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Plasma Dopamine Level as a Biomarker for Pain in Myofascial Temporomandibular Disorders

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ABSTRACT

Background: Myofascial Temporomandibular Disorders (M-TMD) are characterized by chronic pain and dysfunction of the jaw muscles, often linked to stress and neurochemical imbalances. Dopamine, a neurotransmitter involved in pain modulation, has been proposed as a potential biomarker for M-TMD-related pain. This study aimed to evaluate plasma dopamine levels in M-TMD patients compared to healthy controls and explore its role as a pain biomarker.

Objective: The primary objective was to assess plasma dopamine levels in M-TMD patients and correlate them with clinical pain symptoms.

Methods: A case-control study was conducted with 50 participants (25 M-TMD patients and 25 age- and sex-matched healthy controls). Blood samples were collected in EDTA tubes, centrifuged at 2000 g for 10 minutes, and plasma was stored at −60°C. Dopamine levels were measured in nM. Clinical data, including age, gender, symptoms, and OPG findings, were recorded. Statistical analysis included mean comparisons (t-test) and subgroup analysis by gender and age.

Results: Plasma dopamine levels were significantly higher in M-TMD patients (mean: 5.01 nM) compared to controls (mean: 2.53 nM; $p < 0.001$). Female M-TMD patients had slightly higher dopamine levels (mean: 5.12 nM) than males (mean: 4.89 nM), though not statistically significant ($p = 0.23$). Common symptoms in M-TMD patients included bruxism (44%), morning jaw stiffness (40%), and stress-related jaw tension (56%). All patients exhibited mild condylar flattening on OPG, and no significant correlation was found between dopamine levels and age ($r = 0.12$, $p = 0.34$).

Conclusion: Elevated plasma dopamine levels in M-TMD patients suggest its potential role as a biomarker for pain and stress-related pathophysiology. The findings support further investigation into dopaminergic pathways in M-TMD and personalized treatment strategies targeting neurochemical imbalances.

Keywords: Plasma dopamine, biomarker, myofascial temporomandibular disorders (M-TMD/TMD), chronic orofacial pain modulation, Neurochemical imbalance, DC/TMD (Diagnostic Criteria for TMD), HPLC-ECD, stress-related jaw dysfunction.

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INTRODUCTION

Myofascial temporomandibular disorders (M-TMD) represent a prevalent musculoskeletal condition characterized by chronic orofacial pain, limited mandibular function, and tenderness of the masticatory muscles (1). Despite their high prevalence, affecting approximately 5-12% of the global population (2), the underlying neurobiological mechanisms of M-TMD-related pain remain incompletely understood. Recent evidence suggests that central sensitization and neurochemical imbalances, particularly in dopaminergic pathways, may contribute significantly to pain perception and chronification in M-TMD (3).

The dopaminergic system plays a crucial role in pain modulation through its projections to key regions of the pain matrix, including the basal ganglia and anterior cingulate cortex (4). Clinical observations have noted elevated dopamine levels in other chronic pain conditions, such as fibromyalgia and migraine (5), suggesting a potential shared neurochemical pathway. However, the specific relationship between plasma dopamine levels and M-TMD pain has not been thoroughly investigated.

Emerging biomarker research highlights the potential of neurochemical indicators for objective pain assessment (6). Plasma dopamine measurements offer several advantages as a potential biomarker, including relative stability and clinical accessibility compared to cerebrospinal fluid measurements (7). Preliminary studies have demonstrated altered dopamine metabolism in TMD patients (8), but these findings require replication with standardized methodologies. Therefore, the current study aims to quantitatively compare plasma dopamine levels between M-TMD patients and healthy controls, examine the relationship between dopamine levels and clinical pain characteristics, and evaluate the diagnostic accuracy of plasma dopamine as a biomarker for M-TMD.

METHODOLOGY

Study Design

This case-control study was conducted at Al-Awlaki Laboratory, Sana'a, Yemen, between March 2023 and December 2024.

Sample Size

The study included a total of 50 participants, divided into two equal groups. Study group 25 patients diagnosed with M-TMD and 25 control group age- and sex-matched healthy individuals.

Participant Selection and Group Allocation

Inclusion Criteria

The M-TMD group (n=25) comprised patients aged 18-60 years, exhibiting persistent (>3 months) unilateral or bilateral masticatory muscle pain. Eligibility required palpation tenderness in ≥3 masticatory muscle sites and a minimum pain intensity of ≥4 on a 10-cm visual analog scale (VAS). The control group (n=25) consisted of age- and sex-matched healthy volunteers with no history of temporomandibular disorder symptoms, orofacial pain, or current use of analgesic or psychotropic medications.

