DOI: 10.7860/JCDR/2024/68440.19195

Review Article

Dentistry Section

Malondialdehyde: A Toxic Stress Marker for Periodontitis

AFSHAN BEY[1], ARTHY ARRVIND[2], PRAMOD KUMAR YADAV[3], SHUBHAM SAREEN[4]

ABSTRACT

Recently, it has been discovered that one of the primary causes of a variety of inflammatory illnesses, including periodontitis, is an excess of Reactive Oxygen Species (ROS). It is recognised that the host's response to pathogens plays an equal or even bigger part in determining how connective tissue breaks down. The process of Polymorphonuclear (PMN) phagocytosis greatly increases ROS formation through the metabolic pathway known as the "respiratory burst." Because the antioxidant defense system is unable to neutralise these high levels or activities of ROS, Oxidative Stress (OS) and tissue damage ensue. ROS can directly affect tissue through Lipid Peroxidation (LPO), Deoxyribonucleic Acid (DNA) damage, protein breakdown, and the oxidation of essential enzymes. Numerous aldehydes can be produced as byproducts of LPO, including Malondialdehyde (MDA), propanal, hexanal, and 4-Hydroxynonenal (4-HNE). They can be detected in bodily fluids and suggest a pro-oxidant state. MDA is a by-product created by the enzymatic or non enzymatic breakdown of Arachidonic Acid (AA) and larger Polyunsaturated Fatty Acids (PUFAs). MDA is the most studied OS tissue damage indicator. After it is formed, MDA can either be broken down by enzymes or combine with DNA or proteins in cells and tissues to form adducts that can cause harm to biological molecules.

Keywords: Lipid peroxidation, Oxidative stress, Reactive oxygen species

INTRODUCTION

Chronic illnesses are becoming more common worldwide and are affecting people from all socio-economic backgrounds. Since periodontal disease and other chronic illnesses share many risk factors, they contribute to the increasing worldwide burden of disease. Approximately 320 million adults in India, or roughly one in two, suffer from periodontal disease. The prevalence of periodontal disease among American adults (47.2%) is comparable to this estimate [1].

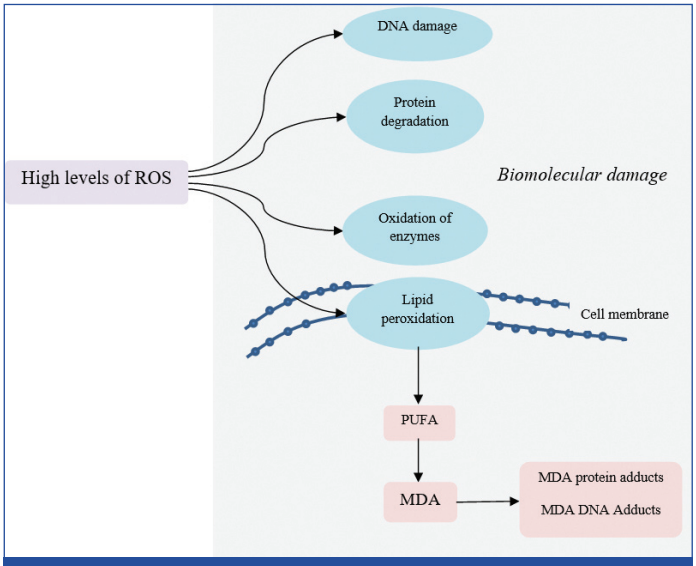
Periodontitis is a chronic, multifactorial inflammatory disease characterised by host-mediated inflammation that results in the progressive breakdown of periodontal attachment. According to a growing body of recent research, ROS have been implicated in the establishment of an oxidatively stressed environment that underpins the pathogenesis of many long-term chronic inflammatory diseases, such as type 2 diabetes, atherosclerosis, Rheumatoid Arthritis (RA), cancer, inflammatory lung disease, and periodontitis [2]. While pathogenic bacteria are an important cause in the development of periodontitis, periodontal breakdown is ultimately caused by an overreaction of the immune system. The host's defense mechanism against spreading periodontal pathogenic bacteria is mostly mediated by PMN leukocytes. The antioxidant defense system is unable to combat the excessive production of Reactive Oxygen or Nitrogen Species (ROS/RNS) like Hydrogen Peroxide (H_2O_2) and superoxide (O_2^-) that are produced by hyperactivated neutrophils or from the direct release of microbes. This leads to oxidative stress and subsequently apoptosis of connective periodontal tissue [3]. The pathogenesis of periodontitis has drawn more attention to the importance of LPO products and antioxidant biomarkers so far.

