 women who reported to the outpatient department for over 6 months between September 2021 and February 2022 were included.

Study participants: The study participants were categorized as premenopausal [group 1; n = 15], perimenopausal [group 2; n = 15], and postmenopausal [group 3; n = 15] groups based on their menstrual history. Women were categorized into the premenopausal group if their menstrual cycles were regular during the last 3 months. Participants were considered to be in the perimenopausal stage if there was increased menstrual irregularity or amenorrhea in the past 3-11 months.[9] If there had been 12 or more months of amenorrhea caused by natural or surgical interventions, such as bilateral oophorectomy, women were regarded as postmenopausal.[10,11] The study excluded women with gingivitis, high decay-missing-filled indices, high Oral Hygiene Index-Simplified indices, any oral lesions, systemic diseases, heavy alcohol intake, women taking vitamin supplements, antibiotics, anti-inflammatory drugs, or any other medications. The participants were instructed not to intake food or exercise for 1 to 2 hours before the sample collection.

Methods for Collecting Saliva

The participants were told to use povidone–iodine mouthwash for 2 minutes. After 1 minute, participants were instructed to sit comfortably with their heads tilted, eyes open, and eyes slightly forward. Saliva was then permitted to collect on the floor of their mouths. The spitting method collected saliva that had not been provoked into a test tube.

Standard known MDA solutions in varying concentrations from 0.2 to 1 nmol/mL were prepared, and test tubes were labeled M1- M5, respectively. Aliquots of these solutions were heated with thiobarbituric acid (TBA) in a water bath for 15 minutes, which led to the formation of MDA-TBA2 adducts. These adducts produced a reddish-pink color that was seen spectrophotometrically at 532 nm. The experiment was conducted at 95°C in an acidic environment (pH 4). A standard curve was generated based on the known concentrations of salivary MDA levels with their obtained standard optical density (SOD). The samples were run in duplicates to minimize potential sources of error.

Determination of Salivary Malondialdehyde

In the same way, 1 mL of the saliva sample was taken from each patient in our study group and heated with TBA. The color change in the test tube was read in a spectrophotometer at 532 nm, and absorbance was recorded. This represents the test optical density (TOD). The concentration of MDA in the saliva was calculated using the formula TOD/SOD × concentration of the standard solution.

Statistical Analysis

Statistical Package for the Social Sciences Statistics version 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The Kruskal–Wallis test was used to compare the mean MDA levels of the 3 groups. Intergroup comparison was done using post hoc Dunn's test. The association between the variables was determined using Spearman's correlation test. A *P*-value of .05 was regarded as statistically significant.

Results

The mean age of the group 1 participants was 30.53 ± 3.48 years, in group 2 it was 42.87 ± 4.01 years, and in group 3 it was 53.07 ± 1.61 years. The mean MDA level was highest in group 3 (0.94 ± 0.18 nmol/mL), followed by group 2 (0.78 ± 0.08 nmol/mL), and group 1 (0.47 ± 0.09 nmol/mL). The mean salivary MDA levels among the groups were statistically significant ($P < .001$). (Table 1) When intergroup comparison was done, a significant difference was found between group 1 and group 2 and between group 1 and group 3 ($P < .001$). While the difference in salivary MDA levels between group 2 and group 3 was not significant ($P = .07$).

When all the participants' ages were correlated with MDA levels, a strong positive correlation was found with an *r*-value of 0.79 and $P < .001$. (Figure 1). A strong positive correlation was found between the duration of menopause and MDA levels in group 3 participants with an *r*-value of 0.609, which was statistically significant ($P = .015$) (Figure 2).

The multiple regression analysis was performed for group 3 with salivary MDA levels as the dependent variable and the duration of menopause as the independent variable. Age was excluded from the analysis as it did not significantly influence the effect of the duration of menopause on the salivary MDA level. Table 2 shows an adjusted R-square of 0.371, indicating that the duration of menopause can predict 37.1% of the change in the salivary MDA levels in the postmenopausal group. The following regression formula was obtained:

Salivary MDA level = 0.6345 + (0.062 × duration of menopause).

