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Does salivary cortisol serve as a potential biomarker for temporomandibular disorders in adults?

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Abstract

Background The etiology of temporomandibular disorders (TMD) is multifactorial, involving a complex interplay of psychological and physiological factors. While salivary biomarkers, particularly cortisol, play an important role in TMD pathophysiology, evidence in the literature is still scarce and inconsistent. Hence, this study aims to evaluate the applicability of salivary cortisol as a potential biomarker for TMD in adults.

Methods The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) were used to accurately diagnose TMD patients. The study included adults, both male and female, aged 18–40 in the TMD group ($n=66$) and non TMD participants ($n=66$) matched for age and gender. Salivary samples were collected from participants at two time points: early and late morning. Cortisol levels in the samples were quantified using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using a one-way ANOVA to evaluate the correlations between cortisol levels and the study variables. Tukey's post-hoc tests were applied to adjust for multiple comparisons.

Results Salivary cortisol levels were significantly higher in the TMD group than in the corresponding controls ($p=0.034$). In the TMD group, the mean cortisol levels early in the morning were 29.95 ± 75.05 (0-398.64), while the late morning levels were recorded as 4.87 ± 3.96 (0-17.13). In the control group, the mean cortisol levels early in the morning were 10.98 ± 16.83 (2.16–92.90), and late morning mean cortisol levels were 6.15 ± 6.13 (0-20.42). This indicates that the early morning levels of cortisol are higher in TMD patients ($p=0.046$). In the subgroup analysis of the TMD, the mean salivary cortisol levels recorded were highest at 82.49 ± 124.34 (8.32-398.64) in patients having disc displacement without reduction with limited mouth opening. Furthermore, the mean salivary cortisol levels in the early morning were statistically higher (84.83 ± 132.80) in males compared to females (9.36 ± 9.01) ($p=0.008$) with TMD.

Conclusion The result of this study suggests that salivary cortisol could be a potential biomarker for a specific TMD subtype (disc displacement without reduction with limited mouth opening). However, further studies are needed to better understand the role of cortisol biomarker in the underlying pathogenesis of TMD.

Keywords Temporomandibular disorders, Salivary biomarkers, Salivary cortisol, Enzyme immunoassay

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Introduction

Temporomandibular disorders (TMD) are a broad term for musculoskeletal and neuromuscular conditions that affect the masticatory muscles, the temporomandibular joint (TMJ), and related structures [1]. Symptoms can vary from minor discomfort to severe myofascial pain, restriction of jaw movement, and psychological distress [2]. Both acute and chronic TMD lead to a detrimental quality of life [3]. A recent National Institute of Health survey demonstrated that TMD affects 5 to 15% of young and middle-aged individuals and it is the second most common musculoskeletal and neuromuscular disorder [4]. In terms of gender prevalence, it has been found that the prevalence of TMD is higher in females than in males [4]. The etiology and pathophysiology associated with this condition are multifactorial and complex, involving various social, psychological, and biological factors [5]. Recent research in the field has highlighted the potential of salivary biomarkers as valuable tools for enhancing our understanding of TMD [6, 7].

Research into the structural and compositional changes in TMJ highlights the complexity of TMD and underscores the potential role of biomarkers in identifying and monitoring these changes [8, 9]. Even though there is an increasing interest in biomarkers and their association with TMD development, the existing evidence is scant. Previously published studies have reported conflicting findings, with variations in the selection of salivary biomarkers, study design, and analysis of the findings. Saliva has shown a promising outcome for obtaining biomarkers as it is an accessible biofluid that offers various diagnostic advantages, such as cost-effectiveness, non-invasiveness, and ease of collection [10]. The salivary fluid contains biomarkers that serve as an analyst for both local and systemic diseases. Salivary biomarkers, including proteins, enzymes, inflammatory mediators, and genetic markers, show potential as objective indicators for the presence, progression, and treatment outcomes of temporomandibular disorders [10]. Salivary biomarkers investigated in relation to TMD include Cortisol, IL-1, Glutamate, 5-HT, NGF, BDNF, SP, Salivary alpha-amylase (SAA), Phenyl acetate (PA), Dimethylamine (DMA), Maltose, Acetoin, Isovalerate, Total Antioxidant Capacity (TAC), Catalase, Malondialdehyde (MDA), TNF-MMP-3, 8-OHdG, 6Ckine, ANG, CXCL16, ENA-78, GM-CSF, IFN-, IL-1, IL-6, PAI-1, TGF-1, TIMP-1, VE-Cadherin, and VEGF [10–15].