The OS is characterised by elevated LPO metabolites or end products, protein damage, and DNA damage. When PUFAs in cell membranes are peroxidised by ROS, carbon-centered radicals (PUFA radicals) or lipid peroxide radicals are produced, which can lead to a loss of membrane function. Compared to free radicals, the byproducts of LPO are more stable. MDA, 4-hydroxy-2-nonenal (4-HNE), and isoprostanes are examples of such LPO breakdown products. Additionally, DNA can be affected by OS, which generates 8-hydroxy-2'-deoxyguanosine (8-OHdG) [4]. MDA has been the subject of the most research since it is a dependable indication of OS tissue injury in a variety of biological samples. The present narrative review aimed to summarise the key facts about MDA synthesis and metabolism and to distill the various approaches to estimating MDA levels in individuals with periodontitis.

The Defective Host Response in Periodontitis

The tissue destruction in the periodontium is primarily caused by host-derived enzymes called matrix Metalloproteinases (MMPs) and changes in osteoclast activity triggered by cytokines and prostanoids. As subgingival plaque bacteria accumulate, various microbial components, including chemotactic elements like Lipopolysaccharide (LPS), microbial peptides, and other bacterial antigens, penetrate the gingival connective tissues over the junctional epithelium. An inflammatory response occurs in the tissues due to the stimulation of epithelial and connective tissue cells to produce inflammatory mediators. The gingival vasculature expands (also known as vasodilation) and opens up to more fluid and cells. The tissues fill with fluid, and defense cells migrate from the circulation to the gingival crevice, where the bacteria and their byproducts serve as the source of chemotactic stimulation. In the early stages of gingival inflammation, neutrophils, a type of PMN leukocyte, predominate to phagocytose and eliminate plaque microorganisms. PMNs utilise both intracellular and extracellular mechanisms to destroy bacteria. Committed lymphocytes return to the infection area as bacterial products circulate, and B lymphocytes transform into plasma cells that produce antibodies to specific bacterial antigens. Antibodies generated in gingival tissues aid and enhance PMN phagocytosis and bacterial killing in the presence of complement [5]. During the process of PMN phagocytosis, ROS formation is significantly increased through the metabolic pathway known as the "respiratory burst" [6]. Due to the inadequate antioxidant defense system to counteract high levels or activities of ROS, oxidative stress and tissue damage occur. While ROS function as signalling molecules or inflammatory mediators, they can also directly damage tissue through processes such as lipid peroxidation, DNA damage, protein degradation, and the oxidation of essential enzymes when they accumulate to toxic levels [7].

Lipid peroxide radicals or carbon-centered radicals (PUFA radicals) are formed when PUFAs undergo peroxidation in cell membranes, leading to membrane dysfunction [Table/Fig-1]. During the LPO of PUFAs, Malondialdehyde (MDA), also known as MDA, can be generated through the actions of polyamine oxidase and amine oxidase on spermine, as well as by human platelet thromboxane synthetase on prostaglandins PGH2, PGH3, and PGG2. In biological fluids, breakdown products of LPO such as MDA, 4-hydroxy-2-nonenal (4-HNE), and isoprostanes are detected, indicating a pro-oxidant state [4]. It is noteworthy that individuals with this "hyperactivated" PMN neutrophil response, characterised by an excess of ROS and proteases, are more susceptible to periodontitis [8].



[Table/Fig-1]: A simplified schematic diagram to illustrate the formation of MDA from excessive production of Reactive Oxygen Species (ROS).

The Production of MDA

Numerous oxidation products are generated during LPO. Lipid Hydroperoxides (LOOH) are the primary byproducts of LPO. Several aldehydes, including MDA, propanal, hexanal, and 4-HNE, can be formed as secondary products during LPO. Esterbauer H et al., conducted significant research on these compounds in the 1980s [9,10].

The MDA is a by-product created through the enzymatic or non enzymatic breakdown of Arachidonic Acid (AA) and larger Polyunsaturated Fatty Acids (PUFAs). Arachidonic acid is acted upon by cyclooxygenases to produce PGH2. The enzyme thromboxane A2 synthase converts prostaglandin endoperoxide or Prostaglandin H2 (PGH2) into Thromboxane A2 (TXA2), a physiologically active metabolite of AA [11]. MDA can originate in-vivo as a by-product of enzymatic events during the formation of thromboxane A2 [12].

The process of LPO leads to the creation of a mixture of LOOHs. Hydroperoxides with a homoallylic cis-double bond to the peroxyl group can cyclically generate new radicals by introducing an intramolecular radical to the double bond. Cycle-generated intermediate free radicals can form bicyclic endoperoxides, which structurally resemble prostaglandins and can further break down to produce MDA. Arachidonic acid is the primary precursor of bicyclic endoperoxide through a non enzymatic oxygen radical-dependent process. To produce MDA, this compound subsequently undergoes additional reactions, either independently or in conjunction with other compounds. However, other eicosanoids that can also be formed through non enzymatic oxygen radical-dependent reactions may serve as precursors of bicyclic endoperoxide and MDA [11,13].

