**INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH**
**(ISSN: 2454-4191)**
www.ijmsdh.org (2026)
The Second International Conference for Medical and Applied Sciences (ICMAS-2026)



**Received:** 27 June 2026
**Revised:** 16 July 2026
**Accepted:** 04 August 2026
**Published:** 22 August 2026

**Page No - 01-09**
**DOI** - 10.55640/ijmsdh-icmas-2026-01
**Volume 12 Issue - ICMAS-2026 Special Issue | Selected Conference Papers**

**Article Citation:** Abbas, B. M., Kaem, G. G., & Hussein, H. S. (2026). Serum Cgrp Can Serve as A Clinically Useful Biomarker for Differentiating Migraine from Tension-Type Headache. International Journal of Medical Science and Dental Health, 01-09. https://doi.org/10.55640/ijmsdh-icmas-2026-01



# Serum Cgrp Can Serve as A Clinically Useful Biomarker for Differentiating Migraine from Tension-Type Headache

**Batoul Munir Abbas**

Department of Pathology Analysis, College of Applied Medical Sciences, University of Kerbala, Kerbala, Iraq.

**Ghosoon Ghanim Kaem**

Department of Pathology Analysis, College of Applied Medical Sciences, University of Kerbala, Kerbala, Iraq.

**Haider Shafi Hussein**

Consultant Neurologist, Karbala Health Directorate, Kerbala, Iraq.

## Abstract

**Background:** Migraine and tension-type headache (TTH) are the two most prevalent primary headache disorders and remain a major cause of disability worldwide. Despite their high prevalence, differentiating these conditions in clinical practice still relies primarily on symptom-based diagnostic criteria. The present study aimed to evaluate serum CGRP concentrations in patients with migraine, patients with tension-type headache, and healthy individuals. **Methods: This cross-sectional study included 100 subjects, recruited from November 2025 to March 2026: 35 migraine patients, 35 tension-type headache patients, and 30 healthy controls. Diagnosis of migraine and TTH was made by a consultant neurologist according to established clinical criteria. Serum CGRP levels were measured with a sandwich enzyme-linked immunosorbent assay (ELISA). Results: The serum concentrations of CGRP were significantly different between the three study groups (P < 0.001). The highest CGRP levels were observed in migraine patients (355.57 ± 86.29 pg/mL) followed by TTH patients (220.59 ± 42.25 pg/mL) and the lowest in healthy controls (171.27 ± 32.62 pg/mL). CGRP levels were significantly higher in migraine patients than TTH patients (P<0.001). Thus, migraine is associated with increased trigeminovascular activation. Serum CGRP showed good**

**diagnostic performance in the ROC curve analysis with AUC of 0.879, optimal cutoff value of 221.47 pg/mL, sensitivity of 67.14%, and specificity of 96.67%. The serum CGRP could discriminate patients with primary headache disorders from healthy controls, as confirmed by ROC curve analysis. Conclusions:** Serum CGRP is markedly elevated in migraine compared with both tension-type headache and healthy controls, reflecting its central role in migraine pathophysiology. Its high diagnostic accuracy, particularly its excellent specificity, highlights its potential as a clinically useful biomarker for differentiating primary headache disorders and supports its future integration into diagnostic and therapeutic strategies.

**Keywords:** Migraine; Tension type headache; Calcitonin gene related peptide; CGRP

## 1. Introduction

Primary headache disorders represent one of the leading causes of disability worldwide, affecting individuals during their most productive years and imposing substantial personal, social, and economic burdens. Migraine and tension-type headache (TTH) are the most common of these disorders and account for the majority of primary headaches seen in clinical practice. Although the two conditions exhibit overlapping clinical presentations such as recurrent episodes of headache and impaired quality of life, they differ widely in biological mechanisms, disease severity and therapeutic response (Zhao et al., 2025). Accurate differentiation between migraine and TTH is crucial for treatment Selection and better patient outcomes (AlBarqi et al., 2022).

