Review Article

The relationship between oxidative stress markers and temporomandibular disorders: A systematic review and meta-analysis

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Background: Oxidative stress has a role in many pathologic conditions, including oral diseases and temporomandibular joint disorders (TMDs) pathophysiology. This study compared the selected oxidative biomarkers' levels in TMD patients and healthy controls in a systematic review and meta-analysis. **Materials and Methods:** Medline/PubMed, Scopus, Web of Science, Google Scholar, and Embase were systematically searched for English articles up to October 2022 using MeSH and free keywords. Joanna Briggs Institute checklist was used to assess the risk of bias. Differences between biomarker levels in TMD patients were compared to the control group. **Results:** Ten case–control studies were included based on inclusion and exclusion criteria with a total of 659 patients: 314 with TMD and 345 healthy controls. The studies investigated 15 markers, including total oxidant status (TOS), total antioxidant status, and malondialdehyde (MDA). There was a significant difference in the salivary MDA of patients with TMD in comparison with healthy people; standard mean difference = 3.22 (95% confidence interval [CI]: 0.28–6.16); I^2 = 96.0%). The Antioxidant status in serum was significantly lower in patients with TMD in comparison with healthy people; weighted mean difference = −0.52 (95% CI: −0.90 to −0.14; I^2 = 97.0%). The result of TOS was inconclusive. **Conclusion:** Salivary MDA and serum total antioxidative status measurements may be used as a biomarker for diagnosing TMD. Due to the lack of sufficient evidence, it is not possible to express a definite relation between the amount and type of marker and TMD diagnosis, which suggests that more case–control studies with larger sample sizes are required.

Key words: Antioxidants, biomarkers, meta-analysis, oxidative stress, saliva, temporomandibular joint disorders

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INTRODUCTION

Temporomandibular joint disorders (TMDs) are a group of disorders that affect the temporomandibular joint and masseteric muscles.[1] TMD is considered a multifactorial disease, and many factors, such as genetic, biological, behavioral, environmental, social, and emotional factors could play a part.[2] Diagnosing the origin of the pain is challenging, and the treatment plan depends on it.[3] TMD is determined by pain or discomfort in the temporomandibular joint, the area around the ear, and the masseteric muscles or neck on one or both sides.[4] It could also be accompanied by joint sounds, limited movement, or deviation of the mandible.[1,4]

Exposure to chronic stress could cause hyperalgesia due to the hypothalamus–hypophysis–adrenal axis.[5,6] Stresses such as parafunctional habits (bruxism and clenching) may cause irreparable damage to the TMJ.[6,7] Loading stress will lead to free oxygen radicals, arachidonic acid catabolites, neuropeptides, cytokines, and matrix metalloproteinase enzymes released from the TMJ tissues.[8,9]

Reactive oxygen species (ROS) is a group of reactive molecules necessary in specific amounts for some

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physiologic cell functions such as signaling.[10-13] Still, at higher rates, it could cause cell structure destruction, such as lipids, proteins, and nucleic acids and lead to oxidative stress.[14,15] Oxidative stress results from the production of unbalanced pro-oxidant/antioxidant factors, generating ROS products such as H_2O_2, organic hydroperoxides, nitric oxides, superoxide, and hydroxyl radicals.[13-17]

Considering that TMD pain and discomfort affect life quality and daily activities, understanding the pathophysiology behind TMD, the mechanisms involved in the onset of pain, and its intensity is crucial for determining the prognostic factors and improving treatment strategies.[11]

Since oxidative stress markers could show promising potential as biological markers for TMD diagnosis and treatment, and considering the studies measuring salivary oxidative markers in TMD patients, this systematic review and meta-analysis study is conducted to determine the relationship between oxidative stress markers and TMD.

METHODS

This systematic review was performed based on the guidelines recommended by the PRISMA statement for writing systematic reviews and has been approved by the Regional Ethics Committee (IR.TBZMED.REC.1401.269).

The question addressed by this review was based on the control, comparison, and outcomes model. The main question was: is there a difference between salivary and serum oxidative markers (outcome) in TMD patients (comparison) and healthy individuals (Control)?.

Literature searching and study selection criteria

Medline/PubMed, Scopus, Web of Science, Google Scholar, and Embase were systematically searched for English articles up to October 2022 using MeSH and free keywords. No restriction was put on the start date. In addition, selected studies' lists of references and related conferences were manually searched.