MDA Metabolism

After its production, MDA can either be broken down by enzymes or combine with proteins or DNA in cells and tissues to form adducts that can harm biological molecules. Early research suggested that MDA is oxidised by mitochondrial aldehyde dehydrogenase, followed by decarboxylation to produce acetaldehyde. Acetaldehyde is then oxidised by aldehyde dehydrogenase to acetate, which is further converted to CO_2 and H_2O [11,14]. On the other hand, cytoplasmic MDA is likely converted by phosphoglucose isomerase to Methylglyoxal (MG), which is subsequently transformed into D-lactate by glyoxalase system enzymes with the help of Glutathione (GSH) as a cofactor [15]. Certain enaminals (RNH-CH-CH-CHO), such as N-epsilon-(2-propenal)lysine or N-2-(propenal) serine, are among the distinct fractions of MDA that are eliminated in the urine [11].

The MDA is a bifunctional aldehyde electrophile whose reactivity varies with pH. The enolate ion, a conjugate base with a negative charge on oxygen and an adjacent C-C double bond, is present at healthy pH levels and exhibits low reactivity. Beta-hydroxyacrolein, the form of MDA that arises when pH drops, is more reactive [11]. MDA's electrophilicity, which makes it highly reactive towards nucleophiles such as basic amino acid residues (lysine, histidine, or arginine), is the main reason for its high reactivity. Advanced LPO end-products (ALE), also known as Schiff-base adducts, result from early interactions between MDA and free amino acids or proteins [16]. Malondialdehyde Acetaldehyde (MAA) adducts are formed by acetaldehyde (a by-product of MDA metabolism) in the presence of MDA under oxidative stress conditions [17]. Evidence suggests that MAA adducts are highly immunogenic [17-20]. Research reveals a list of up to 33 proteins, including enzymatic proteins, carrier proteins, cytoskeletal proteins, mitochondrial proteins, and antioxidant proteins, that are known to be modified by MDA [21].

Adducts of deoxyguanosine and deoxyadenosine have been proposed as the result of several nucleosides, such as cytidine and deoxyguanosine, reacting physiologically with MDA. The primary by-product of this reaction is pyrimido (1,2-a) purin-10 (3H-) one, also referred to as M1G or M1dG. MDA plays a significant role in DNA damage and mutation [22]. The Nucleotide Excision Repair (NER) pathway is believed to be the primary route for repairing M1dG residues in genomic DNA. MDA-DNA adducts have the potential to cause strand breakage, apoptosis induction, point and frameshift mutations, and cell cycle arrest if left unrepaired. Research also indicates that long-lasting M1dG adducts in mitochondrial DNA inhibit the transcription of mitochondrial genes [23]. Lower levels of DNA oxidation markers (M1dG and 8-oxodG) in peripheral white blood cells of healthy individuals have been associated with the consumption of specific antioxidants, such as vitamins [24].

Detection of MDA in Body Fluids

The MDA is utilised as a versatile biomarker in various disease indicators to differentiate between health and illness. The main technique used to measure plasma MDA levels is the colorimetric reaction with Thiobarbituric Acid (TBA). Standard Enzyme-linked Immunosorbent Assay (ELISA) kits, validated against High-Performance Liquid Chromatography (HPLC), can be used to conduct novel antibody-based tests and have produced reliable and precise results [25]. Recently, a self-assembled organic-inorganic nanohybrid technology was employed to develop a non invasive method for measuring the MDA biomarker in human exhaled breath condensate. This technique has shown promise as a suitable, dependable, and cost-effective diagnostic tool for lung diseases [26]. Long-term clinical studies on circulating MDA as a biomarker of LPO have determined that gas chromatography coupled with tandem mass spectrometry (GC-MS/MS) is a useful approach [27]. In 2017, a study by Hanff E et al., revealed that measuring nitrite and MDA in human urine using GC-Electron-Capture Negative Ion Chemical Ionisation (ECNICI)-MS is crucial as a surrogate internal

standard for MDA [28]. Takamura T aki et al., also demonstrated that MDA-modified Low-density Lipoprotein (MDA-LDL) was a favourable option for predicting the outcomes of endovascular therapy in patients with peripheral artery disease [29].

MDA Assay Methods and Studies that Evaluated the Association of MDA with Periodontitis

In 2023, Mohideen K et al., conducted a comprehensive systematic review and meta-analysis of the literature on the OS-mediated LPO end product MDA in periodontitis. The meta-analysis utilised the standardised mean differences approach and a random-effects model with a 95% confidence interval. The trials examined showed that the periodontitis group had signalling higher MDA levels in gingival crevicular fluid, saliva, and blood samples compared to the healthy control group. A total of 16 studies provided consistent data suitable for quantitative synthesis [30]. Veljovic T et al., also found a statistically significant positive correlation between periodontitis and MDA levels in blood and saliva. They observed that scaling and root planing resulted in reduced levels of probing depth and MDA in the blood and saliva of periodontitis patients [31]. Another study by Altngöz SM et al., assessed the relationship between OS and periodontitis in patients with and without diabetes [4]. The study revealed a positive association between the Clinical Attachment Level (CAL) and MDA levels in saliva. The results of the research using MDA evaluation methods on patients with periodontitis clearly indicate that MDA levels in patients with chronic periodontitis are signalling higher than those in periodontally healthy individuals. The reaction with thiobarbituric acid (TBA) is used in the majority of MDA assay procedures to produce a chromogen that can be quantified spectrophotometrically [Table/Fig-2] [31-50].