Migraine is a complex neurovascular disorder which is characterized by recurrent attacks of moderate to severe headache with nausea, vomiting, photophobia and phonophobia (Maiese, 2024).There is an increasing body of evidence suggesting that migraine is a multifactorial neurological disease not just a vascular disorder with the abnormal activation of the trigeminovascular system, cortical and brain stem dysfunction, peripheral and central sensitization, and neurogenic inflammation (Hoffmann et al., 2019)By contrast, tension-type headache is generally thought to be caused by sustained activation of pericranial myofascial nociceptors, together with alterations in central pain processing, leading to a less prominent neuroinflammatory response than that seen in migraine. Although these mechanisms are different, there is often a substantial overlap in clinical symptoms, which frequently complicates the differential diagnosis, especially in patients with atypical or chronic headache presentations. (Pourahmadi et al., 2019).

CGRP is a 37 amino acid neuropeptide that is widely distributed in the central and peripheral nervous systems. Expression of CGRP is especially high in trigeminal sensory neurons. When the trigeminovascular pathway is active (L. Edvinsson, 2022). CGRP is released from peripheral nerve terminals and binds to the calcitonin receptor-like receptor (CLR) with receptor activity-modifying protein 1 (RAMP1) to activate intracellular signaling pathways that promote vasodilation, neurogenic inflammation, mast-cell activation and increased nociceptive transmission (Ramٍrez-Expósito et al., 2026). These biological effects are involved in peripheral and central sensitisation and thus in the initiation and the maintenance of migraine attack. The role of this pathway in migraine pathophysiology has been further supported by the clinical efficacy of monoclonal antibodies and small molecule antagonists that target the CGRP pathway (De Matteis et al., 2020).

In addition to its pathogenic role, CGRP has been of great interest as a possible diagnostic biomarker. Several studies have shown high circulating levels of CGRP in migraine patients, especially during acute attacks, and have linked this to disease activity, frequency of attacks and treatment response (Alpuente et al., 2024; Kamm, 2022) However, the clinical utility of serum CGRP is not fully established, as most of the studies published have only compared migraine patients with healthy controls. Comparatively few investigations have evaluated whether circulating CGRP can reliably distinguish migraine from other primary headache disorders, especially tension-type headache, which remains the most frequent differential diagnosis in routine neurological practice.

Therefore, the present study aimed to evaluate serum CGRP concentrations in patients with migraine, patients with tension-type headache, and healthy individuals, and to determine its diagnostic performance using receiver operating characteristic (ROC) curve analysis. The aim of this study is to provide evidence on the potential value of serum CGRP as a clinically applicable biomarker to enhance diagnostic accuracy and enable personalized management of headache disorders by investigating its discriminatory ability in the most prevalent primary headache disorders.

## 2. Materials and Methods

Study Design and Participants To evaluate the diagnostic value of serum calcitonin gene-related peptide (CGRP) in patients with primary headache disorders in a hospital based cross sectional study from November 2025 to March 2026. A total of 100 participants with age ranging between 18 and 45 years were enrolled and categorized into three groups; 35 patients

diagnosed with migraine, 35 patients diagnosed with tension type headache (TTH) and 30 apparently healthy individuals as control group. Patients were recruited from Al-Hindiya General Hospital and Imam Al-Hassan Al-Mujtaba Teaching Hospital, Iraq.

Migraine and TTH were diagnosed by a consultant neurologist according to the diagnostic criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3). Healthy controls had no previous history of primary headache disorders or chronic systemic diseases.

## 3.Inclusion and Exclusion Criteria

Eligible participants were adults between 18 and 45 years of age who provided written informed consent before enrollment. Individuals with secondary headache disorders, brain tumors, neurological diseases other than primary headaches, malignancies, diabetes mellitus, autoimmune disorders, chronic inflammatory diseases, severe hepatic or renal dysfunction, pregnancy, or any condition that might influence inflammatory biomarker levels were excluded from the study.

Venous blood was collected from each participant (5 mL) using aseptic technique. Two milliliters were sent to EDTA tubes for complete blood count (CBC) analysis and the other three milliliters were transferred to plain gel tubes for serum separation. The blood samples were allowed to clot at room temperature and centrifuged at 4000rpm for 10min. The isolated serum was divided into sterile microtubes and stored at −20°C until laboratory analysis.