MeSH and free keywords with a combination of (OR) and (AND) were used for data collection using the following keywords: "Temporomandibular disorder(s)," "Temporomandibular joint disorder(s)," "Temporomandibular joint dysfunction," "TMJ disorder(s)" OR "TM disorder(s)," "Temporomandibular joint pain," "Temporomandibular pain," "TM pain," "TMJ pain," "TMD," "Osteoarthritis," "Temporomandibular joint dysfunction syndrome," "TAOC," "total antioxidant capacity," "MDA," "malondialdehyde," "SOD," "superoxide dismutase," "GPX," "glutathione peroxidase," "NO," "nitric oxide," "TOS," "total oxidant status" and: 8-OHdG" "8-hydroxy-deoxyguanosine" OR "reactive oxygen species," "ROS," "oxidant*," "antioxidant*."

Inclusion and exclusion criteria

Studies comparing an oxidative stress marker in patients with TMD and controls were included. The studies in which an intervention was done, or the samples were taken from synovial fluid, were excluded. Review studies, case reports, letters to the editor, animal and laboratory studies, studies of poor quality, studies with no control group, and non-English articles were excluded.

Data extraction and quality assessment

After extracting potentially eligible studies from databases, studies were reviewed by two independent specialists (K.K and H.E), who scanned the articles' titles and abstracts based on inclusion and exclusion criteria. Any disagreements were solved by consulting a third reviewer (M.H). In the next step, full texts of the selected studies were extracted.

Two independent reviewers (K.K and M.H) used the Joanna Briggs Institute (JBI) checklist to measure the risk of bias. In the case of a disagreement on scores between two reviewers, a final mutual decision was made. Articles were assessed regarding sample selection, sample size, study context, outcome measurement quality, statistical analysis, and confounding factors. The risk of bias was classified as low when the study reached a "yes" score of >70, moderate when the study reached a "yes" score of 50%–70%, and high when the study reached a "yes" score of <49%. Only articles receiving low and moderate risk of bias were included in meta-analysis.[18]

Data regarding the country of the studies, type of TMD, characteristics of the control group, sample size, age of the participants, and the source of the samples were extracted from the studies. The outcome was oxidative markers which were extracted for TMD and controls. Cross-sectional studies investigating the difference between oxidative stress marker levels in TMD patients and the control group were analyzed.

Statistical analysis

Weighted mean differences (WMD), endpoint scores, or change scores representing the difference between intervention and control groups were used as effect sizes. Standard mean difference (SMD) was used when no same rating scale was used for assessing oxidative stress markers in the study groups. The pooled WMD and SMD with 95% confidence intervals (CIs) were calculated using the Der Simonian and Laird method through the random effects model. Cochran's Q-test and I^2 were performed for assessing the heterogeneity between the studies. Due to heterogenicity among studies, random-effects model was used for the

meta-analysis.[19] To identify sources of heterogeneity, sensitivity analysis was done by removing a particular study that had the highest impact on the heterogeneity. Since there were less than ten studies in each meta-analysis, evaluation of publication bias and subgroup analysis was not applicable.[19] All statistical analyses were performed using STATA version 14.0 (STATA Corporation, College Station, Texas, USA). The significance level for $P < 0.05$.

RESULTS

Search results

One hundred and forty-one papers were initially identified, and after removing duplicate studies and irrelevant studies, 18 studies remained, two studies were review studies,[10] one was a laboratory study,[20] one was an animal study,[21] and four studies did not have a control group,[22-25] which were all excluded. Finally, ten studies fulfilled the criteria for the study [Figure 1].

The results of evaluating the risk of bias

According to the JBI checklist, one study showed a moderate risk of bias,[11] and the others had a low risk.[17,26-31] None of the studies had a high risk of bias. Details are presented in Table 1.

Characteristics of the studies

A total of 10 studies were assessed with a total of 659 patients: 314 with TMD and 345 healthy controls. The sample size ranged from 30 to 140. The studies investigated a total of 15 markers. Sample sources were either serum or saliva. The descriptive characteristics of the included articles are presented in Table 2.