Association of MDA with other Oral Diseases

Numerous studies have demonstrated that OS contributes to the pathophysiology of Oral Lichen Planus (OLP) [51]. Salivary ROS, LPO, nitric oxide, and nitrite levels were signalling higher in OLP patients compared to control subjects [52,53]. In OLP patients with higher salivary MDA levels than the healthy control group, total antioxidant activity was considerably lower, suggesting a potential role for oxidants in driving the disease through an LPO-mediated pathway [54,55]. Additionally, patients with oral leukoplakia and oral squamous cell carcinoma exhibited signalling higher levels of LPO, as evidenced by salivary MDA levels [56,57]. OS biomarkers have been used in studies as markers for various oral pathologies, including odontogenic cysts, inflammatory disorders of the oral mucosa, and salivary gland pathologies [58].

Various pathological issues, such as pericoronitis, swelling, odontogenic cysts or tumours, bone loss, or root resorption of adjacent teeth, are commonly associated with impacted mandibular third molars. These diseases can disrupt normal oral functions and reduce a patient's quality of life, even if they remain unnoticed for the rest of their lives. Tekin U et al., compared MDA levels in 40 dental follicle samples from asymptomatic impacted mandibular third molars with 40 samples from healthy gingival tissue. They found higher MDA levels in the dental follicles of impacted mandibular third molars, with a statistically significant difference [59]. In a long-term study, blood serum samples were used to investigate the decrease in inflammation and MDA levels after impacted third molar extraction [60]. Fabio Camacho-Alonso F et al., reported that myeloperoxidase and MDA salivary concentrations were higher in patients with impacted mandibular third molars compared to participants without impacted third molars [61].

Association of MDA with systemic diseases linked to periodontitis

According to a study by Isola G et al., patients with Coronary Heart Disease (CHD) who also have periodontitis exhibit higher levels of serum and salivary MAA and C-reactive protein. The observed

S. No.	Study for periodontitis	Sample	MDA levels		Unit of measurement	MDA assay
			Chronic periodontitis	Periodontally healthy		
1.	Veljovic T et al., [31] 2022	Saliva	2.99±1.21 (1.11-4.80)	1.33±0.92 (0.23-3.70)	pmol/µL	Commercial MDA Adduct ELISA Kit*
		Plasma	0.5±0.13 (0.29-0.70)	0.4±0.13 (0.13-0.62)		
2.	Warad SB et al., 2021 [32]	saliva	8.96±2.59	5.42±1.55	µmol/mL	Stalnaya and Garishvili 1997
3.	Shiny I et al., 2020 [33]	Saliva	1.78 ± 0.45	0.48 ± 0.3	µM/L	Buege JA and Aust SD [34]
		Serum	1.8 ± 0.89	0.85± 0.46		
4.	Sánchez Villamil JP et al., 2020 [35]	Saliva	2.1±1.54	0.46±0.3	µmol/g protein	Sigma-Aldrich assay
5.	Cherian DA et al., 2019 [36]	Saliva	281.6 ±83.5	89.45±46.47	µM/100 mL	Esa
6.	Narendra S et al., 2018 [37]	GCF	1.98±0.32; GAP: 3.33±0.38	0.63±0.12	nmol/mL	Satoh K [38]
		Serum	2.02±0.32; GAP: 3.61±0.39	0.59±0.14		
7.	Tripathi V et al., 2018 [39]	Saliva	0.16; GAP: 0.16	0.07	µM	Young IS and Trimble ER [40]
		Serum	0.68; GAP: 0.65	0.61		
8.	Lutfioğlu M et al., 2017 [41]	GCF	802.1±88.2	144.1±4.15	µM	Bioxy tech, MDA-586†
9.	Dahiya P et al., 2016 [42]	Serum	308±58.5	194.4±22	nmol/dL	Yagi K [43]
10	Ghallab N et al., 2016 [44]	GCF	1.1±0.2 (0.8-1.4); GAP: 1.8±0.4 (0.8-2.3)	0.5±0.1 (0.4-0.5)	µM	High-Performance Liquid Chromatography (HPLC) using Thiobarbituric Acid (TBA)
11.	Nguyen TT et al., 2016 [45]	Saliva	1.55±0.52	0.36±0.44	µM	Ohkawa method [46]
12.	Fentoglu O 2015 [47]	Serum	31.64±11.51	39.11±10.01	nmol/g	Method of Draper and Hadley [48]
13.	Canakci V et al., 2007 [49]	Saliva	6.71±1.69	6.41±1.77	nmol/mL	Jain SK et al., [50]
		Serum	4.21±0.88	3.46±0.94		
		GCF	3.37±0.23	3.06±0.32		