Serum CGRP concentrations were determined using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biotechnology Co., Wuhan, China). All assays were performed according to the manufacturer's instructions. Absorbance values were registered using an ELISA microplate reader and serum concentrations were calculated from the standard curve included in the kit. All samples and standards were analyzed under the same laboratory conditions to minimize analytical variability.

## 4.Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequency and percentage. Normality of data distribution was tested by Shapiro–Wilk test and homogeneity of variances was evaluated by Levene's test. One-way analysis of variance (ANOVA) was used to compare the three study groups, with appropriate post hoc comparisons when significant differences were found. Independent-samples t-tests were used to make comparisons between two groups. Pearson's correlation coefficient was calculated to assess the relationship between levels of CGRP and selected clinical and laboratory variables. The diagnostic performance of serum CGRP was evaluated using receiver operating characteristic (ROC) curve analysis. The diagnostic discriminatory ability of CGRP was evaluated using the area under the curve (AUC), sensitivity, specificity, optimum cut-off value and 95% confidence intervals. Statistical significance was considered at two-tailed P value $<0.05$ and P $<0.01$ was considered as highly statistically significant.

## 5.Ethical Approval

This study was approved by the Ethics Committee of the Department of Clinical Laboratories, College of Applied Medical Sciences, University of Karbala (Reference No.: PAAMSKU/18). Permission to conduct the study was obtained from Ministry of Health and Environment prior sample collection. All participants were apprised of the study and furnished formal informed consent prior to their involvement. All participants also provided consent for socio-demographic data collection and laboratory analysis, with strict adherence to patient confidentiality.

## 6. Results

### *6.1 Demographic Characteristics of the Study Population*

The study was carried out in 100 subjects, 35 migraine patients, 35 patients with tension-type headache (TTH) and 30 healthy controls. The demographic characteristics of the study population are shown in **(Table 1).** There was a significant difference in sex distribution among study groups (P = 0.004). The majority of migraine patients were females (94.3%) followed by TTH patients (71.4%) and healthy controls (60.0%). Males were only 5.7% of the migraine group. Regarding age distribution, no statistically significant difference was found among the three groups (P = 0.139). Participants aged over 30 years constituted 60.0% of the migraine group and 62.9% of the TTH group, compared with 40.0% of the control group.

Similarly, body mass index (BMI) categories did not differ significantly among the study groups (P = 0.110). Normal BMI was the most common category in the control (50.0%) and TTH (51.4%) groups, whereas overweight participants represented the largest proportion in the migraine group (42.9%). Comparison of

the mean age also showed no statistically significant differences among the three groups. The overall mean age was **30.12 ± 7.63 years**, with mean ages of **28.10 ± 7.35 years** in controls, **30.40 ± 7.30 years** in migraine patients, and **31.57 ± 8.02 years** in patients with TTH (P = 0.182). Overall, the study groups were comparable with respect to age and BMI, while a significant predominance of females was observed among patients with migraine.

(**Table 1)** Demographic Characteristics of the Study Population

| Parameters | Group | Control | Migraine | Head tension | Total | P. value |
|---|---|---|---|---|---|---|
| Sex | Male | 12<br>%40.0 | 2<br>%5.7 | 10<br>%28.6 | 24<br>%24.0 | **0.00403 |
| | Female | 18<br>%60.0 | 33<br>%94.3 | 25<br>%71.4 | 76<br>%76.0 | |
| Age Group | Less than 30 | 18<br>%60.0 | 14<br>%40.0 | 13<br>%37.1 | 45<br>%45.0 | 0.13850 |
| | Greater than 30 | 12<br>%40.0 | 21<br>%60.0 | 22<br>%62.9 | 55<br>%55.0 | |
| BMI Group | Normal | 15<br>%50.0 | 13<br>%37.1 | 18<br>%51.4 | 46<br>%46.0 | 0.10972 |
| | Overweight | 8<br>%26.7 | 15<br>%42.9 | 5<br>%14.3 | 28<br>%28.0 | |
| | Obese | 7<br>%23.3 | 7<br>%20.0 | 12<br>%34.3 | 26<br>%26.0 | |
| Age (Mean ± Std. dev) | Less than 30 | 23.055 ± 3.572 | 23.214 ± 4.423 | 23.307 ± 4.069 | 23.177 ± 3.903 | 0.98424 |
| | Greater than 30 | 35.666 ± 4.313 | 35.190 ± 4.190 | 36.454 ± 5.243 | 35.800 ± 4.616 | 0.67230 |
| | Overall | 28.100 ± 7.350 | 30.400 ± 7.297 | 31.571 ± 8.023 | 30.120 ± 7.630 | 0.18216 |

- *. Association is significant at the 0.05 level.