Studies have shown that increasing cortisol and stress-related indicators are found in the saliva of patients affected by oral diseases, including TMD [16–18]. Salivary cortisol levels indicate unbound active cortisol levels compared to bound plasma cortisol measurements [19]. Recent research has highlighted a significant association between elevated salivary cortisol levels and temporomandibular disorders (TMD) in young adults. A systematic review revealing that individuals with TMD often exhibit higher cortisol levels compared to healthy controls, suggesting a potential link between psychological stress and TMD. This review calls for further investigation into the underlying connection between cortisol levels and TMD pathophysiology [20]. Studies have correlated stress levels, salivary cortisol, and their association with the development of TMD [16, 21]. Contradictory, few studies was observed no statistical association between psychological symptoms and cortisol levels in individuals with different types of TMD [19, 22, 23].

Cortisol is a stress biomarker, and studies have found an association between cortisol and TMD in women [24]. Moreover, most of the research has demonstrated cortisol levels and their association with TMD in only female participants [25]. Evidence related to the levels of cortisol and their association with TMD amongst the genders is scarce [12]. In a systematic review by Alam et al., the emphasis was given to separately considering each salivary biomarker to establish its association with TMD development [26]. This review revealed a complex relationship between salivary cortisol levels and TMD. By examining salivary biomarkers, investigators have attempted to unravel the complex pathophysiological association between TMD and salivary cortisol. This complexity underscores the necessity for further studies to understand this relationship fully.

Therefore, in the current study, we aim to measure cortisol levels in saliva among different groups of patients with TMD to understand the applicability of salivary cortisol as a potential biomarker in TMD compared to control. This could pave the way for a more holistic, precise, and patient-centered approach to TMD management. The null hypothesis established was that salivary cortisol cannot serve as potential biomarkers of TMD in adults.

Material and method

Study design, participants, and protocol

The protocol for this case-control study was developed, ethical approval was obtained from the Institutional Review Board (IRB) at King Saud University under project number (E-23-7619), according to the ethical code (Declaration of Helsinki) before proceeding with the study. The reporting of this study followed STROBE guidelines.

Young adults aged 18–40 were recruited from the University Dental Hospital, King Saud University, Riyadh, Saudi Arabia between November 2022, and April 2023.

Inclusion of study participants

Sixty-six consecutive subjects referred to the oral medicine clinic of Dental University Hospital, King Saud

University, complaining of orofacial pain, were included in this study. The inclusion criteria were symptomatic disc displacement (DD) or/and myofascial pain according to the diagnostic criteria for temporomandibular joint disorders (DC/TMD) [27], with symptoms experienced for at least three months and an average pain intensity of ≥4/10 on a Visual Analogue Scale (VAS). Two calibrated dentists diagnosed the patients with TMD and divided them into subgroups according to their diagnosis. Participants in the control group (n=66) were volunteers of the same age, without any complaint of myofascial pain. The same dentists examined controls to ensure they had no clinical symptoms associated with TMD.