[Table/Fig-2]: List of studies that evaluated the levels of MDA in periodontally healthy individuals and chronic periodontitis patients [31-50].
GAP: Generalized aggressive periodontitis; *Cell Biolabs' OxiSelect, San Diego, CA, USA; †Bioxytech, MDA-586, Cat. No. 21,044; OxisResearch, Burlingame, CA, USA

decrease in endothelial function due to elevated MAA levels in CHD patients may be attributed to the co-existence of periodontitis. In instance, periodontal therapy dramatically lowered serum MAA levels in periodontitis patients [62].

It has been suggested that the transition from subclinical autoimmunity to clinically evident arthritis may be influenced by the production of malondialdehyde acetaldehyde (MAA) and immune responses against MAA. In rheumatoid arthritis (RA) inflamed synovial tissues, MAA adducts localise independently and, more signalling, colocalise with citrullinated proteins. Notably, MAA-modified proteins have been identified in inflamed periodontal tissue due to oxidative damage induced by inflammation. Further research is needed; however, the available data suggest a potential role for anti-MAA autoantibodies in the development of RA [63]. RA (autoimmune) and periodontal disease (dysbiotic microbial biofilm) have distinct aetiologies, but they share parallel biological processes, such as citrullination, autoantibody response [64], and the crucial role of bacterial dysbiosis, which may serve as direct links between these two conditions [65]. Monea A et al., discovered that diabetics had higher tissue MDA levels than controls in their study. Elevated tissue MDA levels could support the hypothesis that oxidative stress contributes to the development of periodontal disease in diabetics [66].

CONCLUSION(S)

A substantial body of research has demonstrated that OS is the main cause of the development of various inflammatory diseases, including periodontitis. Given this, it is no surprise that Malondialdehyde (MDA) is considered one of the most valuable biomarkers in numerous diseases. In conclusion, MDA serves as a crucial biomarker for assessing OS and potential cellular damage. Its measurement offers valuable insights into the extent of LPO, reflecting the body's response to different stressors, toxins, or pathological conditions. As a reliable indicator, MDA helps in understanding the complex mechanisms of OS-related diseases. Ongoing research on MDA and its associations with various stressors holds promise for enhancing our understanding of cellular damage and developing targeted treatments to mitigate its adverse effects. The advancements in detecting OS in patients with periodontitis will be intriguing to follow, and further research in this area is recommended.

REFERENCES

[1] Janakiram C, Mehta A, Venkitachalam R. Prevalence of periodontal disease among adults in India: A systematic review and meta-analysis. J Oral Biol Craniofacial Res. 2020;10(4):800-06.

[2] Chapple ILC, Matthews JB. The role of reactive oxygen and antioxidant species in periodontal tissue destruction. Periodontol 2000. 2007;43(1):160-232.

[3] Sczepanik FSC, Grossi ML, Casati M, Goldberg M, Glogauer M, Fine N, et al. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. Periodontol 2000. 2020;84(1):45-68.

[4] Altıngöz SM, Kurgan Ş, Önder C, Serdar MA, Ünlütürk U, Uyanık M, et al. Salivary and serum oxidative stress biomarkers and advanced glycation end products in periodontitis patients with or without diabetes: A cross-sectional study. J Periodontol. 2021;92(9):1274-85.

[5] Ryan ME, Gu Y. Host Modulation. In: Textbook of Newman and Carranza's Clinical Periodontology and Implantology. 14th edition. 2023. Pp. 669-71.

[6] Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 2014;20(7):1126-67.

[7] Wang Y, Andrukhov O, Rausch-Fan X. Oxidative stress and antioxidant system in periodontitis. Front Physiol. 2017;8:910.

[8] Ikeda E, Ikeda Y, Wang Y, Fine N, Sheikh Z, Viniegra A, et al. Resveratrol derivative-rich melinjo seed extract induces healing in a murine model of established periodontitis. J Periodontol. 2018;89(5):586-95.

[9] Esterbauer H, Lang J, Zadravec S, Slater TF. Detection of malonaldehyde by high-performance liquid chromatography. In: Methods in Enzymology [Internet]. Academic Press; 1984 Pp. 319-28. [cited 2023 May 21]. (Oxygen Radicals in Biological Systems; vol. 105). Available from: https://www.sciencedirect.com/science/article/pii/S0076687984050412.

[10] Esterbauer H, Cheeseman KH. Determination of aldehydic lipid peroxidation products: Malonaldehyde and 4-hydroxynonenal. Methods Enzymol. 1990;186:407-21.

[11] Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic Biol Med. 1991;11(1):81-128.