- **. Association is significant at the 0.01 level.

***6.2 Neuroinflammatory Biomarker Profile Among Migraine, Tension-Type Headache, and Healthy Controls***

As shown in (**Table 2)** Serum CGRP concentrations were significantly different among the three study groups (P = 0.00004) . The mean serum CGRP level was highest in patients with migraine (355.57 ± 86.29 pg/mL) and the second highest in patients with tension-type headache (220.59 ± 42.25 pg/mL) and lowest in healthy controls (171.27 ± 32.62 pg/mL). The respective confidence intervals of 95% were 325.93–385.21 pg/mL for migraine, 206.07–235.10 pg/mL for TTH, and 159.09–183.45 pg/mL for the control group, which shows a gradual increase of serum CGRP levels in the study groups.

**(Table 2) Comparison of Serum CGRP Levels Among Migraine Patients, Tension-Type Headache Patients, and Healthy Controls**

| Parameters | Groups | Mean | Std. Deviation | 95% Confidence Interval for Mean | | P. value |
|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | |
| CGRP | Control | 171.266 | 32.615 | 159.087 | 183.445 | **0.00004 |
| | Head tension | 220.588 | 42.253 | 206.074 | 235.103 | |
| | Migraine | 355.573 | 86.288 | 325.932 | 385.214 | |

### *6.3 Diagnostic Accuracy of CGRP*

Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance of serum calcitonin gene-related peptide (CGRP) to differentiate patients with headache from healthy controls **(Table 3).** The serum CGRP showed an excellent diagnostic accuracy with an area under the curve (AUC) of 87.91 % (95% confidence interval [CI], 81.40–94.40 %, P = 0.002). The optimal cutoff value was 221.47 pg/mL with a sensitivity of 86.14% and specificity of 96.67% in distinguishing headache patients from healthy controls. These results suggest that serum CGRP has high diagnostic performance and excellent discriminatory power to differentiate patients with primary headache disorders from healthy controls.

**(Table3)** Receiver Operation Characteristic (ROC) Analysis of CGRP, for Differentiating Headache Patients from Healthy Controls

| Metrics | | CGRP |
|---|---|---|
| Std. Error | | 0.033 |
| Asymptotic Sig. | | 0.002 |
| Asymptotic 95% Confidence Interval | Lower Bound | 0.814 |
| | Upper Bound | 0.944 |
| Cutoff Point | | 221.469 |
| Area Under Curve (AUC) | | %87.905 |
| Sensitivity | | %86.143 |
| Specificity | | %96.667 |

### *6.4 Correlation Analysis of Serum CGRP and Blood Parameters*

Correlation analysis was used to evaluate the relationships between serum CGRP concentrations and selected clinical and laboratory parameters in headache patients **(Table 4).** Serum CGRP levels showed a significant positive correlation with IL-1β levels ($r = 0.726$, $P < 0.001$). By contrast, no significant correlations were found between serum CGRP and age ($r = 0.032$, $P = 0.795$), white blood cell (WBC) count ($r = 0.021$, $P = 0.860$), or hemoglobin (Hb) level ($r = –0.118$, $P = 0.329$). No significant correlation was observed between platelet count and serum CGRP ($r = 0.127$, $P = 0.296$), IL-1β ($r = 0.140$, $P = 0.248$), age ($r = −0.198$, $P = 0.101$) and WBC count ($r = 0.123$, $P = 0.309$). However, a significant negative correlation between platelet count and hemoglobin level was noted ($r = –0.416$, $P < 0.001$). In addition, IL-1β did not significantly correlate with age ($r = 0.104$, $P = 0.393$), WBC count ($r = 0.005$, $P = 0.965$), or hemoglobin level ($r = −0.202$, $P = 0.094$). Correlation analysis showed only a significant positive correlation between serum CGRP and IL-1β levels, and no significant correlations between CGRP and the demographic and hematological parameters studied.

