Shiraz E-Med J. 2023 July; 24(7):e137608. https://doi.org/10.5812/semj-137608.
Published online 2023 August 26. **Systematic Review**

Association Between Temporomandibular Joint Disorders and Salivary Cortisol Levels: A Systematic Review and Meta-analysis

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Received 2023 May 20; **Revised** 2023 August 01; **Accepted** 2023 August 13.

Abstract

Context: Salivary cortisol could be a good marker for temporomandibular joint disorders. This article aimed to study the association between salivary cortisol and temporomandibular joint disorders (TMD).
Methods: PubMed, Web of Science, Scopus, and Embase were searched according to the PRISMA guidelines without restricting the publication start date until October 2022. Only case-control studies were included in the study. The critical appraisal checklist of the Joanna Briggs Institute was utilized to appraise the selected articles.
Results: Of 1173 articles found, 23 studies were eligible, and 18 were meta-analyzed. A total of 696 TMD patients and 785 controls were included. Meta-analysis showed that salivary cortisol was significantly higher in patients with TMD than the controls. Meta-regression showed that the difference in mean salivary cortisol decreased significantly between the two groups with increasing age.
Conclusions: The salivary cortisol in patients with TMD is significantly higher than in the controls. As the heterogeneity among the studies was high, more studies are required to verify this association.

Keywords: Temporomandibular Joint Disorders, Hydrocortisone, Saliva, Stress, Meta-analysis

1. Context

Temporomandibular disorders (TMDs) are a diverse group of diseases that affect the temporomandibular joint (TMJ), the muscles of mastication, and related structures (1). TMD is the most prevalent chronic orofacial disorder that affects many people (2) and is more prevalent in 20-40-year-old females (3). The most important clinical signs of TMD include joint sounds, TMJ or muscular pain, and deviations or limitations in mouth opening (4). TMD is typically characterized by pain as the main symptom, and those affected often experience frequent stress in their daily lives (2). The nature of TMD involves multiple factors, but there is debate regarding the specific factors involved (5).

Patients with TMD usually have psychological stress as a significant triggering factor (6, 7). Patients with higher stress are more inclined to bruxism and TMD (8). The significance of psychosocial factors in the etiology of TMD might suggest that these disorders are part of somatoform disorders (9). Therefore, some studies have suggested that the hypothalamic-pituitary-adrenal (HPA) axis plays a role in the pathogenesis of these disorders, and patients with TMD who have inadequate stress responses exhibit increased cortisol secretion (10). Physiological stress activates the HPA axis, which leads to the secretion of cortisol (11, 12), which is then filtered in the acinar cells of the salivary glands and released freely into the saliva (13, 14).

Plasma cortisol is a reliable means to assess the HPA axis, as is salivary cortisol (15). The main advantages of salivary cortisol over serum are the possibility of non-invasive and non-stressful sampling (16). The cause of TMD is not fully understood, but some researchers have explored a potential link between cortisol and TMD. Specifically, they have studied the relationship between salivary cortisol levels and TMD in several different studies (17-25). This systematic review examined the findings from these studies to determine whether there is a correlation between cortisol levels and TMDs.

2. Methods

This systematic review was done according to the PRISMA guidelines (26). The Regional Ethics Committee approved this study (IR.TBZMED.REC.1401.268). The main question was devised according to the "PECO" (population, exposure, comparison, and outcome) approach, where "P" is the whole population, "E" is patients with Temporomandibular joint disorders, "C" is healthy people, and "O" is salivary cortisol levels.

2.1. Eligibility Criteria

Only case-control articles published in English until February 2023 (with no restrictions on publication start dates) were included.

Studies were excluded if they were reprinted articles using information from the same sample, letters to the editor, correspondences, and papers whose full text was unavailable.

2.2. Search Strategy

Electronic research without restriction on publication start date was carried out in October 2022 using four main databases: PubMed, Web of Science, Scopus, and Embase.

All combinations of free and MESH (Medical Subject Heading) terms, including "temporomandibular joint disorders", "temporomandibular joint", "temporomandibular joint dysfunction", "temporomandibular joint disk", "temporomandibular joint disk displacement", "myofascial pain", "myofascial pain and dysfunction", "myofascial pain disorder syndrome", "myofascial pain dysfunction", "cortisol", "cortisone", "corticosteroid", "salivary cortisol", "serum cortisol", "blood cortisol", "serum hydrocortisone", "corticosteroid hormone", "hypothalamic pituitary adrenal axis" with "OR" and "AND" operators were searched. The exact search strategy is presented in Appendix 1 in the Supplementary File. The reference lists of the included articles were also searched to identify more papers. The EndNote Basic software was used to identify and remove duplicate references.