All exclusion criteria apply to both the TMD and control groups to ensure participant selection consistency. Exclusion criteria were: (1) participants with conditions that can influence the pain sensitivity, including chronic widespread pain (e.g., fibromyalgia), systemic muscular or joint diseases (e.g., rheumatoid arthritis), autoimmune diseases, migraines, and neurological or neuropsychiatric disorders; (2) Participants using anti-inflammatory drugs, opioids, analgesics, or steroids within the last 30 days were excluded but those not currently using them were eligible. (3) use of drugs that affect saliva secretion (e.g., calcium channel blockers, antidepressants, antihistamines); (4) pregnancy or lactation; (5) obesity; (6) smoking; (7) diseases of the salivary glands (e.g., salivary gland tumor, salivary gland stones, hyposalivation); (8) participants complaining of dry mouth; (9) edentulism; (10) prosthodontic rehabilitation (complete or partial dentures); (11) poor oral hygiene (evaluated using the Plaque Index (PI) and the Gingival Index (GI), with individuals scoring above 2.0 on either index); (12) severe periodontal disease (defined according to the criteria established by the 2017 World Workshop on the Classification of Periodontal and Peri-Implant, including clinical attachment loss of ≥5 mm, probing depths of ≥6 mm, and radiographic evidence of bone loss extending to the middle third of the root and beyond); (13) untreated mental health disorders or those under active treatment for depression, anxiety, or Post-traumatic stress disorder (PTSD) are excluded.(14) patient with obstructive sleep apnea (OSA), (15) patients with any form of malignancy (16) patients under radiotherapy and\or chemotherapy (17) adrenal hyperfunction (18) Cushing disease. All the exclusion criteria were evaluated in each participant by taking a thorough medical and dental history by a single dentist.

Calculation of sample population

The sample size for this study was determined using a formula based on a previous study evaluating cortisol levels in TMD patients (Da silva et al., 2008) [24].

The following formula was applied:

Where n=sample size for each group; Z1 is the Z score for α error of 5% (1.96), (95% confidence level); Z2 is the Z score for 80% estimated study power (0.84); S is the standard deviation of the mean salivary cortisol [12.24], and μ2-μ1 is the expected minimum difference between group means [7]. Using these values, the required sample size per group was calculated as $n=(1.96+0.84)^2\times 2(12.24)^2 / (7)^2 = 48$. Allowing for a 10% attrition rate, the minimum sample size per group was 53 participants. This study included a total of 132 participants, exceeding the required minimum and ensuring sufficient power for statistical analysis.

Participants were divided into two groups, sixty-six subjects in each group (Group 1=TMD; Group 2=controls without TMD), where Group 1 was further subdivided into four groups [Group 1 A=Disc displacement with reduction (n=10); Group 1B=Disc displacement without reduction with limited mouth opening (n=10); Group 1 C=Myofascial pain (n=10); Group 1D=Myalgia (n=36)].

Saliva collection and the measurement of salivary cortisol levels

To determine the salivary cortisol levels, the unstimulated early and late morning saliva were collected at two intervals, early morning at 7 a.m. and late morning at 10 a.m. All participants were instructed not to brush their teeth, to avoid blood contamination, and not to eat before saliva collection. However, they were asked to rinse their mouth thoroughly to eliminate any debris. Two mL of unstimulated saliva was collected from both groups in (pre-graduated polypropylene vials, conical-bottom centrifuge tubes) and restored at -20^{0}C in Thermo Scientific™ TSX Series Ultra-Low Temperature Freezers (TSX60086A, Thermo Fisher Scientific, Waltham, Massachusetts, USA). Collected saliva was centrifuged to remove the mucins in Andreas Hettich GmbH & Co. KG (EBA 270, Tuttlingen, Germany) at 3000 RPM for 5 min. Investigators did not utilize protease inhibitors while collecting saliva. To conjugate salivary samples for cortisol, 16 μl of sterile dH_2O was reconstituted, and the solution was kept at room temperature (37°C^0) for 10 min till the solution was dissolved completely. The supernatant sample was removed to estimate the cortisol levels, salivary cortisol levels were determined for all the samples using ELISA kit (IBL International corporation, Switzerland) in similar manners and within the same time for both the TMD and control groups.

Statistical analysis

The data were tabulated in Microsoft Excel (Microsoft, USA) and analyzed using the SPSS version 21.0 (the statistical package for social science, Armonk, USA). The power of the study was calculated at 80%. The descriptive

Table 1 Mean cortisol levels (early and late morning), age distribution, and standard deviation by gender in Control and TMD groups

Parameter	Mean ± SD (ng/ml)	Minimum (ng/ml)	Maximum (ng/ml)	Overall Mean Age (SD)	Male Mean Age (SD)	Female Mean Age (SD)
TMD Group - Early Morning	29.95 ± 75.05	0.0	398.64	29.54 (5.38)	32.17 (4.85)	28.42 (5.29)
TMD Group - Late Morning	4.87 ± 3.96	0.0	17.13	29.25 (5.34)	30.68 (5.31)	28.50 (5.29)
Control Group - Early Morning	10.98 ± 16.83	2.16	92.9	29.25 (5.34)	28.73 (5.48)	29.21 (5.32)
Control Group - Late Morning	6.15 ± 6.13	0.0	20.42	29.70 (5.38)	31.93 (7.45)	28.20 (5.23)