**Table4** Correlation Analysis of Platelets Count, CGRP, and IL-1β in Headache patients

| Parameters | Value | CGRP | IL-1beta | Age | WBC | HB |
|---|---|---|---|---|---|---|
| Platelets | R. value | 0.127 | 0.140 | 0.198- | 0.123 | **416.- |
| | P. value | 0.296 | 0.248 | 0.101 | 0.309 | 0.000 |
| CGRP | R. value | 1 | **726. | 0.032 | 0.021 | 0.118- |
| | P. value | | 0.000 | 0.795 | 0.860 | 0.329 |
| IL-1beta | R. value | | 1 | 0.104 | 0.005 | 0.202- |
| | P. value | | | 0.393 | 0.965 | 0.094 |

- *. Correlation is significant at the 0.05 level.

- **. Correlation is significant at the 0.01 level

## 7. Discussion

The current study evaluated the diagnostic value of serum calcitonin gene-related peptide (CGRP) in migraine and tension-type headache (TTH) and the potential effect of demographic variables and correlation of CGRP with inflammatory biomarkers. The results indicated that: 1) serum CGRP was significantly increased in migraine compared with TTH and healthy controls; 2) serum CGRP had an excellent diagnostic performance in ROC analysis; 3) serum CGRP was highly correlated with IL-1β but not with age, body mass index (BMI) and routine hematological parameters. These observations, taken together, support the accumulating evidence that CGRP is intricately associated with migraine-related neurogenic inflammation, but not demographic or physiological differences (Lu et al., 2026) .

The demographic analysis revealed a significantly higher proportion of female patients, particularly in the migraine group, whereas no significant differences were observed regarding age distribution or BMI among the study groups. These findings are consistent with previous epidemiological studies demonstrating that migraine predominantly affects women because fluctuations in estrogen influence trigeminovascular activation, neuronal excitability, and CGRP (Godley III et al., 2024; Krause et al., 2021).

Nevertheless, the absence of significant differences in age and BMI suggests that these variables were unlikely to act as confounding factors affecting serum CGRP concentrations in the present study. Consequently, the observed differences in CGRP levels are more likely attributable to disease-specific mechanisms rather than demographic characteristics . The principal finding of the current study was the significant elevation of serum CGRP in migraine patients compared with both TTH patients and healthy controls. Migraine patients exhibited a mean serum CGRP concentration of 355.57 ± 86.29 pg/mL, whereas concentrations were substantially lower in TTH (220.59 ± 42.25 pg/mL) and controls (171.27 ± 32.62 pg/mL).

This progressive increase across the three groups strongly supports the central role of CGRP in migraine pathophysiology

. During migraine attacks, activation of the trigeminovascular system results in the release of CGRP from trigeminal sensory nerve endings CGRP then binds to the calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein-1 (RAMP1) resulting in vasodilation, plasma protein extravasation, mast-cell activation and neurogenic inflammation. These mechanisms further enhance peripheral and central sensitization, thus playing a role in headache initiation, persistence and pain severity (J. C. A. Edvinsson et al., 2021; Karsan et al., 2023). Conversely, TTH is thought to be mainly myofascial nociception and altered central pain processing with lesser trigeminovascular activation, which explains the comparatively lower CGRP concentrations in these patients (Bhoi et al., 2021; Vicente et al., 2023) .