[12] Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. 2011;31(5):986-1000.

[13] Tsikas D, Suchy MT, Niemann J, Tossios P, Schneider Y, Rothmann S, et al. Glutathione promotes prostaglandin H synthase (cyclooxygenase)-dependent formation of malondialdehyde and 15(S)-8-iso-prostaglandin $F_{2\alpha}$. FEBS Lett. 2012;586(20):3723-30.

[14] Yin H, Xu L, Porter NA. Free radical lipid peroxidation: Mechanisms and analysis. Chem Rev. 2011;111(10):5944-72.

[15] Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-Hydroxy-2-Nonenal. Oxid Med Cell Longev. 2014;2014:e360438.

[16] Agadjanyan ZS, Dmitriev LF, Dugin SF. A new role of phosphoglucose isomerase. Involvement of the glycolytic enzyme in aldehyde metabolism. Biochem Mosc. 2005;70(11):1251-55.

[17] Pizzimenti S, Ciamporcero E, Daga M, Pettazzoni P, Arcaro A, Cetrangolo G, et al. Interaction of aldehydes derived from lipid peroxidation and membrane proteins. Front Physiol. 2013;4:242.

[18] Tuma DJ, Kearley ML, Thiele GM, Worrall S, Haver A, Klassen LW, et al. Elucidation of reaction scheme describing malondialdehyde- Acetaldehyde- protein adduct formation. Chem Res Toxicol. 2001;14(7):822-32.

[19] Tuma DJ. Role of malondialdehyde-Acetaldehyde adducts in liver injury. Free Radic Biol Med. 2002;32(4):303-08.

[20] Wang G, Li H, Khan MF. Differential oxidative modification of proteins in MRL+/+and MRL/lpr mice: Increased formation of lipid peroxidation-derived aldehyde-protein adducts may contribute to accelerated onset of autoimmune response. Free Radic Res. 2012;46(12):1472-81.

[21] Zarkovic N, Cipak A, Jaganjac M, Borovic S, Zarkovic K. Pathophysiological relevance of aldehydic protein modifications. J Proteomics. 2013;92:239-47.

[22] Niedernhofer LJ, Daniels JS, Rouzer CA, Greene RE, Marnett LJ. Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. J Biol Chem. 2003;278(33):31426-33.

[23] Cline SD, Lodeiro MF, Marnett LJ, Cameron CE, Arnold JJ. Arrest of human mitochondrial RNA polymerase transcription by the biological aldehyde adduct of DNA, M1dG. Nucleic Acids Res. 2010;38(21):7546-57.

[24] Sram RJ, Farmer P, Singh R, Garte S, Kalina I, Popov TA, et al. Effect of vitamin levels on biomarkers of exposure and oxidative damage-The EXPAH study. Mutat Res. 2009;672(2):129-34.

[25] Bevan RJ, Durand MF, Hickenbotham PT, Kitas GD, Patel PR, Podmore ID, et al. Validation of a novel ELISA for measurement of MDA-LDL in human plasma. Free Radic Biol Med. 2003;35(5):517-27.

[26] Jafari M, Solhi E, Tagi S, Hasanzadeh M, Jouyban-Gharamaleki V, Jouyban A, et al. Non-invasive quantification of malondialdehyde biomarker in human exhaled breath condensate using self-assembled organic-inorganic nanohybrid: A new platform for early diagnosis of lung disease. J Pharm Biomed Anal. 2019;164:249-57.

[27] Tsikas D, Rothmann S, Schneider JY, Suchy MT, Trettin A, Modun D, et al. Development, validation and biomedical applications of stable-isotope dilution GC-MS and GC-MS/MS techniques for circulating malondialdehyde (MDA) after pentafluorobenzyl bromide derivatization: MDA as a biomarker of oxidative stress and its relation to 15(S)-8-iso-prostaglandin F 2α and nitric oxide (NO). J Chromatogr B. 2016;1019:95-111.

[28] Hanff E, Eisenga MF, Beckmann B, Bakker SJL, Tsikas D. Simultaneous pentafluorobenzyl derivatization and GC-ECNICI-MS measurement of nitrite and malondialdehyde in human urine: Close positive correlation between these disparate oxidative stress biomarkers. J Chromatogr B. 2017;1043:167-75.

[29] Takamura T aki, Tsuchiya T, Oda M, Watanabe M, Saito R, Sato-Ishida R, et al. Circulating malondialdehyde-modified low-density lipoprotein (MDA-LDL) as a novel predictor of clinical outcome after endovascular therapy in patients with peripheral artery disease (PAD). Atherosclerosis. 2017;263:192-97.

[30] Mohideen K, Chandrasekar K, Ramsridhar S, Rajkumar C, Ghosh S, Dhungel S. Assessment of oxidative stress by the estimation of lipid peroxidation marker Malondialdehyde (MDA) in patients with chronic periodontitis: A systematic review and meta-analysis. Chien HH, editor. Int J Dent. 2023;2023:6014706.