Four studies assessed total oxidant status (TOS) among them; one study measured serum total oxidative stress levels,[26] and three studies measured salivary TOS levels [Table 3]. Total antioxidant status (TAS)

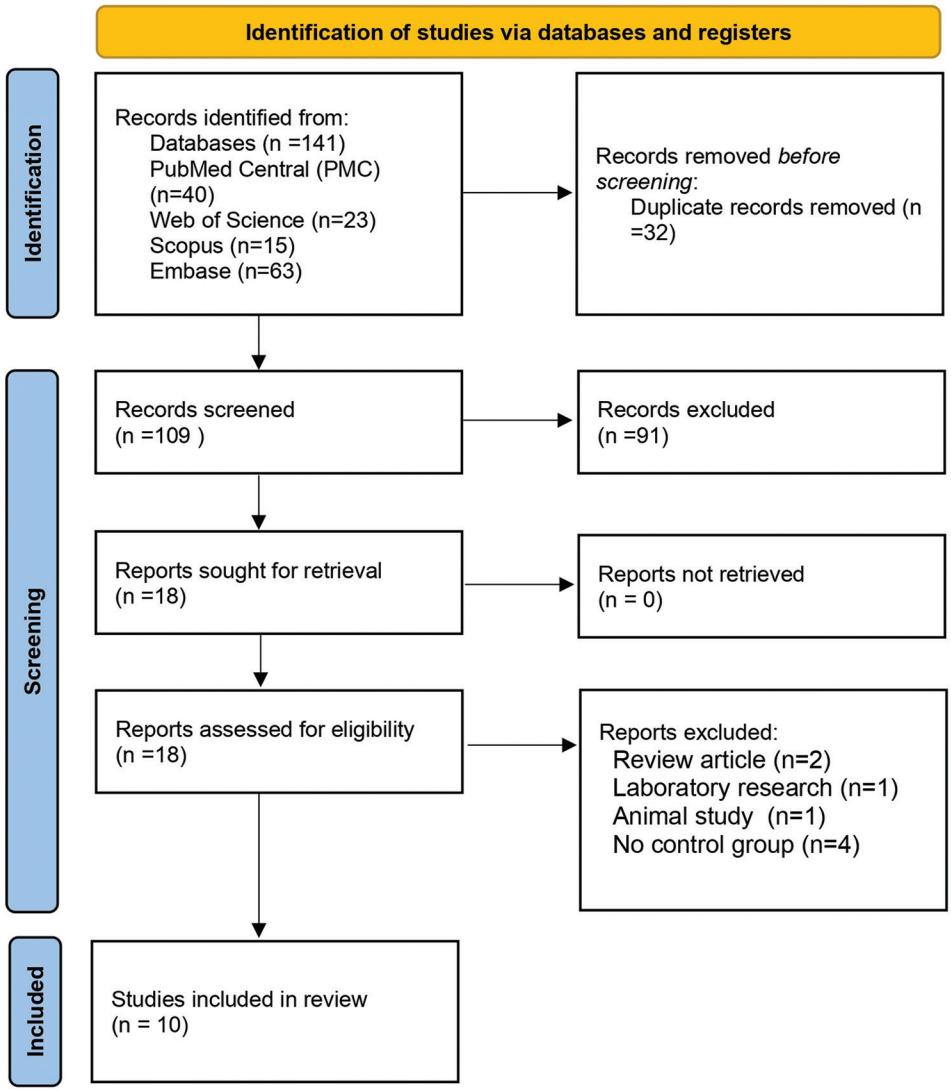

Figure 1: The PRISMA flowchart of the selection process of the study

Table 1: The results of the Joanna Briggs Institute checklist of quality assessment

Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total	Risk of bias
Ege, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9/10	Low
Basi, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10	Low
Demir, 2018	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8/10	Low
de Sotillo, 2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/10	Low
Lawaf, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10	Low
de Almeida, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	8/10	Low
Madariaga, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9/10	Low
Omidpanah, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No	7/10	Moderate
Yaman, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10	Low
Vrbanovic, 2018	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	8/10	Low

NA=Not applicable; Q1=Was the sample representative of the target population?; Q2=Were study participants recruited appropriately?; Q3=Was the sample size adequate?; Q4=Were the study subjects and the setting described in detail?; Q5=Was the data analysis conducted with sufficient coverage of the identified sample?; Q6=Was objective, standard criteria used for the measurement of the condition?; Q7=Was the condition measured reliably?; Q8=Was there appropriate statistical analysis?; Q9=Are all important confounding factors/subgroups/differences identified and accounted for?; Q10=Were subpopulations identified using objective criteria?