The current results are in line with abundant clinical studies showing increased circulating CGRP levels in migraine (Leira et al., 2019; Różycka et al., 2026). identified CGRP as the key neuropeptide in the pathogenesis of migraine and noted that increased circulating CGRP is a sign of activation of the trigeminal nociceptive pathways (Greco et al., 2020). most studies consistently showed significantly increased serum or plasma CGRP concentrations in migraine, especially in symptomatic periods. CGRP signaling facilitates neurogenic inflammation and sensitization, thus contributing to migraine chronification

(Alpuente, 2023; Spekker et al., 2021) . The receiver operating characteristic (ROC) analysis revealed excellent diagnostic performance of serum CGRP in differentiating headache patients from healthy controls with AUC 0.879, sensitivity 86.14% and specificity 96.67%. The very high specificity observed in the present study indicates that it is unlikely that non-migraineurs will have high serum CGRP concentrations above the identified cut-off value (221.47 pg/mL) and thus decreasing false positive diagnoses. The sensitivity was somewhat less than the specificity although the overall diagnostic accuracy suggests that serum CGRP may be a useful adjunct biomarker when used in conjunction with clinical assessment and established diagnostic criteria. These results are consistent with recent evidence suggesting that biomarkers targeting the CGRP pathway may improve diagnostic confidence and enable personalized management of Primary headache disorders (Martin et al., 2021; ضzge et al., 2024).

Serum CGRP concentrations were strongly and positively correlated with IL-1β concentrations ($r = 0.726$, $P < 0.001$) but not significantly correlated with age, BMI, white blood cell count, hemoglobin concentration, or platelet count. These data suggest that increased CGRP release is more strongly associated with inflammatory activation than routine hematological or demographic parameters. IL-1β activates inflammatory signaling pathways that might upregulate neuronal CGRP expression, and CGRP may amplify inflammatory responses through interactions with immune cells, creating a positive feedback loop that perpetuates neurogenic inflammation during migraine attacks (Afroz et al., 2020; Mosaddeghi-Heris et al., 2026). Experimental studies have demonstrated that. Therefore, the strong correlation observed in the current study adds further evidence to the interaction of CGRP and inflammatory cytokines in the pathophysiology of migraine (Biscetti et al., 2022; Thuraiaiyah et al., 2022).

Finally, subgroup analyses performed by sex and age demonstrated no consistent effect of these demographic factors on circulating CGRP levels. A sex difference was observed in the migraine group but this was not present across all study groups and age-stratified analyses remained statistically non-significant. These results imply that serum CGRP levels are affected by disease status and not by demographic difference. To summarize, the findings of this study are consistent with the hypothesis that serum CGRP is a biologically plausible and clinically useful biomarker that differentiates between migraine and tension-type headache and reflects the underlying neurogenic inflammatory processes that drive migraine pathogenesis (Różycka et al., 2025; Wu et al., 2025).

## 8 .Conclusions

The present study shows that serum CGRP (calcitonin gene-related peptide) is significantly elevated in migraine patients as compared to patients with tension-type headache (TTH) and healthy controls. This indicates its important role in the pathophysiology of migraine and trigeminovascular activation. The significant variance in serum CGRP levels among the three groups suggests that CGRP is indicative of the biological processes underlying the distinction of migraine from other primary headache disorders. ROC curve analysis demonstrated good diagnostic performance of serum CGRP with excellent specificity, providing supporting evidence for its potential as a valuable adjunctive biomarker to improve the differential diagnosis of migraine and TTH with the established clinical criteria. In addition, the strong positive correlation between CGRP and IL-1β indicates a close interaction between neurogenic inflammation and inflammatory cytokines in migraine, providing further evidence for the role of

inflammatory pathways in pathogenesis of the disease. The increase of CGRP seems to be mostly associated with disease activity rather than demographic or physiological factors as no strong correlations were found with age or routine hematological parameters. Together, these findings indicate that serum CGRP is a biologically relevant and clinically promising biomarker that may allow for improved diagnosis, patient stratification and personalized treatment decision making in primary headache disorders. Although the present study provides encouraging evidence, additional multicenter studies with larger and more diverse populations are recommended to validate these findings, establish standardized reference ranges and diagnostic cut-off values, and clarify the utility of serum CGRP as a routine clinical biomarker in headache practice.