[31] Veljovic T, Djuric M, Mirnic J, Gusic I, Maletin A, Ramic B, et al. Lipid peroxidation levels in saliva and plasma of patients suffering from periodontitis. J Clin Med. 2022;11(13):3617.

[32] Warad SB, Pattanashetti J, Kalburgi N, Koregol A, Rao S. Estimation of salivary malondialdehyde levels in smokeless tobacco chewers with chronic periodontitis-A cross sectional clinico-biochemical study. Odovtos- Int J Dent Sci. 2021;3(3):56-65.

[33] Shiny I, Talwar A, Kumari S, Thomas B. Malondialdehyde-an end product of tissue destruction in periodontal disease. Int J Sci Res. 2020;11(08 C):39518-21.

[34] Buege JA, Aust SD. Microsomal lipid peroxidation. In: Fleischer S, Packer L, editors. Methods Enzymol. 1978:52:302-10. Available from: https://www.sciencedirect.com/science/article/pii/S0076687978520326.

[35] Sánchez-Villamil JP, Pino-Vélez C, Trejos-Suárez J, Cardona N, España AL, Alfonso PA. Salivary markers of oxidative stress and periodontal pathogens in patients with periodontitis from Santander, Colombia. Biomédica. 2020;40(Suppl 1):113-24.

[36] Cherian DA, Peter T, Narayanan A, Madhavan SS, Achammada S, Vynat GP. Malondialdehyde as a marker of oxidative stress in periodontitis patients. J Pharm Bioallied Sci. 2019;11(Suppl 2):S297-300.