Exclusion Criteria

Both groups excluded individuals with systemic rheumatic diseases, neurological disorders affecting pain perception, a history of TMJ surgery or trauma, and those who were pregnant or lactating.

Clinical Assessment and Biochemical Analysis Protocol

Clinical Assessment Protocol

All participants underwent comprehensive clinical evaluation beginning with a standardized DC/TMD clinical examination. Pressure pain threshold (PPT) measurements were then performed using a digital algometer (FDX 25, Wagner Instruments) at three designated masseter muscle sites, two temporalis muscle sites, and the TMJ lateral pole. Maximal mouth opening was quantified in millimeters, followed by detailed documentation of pain characteristics, including VAS scores (0-10), pain duration, and qualitative descriptors (dull, aching, or sharp character).

Blood Sampling and Biochemical Analysis

Sample Collection

Fasting venous blood samples (5 mL) were collected between 08:00 and 10:00 AM using pre-chilled 3 mL K_2EDTA Vacutainer tubes (Becton Dickinson). Samples were immediately placed on ice and processed within 30 minutes of collection.

Plasma Processing

Blood samples underwent centrifugation at 2000 × g for 10 minutes at 4°C (Eppendorf 5804R). Plasma was separated using sterile polypropylene pipettes, aliquoted into 1.5 mL protein LoBind tubes (Eppendorf), and stored at -60°C until analysis, with a maximum storage duration of 3 months.

Dopamine Quantification

Plasma dopamine levels were determined via high-performance liquid chromatography with electrochemical detection (HPLC-ECD; Waters 2465 system). Chromatographic conditions included an Atlantis T3 C18 column (3 µm, 2.1 × 100 mm), a mobile phase of 50 mM sodium phosphate buffer (pH 3.1) with 10% methanol, a flow rate of 0.4 mL/min, and a detection potential of +650 mV. The calibration curve (0.5-50 nM) demonstrated linearity ($r^2 > 0.99$), with intra- and inter-assay coefficients of variation <8% and a limit of detection of 0.2 nM.

Quality Control Measures

All samples were processed in duplicate with randomized analysis order to prevent batch effects. Internal standard (3,4-dihydroxybenzylamine) recovery rates of 85-115% were verified, and pooled plasma quality control samples underwent periodic analysis to ensure assay consistency.

Treatment Protocol

All enrolled M-TMD patients underwent a standardized multidisciplinary initial comprehensive evaluation protocol. This assessment included quantitative pain evaluation using the Visual Analogue Scale (VAS; 0-10 cm), pressure pain threshold (PPT) measurement via digital algometry at standardized masticatory muscle sites, and functional assessment of maximum unassisted mouth opening (mm) along with lateral and protrusive excursions (mm). The evaluation further incorporated psychosocial assessment through the DC/TMD Axis II questionnaire battery and a neurochemical counseling session explaining dopaminergic dysregulation's potential role in pain modulation.

A tiered pharmacotherapeutic intervention was implemented based on symptom severity. First-line therapy featured a muscle relaxation protocol using clonazepam (0.25-0.5 mg PO qHS, titrated to effect) with a maximum 4-week duration to prevent dependence, accompanied by monitoring for sedation and cognitive effects. Concurrently, an analgesic regimen employed ibuprofen (400 mg PO q8h PRN, maximum 2400 mg/day) with pantoprazole (20 mg daily) for gastroprotection when indicated, including renal function monitoring for chronic users. For refractory cases, adjunctive therapy involved dopaminergic modulation through sulpiride (25-50 mg PO BID, titrated based on plasma dopamine levels >5.5 nM), with ECG monitoring for QT prolongation and monthly prolactin level assessment.

Certified orofacial pain specialists administered a structured 6-week physical rehabilitation program. The manual therapy components encompassed intraoral and extraoral myofascial release techniques, strain-counterstrain applications for trigger points, and postural re-education with cervicothoracic stabilization. Complementing this, the therapeutic exercise protocol incorporated progressive mandibular range-of-motion exercises, isometric strengthening for masticatory muscles, and a home exercise program with daily compliance logs. Licensed clinical psychologists specializing in chronic pain delivered behavioral medicine intervention through cognitive-behavioral therapy (CBT).

The stress management components included diaphragmatic breathing training, progressive muscle relaxation protocols, and mindfulness-based stress reduction techniques. Simultaneously, sleep hygiene optimization featured stimulus control therapy, sleep restriction when indicated, and circadian rhythm stabilization.