SD-standard deviation

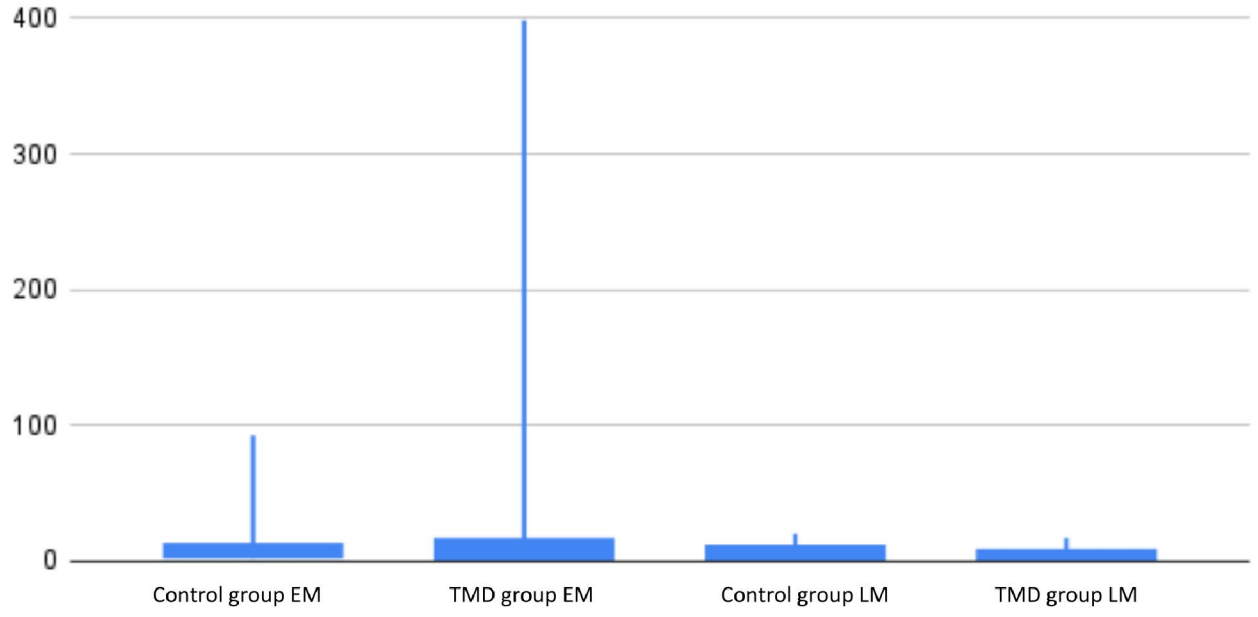

Fig. 1 The mean cortisol levels early morning and late morning in the study participants in both groups
EM: Early morning, LM: Late morning

data were presented in mean, median, and interquartile range. A one-way ANOVA was used to assess the strength of the statistical correlation between the variables. The correlations were adjusted for multiple comparisons using Tukey's post-hoc tests. A *p*-value for significance was established at <0.05. A logistic regression model was used to test the variability of dependable variables.

Results

A total of 132 participants were included in this study, with 66 participants with TMD (20 males and 46 females) and 66 participants in the control group (20 males and 46 females).

Table 1 demonstrates the mean cortisol level among both groups in two points of time. In the TMD group, the mean cortisol levels in the early morning were 29.95±75.05 (0-398.64), while the late morning levels were recorded as 4.87±3.96 (0-17.13). In the control group, the mean cortisol levels early morning were 10.98±16.83 (2.16–92.90), while the late morning cortisol levels were 6.15±6.13 (0-20.42). The accompanying boxplot visually highlights the maximum cortisol levels for each group at the two time points, providing a clear comparison of peak values between the TMD and control groups (Fig. 1). This indicates that the early morning salivary levels in patients with TMD have higher cortisol levels. The late morning mean cortisol level in the control group, though not statistically significant, was higher than the corresponding value in the TMD group.

