



Role Of Oxidative Stress as An Etiological Agent in Temporomandibular Disorders: A Systematic Review

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ABSTRACT

Introduction: Since oxidative stress is related to the pathogenesis of TMD, it has been shown that an increase in the generation of free radicals, the release of neuropeptides and cytokines, and the activation of matrix-degrading enzymes from various TMJ tissues were observed. Few studies reported reactive oxygen species (ROS) in TMD. This systematic review aimed to evaluate the role of oxidative stress as an etiological agent in temporomandibular disorders.

Materials And Methods: The search was done on Pubmed, Embase, and Cochrane till January 2023. A title scan was done to identify relevant articles, which were further analyzed for inclusion criteria. Studies that assessed the oxidative stress markers before and after any treatment modality in TMD patients, were included.

Results: A total of three studies were included in this review, which consisted of prospective clinical trials. Risk of bias assessment was done by RevMan software. All the studies show low risk of bias. The included studies show occlusal splints is proven to be effective in the management of TMD with reduction of oxidative stress marker levels.

Conclusion: It is evident that improvement of the oxidative stress would raise the possibility of constructing novel treatment strategies for TMD. We could postulate new treatment strategies such as antioxidant therapy for TMD in the near future.

Keywords: TMD, Temporomandibular disorders, TMJ, oxidative stress, splints

INTRODUCTION

The temporomandibular joint is a fibrous avascular disc. It is known as a diarthrodial and bilateral joint with two condyles of the mandibular bone fitting the reciprocally concave surface of the temporal bone just in front of the ear. It permits movement of the mandible both in the horizontal and transverse axis.

It works synchronously with the dentition along with the masticatory muscles and occlusal loading contributing to a healthy stomatognathic system[1,2]. Any interference or disturbance in any one of the components of this system will affect the TMJ[3].

The term “Temporomandibular disorders” confines a wide range of conditions. It is the second most common cause of musculoskeletal pain. It is a condition that includes musculoskeletal and neuromuscular abnormalities that result in pain and dysfunction of the masticatory muscles, temporomandibular joint, and its associated structures[4]. The common symptoms of TMD include pain in the joints and their associated structures, reduced mouth opening/ trismus, and joint sounds like clicking or crepitations[5]. The intensity of pain can be mild to severe, the latter would hamper the normal daily activities of the affected individual and impact the patient’s psychological functioning and quality of life. The other symptoms of TMD include pain in the face, head, and ear region, tinnitus, ear fullness, and vertigo. It causes a great deal of suffering in society and widespread problems in clinical practices[2].

The prevalence of TMD includes 5-12% in the general population[6]. The equal predilection of male and female. Few studies report female predilection with a female-to-male ratio of 2:1 in the general population. Rauch A et al, 2021 reported incidence of TMD is around 2% with a peak at 20-40 years of age[7]. The etiology of TMD is highly unresolved[8]. In literature, there is no primary etiological factor or there is no unified opinion about the exact primary etiological factor. Studies suggest that it is of multifactorial origin and associated with various risk factors like biological factors, individual anatomy, injuries, stressors, pharmacotherapy, occlusal interferences or occlusal factors, behavioral factors, neuroendocrine elements, genetics, and systemic disease stress, characterized by a disturbance between the formation of free radicals and uptake by antioxidant defenses, has been related to the pathophysiology of several diseases, including those of the stomatognathic system, such as temporomandibular disorders (TMDs)[9]. Recent evidence suggests that oxidative stress plays a role in the pathogenesis of TMD[10]. With the presence of pain conditions, there is increased neural activity with increased production of ROS. When the pain is chronic, the production of ROS can overcome the limitations of the protective mechanisms resulting in

oxidative stress. It is believed that in TMD, the mechanical stress on the joint and on the masticatory muscles can generate free radicals, triggering a cascade of reactions that can exacerbate tissue damage, inflammation, and pain[11].

Despite numerous publications on oxidative stress of temporomandibular disorders, limited information is available on the oxidative stress levels in the intervention of temporomandibular disorders. Therefore, this systematic review aims to assess oxidative stress levels in the management of temporomandibular disorders.