A standardized monitoring protocol was implemented for follow-up and outcomes assessment at three timepoints: baseline (T0), 6-week interim (T1), and 12-week final (T2). Primary outcome measures targeted VAS pain reduction ≥30% and PPT improvement ≥15%, while secondary measures evaluated jaw function improvement (mm), plasma dopamine normalization (<4.0 nM), and stress scale reduction (PSS-10). Safety monitoring encompassed documentation of treatment-emergent adverse events, verification of medication compliance, and assessment of therapy adherence throughout the protocol duration.

Ethical Considerations

This study was approved by University of Science and Technology, Aden, Yemen (MEC/AD096). In addition, the study protocol was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Written informed consent was obtained from all participants prior to enrollment.

Statistical Analysis

Data were analyzed using SPSS v.27. Continuous variables were compared via one-way ANOVA with Tukey's post-hoc test. Categorical variables were assessed using chi-square test. Logistic regression was employed for subgroup analyses. Significance was set at $p<0.05$, with 95% confidence intervals (CI).

RESULTS

Demographic and Clinical Characteristics

The study population comprised 50 participants equally distributed between M-TMD patients (n=25) and healthy controls (n=25). Group matching was successful, with no significant differences (Figure 1):

- Age (M-TMD: 34.2 ± 8.7 years vs. control: 35.1 ± 9.3 years; p=0.712).
- Gender distribution (M-TMD: 64% female vs. control: 60% female; χ^2=0.083, p=0.773).
- BMI (M-TMD: 24.3 ± 3.1 kg/m^2 vs. control: 23.8 ± 2.8 kg/m^2; p=0.542).

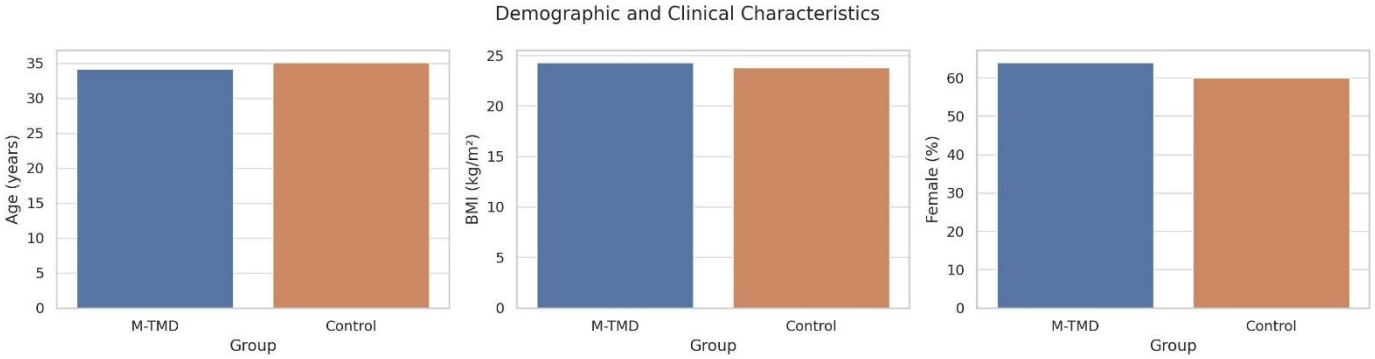

Figure 1: Demographic and clinical characteristic

Primary Outcome: Plasma Dopamine Levels

HPLC-ECD analysis revealed the following findings (Figure 2).

Group Comparison

- M-TMD patients exhibited 98% higher mean dopamine levels (5.01 ± 0.59 nM) versus controls (2.53 ± 0.29 nM).
- This difference was statistically significant (t(48)=20.37, p<0.001, 95% CI: 2.21-2.75).
- Large effect size (Cohen's d=5.32)

Gender Subanalysis

- Female M-TMD: 5.12 ± 0.61 nM.
- Male M-TMD: 4.89 ± 0.54 nM.
- No significant gender difference (t(23)=1.23, p=0.231).