[37] Narendra S, Das U, Tripathy S, Sahani N. Superoxide dismutase, uric acid, total antioxidant status, and lipid peroxidation assay in chronic and aggressive periodontitis patients. J Contemp Dent Pract. 2018;19(7):874-80.
[38] Satoh K. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. Clin Chim Acta Int J Clin Chem. 1978;90(1):37-43.
[39] Tripathi V, Singh ST, Sharma V, Verma A, Singh CD, Gill JS. Assessment of lipid peroxidation levels and total antioxidant status in chronic and aggressive periodontitis patients: An in vivo study. J Contemp Dent Pract. 2018;19(3):287-291.
[40] Young IS, Trimble ER. Measurement of malondialdehyde in plasma by high performance liquid chromatography with fluorimetric detection. Ann Clin Biochem Int J Lab Med. 1991;28(5):504-08.
[41] Lütfioğlu M, Aydoğdu A, Atabay V, Sakallıoğlu E, Avci B. Gingival crevicular fluid oxidative stress level in patients with periodontal disease and hyperlipidemia. Braz Oral Res. 2017;31.
[42] Dahiya P, Kamal R, Gupta R, Saini H. Evaluation of the serum antioxidant status in patients with chronic periodontitis. Indian J Multidiscip Dent. 2016;6:03-06.
[43] Yagi K. Lipid peroxides and human diseases. Chem Phys Lipids. 1987;45(2-4):337-51.
[44] Ghallab N, Hamdy E, Shaker O. Malondialdehyde, superoxide dismutase and melatonin levels in gingival crevicular fluid of aggressive and chronic periodontitis patients. Aust Dent J. 2016;61(1):53-61.
[45] Nguyen TT, Ngo LQ, Promsudthi A, Surarit R. Salivary lipid peroxidation in patients with generalized chronic periodontitis and acute coronary syndrome. J Periodontol. 2016;87(2):134-41.
[46] Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-58.
[47] Fentoğlu Ö, Kırzıoğlu FY, Bulut MT, Kumbul Doğuç D, Kulaç E, Önder C, et al. Evaluation of lipid peroxidation and oxidative DNA damage in patients with periodontitis and hyperlipidemia. J Periodontol. 2015;86(5):682-88.
[48] Draper HH, Hadley M. Malondialdehyde determination as index of lipid peroxidation. Methods Enzymol. 1990;186:421-31.
[49] Canakci V, Yildirim A, Canakci CF, Eltas A, Cicek Y, Canakci H. Total antioxidant capacity and antioxidant enzymes in serum, saliva, and gingival crevicular fluid of preeclamptic women with and without periodontal disease. J Periodontol. 2007;78(8):1602-11.
[50] Jain SK, McVie R, Duett J, Herbst JJ. Erythrocyte membrane lipid peroxidation and glycosylated hemoglobin in diabetes. Diabetes. 1989;38(12):1539-43.
[51] Batu Ş, Ofluoğlu D, Ergun S, Warnakulasuriya S, Uslu E, Güven Y, et al. Evaluation of prolidase activity and oxidative stress in patients with oral lichen planus and oral lichenoid contact reactions. J Oral Pathol Med. 2016;45(4):281-88.
[52] Mehdipour M, Taghavi Zenouz A, Dastanpour S, Bahramian A, Gholizadeh N, Azari-Marhabi S. Evaluation of serum Malondialdehyde level in patients with oral lichen planus. Caspian J Dent Res 2017;6(1):45-48. Available from: https://doi.org/10.22088/cjdr.6.1.45.
[53] Tvarijonaviciute A, Aznar-Cayuela C, Rubio CP, Ceron JJ, López-Jornet P. Evaluation of salivary oxidate stress biomarkers, nitric oxide and C-reactive protein in patients with oral lichen planus and burning mouth syndrome. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol. 2017;46(5):387-92.
[54] Shiva A, Arab S. Evaluation of uric acid, total antioxidant and lipid peroxidation parameters in serum and saliva of patients with oral lichen planus. Glob J Health Sci. 2016;8(12):225.
[55] Lopez-Jornet P, Martinez-Canovas A, Pons-Fuster A. Salivary biomarkers of oxidative stress and quality of life in patients with oral lichen planus. Geriatr Gerontol Int. 2014;14(3):654-59.
[56] Malik UU, Siddiqui IA, Hashim Z, Zarina S. Measurement of serum paraoxonase activity and MDA concentrations in patients suffering with oral squamous cell carcinoma. Clin Chim Acta. 2014;430:38-42.
[57] Metgud R, Bajaj S. Evaluation of salivary and serum lipid peroxidation, and glutathione in oral leukoplakia and oral squamous cell carcinoma. J Oral Sci. 2014;56(2):135-42.
[58] Giebułtowicz J, Wroczyński P, Samolczyk-Wanyura D. Can lower aldehyde dehydrogenase activity in saliva be a risk factor for oral cavity cancer? Oral Dis. 2013;19(8):763-66.
[59] Tekin U, Kısa Ü, Güven O, Kurku H. Malondialdehyde levels in dental follicles of asymptomatic impacted third molars. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2011;69(5):1291-94.
[60] Graziani F, D'Aiuto F, Gennai S, Petrini M, Nisi M, Cirigliano N, et al. Systemic inflammation after third molar removal: A case-control study. J Dent Res. 2017;96(13):1505-12.
[61] Camacho-Alonso F, Tudela-Mulero MR, Peñarrocha-Oltra D, Peñarrocha-Diago M, Balaguer-Martí JC, Sánchez-Siles M. Salivary myeloperoxidase and malondialdehyde are increased in patients exhibiting an asymptomatic mandibular impacted third molar. Med Oral Patol Oral Cirugia Bucal. 2019;24(4):e537-44.
[62] Isola G, Polizzi A, Santonocito S, Alibrandi A, Ferlito S. Expression of salivary and serum malondialdehyde and lipid profile of patients with periodontitis and coronary heart disease. Int J Mol Sci. 2019;20(23):6061.
[63] Mikuls TR, Edison J, Meeshaw E, Sayles H, England BR, Duryee MJ, et al. Autoantibodies to malondialdehyde-acetaldehyde are detected prior to rheumatoid arthritis diagnosis and after other disease specific autoantibodies. Arthritis Rheumatol Hoboken NJ. 2020;72(12):2025-29.
[64] Bright R, Thiele GM, Manavis J, Mikuls TR, Payne JB, Bartold PM. Gingival tissue, an extra synovial source of malondialdehyde-acetaldehyde adducts citrullinated and carbamylated proteins. J Periodontal Res. 2018;53(1):139-43.
[65] Laugisch O, Wong A, Sroka A, Kantyka T, Koziel J, Neuhaus K, et al. Citrullination in the periodontium- A possible link between periodontitis and rheumatoid arthritis. Clin Oral Investig. 2016;20(4):675-83.
[66] Monea A, Mezei T, Popsor S, Monea M. Oxidative stress: A link between diabetes mellitus and periodontal disease. Int J Endocrinol. 2014;2014:917631.

PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Periodontics and Community Dentistry, Dr. Ziauddin Ahmad Dental College, Aligarh, Uttar Pradesh, India.
2. Junior Resident, Department of Periodontics and Community Dentistry, Dr. Ziauddin Ahmad Dental College, Aligarh, Uttar Pradesh, India.
3. Assistant Professor, Department of Periodontics and Community Dentistry, Dr. Ziauddin Ahmad Dental College, Aligarh, Uttar Pradesh, India.
4. Senior Resident, Department of Periodontics, PGIMER, Chandigarh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Arthy Arrvind,
Room No. 8, Fazal Resiplex, Al-Shafi Compound,
Medical Road, Aligarh, Uttar Pradesh-202001, India.
E-mail: art10.dent@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 07, 2023
- Manual Googling: Dec 30, 2023
- iThenticate Software: Feb 03, 2024 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Nov 04, 2023**
Date of Peer Review: **Dec 23, 2023**
Date of Acceptance: **Feb 05, 2024**
Date of Publishing: **Mar 01, 2024**