Research Question

Can oxidative stress be an etiological agent of temporomandibular disorders?

Are there any changes in the level of oxidative stress markers during the management of temporomandibular disorders?

PICO Analysis

P (Population) - Temporomandibular Disorders
 I (Intervention) - Pharmacological Agents /Agents/Splints Therapy / Surgical Management
 O (Outcome) - Changes In The Level Of Oxidative Stress Markers

MATERIALS AND METHODS

Search Methods And Sources

The present systematic review followed the PRISMA guidelines and was registered. We searched three databases for relevant articles published till January 2023. The sources included were PubMed, Cochrane Library, Google Scholar, and grey literature. A detailed personalized search strategy was used for the following electronic databases: PubMed, and Cochrane Library. Google was chosen as the search engine for studying grey literature.

Inclusion Criteria

Studies that analyzed the level of oxidative stress markers at pre & post treatment of TMD patients
 English language

Exclusion Criteria

- Studies that did not have follow-up/intervention for TMD
- Studies that did not assess oxidative stress levels in the management of TMD
- Case reports, case series, and discussion papers

Study selection

Search and study selections were made by the first author and checked by the second author. After the initial search, potentially appropriate articles were selected based on the title and summary. The full text of the selected articles was reviewed and three related studies were

identified, which included studies published till January 2023.

Prisma Flow Chart

Data Extraction

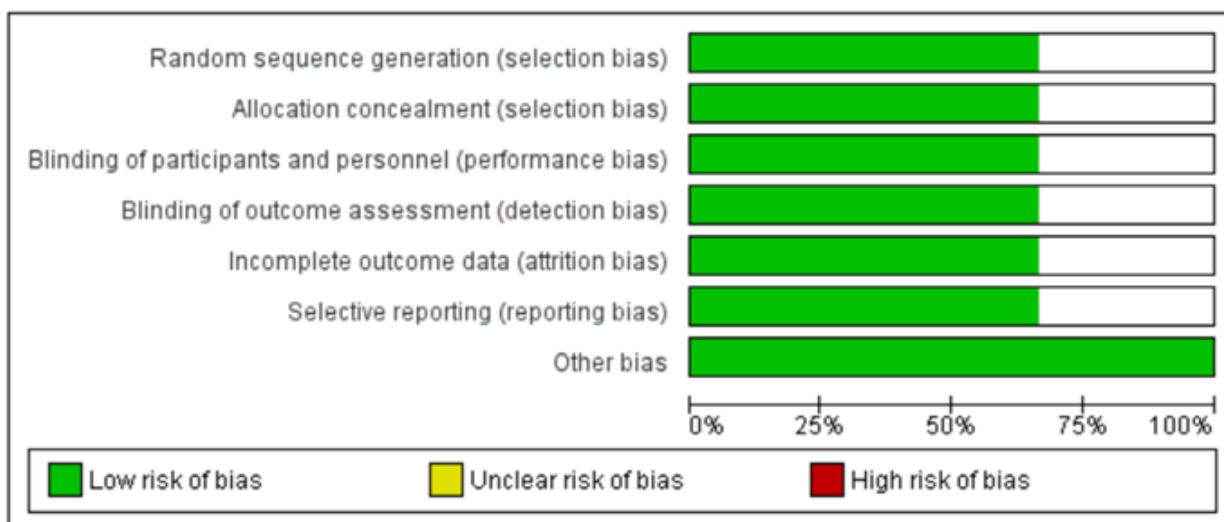
We retrieved a total of 522 articles from electronic and hand searches. After the removal of duplicates, was screened 123 articles for further evaluation and, therefore, excluded 87 based on their title or abstract. Of the 36 articles selected for full-text assessment, we considered 3 of them eligible for inclusion in the review. We excluded the other 33 articles because they did not fulfill the eligibility criteria. The general information of the included studies was tabulated.