Table 2: The descriptive characteristics of the included articles

Study	Country	Type of TMD	Control group	Study groups	Sample size	Mean age±SD
de Sotillo, 2011	USA	Temporomandibular muscle and joint disorders	Non-TMD, nonsmoker females	TMD	20 female	40.5±15.5
				Control	10 female	42.5±11.9
Basi, 2012	USA	Temporomandibular muscle and joint disorders and Myofascial pain	No history of TMD symptoms, absence of TMJ noise, locking or catching of the jaw, pain in the jaw or the temporal area	TMD	23	23.9±6.9
				Control	27	24.8±5.8
Lawaf, 2015	Iran	Patients with TMD	Healthy individuals with no systemic condition or drug use, matched for smoking and periodontal disease	TMD	56 (28 female, 28 male)	29.1±3.9
				Control	28 (14 female, 14 male)	28.5±3.9
de Almeida, 2016	Brazil	Temporomandibular disorders and pain	Healthy age-matched students and staff from the University	TMD	30 (27 female, 3 male)	10–60*
				Control	30 (27 female, 3 male)	10–60*
Vrbanovic, 2018	Croatia	Painful disc displacement or myofascial pain TMD	Healthy age-matched Females	TMD	20 female	39.3±12.0
				Control	15 female	34.3±7.8
Demir, 2018	Turkey	Patients with TMJ disorders	Healthy age-matched individuals	TMD	32 (22 female, 10 male)	27.4±9.4
				Control	32 (20 female, 12 male)	27.4±8.8
Ege, 2019	Turkey	TMJ internal derangement	Healthy age-matched individuals with no systemic disease, no history of drug use or TMD	TMD	70 (60 female, 10 male)	27.3±11.0
				Control	70 (35 female, 35 male)	26.8±7.7
Yaman, 2020	Turkey	Rheumatoid arthritis	Age and sex-matched healthy individuals	TMD	30 (25 female, 5 male)	42.6±10.8
				Control	30 (25 female, 5 male)	42.6±10.8
Omidpanah, 2020	Iran	Patients with temporomandibular disorders	Age- and sex-matched healthy individuals without any systemic disease or history of taking medications, smoking, or alcohol use	TMD	30 (25 female, 5 male)	30.7±13.2
				Control	30 (25 female, 5 male)	29.1±11.2
Madariaga, 2021	Sweden	Myelogenous temporomandibular disorders	Self-reported healthy individuals with no evidence of disease or current pain	TMD	39 (32 female, 7 male)	27.0±8.2
				Control	37 (31 female, 6 male)	28.2±10.7

*Age reported as range in this study. TMD=TMJ disorders; TMJ=Temporomandibular joint

levels were reported in seven studies, among which three studies measured TAS levels in serum and six in saliva [Table 3].

Malondialdehyde (MDA) was investigated in four studies, and two reported MDA levels in serum [Table 4]. 8-hydroxy-deoxyguanosine was mentioned in two studies [Table 4], which indicated that the levels of 8-OHdG in saliva ($P < 0.0001$) and serum ($P = 0.0008$) of TMD patients were statistically higher than the control group. The comparison of other markers' levels is shown in Table 5.

Meta-analysis

The random-effects analysis demonstrated a higher level of serum MDA in patients with TMD than controls although this was not significant; WMD = 0.75 (95% CI: −0.23–1.74; $I^2 = 97.0\%$). Figure 2a shows the meta-analysis of pooled WMD of MDA in serum (mmol/L) between patients with temporomandibular disorders and healthy people.

There was a significant difference in the pooled estimate SMD of MDA in saliva in patients with TMD in comparison with healthy people; SMD = 3.22 (95% CI: 0.28–6.16);