Table 1. Comparison of Mean Salivary Malondialdehyde Levels Among the Study Groups

	Salivary MDA levels (nmol/mL)		
Groups	**Mean ± SD**	**Interquartile Range**	***P***
Group 1	0.48 ± 0.09	0.14	<.001
Group 2	0.78 ± 0.08	0.1	
Group 3	0.94 ± 0.18	0.26	

P-values on intergroup comparison: group 1 vs. group 2 < .001; group 1 vs. group 3 = .070 and group 2 vs. group 3 < .001.

MAIN POINTS

- Malondialdehyde (MDA) is considered one of the biological indicators of oxidative stress.
- Salivary MDA levels were increased in postmenopausal women compared to peri- and premenopausal women.
- It is essential to maintain the oxidant–antioxidant equilibrium during the early stages of menopause.

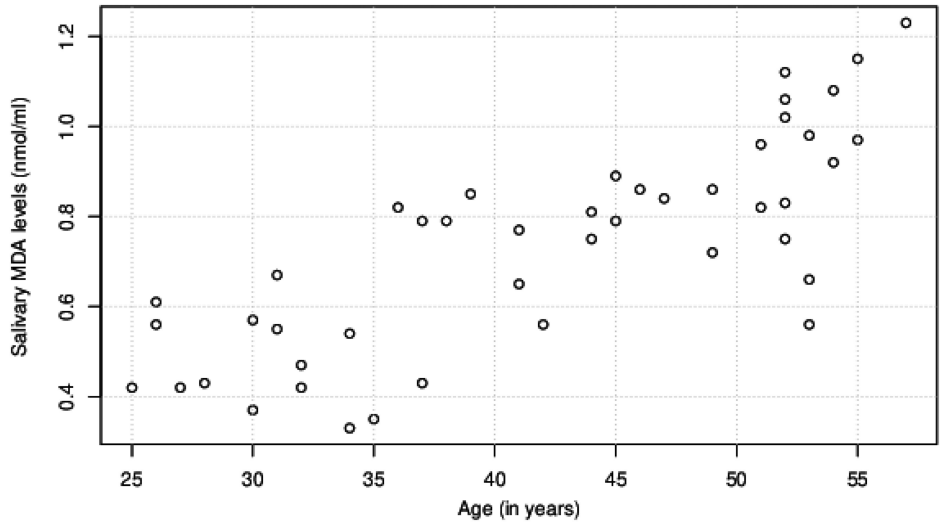

Figure 1. Scatter plot representing a strong positive correlation between salivary malondialdehyde levels and age.

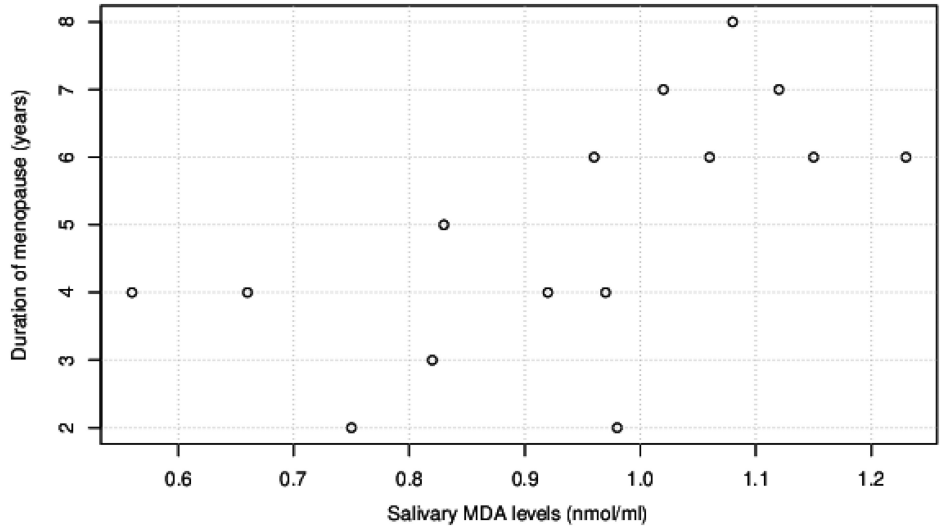

Figure 2. Scatter plot representing a strong positive correlation between salivary malondialdehyde levels and duration of menopause among group 3 participants.