Table 2 shows patients' mean salivary cortisol levels divided into four subgroups for TMD and control groups. The mean value represented in Table 2 is the average value of saliva collected at both intervals. For the participants having disc displacement with reduction, the mean cortisol was 0.83±1.34 (0-3.67). Those having disc displacement without reduction with limited mouth opening had the highest salivary cortisol levels among the subgroups, with a mean 82.49±124.34 (8.32-398.64). In patients with myofascial pain, the mean salivary cortisol levels were 13.03±3.90 (5.69–34.68), while in those with Myalgia, the mean was 4.83±3.90 (0-15.53). Cortisol

Table 2 Mean salivary cortisol levels TMD subgroups and control groups

Group	Salivary cortisol levels			
	Mean	SD	Minimum	Maximum
Disc displacement with reduction	0.83	1.34	0.00	3.67
Disc displacement without reduction with limited mouth opening	82.49	124.34	8.32	398.64
Myofascial pain	13.03	8.46	5.69	34.68
Myalgia	4.83	3.90	0.00	15.53
Control group	8.56	12.80	0.00	92.90

Table 3 Comparison of mean salivary cortisol levels early morning and late morning in both groups

Statistics	dF	Mean square	F	Significance
	3	**4447.146**	**2.980**	**0.034***
Comparison Group				***p*-value**
TMD (Early morning) vs. TMD (Late morning) (ng/ml)				0.046*
TMD (Early morning) vs. Control (Early morning) (ng/ml)				0.196
TMD (Early morning) vs. Control (Late morning) (ng/ml)				0.064
TMD (Late morning) vs. Control (Early morning) (ng/ml)				0.918
TMD (Late morning) vs. Control (Late morning) (ng/ml)				0.999
Control (Early morning) vs. Control (Late morning) (ng/ml)				0.957

levels were highest in participants with disc displacement without reduction with limited mouth opening.

A one-way ANOVA in Table 3 reported a significant difference among both groups ($p=0.034$), indicating increased salivary cortisol in the patients with TMD. Tukey's post hoc analysis reported statistical significance ($p=0.046$) among the TMD group early in the morning and the TMD group late in the morning. However, no statistical significance was recorded among the other groups.

Table 4 presents a gender-wise comparison of mean cortisol levels in the early and late morning among study participants from both groups. Among males in the TMD group, the mean salivary cortisol levels in the early morning were statistically significantly higher (84.83±132.80) compared to females (9.36±9.01) ($p=0.008$). In the late morning, the mean salivary cortisol levels for males and females were 4.83±3.51 and 4.89±4.25, respectively, showing no statistically significant difference. In the control group, among males, the mean salivary cortisol levels in the early morning were 8.78±10.03, while among females, it was 14.36±24. The difference between the two groups was not statistically significant. The mean cortisol levels in the late morning for males and females in the control group were 3.82±5.78 and 6.78±6.18, respectively, with no significant difference.

The regression analysis was applied to different groups of TMD and gender as dependable variables. It was observed that the main predictor variable was gender, with a statistically significant *p*-value of 0.036 (Table 5). While other variable, the TMD, came out to be non-significant with cortisol levels as a dependable variable.

Discussion

This study is one of the few, that aims to investigate salivary cortisol as a potential biomarker of TMD in adults aged between 18 and 40 years. To achieve this objective, we evaluated and compared salivary cortisol levels between individuals with TMD and those without, and further analyzed subgroups within the TMD patients.

Our study found that the salivary cortisol levels were significantly higher in patients with disc displacement without reduction with limited mouth opening compared to control and other TMD groups. These findings reject the null hypothesis, indicating a significant variation in salivary cortisol levels among participants with and without TMD. Our findings align with previous research, which has highlighted that salivary cortisol biomarkers potentially linked to TMD pathophysiology.