Characteristics Of Included Studies

S.No	Author	Study Type	Sample Size	Treatment Given	Follow Up Period	Measurements	Primary Outcome	Secondary Outcome	Results
1	Bas (2019)	Prospective randomized trial	24 patients	GROUP 1: Arthrocentesis followed by splint therapy GROUP 2: Arthrocentesis alone	Baseline and 3 monthly follow up	TMJ synovial fluid samples	Interleukin 6 Malondialdehyde & 8-hydroxydeoxyguanosine levels in the synovial fluid	VAS Maximal mouth opening	Arthrocentesis has positive effects on patient clinical symptoms, regardless of postoperative splint use. Clinical success after arthrocentesis does not correlate with markers of inflammation and oxidative stress in the synovial fluid
2	E.Vrbanovic (2019)	Prospective study	12 female patients	Hard Acrylic splint	Baseline, 1st month, 3rd month	Saliva	VAS, Maximal comfortable mouth opening, Oral Health Impact Profile	Salivary analysis of MDA, TAC, Superoxide dismutase and uric acid	Occlusal splint therapy in female patients contributes to increasing their capacity to remove free radicals

							(OHIP-14), Level of perceived stress (PSS)		
3	Iva Z (2020)	Randomized controlled trial	34	GROUP 1: Stabilization splint GROUP 2: Placebo splint	Baseline, 3rd month follow up and 6 month follow up	Saliva	VAS Maximal comfortable mouth opening	Generalised Anxiety Disorder (GAD-7) Patient Health Questionnaire (PHQ-9) Biochemical stress markers : Uric acid, Superoxide dismutase, total antioxidant capacity, Total antioxidant status, Malondialde hyde	SS provide additional advantages over PS in the treatment of chronic TMD, especially in reducing symptoms of depression and improving pain-related disability. The efficacy of SS could be reflected in a significant decrease in oxidant/ antioxidant ratio which was not present for PS.

Risk Of Bias



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bas et al 2019	+	+				+	+
E. Vrbanovic 2019			+	+	+		+
Iva Z 2020	+	+	+	+	+	+	+

Risk Of Bias Assessment

An assessment of the risk of bias for all the included studies was done. This study has extracted data from randomized controlled trials (RCTs) and prospective trials. This risk of bias for the RCTs was assessed using the risk of a randomized trial of bias tool, given study bias does not change dependent on our review purpose. Randomized trials were assessed using the Cochrane Risk of Bias (RoB 2.0) tool and Higgins JPT 2016, which involve judgment on seven headings as formulated by the Cochrane group. The risk of bias for each of the domains and the overall risk of bias was made as per the recommendations of the RoB 2.0 tool. Trials were classified as low risk bias and unclear or high risk of bias as described in the RoB 2.0 tool.

RESULTS

Three studies were selected for analysis. Patients reporting symptoms of TMD, particularly pain, were alone taken into the studies. Bas et al (2019) evaluated the oxidative stress markers by using TMJ synovial fluid levels and the remaining two studies included salivary samples. All the three studies suggest that oxidative stress plays an important role in the pathogenesis of TMD. The common outcome measures among the three studies were maximal mouth opening, VAS and

Malondialdehyde levels. Results on use of physical therapy and splints to counter oxidative stress was inconclusive. Based on risk of bias assessment all the three studies shows low risk of bias. Iva Z (2020) reported all the parameters accurately showing low risk of bias comparing to the other two studies.

DISCUSSION

Results from this systematic review indicated that there is a significant difference in the pain intensity and oxidative stress marker levels in TMD subjects treated with splints and arthocentesis. Oxidative stress, characterized by a disturbance between the formation of free radicals and uptake by antioxidant defenses, has been related to the pathophysiology of several diseases, including those of the stomatognathic system, such as temporomandibular disorders (TMDs)[12]. Recent evidence suggests that oxidative stress plays a role in pathogenesis of TMD[13]. With the presence of pain conditions, there is an increased neural activity with an increased production of ROS. When the pain is chronic, the production of ROS can overcome the limitations of the protective mechanisms resulting in oxidative stress. It is believed that in TMD, the mechanical stress on the joint and on the masticatory muscles can generate free

radicals, triggering a cascade of reactions that can exacerbate tissue damage, inflammation and pain[14].