Discussion

Oxidative stress typically increases with age, especially after menopause. The lipids present in the cell membrane are the most frequent targets of oxidative damage. Free radicals alter the unsaturated fatty acids in cell membranes, causing damage that results in a cascade of events known as lipid peroxidation. One of the by-products of lipid peroxidation is MDA. An excess of MDA is produced due to the rise in free radicals. Malondialdehyde is frequently regarded as an indicator of oxidative stress and the antioxidant state in cancer patients.[13] Estrogen is a potent antioxidant due to its hydroxyphenolic structure. Furthermore, estradiol can stimulate cellular antioxidant enzymes.[14] Menopause is associated with a dramatic decrease in estrogen, which has been proven to increase oxidative stress levels in the body. The current study evaluated the use of salivary MDA levels to assess oxidative stress in menopausal women, women in the menopause transition period, and premenopausal women.

Table 2. Model Summary of the Multiple Linear Regression Analysis with Salivary Malondialdehyde Level as a Dependent Variable and the Duration of Menopause as the Independent Variable

Group	*R*	R-Square	Adjusted R-Square	Standard Error	*F*	*P*
Group 3	.609	.371	.323	.15391	7.673	.016

Oxidative stress affects the function and integrity of cellular structures by producing ROS, which damages cellular DNA, lipids, and proteins and plays a key role in the pathophysiology of disorders linked with menopause, like CVD, osteoporosis, and hot flashes. In postmenopausal women, estrogen deprivation impairs endothelial function and the production of pro-oxidants. This oxidative stress is a forerunner of hyperlipidemia that will, in turn, lead to CVD. In a study by Amritha J et al,[15] lipid oxidation was assessed by evaluating MDA levels and demonstrated high serum MDA levels in menopausal

women with hyperlipidemia as well as those with normolipidemia, highlighting the fact that oxidative events begin even in the presence of normal lipid levels, and menopausal women are equally susceptible to CVD risk regardless of their lipid status. Diabetes mellitus also causes the generation of oxygen free radicals. Menopause and type 2 diabetes mellitus have synergistic effects in producing oxidative damage, thereby accelerating the risk of CVD.[16]

In the current study, the salivary MDA levels were higher in postmenopausal women than in perimenopausal and premenopausal women. A similar rise in serum MDA levels in postmenopausal women observed by Zovari F et al[17] also corresponded with a decrease in total antioxidant capacity, suggesting an imbalance in the oxidant–antioxidant system. A similar trend was also observed in salivary MDA levels and total antioxidant capacity. However, the salivary and serum MDA levels did not show a significant relationship, which could be attributed to the difference in the types of antioxidants. In saliva, there are several external sources for generating ROS and reactive nitrogen species like oral bacteria, radiation, diet, air pollution, consuming alcohol, and smoking cigarettes.[17] During menopause, salivary oxidant–antioxidant disequilibrium, along with the changes in estrogen levels, can predispose to oral complications, including xerostomia, dental caries, and gingival atrophy. The salivary oxidant–antioxidant disequilibrium is also linked to diabetes mellitus, CVD, temporomandibular joint disorders, periodontal diseases, recurrent aphthous stomatitis, oral lichen planus, and several other conditions.[18-22] Hence, in our study, intricate inclusion and exclusion criteria were followed to include participants without any oral or systemic diseases to avoid these confounding factors. Khoubnasabjafari M et al[23] stated that salivary or serum MDA is not a reliable biomarker for oxidative stress, considering the wide variation observed in the salivary and plasma MDA levels. These substantial variations could have resulted from various factors, such as the analytical technique, sample storage before analysis, saliva sample collection protocol, and several confounding factors affecting the salivary MDA levels.[23]