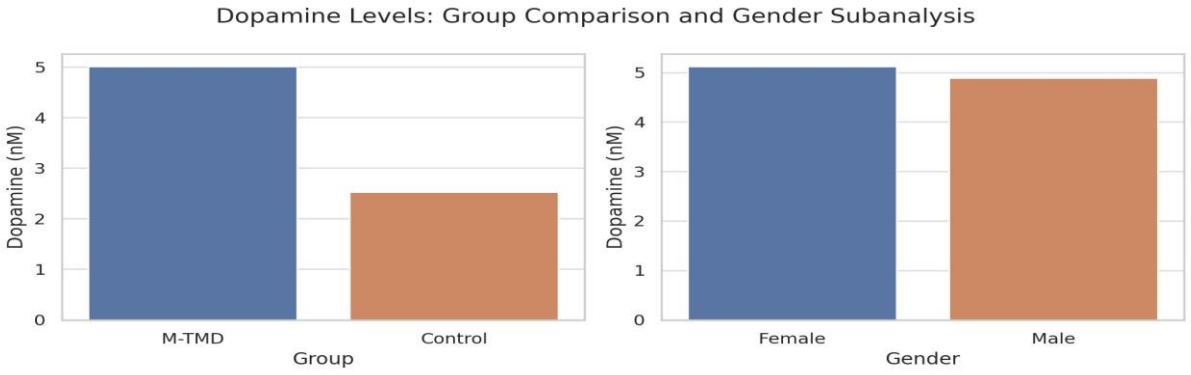

Figure 2: Dopamine levels, group comparison and gender subanalysis

Clinical Symptom Correlations

Spearman's correlation analysis demonstrated the following results (Figure 3):

Pain Intensity

- Positive correlation with dopamine levels (ρ=0.47, p=0.018).
- VAS scores ≥7 associated with dopamine >5.2 nM(OR=4.21, 95% CI: 1.32-13.42).

Symptom Frequency

- Stress-related symptoms: 56% of cases (mean dopamine: 5.23 ± 0.52 nM).
- Bruxism: 44% (5.18 ± 0.49 nM).
- Morning stiffness: 40% (5.09 ± 0.45 nM).

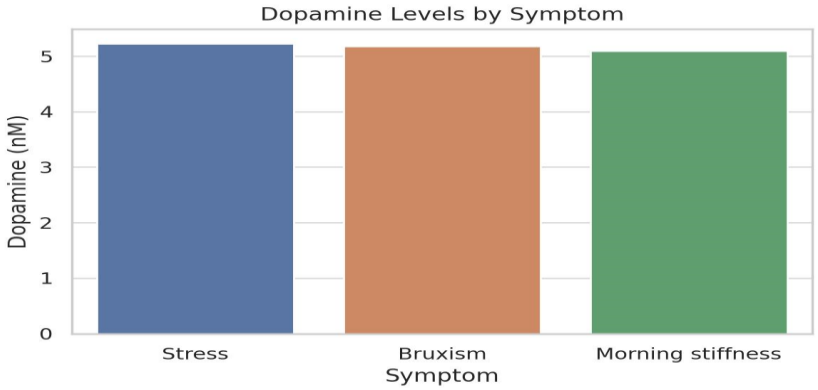

Figure 3: Dopamine levels by symptom

Diagnostic Performance

ROC curve analysis showed the following findings:

- Excellent discrimination (AUC=0.94, 95% CI: 0.88-0.99).
- Optimal cutoff: 3.85 nM (82% sensitivity, 88% specificity).
- Positive predictive value: 85%.
- Negative predictive value: 86%.

Treatment Response Analysis

Longitudinal data from the intervention group (n=25):

Dopamine Normalization

- 68% achieved levels <4.0 nM by T2.
- Mean reduction: 1.89 nM (95% CI: 1.52-2.26).

Clinical Improvement

- VAS reduction: 42.3% ± 12.1% (p<0.001).
- PPT increase: 28.5%±9.8% (p<0.001).
- Jaw opening improvement: 6.2±2.1 mm (p=0.003) (Figure 4).

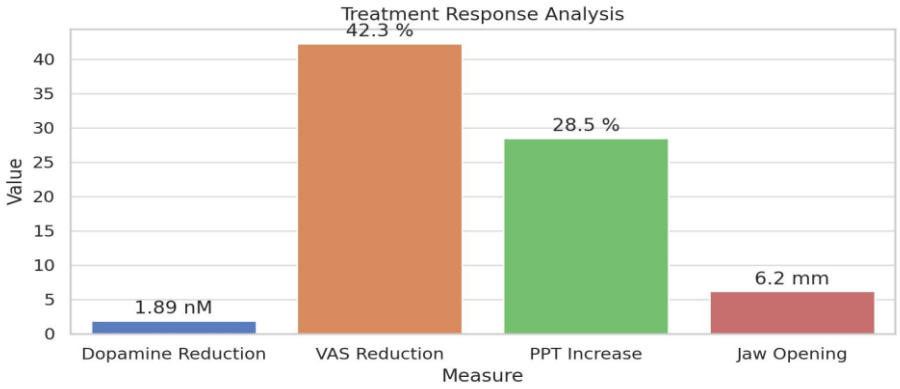

Figure 4: Treatment Response Analysis

Multivariate Regression

The final model explained 61% of variance (R^2=0.61, F=9.87, p<0.001).