2.3. Screening and Selection

The titles were screened by two independent reviewers (H. E. and Z. H.) for compatibility with the research question based on the PECO, and only studies comparing salivary cortisol levels in patients with and without TMD were included. Studies using an intervention, case reports, and studies on patients with fibromyalgia-associated syndromes, sleep apnea, giant-cell arteritis, and autoimmune diseases, such as rheumatoid arthritis, were excluded. Then, the abstracts were reviewed. The authors discussed with the third reviewer (K. K.) whenever there was any disagreement. Then, the full-text articles were examined.

2.4. Data Extraction

After the final selection of studies, the required information was extracted and summarized using a table designed by the Microsoft Excel software.

The first author's name, year of study, country of origin, type of study, gender of participants, mean age, sample size, type of saliva, and cortisol levels were obtained from the studies (when available) by two independent reviewers (K. K. and Z. H.).

2.5. Assessment of the Risk of Bias

The critical appraisal checklist for case-control studies, developed by the Joanna Briggs Institute (JBI) (27), was utilized by two evaluators (B. A. and Z. H.) independently to appraise the articles. Disagreements were resolved by consulting with the third researcher (H. E.).

2.6. Definitions

TMDs: TMDs refer to a group of clinical conditions that affect the masticatory muscles, TMJs, and related structures. These disorders are characterized by facial pain in the region of the TMJs or muscles of mastication, limitation or deviation in mandibular movements, hyperalgesia of the musculoskeletal structures, and TMJ sounds during jaw movement and function (28).

Unstimulated saliva: The saliva produced at rest, which is saliva secreted most of the day, can be collected by spitting and absorbent methods. In the spit method, the patient allows saliva to collect in the mouth and then spit into a pre-weighed tube, usually every 60 seconds for 5 to 15 minutes. The absorbent method uses a pre-weighed sponge placed in the mouth for a predetermined time. To ensure an unstimulated sample, the patient is instructed to refrain from eating, drinking, smoking, chewing gum, and oral hygiene practices or any other oral stimulation for at least 90 minutes prior to the test session. Excessive movement and talking are discouraged during the test period (29).

Stimulated saliva: Stimulation of salivation typically occurs between 10% and 20% of the day, influenced by olfactory, gustatory, and mechanical stimuli. The secretion of salivary fluid and salivary proteins is controlled by both the sympathetic and parasympathetic subsystems of the autonomic nervous system. Upon stimulation, the volume of the saliva increases, and it becomes more hypotonic and less viscous. Chewing an unflavored gum base or an inert substance, such as paraffin wax or a rubber band, at a controlled rate (usually 60 times per minute) is a reliable and repeatable method of inducing salivation. Also, 2% citric acid may be placed on the tongue at 30-second intervals (30).

2.7. Meta-analysis

The mean difference between salivary cortisol levels was calculated for the studies, which provided the required data. I^2 and Q indices were used to measure the heterogeneity between the studies. Also, I^2 greater than 50% was considered a significant heterogeneity. The results were combined by the random-effects model using CMA 2.0. A $P < 0.05$ was considered significant.

3. Results

3.1. Search Results

The electronic search in the mentioned databases produced 1173 articles. After duplicate removal, 940 articles remained, from which interventional studies (n = 495), case reports (n = 136), and studies on autoimmune diseases (n = 181), fibromyalgia-associated syndromes (n = 47), sleep apnea (n = 32), and giant-cell arteritis (n = 17) were excluded, and finally, 32 articles were sought for retrieval. Out of the remaining 32 articles, three articles had not used saliva (31-33), two had no control group (34, 35), and four had discussed other diseases in addition to TMD (18, 36-38). Twenty-three articles entered the systematic review, and 18 papers were meta-analyzed. Also, 5 articles did not provide the required data for meta-analysis (17, 39-42). The PRISMA flow diagram presents the search results in detail (Figure 1).

3.2. Assessing the Risk of Bias

Based on the JBI tool, out of 18 studies in the meta-analysis, 13 had a low risk of bias, while the remaining five studies were identified with a moderate risk of bias. (Table 1)

3.3. Characteristics of the Studies

Some studies collected stimulated saliva (20, 25, 43-46), while others collected unstimulated saliva (19, 21-24, 47-53). Table 2 shows the included studies' descriptive characteristics and related data. Overall, 1467 participants were examined in these 18 studies. The publication date of studies ranged from 2008 to 2022.

3.4. Meta-analysis

The difference between mean salivary cortisol in the case and control groups:

The mean age of 668 participants in the case group was 26.49, and of 799 participants in the control group was 27.03 years. The lack of homogeneity between studies was significant (Q-value = 354.24, df = 17, I-squared = 95.20, and P-value < 0.001). Meta-analysis with the random-effects model indicated that the salivary cortisol in the case group was 0.178 units higher, which was statistically significant (pooled mean difference = 0.178, SD = 0.043, 95% CI = 0.262 - 0.094, z-value = 4.163, and P-value < 0.001). Figure 2 depicts the forest plot of this meta-analysis.