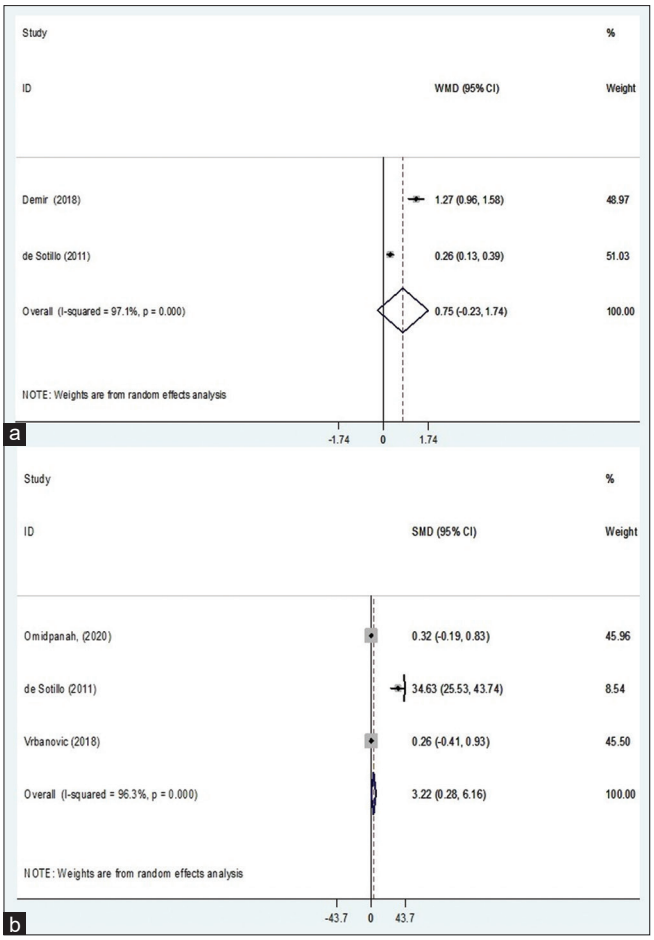

Figure 2: Meta-analysis of pooled mean difference of malondialdehyde in serum (mmol/L) (a) and Saliva (b)

I^2 = 96.0%) [Figure 2b]. Overall, we estimated that the MDA's serum and salivary level are higher in TMD patients.

The random-effects analysis showed that the level of salivary antioxidants is lower in temporomandibular disorders with no significant difference SMD = −0.63 (95% CI: −1.61–0.35; I^2 = 91.7%). Figure 3a indicates the meta-analysis of the pooled SMD of antioxidant status in saliva among patients with temporomandibular disorders and healthy people.

The pooled WMD of antioxidant status in serum was significantly lower in patients with temporomandibular disorders in comparison with healthy people; WMD = −0.52 (95% CI: −0.90–−0.14; I^2 = 97.0%) [Figure 3b].

Sensitivity analysis

The study by Yaman *et al.*[17] included patients with rheumatoid arthritis (RA). Because this disease has an autoimmune base, the meta-analysis of TAS in saliva was repeated without this study. With or without this article, the salivary antioxidant levels were lower in patients than in healthy individuals, although this difference increases by excluding this study [Figure 3c].

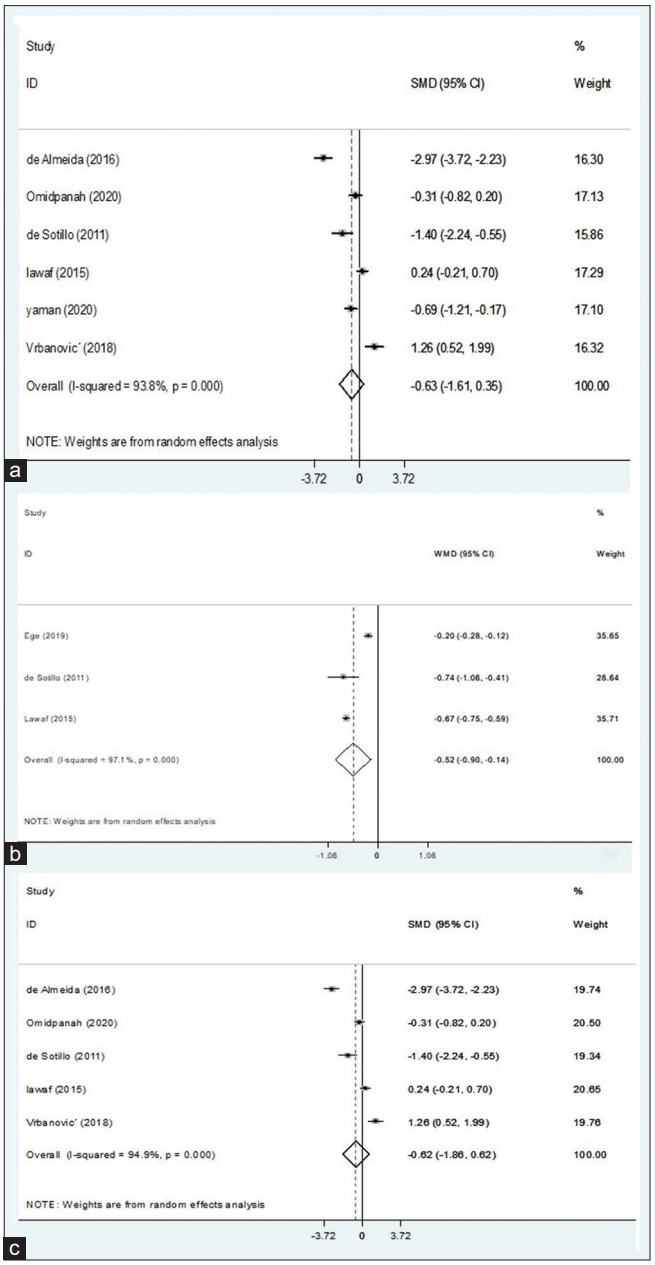

Figure 3: Meta-analysis of pooled mean difference of antioxidant status in saliva (a) and serum (b) (mmol trolox equivalent/L) between patients with temporomandibular disorders and controls and with the exclusion of Yaman *et al.*[17] (c)