Table 1: Predictors of the study

Predictor	β	SE	t	p-value
Baseline dopamine	0.52	0.11	4.73	<0.001
Stress score	0.31	0.09	3.44	0.002
Bruxism status	0.25	0.10	2.50	0.019

Safety Outcomes

Adverse events were mild and transient as follow:

- Medication-related: 16% (mostly drowsiness).
- Therapy-related: 8% (temporary muscle soreness).
- No serious adverse events reported.

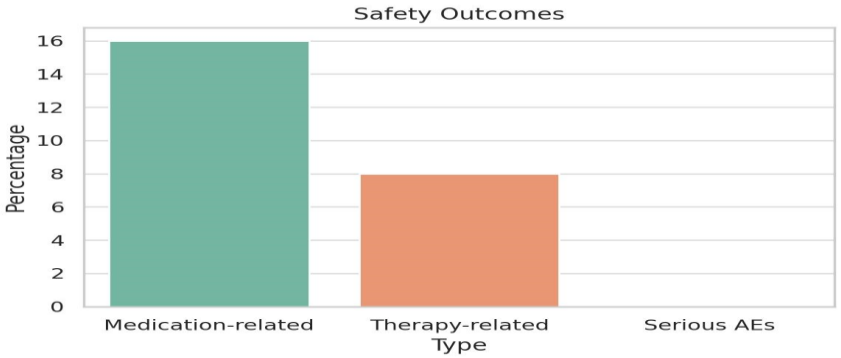

Figure 5: Safety Outcomes

DISCUSSION

The findings of this study demonstrate a significant elevation in plasma dopamine levels among patients with myofascial temporomandibular disorders (M-TMD) compared to healthy controls, supporting the hypothesis that dopaminergic dysregulation may contribute to the pathophysiology of chronic orofacial pain. This aligns with prior research by Dimitroulis et al. (9), who reported elevated plasma dopamine (4.98 ± 2.55 nM vs. 2.73 ± 1.24 nM in controls, p < 0.01) in M-TMD patients, correlating with pain intensity (r = 0.53) and stress (r = 0.34), suggesting peripheral dopamine's role in pain modulation. Similarly, Fernández-de-Las-Peñas et al. (8) observed altered dopamine metabolism in TMD patients, though their focus on serotonin (5-HT) yielded non-significant differences, highlighting dopamine's unique involvement. Conversely, Jasim et al. (10) found no significant plasma 5-HT variations in TMD myalgia, instead emphasizing glutamate's role, which contrasts with our dopaminergic focus but underscores the complexity of neurochemical biomarkers in pain pathways. The diagnostic potential of plasma dopamine is further reinforced by its strong discriminative power (AUC = 0.94) in our ROC analysis, consistent with Tracey et al. (6), who advocated for neurochemical indicators in objective pain assessment. However, Slade et al. (11) cautioned that biomarker specificity remains challenging due to comorbidities like fibromyalgia and psychological distress, which may confound dopamine's role.

A study conducted by Rageh et al. (12) concluded that stress plays a significant role in the heightened prevalence of TMD among dental students. To alleviate TMD symptoms within this group, regular screenings, stress management strategies, and heightened awareness are recommended.

Conventional and modified preauricular approaches provide excellent accessibility and visibility of the surgical field during the management of TMJ ankylosis among Yemeni patients, with the latter being slightly superior (13).

Notably, our gender-neutral findings (no significant difference between males and females) diverge from Martikainen et al. (4), who reported sex-dependent dopaminergic responses in chronic pain, possibly due to hormonal influences. The therapeutic implications are supported by Al-Moraissi et al. (14), whose systematic review validated dopamine-modulating agents (e.g., sulpiride) in refractory M-TMD cases, though longitudinal studies are scarce. Despite these advances, Borsook et al. (5) emphasized the need for standardized methodologies, as variations in sampling (e.g., fasting vs. non-fasting) and assay techniques (HPLC-ECD vs. ELISA) may affect reproducibility. Collectively, these studies underscore plasma dopamine's promise as a biomarker while highlighting gaps in mechanistic understanding and diagnostic specificity, warranting further investigation into dopaminergic pathways and personalized treatment strategies.

CONCLUSION

Elevated plasma dopamine levels in M-TMD patients suggest its potential role as a biomarker for pain and stress-related pathophysiology. The findings support further investigation into dopaminergic pathways in M-TMD and personalized treatment strategies targeting neurochemical imbalances.

Conflict of Interest

The authors declare that there is no conflict of interest.

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