The difference in mean salivary cortisol between study groups based on the type of saliva:

Six studies used stimulated saliva, while 12 used unstimulated saliva. The intragroup difference in the pooled mean salivary cortisol was 0.030 units for stimulated saliva and 0.251 units for unstimulated saliva. This difference was not statistically significant for stimulated saliva but significant for unstimulated saliva. Figure 3 and Table 3 show the results of the subgroup analysis.

3.5. Meta-regression Results Based on Age

Meta-regression was used to explore the effect of age on the mean difference in salivary cortisol in the case and control groups. With increasing age in the studied subjects, the difference in mean salivary cortisol amongst the two groups decreased by 0.006 units, which was statistically significant (regression slope = -0.006, 95% CI =- 0.0077; -0.0052), P-value < 0.001). Figure 4 shows the meta-regression results.

3.6. Publication Bias

The Funnel plot of publication bias is presented in Figure 5. Based on the symmetry in the diagram, there is no publication bias. Also, based on the results of the Egger regression test, the publication bias was not statistically significant (*t*-value = 0.255, df = 16, and P-value = 0.80).

4. Discussion

According to the results of this systematic review, individuals with TMD exhibited significantly higher salivary cortisol levels compared to the control groups. Salivary cortisol is frequently utilized in research due to its simple collection process and low cost. However, cortisol levels can be affected by the time of collection (54); therefore, only morning cortisol levels were taken into account for this meta-analysis.

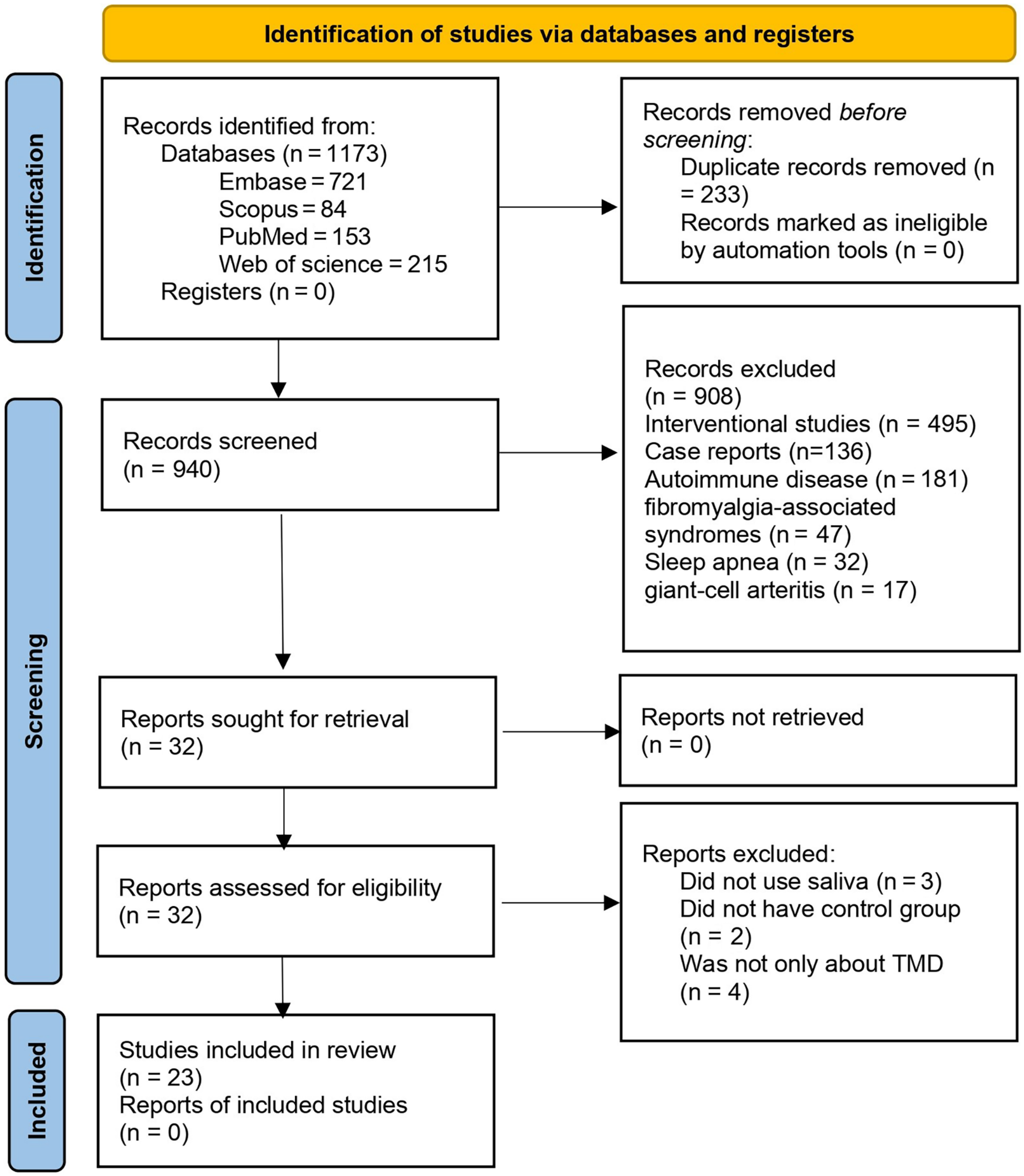

Figure 1. The PRISMA flow diagram shows the article selection process.