DISCUSSION

Mechanical pressure on TMJ and masseteric muscles and degenerative disc disorders could lead to free oxygen radicals' release through different mechanisms, which will cause oxidative stress.[32] Many studies have suggested that the lack of balance between the oxidant and antioxidant factors has a role in TMD and other diseases' pathogenesis in recent years. In this systematic review, the oxidative factors' level was compared in patients with TMD in the healthy control group.

Table 3: Total oxidant status and total antioxidant status levels in serum and saliva

Study	Source	Marker	Study groups	Mean±SD
Ege, 2019	Serum	TOS (mmol H_2O_2 equivalent/L)	TMD	14.61±2.59
			Control	12.27±2.41
de Almeida, 2016	Saliva	TOS (μmol H_2O_2 equivalent/L)	TMD	4.402±0.418
			Control	4.671±0.234
Yaman, 2020		TOS	TMD	14.12±25.37
			Control	3.75±1.63
Madariaga, 2021		TOS	TMD	6*
			Control	9.5*
de Sotillo, 2011	Serum	TAS (mmol trolox equivalent/L)	TMD	0.86±0.41
			Control	1.6±0.46
Lawaf, 2015		TAS	TMD	1.08±0.24
			Control	1.75±0.187
Ege, 2019		TAS	TMD	1.27±0.29
			Control	1.47±0.2
de Sotillo, 2011	Saliva	TAS (mmol trolox equivalent/L)	TMD	1.33±0.77
			Control	2.24±0.26
Lawaf, 2015		TAS	TMD	1.38±0.13
			Control	1.35±0.116
de Almeida, 2016		TAS	TMD	0.13±0.043
			Control	0.264±0.047
Vrbanovic, 2018		TAS	TMD	5.47±2.85
			Control	2.65±0.911
Yaman, 2020		TAS	TMD	0.57±0.25
			Control	0.72±0.18
Omidpanah, 2020		TAS	TMD	751.2±408.7
			Control	939.1±723.8
Madariaga, 2021		TAS	TMD	1350*
			Control	1250*

*SD not reported. SD=Standard deviation; TMD=Temporomandibular joint disorders; TOS=Total oxidant status; TAS=Total antioxidant status

Table 4: Malondialdehyde and 8-hydroxy-deoxyguanosine levels in serum and saliva

Study	Source	Marker	Study groups	Mean±SD
de Sotillo, 2011	Serum	Malondialdehyde (mmol/L)	TMD	1.0±0.2
			Control	0.7±0.1
Demir, 2018		Malondialdehyde	TMD	1.4–0.2±4.27
			Control	0.6–0.1±0.16
de Sotillo, 2011	Saliva	Malondialdehyde (nmol/mL)	TMD	1.415±0.40
			Control	0.92±0.34
Vrbanovic, 2018		Malondialdehyde	TMD	412.4±378.6
			Control	329.9±214.5
Omidpanah, 2020		Malondialdehyde	TMD	30.5±(female 29.5, male 8.4)
			Control	24.1±(female 7.3, male 7.8)
de Sotillo, 2011	Serum	8-OHdG (ng/mL)	TMD	0.9±0.7
			Control	0.0±0.4
de Sotillo, 2011	Saliva	8-OHdG (ng/mL)	TMD	2.6±0.3
			Control	1.4±0.4
Vrbanovic, 2018		8-OHdG	TMD	1.7±1.4
			Control	1.9±0.9

SD=Standard deviation; TMD=Temporomandibular joint disorders; 8-OHdG=8-hydroxy-deoxyguanosine; SD=Standard deviation

Nitzan *et al*. suggested that uncontrolled oxidative stress causes the lubrication system's collapse, which is the primary reason for TMJ problems.[33] The presence of inflammation and pain in the muscles or TMJ leads to more free radicals at the site, which initiates a cascade of inflammatory reactions in the joint or muscle.[32] Studies on the mechanism of chronic muscle pain indicate that a local increase in oxidative metabolism, especially in type I muscle fibers, increases the by-products of oxidative metabolism, and stimulates peripheral nociceptors.[34,35]