### *9. Reference*

1. Afroz, S., Arakaki, R., Iwasa, T., Waskitho, A., Oshima, M., & Matsuka, Y. (2020). Role of CGRP in neuroimmune interaction via NF-κB signaling genes in glial cells of trigeminal ganglia. *International Journal of Molecular Sciences*, *21*(17), 6005.
2. AlBarqi, M., AlDablan, M., AlBahr, A., AlAmer, M., AlNaim, A., AlNaim, A., & Almaqhawi, A. (2022). Prevalence, frequency, and disability of migraine headaches and tension headaches among the general population in the Eastern Region of Saudi Arabia. *Journal of Medicine and Life*, *15*(11), 1371.
3. Alpuente, A. (2023). *Migraine molecular phenotyping through the study of the calcitonin gene-related peptide: towards precision medicine*.
4. Alpuente, A., Gallardo, V. J., Asskour, L., Caronna, E., Torres-Ferrus, M., & Pozo-Rosich, P. (2024). Dynamic fluctuations of salivary CGRP levels during migraine attacks: association with clinical variables and phenotypic characterization. *The Journal of Headache and Pain*, *25*(1), 58.
5. Bhoi, S. K., Jha, M., & Chowdhury, D. (2021). Advances in the Understanding of Pathophysiology of TTH and its Management. *Neurology India*, *69*(Suppl 1), S116–S123.
6. Biscetti, L., De Vanna, G., Cresta, E., Bellotti, A., Corbelli, I., Letizia Cupini, M., Calabresi, P., & Sarchielli, P. (2022). Immunological findings in patients with migraine and other primary headaches: a narrative review. *Clinical and Experimental Immunology*, *207*(1), 11–26.
7. De Matteis, E., Guglielmetti, M., Ornello, R., Spuntarelli, V., Martelletti, P., & Sacco, S. (2020). Targeting CGRP for migraine treatment: mechanisms, antibodies, small molecules, perspectives. *Expert Review of Neurotherapeutics*, *20*(6), 627–641.
8. Edvinsson, J. C. A., Reducha, P. V, Sheykhzade, M., Warfvinge, K., Haanes, K. A., & Edvinsson, L. (2021). Neurokinins and their receptors in the rat trigeminal system: Differential localization and release with implications for migraine pain. *Molecular Pain*, *17*, 17448069211059400.
9. Edvinsson, L. (2022). Calcitonin gene-related peptide (CGRP) is a key molecule released in acute migraine attacks—Successful translation of basic science to clinical practice. *Journal of Internal Medicine*, *292*(4), 575–586.
10. Godley III, F., Meitzen, J., Nahman-Averbuch, H., O'Neal, M. A., Yeomans, D., Santoro, N., Riggins, N., & Edvinsson, L. (2024). How sex hormones affect migraine: an interdisciplinary preclinical research panel review. *Journal of Personalized Medicine*, *14*(2), 184.
11. Greco, R., De Icco, R., Demartini, C., Zanaboni, A. M., Tumelero, E., Sances, G., Allena, M., & Tassorelli, C. (2020). Plasma levels of CGRP and expression of specific microRNAs in blood cells of episodic and chronic migraine subjects: towards the identification of a panel of peripheral biomarkers of migraine? *The Journal of Headache and Pain*, *21*(1), 122.
12. Hoffmann, J., Baca, S. M., & Akerman, S. (2019). Neurovascular mechanisms of migraine and cluster headache. *Journal of Cerebral Blood Flow & Metabolism*, *39*(4), 573–594.
13. Kamm, K. (2022). CGRP and migraine: what have we learned from measuring CGRP in migraine patients so far? *Frontiers in Neurology*, *13*, 930383.
14. Karsan, N., Gosalia, H., & Goadsby, P. J. (2023). Molecular mechanisms of migraine: nitric oxide synthase and neuropeptides. *International Journal of Molecular Sciences*, *24*(15), 11993.
15. Krause, D. N., Warfvinge, K., Haanes, K. A., & Edvinsson, L. (2021). Hormonal influences in migraine—interactions of oestrogen, oxytocin and CGRP. *Nature Reviews Neurology*, *17*(10), 621–633.
16. Leira, Y., Ameijeira, P., Domínguez, C., López-Arias, E., Ávila-Gómez, P., Pérez-Mato, M., Sobrino, T., Campos, F., D'Aiuto, F., & Leira, R. (2019). Periodontal inflammation is related to increased serum calcitonin gene-related peptide levels in patients with chronic migraine. *Journal of Periodontology*, *90*(10), 1088–1095.
17. Lu, C.-L., Cheng, Y.-C., & Lu, K.-C. (2026). CGRP–uric acid axis in migraine: A redox–inflammatory framework linking neurovascular signaling and metabolic regulation. *Biomedicine & Pharmacotherapy*, *201*, 119709.
18. Maiese, K. (2024). Migraine Disorders, Neurovascular Disease, and the Underlying Role of Oxidative Stress. In

*Current Neurovascular Research* (Vol. 21, Issue 2, pp. 111–115). Bentham Science Publishers direct.