The oxidant–antioxidant system is one of the several defense mechanisms present in saliva. Oxidant and antioxidant levels in saliva might change due to infection, inflammation, or disease. Increased salivary MDA has been associated with the number of carious lesions, which dramatically decreased after treatment, demonstrating the contribution of oxidative stress to the development of dental caries.[24] When periodontopathogens or their by-products interact with neutrophils in periodontal tissues or pockets, superoxide anions are generated, resulting in a rise in salivary MDA levels. Free radical-induced lipid peroxidation increases with the severity of periodontitis, indicating the degree of tissue damage.[25] Oxidative stress is also a major trigger for oral lichen planus wherein T-cells activate cytokines to attract inflammatory cells, thereby generating ROS and destroying keratinocytes. In a study by Singh S et al,[26] salivary MDA levels were greater in the erosive type of oral lichen planus when compared to the reticular type.[26] Betel nut chewing is known to cause oral submucous fibrosis (OSMF) through various molecular pathways, including altered collagen metabolism, changes in micronutrient levels, inflammation, and lipid peroxidation. Salivary MDA levels increase as the clinical and histological phases advance, suggesting that MDA can be a prognostic marker in the OSMF treatment regimen.[27] Betel quid components also play a role in carcinogenesis by generating ROS, which form aldehydes like MDA. Malondialdehyde, in turn, reacts with DNA to form adducts, which serve as mutagens. Assessing MDA levels in potentially malignant oral disorders and oral cancer may be useful for determining the severity of the condition for preventive and therapeutic intervention.[28-30]

Oxidative stress accompanies the process of aging. In our study, age was found to correlate with MDA levels. Several studies have recorded a similar increase in oxidative stress and MDA levels with increasing age.[31-33] However, in a study by Cakir et al,[34] although serum MDA levels increased in postmenopausal women and were higher than those for men, MDA levels did not correlate with age or duration of menopause. In our study, salivary MDA levels positively correlated with the duration of menopause. In a previous study, when compared to short-term menopausal women (<5 years), MDA levels and the thickness of the intima-media of the common carotid artery wall were found to be higher in women with long menopausal periods (>5 years), suggesting that women are more susceptible to low-density lipoprotein oxidation as menopause progresses.[16] The duration of menopause enhances the risk of oxidative stress, especially in the presence of underlying diseases like CVD or diabetes mellitus.[35] Hence, it is imperative to administer antioxidants such as vitamins E and C based on their salivary MDA levels during the early stages of menopause transition to reduce further complications. Antioxidative stress therapy shows potential benefits in reducing MDA levels, increasing total antioxidant capacity, and reducing glutathione in some subgroups.[36] Monitoring salivary MDA levels can serve as a guide for therapeutic interventions in postmenopausal women. Increased salivary MDA levels in postmenopausal women indicate that intervention to maintain the oxidant–antioxidant equilibrium during the early stages of menopause is essential. The limitation of the current study is that the sample size was small, and that self-reported medical history was only considered. Assessment of hormonal levels (Follicle-stimulating hormone (FSH)/Luteinizing hormone (LH)/estradiol and prolactin) to determine the menopausal status would enhance the reproducibility of the study.

Salivary MDA levels were highest in postmenopausal women, followed by perimenopausal and premenopausal women. The changes observed in salivary MDA levels could be due to oxidative stress during menopause.

Data Availability Statement: All data generated or analyzed during this study are included in this published article.

Ethics Committee Approval: This study was approved by the Ethics Committee of SRM Dental College, Institutional review board University (approval number: SRMU/M&HS/SRMDC/2021/PG/006B; date: 21/08/2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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