Since measuring each oxidative and antioxidative factor is time-consuming, using TOS and total antioxidant capacity (TAC) could save time and money. Previous studies have confirmed that serum and salivary TAC levels decrease in patients with joint and muscular problems.[34] Among the included articles, eight articles investigated TAC and TOS levels of TMD patients' serum and saliva, which stated contradictory results. According to Lawaf *et al*., TAC levels in TMD patients' plasma with/without pain were meaningly less than the control group, showing the imbalance between oxidant/antioxidant levels due to the pain mechanism.[29] Rodríguez de Sotillo *et al*. observed lower serum and salivary TAC levels in TMD patients and stated that salivary biomarkers can be a reliable predictor for pain severity and have a significant correlation with serum antioxidant levels.[31] De Almeida and Amenábar showed that salivary TAC levels in TMD patients with pain are significantly lower, whereas salivary TOS levels were similar in both TMD groups, concluding that oxidate stress increases in TMD patients experiencing pain.[27] Yaman *et al*.'s study also observed lower TAS levels and higher oxidative stress levels in RA patients compared to the control group. However, TOS values were not different from the control group.[17] Ege *et al*. stated that the significant increase in TOS and oxidative stress index (OSI) in patients with TMD may be related to long-term collagen tissue damage and inflammation and could be effective in the etiology of TMD.[26] The studies of Omidpanah *et al*. and Madariaga *et al*. reported different results. Omidpanah *et al*. showed that TAC levels in saliva in TMD patients were similar to healthy individuals.[6] A study on myogenic temporomandibular disorders patients by Madariaga *et al*. showed higher levels of antioxidant markers (TAC) and lower levels of oxidative markers (TOS).[11] Vrbanović *et al*. similarly observed higher levels of TAC in TMD patients.[36] The results of these studies are partly related to chronicity and adaptation to the disease and other factors such as psychological stress.[11]

In a study performed on TMJ patients with and without pain, although there is no relationship between TAC and the severity of patients' pain, plasma TAC levels were significantly lower in patients with limited mouth opening.[23] According to the meta-analysis results, the level of antioxidants in saliva and serum is lower in temporomandibular disorders than in healthy controls. Our

Table 5: Other marker levels from serum and saliva

Marker	Study	Source	Study groups	Mean±SD
SOD (U/mg)	Demir, 2018	Serum	TMJ disorders	1.78–1.31*
			Control	8.24–0.59*
	Madariaga, 2021	Saliva	Myogenous temporomandibular disorders	3.1†
			Control	3†
Glutathione (nmol/mL)	Demir, 2018	Serum	TMJ disorders	21–140*
			Control	93–6,060,000*
	Ege, 2019		TMJ derangement	10.30±2.09
			Control	10.98±2.30
Prolidase (ng/mL)	Ege, 2019	Serum	TMJ internal derangement	248.79±46.34
			Control	167.67±51.83
OSI	Ege, 2019	Serum	TMJ internal derangement	1.12 (0.72–3.08)*
			Control	0.80 (0.53–1.54)*
	de Almeida, 2016	Saliva	Temporomandibular disorders and pain	4.2±0.4
			Control	1.5±0.2
	Yaman, 2020		Rheumatoid arthritis+TMD	2.12±3.15
			Control	0.54±0.28
FRAP (nmol/mL)	Ege, 2019	Serum	TMJ internal derangement	8.20 (2.33–14.65)*
			Control	10.18 (7.50–15.46)*
AOPP (nmol/nL)	Ege, 2019	Serum	TMJ internal derangement	0.44 (0.25–2.34)*
			Control	0.30 (0.19–1.49)
LOOH (nmol/mL)	Ege, 2019	Serum	TMJ internal derangement	0.94 (0.69–4.70)*
			Control	0.55 (0.23–6.76)*
F2-isoprostan (pg/mL)	Basi, 2012	Serum	Temporomandibular muscle and joint disorders and myofascial pain	8.8 (7.8–9.9)*
			Control	8.7 (7.7–9.7)*
CAT (U/mg)	Demir, 2018	Serum	TMJ disorders	0.0077–0.00018*
			Control	0.274–0.237*
	Omidpanah, 2020	Saliva	Temporomandibular disorders	0.535±0.405
			Control	0.466±0.37
Arylesterase (U/L)	Yaman, 2020	Saliva	Rheumatoid arthritis+TMD	314.20±29.75
			Control	318.60±11.44
GPX (U/g)	Vrbanović, 2018	Saliva	Painful disc displacement or myofascial pain	56.59†
			Control	91.74†

*The data is presented as median-interquartile range; †SD not reported. FRAP=Ferric reducing antioxidant power; AOPP=Advanced oxidation protein products; LOOH=lipid hydroperoxide; SD=Standard deviation; TMJ=Temporomandibular joint; TMD=TMJ disorders; OSI=Oxidative stress index; SOD=Superoxide dismutase; GPX=Glutathione peroxidase; CAT=Catalase

results also indicate a lower salivary TOS in patients with TMD than the controls.