Cai et al. reported that the antioxidant enzyme, superoxide dismutase levels were increased in TMD patients compared to healthy individuals[15]. Güven et al. observed that the activity of SOD seemed progressively reduced as the stage of the disease increased, which they explained as an insufficient scavenging capacity of free radicals[16]. Nitzan et al. investigated the hypothesis that uncontrolled oxidative stress causes the collapse of the lubrication system. They analyzed the synovial fluids by measuring their overall reducing power and found that the capacity to cope with oxidative stress is lower in joints with anchored disc phenomenon. They suggested that increased oxidative stress caused by free radicals in the TMJ could cause an imbalance of local antioxidant defenses[17]. The authors proposed the explanation that the overactivity of oxygen free radicals can lead to the overgeneration of antioxidant enzymes[18].

Rodríguez de Sotillo et al. reported increased OS products in TMD patients, with the oxidants MDA and 8-OHdG being statistically higher in patients with TMD compared to the control and a significant association between pain intensity and salivary OS markers. Moreover, significant differences in the MDA/total antioxidant status (TAS) and 8-OHdG/TAS ratios between patients with TMD and the controls indicate that oxidative stress plays a role in TMD pathophysiology[19]. Richards et al. evaluated blood oxidative stress in individuals with temporomandibular dysfunction who also suffer from chronic fatigue syndrome and found out that jaw muscle pain and TMJ clicking and/or locking was associated with an increase in malondialdehyde levels[18]. De Almeida and Amenábar determined a lower TAC in patients with pain-related TMD but found no correlation between TAC and pain intensity[20]. A study that compared the treatment effect and outcomes in female TMD patients after a 3-month stabilization splint therapy showed a significant reduction in afternoon TAC and a significant reduction in afternoon MDA. A decrease in afternoon MDA to the superoxide dismutase ratio was present in high-intensity pain patients. The

effect of treatment on the self-perceived quality of life was more pronounced in Myofascial pain patients while the reduction of spontaneous pain was significantly greater in high-intensity pain patients[21]. Etöz et al. support the role of OS in the intensity of pain in TMD but specimens other than saliva were used in these studies[22]. In the pilot study, Vrbanović et al. found that TAC was significantly higher in TMD patients than in the controls. Significant differences were also observed when the TAC levels between high-intensity pain patients and controls were compared. In addition, the TAC levels differed significantly between patients with disc displacement and the controls suggesting that the salivary oxidant status in chronic TMD is dependent on the intensity and source of pain[23]

Based on our research, only three studies assessed the oxidative stress markers levels in the pre and post management of TMD. There are various treatment modalities in the management of TMD like physical therapy, drug therapy, behavioral therapy etc. Therefore, assessment of oxidative stress levels in each treatment modality is required.

Our team has extensive knowledge and research experience that has translate into high quality publications(J et al. 2018)(J et al. 2018; Atul Tanaji Lakde & Dr. Laxman Babasaheb Patil 2023) (Chandrasekar et al. 2020) (Kanimozhi et al. 2018) (Kavarthapu and Gurumoorthy 2021)(Kavarthapu and Gurumoorthy 2021; J et al. 2018) (Kavarthapu and Gurumoorthy 2021; J et al. 2018)(Vijayashree Priyadharsini, Smiline Girija, and Paramasivam 2018)(Govindaraju and Jeevanandan 2023) (Jeevanandan et al. 2021) (Marimuthu et al. 2018)(Marimuthu et al. 2018; Ramesh et al. 2019)(Gupta, Ariga, and Deogade 2018)

CONCLUSION

It is hypothesized that, the mechanical stress on the temporomandibular joint and on the masticatory muscles can generate free radicals, triggering a cascade of reactions that can exacerbate tissue damage, inflammation and pain. To advance this evidence, studies evaluated oxidative stress levels in TMD patients treated with arthrocentesis and splint therapy. It is

evident that improvement of the oxidative stress would raise the possibility of constructing novel treatment strategies for TMD. We could postulate new treatment strategies such as antioxidant therapy for TMD in the near future.

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