**19.** Martin, V. T., Feoktistov, A., & Solomon, G. D. (2021). A rational approach to migraine diagnosis and management in primary care. *Annals of Medicine*, *53*(1), 1969–1980.

**20.** Mosaddeghi-Heris, R., Forghani, N., Dehnavi, N. S., Saberivand, M., Tahavvori, A., Azin, S., Taheri, N., & Martelletti, P. (2026). Sensory Neuroimmunology: Bidirectional Neuro-Immune Circuits Governing Pain, Itch, Inflammation, and Host Defense at Barrier Surfaces. *Biology*, *15*(10), 756.

**21.** Özge, A., Baykan, B., Bıçakçı ,Ş., Ertaş, M., Atalar, A. Ç., Gümrü, S., & Karlı, N. (2024). Revolutionizing migraine management: advances and challenges in CGRP-targeted therapies and their clinical implications. *Frontiers in Neurology*, *15*, 1402569.

**22.** Pourahmadi, M., Mohseni-Bandpei, M. A., Keshtkar, A., Koes, B. W., Fernandez-de-Las-Penas, C., Dommerholt, J., & Bahramian, M. (2019). Effectiveness of dry needling for improving pain and disability in adults with tension-type, cervicogenic, or migraine headaches: protocol for a systematic review. *Chiropractic & Manual Therapies*, *27*(1), 43.

**23.** Ramírez-Expósito, M. J., Cueto-Ureña, C., & Martínez-Martos, J. M. (2026). Calcitonin Gene-Related Peptide (CGRP): Biology, Signaling, Pathophysiological Roles, and Therapeutic Applications. *International Journal of Molecular Sciences*, *27*(11), 4973.

**24.** Różycka, K., Krycia, K., Mulawa, M., Mazur, K., Gałuszka, A., Piaszczyńska, E., Matacz, D., Drabik, S., Gałuszka, M., & Adamczyk, A. (2026). CGRP as a Biochemical Biomarker in Migraine Diagnosis: A Systematic Review. *Journal of Education, Health and Sport*, *90*, 70438.

**25.** Różycka, K., Siwak, N., Rucka, A., Bielewicz, J., & Rejdak, K. (2025). A Review of the Biochemical Diagnostic Biomarkers in Migraine: New Perspectives in Diagnostics. *Pain Research and Management*, *2025*(1), 9478767.

**26.** Spekker, E., Tanaka, M., Szabó ,Á., & Vécsei, L. (2021). Neurogenic inflammation: the participant in migraine and recent advancements in translational research. *Biomedicines*, *10*(1), 76.

**27.** Thuraiaiyah, J., Erritzøe-Jervild, M., Al-Khazali, H. M., Schytz, H. W., & Younis, S. (2022). The role of cytokines in migraine: A systematic review. *Cephalalgia*, *42*(14), 1565–1588.

**28.** Vicente, B. N., Oliveira, R., Martins, I. P., & Gil-Gouveia, R. (2023). Cranial autonomic symptoms and neck pain in differential diagnosis of migraine. *Diagnostics*, *13*(4), 590.

**29.** Wu, J., Fu, L., Deng, Z., Li, H., Zhong, L., Gao, R., & Gui, W. (2025). A study of changes in hematologic parameters in patients with migraine. *Clinical and Experimental Immunology*, *219*(1), uxae113.

**30.** Zhao, Y., Yi, Y., Zhou, H., Pang, Q., & Wang, J. (2025). The burden of migraine and tension-type headache in Asia from 1990 to 2021. *The Journal of Headache and Pain*, *26*(1), 49.