MDA is a valuable indicator showing the high lipid peroxidation level, which leads to cell dysfunction.[38] Inflammatory cells, fibroblasts, endothelial cells, and osteoclasts can produce ROS.[37] MDA is the product of membrane lipids' peroxidation by free radicals, which have a low-molecular weight. Due to its simplicity, MDA measurement is the most used technique to assess the extent of oxidative stress damage to lipids.[39] Previous studies have shown increased MDA levels in patients with inflammatory diseases and acute pain.[40-42] Demir *et al*. also stated that antioxidant treatment may delay the progression of oxidative stress damage, reduce inflammation, and slow the progression of TMD. This case–control study showed that oxidative stress in TMJ disorders is associated with high levels of MDA.[30] An increase in MDA with increasing pain intensity in TMD patients was also observed in the studies of Rodríguez de Sotillo *et al*. and Omidpanah *et al*.[6,31] The meta-analysis results showed that patients with TMD had higher levels of serum MDA.

Antioxidant defense mechanisms are to prevent redox imbalance (oxidation and reduction) and oxidative damage, which are divided into two groups: antioxidant enzymes and nonenzymatic antioxidants. Superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) are among the antioxidant enzymes.[43,44] The results of Demir *et al*. showed reduced levels of the antioxidants such as CAT and SOD in the serum which resulted in oxidative stress in TMJ disorders.[30] However, another study showed that an increase in the production of free radicals increases the production of antioxidant enzymes.[25] Similarly, Vrbanović *et al*. stated higher salivary GPX levels in TMD patients.[36]

Glutathione (GSH) is an antioxidant enzyme that plays a key role against oxidative stress and is essential for eliminating

free radical species and protecting the membrane proteins.[45] Therefore, GSH may help reduce inflammation and TMD progression.[46] In the study of Demir *et al*., the serum level of GSH in the control group was significantly higher than in the TMD group.[30] In the study of Ege *et al*., the groups had no significant difference in GSH levels.[26]

Lipid peroxidation and protein oxidation are the indicators of oxidative stress. Lipid hydroperoxides (LOOHs) are nonradical mediators of lipid peroxidation.[47] Advanced oxidation products (AOPP) are biological indicators of protein oxidation. In other words, AOPPs are proteins that are damaged by oxidative stress.[48] Ege *et al*. stated that the significant increase of prolidase activity and oxidative stress (TOS, OSI, AOPP, and LOOH) in patients with TMD may be related to long-term collagen tissue damage and inflammation and could be effective in the etiology of TMD.[26] Studies have shown an increase in lipid peroxidation in patients with TMD (anterior disc displacement with reduction, anterior disc displacement without reduction, and osteoarthritis).[25]

8-hydroxydeoxyguanosine is produced when DNA is exposed to oxidative stress. The effect of free radicals on DNA is the activation of metabolic systems that cause DNA chain cleavage. Damaged DNA becomes immunogenic and causes autoantibody production.[31] The level of 8-OHdG is used as a biomarker to assess DNA damage. Rodríguez de Sotillo's study reported increased salivary and serum 8-OHdG levels in TMD patients.[31]

Biomarkers can be both a diagnostic marker and a target for treatment, but it should be noted that metabolic and environmental factors, stress, infection, and body microbiota[49-51] may affect the level of the biomarkers, therefore be the source of heterogenicity between the studies. Furthermore, the chronic nature of TMD disease can affect oxidative markers' levels, causing different results in different studies.[52] Therefore, changes in the levels of multiple markers in a certain period may provide more reliable data than a single measurement.

In general, oxidative stress plays a role in the pathogenesis of TMD in both joint and muscle conditions, and free radical inhibitory agents may prevent the pathological process. In other words, antioxidants may be a potential therapeutic agent to prevent the progression of TMD. One of the limitations of the present study, which limits any definitive conclusions, is the small number of studies, especially considering the wide range of biomarkers.

CONCLUSION

Based on the results of this study, it is concluded that salivary MDA and total antioxidative status measurements may be considered a diagnostic tool. However, a definite result regarding the amount and type of markers is not possible, and it is necessary to conduct larger case–control studies with a larger sample size. Furthermore, comparative studies between markers may be considered.

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Conflicts of interest
There are no conflicts of interest.

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