Table 4 Gender-wise mean cortisol levels early morning and late morning among groups

Cortisol level by (ng/ml)	Gender	Mean	SD	dF	Mean Difference	*p*-value
TMD (Early morning)	Males	84.83	132.80	31	75.46	0.008*
	Females	9.36	9.01			
TMD (Late morning)	Males	4.83	3.51	31	-0.05	0.970 NS
	Females	4.89	4.25			
Control (Early morning)	Males	8.78	10.03	31	-5.57	0.361 NS
	Females	14.36	24.00			
Control (Late morning)	Males	3.82	5.78	31	-2.95	0.265 NS
	Females	6.78	6.18			

Table 5 Regression coefficient

Model	Unstandardized coefficients		Standardized coefficient Beta	t	Significance
	B	Standard error			
Gender	-15.408	7.271	-0.180	-2.119	0.036*
TMD	8.844	6.668	0.112	1.326	0.187

The elevated cortisol levels in certain TMD subgroup may point to underlying biological mechanisms contributing to the disorder's progression [26]. In this study, we used the English version of the most reliable tool for clinically diagnosing TMD, the diagnostic criteria for temporomandibular disorders (DC/TMD axis I) [27], to categorize patients into different TMD groups based on physical and clinical aspects, which the DC/TMD axis-I form comprehensively covers. Since the primary objective of this study was examining the relevance of salivary cortisol as a potential biomarker for TMD in adults, psychological factors were not the focus of this research. Therefore, the DC/TMD Axis II form, which assesses psychological status and pain-related disability, was not utilized. Previous studies have shown that salivary cortisol levels are higher in patients with psychological disorders [28, 29]. However, in this study, the authors aimed to evaluate salivary cortisol specifically in the context of physical manifestations of TMD. One study found that patients with muscular pain had 35–55% higher cortisol levels than controls [10]. A systematic review by Alam et al. confirms that salivary cortisol levels tend to be higher in patients with various types of TMD than in the control group suggesting an association between salivary cortisol levels and the development of TMD [30].

The results of a one-way ANOVA showed a statistically significant difference in cortisol levels among the groups ($p=0.036$). Previous studies have also reported a significant increase in cortisol levels in patients with TMD, often as a response to stress [31, 32]. The timing of saliva collection is crucial due to the circadian rhythm of glucocorticoid hormone secretion, which peaks during the morning hours. In this study, saliva collection time was based on findings from previous studies that reported higher cortisol levels between 6.00 a.m. and 10.00 a.m [12, 33]. Our results indicate that cortisol levels were generally higher in the early morning than in the late morning across all groups, although this difference was not statistically significant. These findings were consistent with studies by Wilhelm et al. and Goyal et al., who also observed a distinct rise in early morning salivary cortisol levels in both plasma and saliva, reflecting adrenocortical activity. This emphasizes the importance of standardized collection times in research and clinical practice to ensure accurate assessments of cortisol levels and their implications for TMD.

Early-morning salivary cortisol levels were higher in TMD compared to late-morning, especially among males. This suggests that cortisol influences stress-related pain pathways that may exacerbate TMD. While TMD subgroups showed higher morning cortisol levels than controls, these differences were not statistically significant. Similar findings have been reported by Venkatesh et al. [11] and Khayam et al. [34], who observed higher cortisol levels in patients with TMD with disc displacement groups compared to controls. Both studies have also evaluated the psychological stress level of the participants. Conversely, Ornek et al. [19], found no significant association between cortisol levels, depression, and various types of TMD, though cortisol levels were slightly higher in TMD patients. However, by late morning, the control group had higher cortisol levels than the TMD group. Despite not reaching significance, this pattern in TMD patients could be explained by the alteration of cortisol rhythm due to chronic pain. As the body conserves cortisol after the initial Cortisol Awakening Response (CAR) [35], TMD patients may conserve cortisol leading to lower levels later in the morning. In contrast, the control group, without such chronic pain, maintains a typical cortisol rhythm with higher late morning levels.

The linear regression model result indicates that females had higher overall cortisol levels, which is consistent with other research by Venkatesh SB et al. [11], Jasmin et al. [12], and Ce et al. [36] all of which reported higher salivary biomarker levels in females than in males. However, in the context of TMD, the linear regression analysis did not show a significant correlation with cortisol levels, possibly due to the complexity of the relationship between cortisol and TMD which influenced by multiple interacting factors. It is important to consider that salivary cortisol is highly sensitive to other variables such as the time of day, psychological stress, and pain severity.