Table 1. Risk of Bias of the Included Studies [a]

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total	Risk of Bias
Da Silva Andrade et al.(43)	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	90	Low
Nilsson and Dahlstrom (44)	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90	Low
Barabosa et al. (45)	Y	N	Y	Y	Y	Y	Y	Y	U	Y	80	Low
De Almeida et al. (46)	Y	N	Y	Y	Y	N	N	Y	N	Y	60	Moderate
Kobayashi et al. (20)	Y	Y	Y	Y	Y	N	N	Y	U	Y	70	Low
Venkatesh et al. (25)	Y	Y	Y	Y	Y	Y	U	Y	U	Y	80	Low
Jasim et al. (47)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100	Low
Nadendla et al. (21)	Y	Y	Y	Y	Y	Y	N	Y	U	Y	80	Low
Salameh et al. (24)	Y	Y	Y	Y	Y	Y	N	Y	U	Y	80	Low
Poorian et al. (22)	Y	U	Y	U	Y	N	N	Y	U	Y	50	Moderate
Galvão-Moreira et al. (48)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	90	Low
Vrbanovic et al. (49)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	80	Low
Chinthakanan et al. (19)	Y	N	Y	Y	Y	N	N	Y	U	Y	60	Moderate
Staniszewski et al. (50)	Y	Y	Y	Y	Y	N	N	Y	U	Y	70	Low
Alresayes et al. (51)	Y	U	Y	Y	Y	Y	N	Y	U	Y	70	Low
Barakian et al. (52)	Y	U	Y	U	U	N	N	Y	Y	Y	50	Moderate
Goyal et al. (53)	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90	Low
Cheon et al. (23)	Y	N	Y	Y	Y	N	N	Y	U	Y	60	Moderate

[a] Y, yes; N, no; U, unclear; NA, not applicable; Q, question. Q1: Were the groups comparable other than the presence of disease in cases or the absence of disease in control? Q2: Were cases and controls matched appropriately? Q3: Were the same criteria used to identify cases and controls? Q4: Was the exposure measured in a standard, valid, and reliable way? Q5: Was the exposure measured the same way for cases and controls? Q6: Were confounding factors identified? Q7: Were strategies to deal with confounding factors stated? Q8: Were outcomes assessed in a standard, valid, and reliable way for cases? Q9: Was the exposure period of interest long enough to be meaningful? Q10: Was appropriate statistical analysis used? Total = ΣY/applicable items (not applicable (NA) items were excluded from the sum). The risk of bias was classified as high when the study reached a "yes" score of up to 49%, moderate when the study reached a "yes" score of 50 to 69%, and low when the study reached a "yes" score of more than 70%.

In 6 articles that studied stimulated saliva, there was no significant association between the salivary levels of TMD patients and controls, although there were some contradictory results between the studies. Venkatesh et al. showed a significant correlation between salivary cortisol levels and TMD. They suggested that salivary cortisol could be a useful marker to assess the severity of TMD in individuals who experience stress (25). Additionally, Da Silva Andrade et al. showed that females with TMD had higher cortisol levels than the control group; however, there was no significant difference between the two groups in general (43). This could be because males and females respond differently to stress. It is worth noting that in most of these studies, the female-to-male ratio was over 50%, and three studies only included females (44, 47, 49).

In the articles that used unstimulated saliva, salivary cortisol was significantly higher in TMD patients in comparison with controls, although there were inconsistencies between the studies. The differences in the studies could be due to varying types of pain, duration of disease, and study population. Jasim et al. conducted research on salivary cortisol levels in cases of chronic and acute orofacial pain and compared it to a control group consisting of only female patients. The results showed that salivary cortisol levels were not significantly different between the three groups (47). However, Chinthakanan et al. studied TMD patients of both genders who had experienced TMD pain for at least three months. They reported that salivary cortisol levels in the TMD group did not correlate with the visual analog scale (VAS) score (19). This finding is consistent with that of Kobayashi et al., who demonstrated that salivary cortisol levels are not correlated with mild TMD pain, but there is a positive correlation between moderate and severe TMD pain and salivary cortisol levels (20). The pain intensity in the TMD group in the study by Chinthakanan et al. (19) was mild to moderate; hence, no correlation was found between pain and salivary cortisol levels. Thus, it is suggested that salivary cortisol levels are associated with the severity of pain.

The possible explanation is a relationship between the

Table 2. The Characteristics of the Included Studies [a]

Author	Country	Sex (Female %)	Participants' Age (year) in the Case/ Control Group	Sample Size in the Case/ Control Group	Type of Saliva	Cortisol Levels (μg/dL) in the Case Group (Mean ± SD)	Cortisol Levels (μg/dL) in the Control Group (Mean ± SD)
Da Silva Andrade et al. (43)	Brazil	50	22.5/22.8	20/20	Stimulated	0.27 ± 0.10	0.39 ± 0.33
Nilsson and Dahlstrom (44)	Sweden	100	19.7/21.2	30/30	Stimulated	0.41 ± 0.24	0.49 ± 0.36
Barabosa (45)	Brazil	66	11/11	86/59	Stimulated	0.21 ± 0.16	0.16 ± 0.12
De Almeida et al. (46)	Brazil	75	21.8/21.2	25/23	Stimulated	0.27 ± 0.2	0.39 ± 0.33
Kobayashi et al. (20)	Brazil	63	10.6/10.6	38/38	Stimulated	0.15 ± 0.09	0.15 ± 0.09
Venkatesh et al. (25)	India	53	20.5/20.5	107/241	Stimulated	1.10 ± 0.17	0.69 ± 0.16
Jasim et al. (47)	Sweden	100	42.3/45.7	27/27	Unstimulated	0.20 ± 0.26	0.21 ± 0.14
Nadendla et al. (21)	India	55	36.6/36.6	20/20	Unstimulated	1.7 ± 0.29	0.53 ± 0.13
Salameh et al. (24)	Syria	70	29.1/29.1	60/60	Unstimulated	0.21 ± 0.13	0.07 ± 0.04
Poorian et al. (22)	Iran	54	32.4/39.6	15/60	Unstimulated	2.90 ± 0.52	0.88 ± 0.95
Galvão-Moreira et al. (48)	Brazil	64	28.5/28.5	39/33	Unstimulated	0.10 ± 0.04	0.084 ± 0.04
Vrbanovic et al. (49)	Croatia	100	39.3/34.3	20/15	Unstimulated	0.41 ± 0.28	0.24 ± 0.16
Chinthakanan et al. (19)	Thailand	72	22/26.0	23/21	Unstimulated	0.29 ± 0.12	0.22 ± 0.06
Staniszewski et al. (50)	Norway	86	44/46	44/44	Unstimulated	0.26 ± 0.22	0.17 ± 0.13
Alresayes et al. (51)	Saudi Arabia	88	16.3/16.5	18/18	Unstimulated	0.31 ± 0.03	0.05 ± 0.00
Barakian et al. (52)	Iran	NR	NR	24/36	Unstimulated	0.49 ± 0.37	0.45 ± 0.20
Goyal et al. (53)	India	50	25.5/23.6	40/20	Unstimulated	0.36 ± 0.22	0.12 ± 0.42
Cheon et al. (23)	Korea	50	28.2/25.9	32/34	Unstimulated	0.2 ± 0.12	0.11 ± 0.03

[a]Unstimulated saliva: The saliva produced at rest, which is saliva secreted most of the day, can be collected by spitting and absorbent methods. Stimulated saliva: Stimulation of salivation typically occurs between 10% and 20% of the day, influenced by olfactory, gustatory, and mechanical stimuli. The sympathetic and parasympathetic subsystems of the autonomic nervous system control the secretion of salivary fluid and proteins. Upon stimulation, the saliva volume increases and becomes more hypotonic and less viscous.

Table 3. The Results of the Meta-analysis in Subgroups

Groups	Effect Size and 95% Confidence Interval					Test of the Null Hypothesis (2-Tail)		Heterogeneity			
	Number of Studies	Point Estimate	Standard Error	Lower Limit	Upper Limit	Z-Value	P-Value	Q-Value	df (Q)	P-Value	I-Squared
Stimulated saliva	6	0.03	0.10	-0.17	0.23	0.30	0.76	291.13	5	0	98.28
Unstimulated saliva	12	0.25	0.05	0.15	0.35	4.83	0.00	687.96	11	0	98.40

severe pain experienced by the patients and an increase in stress psychobiology, including anxiety and depression. Anxiety can lead to an imbalance of the HPA, and cortisol is the major factor associated with the HPA imbalance (55).

The duration of the TMD could explain why the study results differed. In the study by Vrbanovic et al., patients had experienced pain lasting more than six months (49); therefore, higher cortisol might imply a compensatory increase in the function of the HPA axis. Some articles did not report how long their patients experienced TMD pain.