In the specific case of TMD, a significant difference was observed in early morning cortisol levels between males and females, with males showing higher levels (84.83 ± 132.80) than females (9.36 ± 9.01) ($p=0.008$). No significant gender difference was observed in the late morning cortisol levels within the TMD group, suggesting that gender may influence cortisol levels in the early morning only for individuals with TMD. Similarly, a previous study reported higher cortisol levels in males during late afternoon hours and speculated that these variations could be due to the time of saliva collection [37], while another study reported no gender differences in morning cortisol levels for facial pain [24]. Despite these findings, serum and salivary cortisol levels found a significant association with males' early morning cortisol levels [14]. Stirni et al., also observed that gender differences in pain scores were evident in patients with myofascial pain, although cortisol levels remained similar between genders [38].

Limitation and strength

Larger sample sizes are needed in the TMD subgroups to enhance the robustness and generalizability of the study's findings. Although patients with stress and mental disorders were excluded from the study, incorporating a tool

for subjective measurements of depression, anxiety, and stress would further enhance the ability to control factors that could affect saliva cortisol levels. This additional measure would help to minimize potential influences on the results and ensure a more precise assessment of cortisol biomarkers.

A potential limitation of this study is that protease inhibitors were not used during saliva collection. This choice might have introduced some variability in protein stability. Although the samples were preserved at a temperature that maintains protein integrity and were analyzed within a proper timeframe, the absence of protease inhibitors could still impact the stability of certain proteins. Future research could benefit from including protease inhibitors to help preserve protein integrity and improve data accuracy.

Clinical significance

This study introduces a novel clinical insight by demonstrating that salivary cortisol levels are significantly elevated in patients with disc displacement without reduction with limited mouth opening compared to those with other types of TMD and healthy controls. Notably, the study highlights that early morning cortisol levels are particularly elevated in males with TMD, revealing a distinct temporal and gender-related variation in cortisol secretion associated with TMD. This finding underscores the importance of considering both the time of day and gender when assessing cortisol levels in TMD patients.

Furthermore, the observed variations in cortisol levels among different TMD subgroups, especially in the context of disc displacement, suggest that salivary cortisol could serve as a potential biomarker for more specific TMD classifications.

Conclusion

While our findings suggest that salivary cortisol levels might be a potential biomarker for TMD, this does not imply causation. Disc displacement without reduction with limited mouth opening has significantly higher cortisol levels compared to the other groups, including the control group. This suggests that salivary cortisol could be a potential biomarker for this specific TMD subtype. Moreover, the data obtained suggests that the regulation of morning salivary cortisol is almost similar in both genders. However, early morning salivary cortisol levels were higher in males with TMD, which requires further investigation. Studies are needed to better understand the role of cortisol biomarkers in the underlying pathophysiology of TMD.

Abbreviations

TMD	Temporomandibular Disorders
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
TAC	Total Antioxidant Capacity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MMP	3-Matrix Metalloproteinase-3
TNF	α-Tumor Necrosis Factor-alpha
IL	1β-Interleukin-1 beta
HPA	Hypothalamic-Pituitary-Adrenal
OA	Osteoarthritis
CAR	Cortisol Awakening Response
PTSD	Post-traumatic stress disorder
ELISA	Enzyme-linked immunosorbent assay
EM	Early morning
LM	Late morning

Supplementary Information

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Supplementary Material 1

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Author contributions

L.A: Project conceptualization and design, patient recruitment and screening, data collection, ensuring proper handling and timing for early and late morning measurements, analysis, interpretation of the result, and main manuscript writing.H.A: patient recruitment and screening, Patient diagnosis, examination, and supervision during collection of salivary samples and coordination with participants, data collection.R.A: patient recruitment and screening, Data collection, ensuring proper handling and timing for early and late morning measurements, analysis, interpretation of the result, main manuscript writing.N.M: Participate in the study, Revising the manuscript, incorporating all necessary adjustments and changes, and ensuring coherence across sections. L.C: Participate in the study, Revising the manuscript, incorporating all necessary adjustments and changes, and ensuring coherence across sections.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Obtained from the Institutional Review Board (IRB),King Saud University under project number (E-23-7619). All participants provided written informed consent prior to their inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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