One of the most frequently suggested mechanisms causing myofascial pain associated with TMDs is

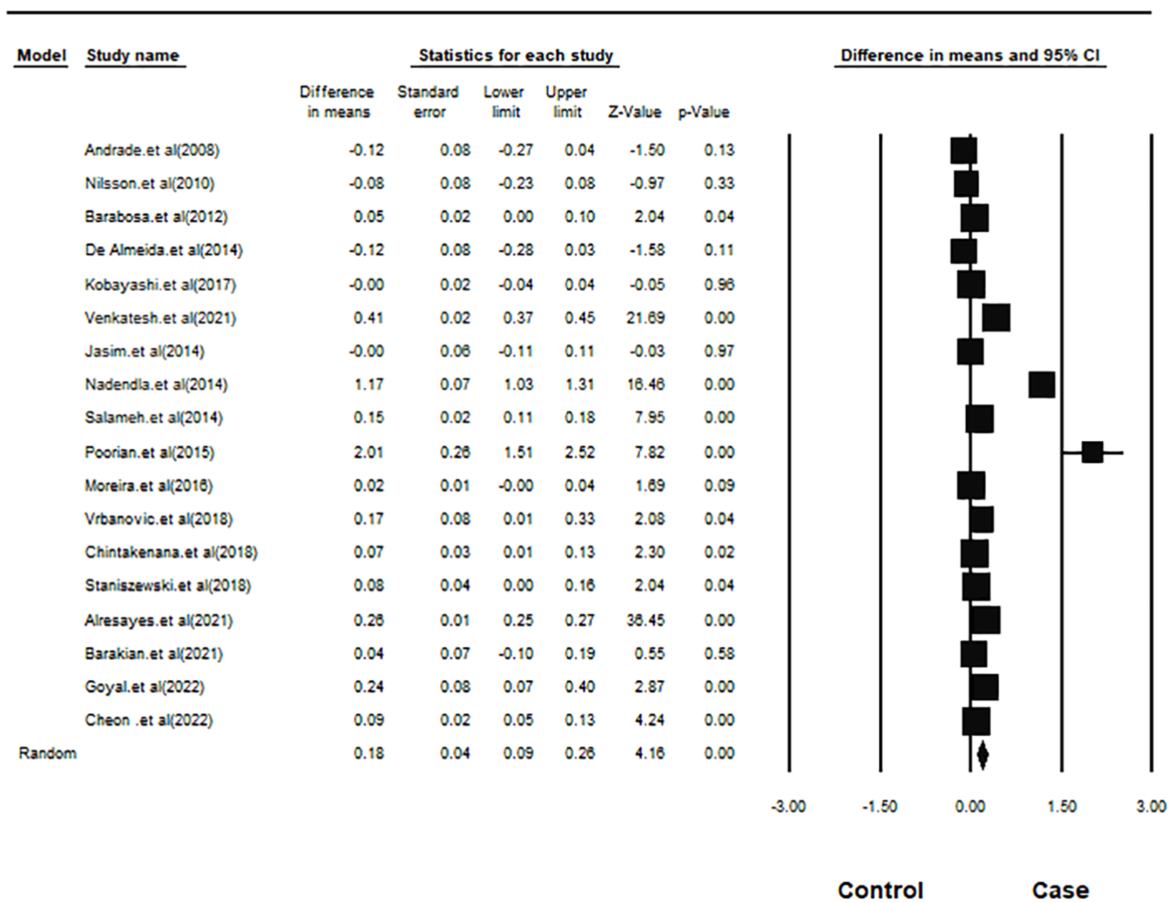

Figure 2. The forest plot depicting the included studies in the present meta-analysis.

hyperactivity of the masticatory muscles (56). When exposed to stress, some patients respond with increased masticatory muscle activity rather than a general increase in body muscle tonus. Such activity manifested as parafunctional habits, can result in muscular fatigue and spasms, leading to myofascial pain and TMD (57).

Bozovic et al. examined 30 university students with myofascial pain and 30 healthy students and found that salivary cortisol levels were higher in students with myofascial pain on both exam days and typical days compared to the control group. Additionally, the salivary cortisol level was found to correlate with psychological factors in students with TMD but not in the control group (17). These findings suggest that preexisting vulnerability, such as TMD, can cause an increase in salivary cortisol levels on stressful days in students with TMD.

As shown in Table 2, the salivary cortisol levels in both stimulated and unstimulated saliva were in a similar range. In general, the concentrations of salivary components that are actively transported, like cortisol, are not significantly reduced in stimulated saliva; however, the concentration of proteins that are not actively transported will tend to decrease in stimulated compared to unstimulated saliva (58).

Higher salivary cortisol levels in TMD patients indicate that stress, either with a role in the development of TMD or pain-related TMD, produces additional stress to the body and further enhances cortisol secretion. For a definite conclusion, longitudinal prospective studies are needed.

Three articles (20, 45, 51) studied children and adolescents, while the others studied adults, which is one of the limitations of this systematic review. Females have higher salivary cortisol levels than men; therefore, gender distribution plays an important role. Seven studies (22, 25, 45-, 51, 52) failed to provide the same female-to-male ratio between the groups, which might contribute to the heterogeneity of the results.

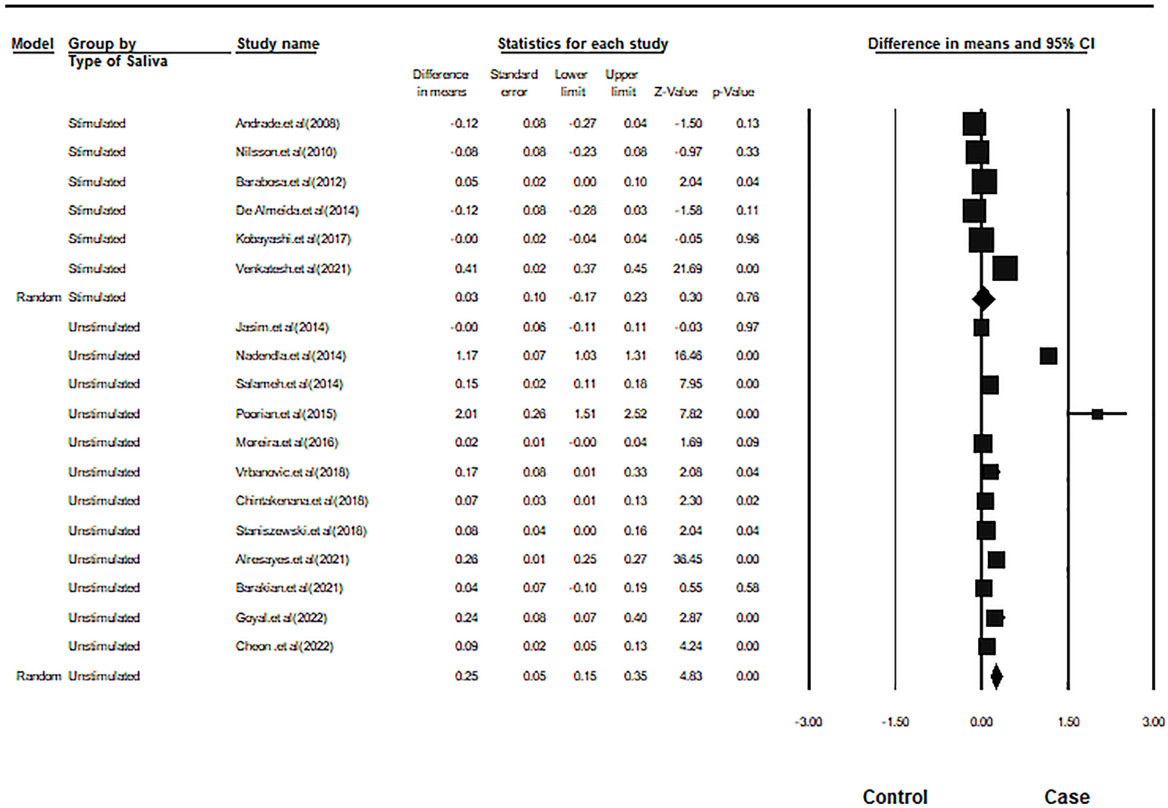

Figure 3. The forest plot of subgroups categorized according to the type of saliva collection method

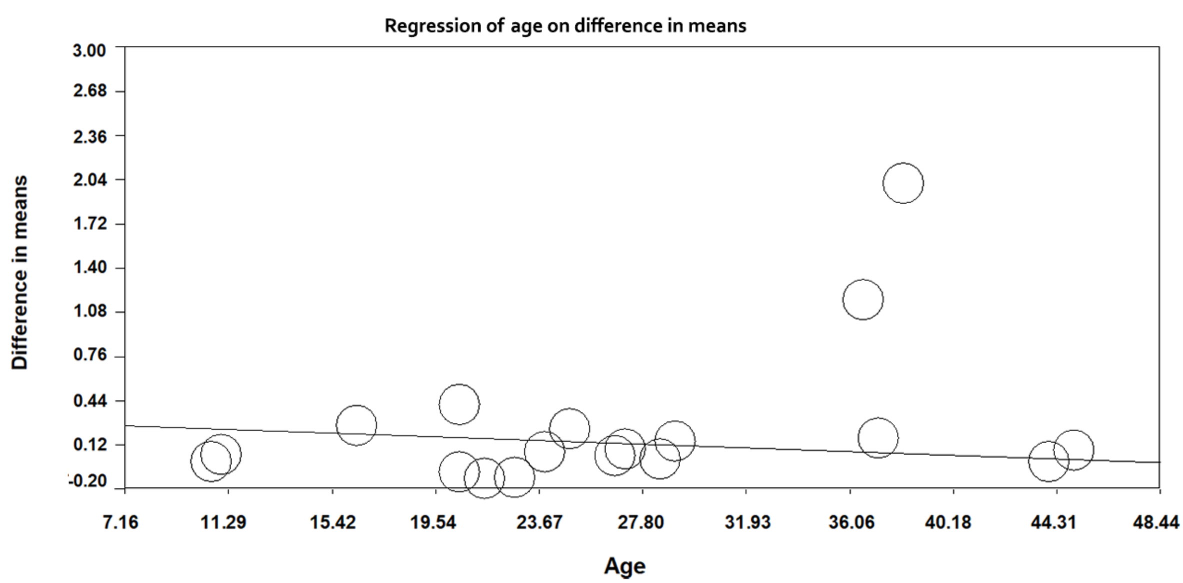

Figure 4. The meta-regression for age in the included articles.

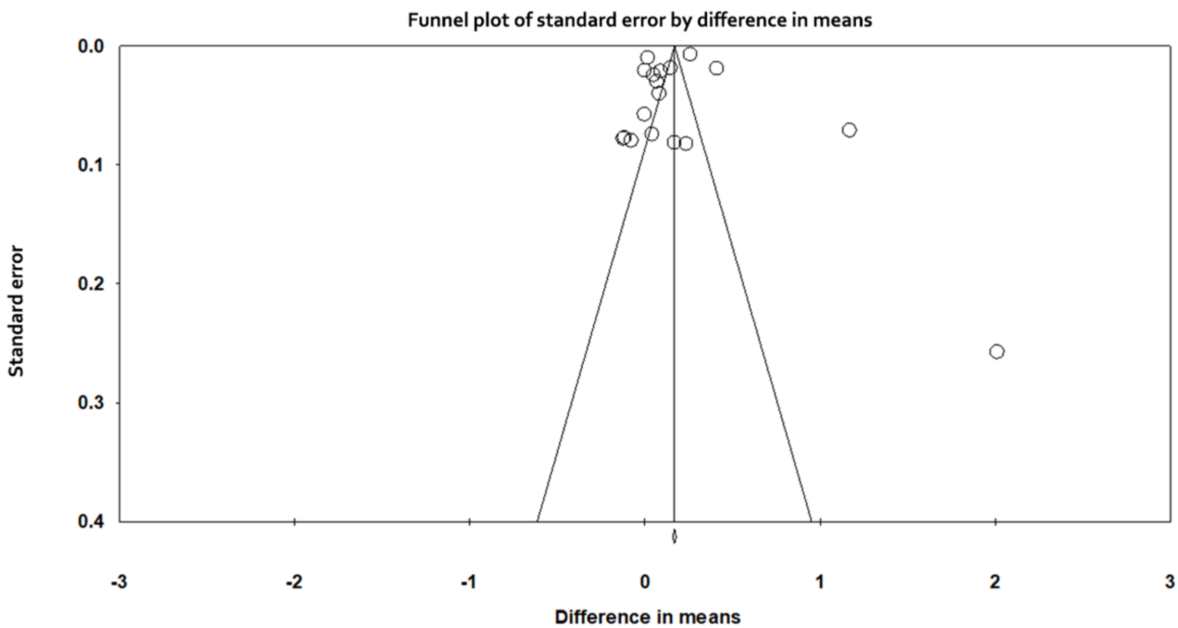

Figure 5. The Funnel plot of publication bias

5. Conclusions

This study showed that individuals with TMD have higher cortisol levels in their saliva than those without TMD. This could be due to stress, anxiety, and depression. It is recommended that psychological support be included in the treatment plan for TMD. However, as there are variations in the findings of different studies, further research with a larger sample size and a prospective design would help gain more insight into this issue.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

The authors would like to thank Mr. Hosein Azizi for his help in statistical analysis.

Footnotes

Authors' Contribution: Study concept and design: KK and HE; Investigations: BA, KK, and ZH; Analysis and interpretation of data: KK, HE, BA, and ZH; Drafting of the manuscript: ZH and BA; Critical revision of the manuscript for important intellectual content: HE and KK; and study supervision: HE. All authors have read and approved the final manuscript.

Conflict of Interests: This research did not receive any funding. None of the authors are employees of any organization that may gain or lose financially through this publication. None of the authors gain or lose financially through this publication.

Data Reproducibility: The data presented in this study are uploaded during submission as a supplementary file and are openly available for readers upon request.

Ethical Approval: This manuscript was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran under the ethical code of IR.TBZMED.REC.1401.268.

Funding/Support: This article results from a DDS degree thesis supported non-financially by the Tabriz University of Medical Sciences, and no funding was received.

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