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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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MIGRAINE AS A NEUROINFLAMMATORY DISEASE: PATHOPHYSIOLOGY, TREATMENT, AND IMPACT OF PHYSICAL EXERCISE

Agnieszka Ozdarska *(Corresponding Author, Email: agnieszka.ozdarska99@gmail.com)*
Independent Public Healthcare Institution in Wyszków, ul. Komisji Edukacji Narodowej 1, 07–200 Wyszków, Poland
ORCID ID: 0009-0008-7083-2140

Agnieszka Floriańczyk
Masovian Bródnowski Hospital, ul. Ludwika Kondratowicza 8, 03-242 Warsaw, Poland
ORCID ID: 0009-0003-5136-0380

Ewa Romanowicz
Independent Public Healthcare Institution in Wyszków, ul. Komisji Edukacji Narodowej 1, 07–200 Wyszków, Poland
ORCID ID: 0009-0004-6612-3174

Aleksandra Kołdyj
District Medical Centre in Grójec, ul. Piotra Skargi 10, 05-600 Grójec, Poland
ORCID ID: 0009-0002-5695-608X

Adrian Krzysztof Biernat
Specialist Provincial Hospital in Ciechanów, ul. Powstańców Wielkopolskich 2, 06-400 Ciechanów, Poland
ORCID ID: 0009-0007-6734-0447

Marcin Lampart
St. John Paul II Independent Public Western Specialist Hospital, ul. Daleka 11, 05-825 Grodzisk Mazowiecki, Poland
ORCID ID: 0009-0005-8485-850X

Anna Rupińska
Independent Public Outpatient Healthcare Group – Warsaw-Ochota, ul. Szczęśliwicka 36, 02-353 Warsaw, Poland
ORCID ID: 0009-0001-8567-5925

Kamila Krzewska
Primary Care Clinic "Zdrowa Rodzina", ul. Generała Tadeusza Pełczyńskiego 22J, 01-471 Warsaw, Poland
ORCID ID: 0009-0002-5672-3796

Hanna Skarakhodava
Health Center of Western Mazovia Sp. o.o., ul. Limanowskiego 30 96-300 Żyrardów, Poland
ORCID ID: 0009-0001-8051-6837

ABSTRACT

Migraine is a common and disabling neurological disorder now recognized as a neuroinflammatory condition. Its pathophysiology involves interactions between neurons, glial cells, vascular structures, and immune pathways, with critical roles played by pro-inflammatory cytokines, CGRP signaling, microglial activation, and mitochondrial dysfunction. These factors contribute to pain sensitization and chronic inflammation in the brain. This review summarizes current understanding of migraine as a neuroinflammatory disease, examining both pharmacological and non-pharmacological treatment strategies. Acute therapies include NSAIDs, triptans, and CGRP antagonists, while preventive options involve antiepileptics, beta-blockers, and monoclonal antibodies targeting CGRP. Beyond medications, lifestyle factors such as stress, sleep disorders, poor diet, and gut dysbiosis are shown to exacerbate migraine through inflammatory pathways. Special emphasis is placed on the role of physical exercise, which has demonstrated anti-inflammatory and neuromodulatory effects. Regular aerobic activity can reduce migraine frequency, duration, and intensity by lowering inflammatory markers and improving vascular and hormonal balance. Other supportive strategies include dietary modifications, probiotic supplementation, and patient education within a biopsychosocial framework. A multidisciplinary and personalized approach, combining medication, exercise, nutrition, and education, offers the most promise for long-term migraine management and improved quality of life.

KEYWORDS

Migraine Pathophysiology, Migraine Prevention, Physical Exercise, Neuroinflammation, Gut-Brain Axis

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Introduction.

Migraine is a highly prevalent primary headache disorder affecting approximately 1 in 9 adults worldwide(Ramachandran, 2018). The condition can significantly reduce the quality of one's life. It's considered to have a severe impact on not only physical state but also cause other neurological and mental conditions such as depression, anxiety, difficulty concentrating and sleeping. Those can have further implications that lead to social and professional consequences oftentimes straining relationships with family and friends and missing work days and having a negative effect on one's performance.

It is increasingly recognized as a complex neuroinflammatory condition, resulting from intricate interactions between neurons, glial cells, the vascular system, and inflammatory signaling pathways(Kursun et al., 2021). Central to migraine pathophysiology are neuroplastic changes that alter brain excitability, neurochemistry, and functional connectivity, leading to central sensitization and impaired pain modulation. Persistent activation of the trigeminovascular system promotes meningeal inflammation, triggering the release of proinflammatory mediators and heightened sensitivity of pain pathways(Tanaka et al., 2024; Viganò et al., 2019).

This paper aims to provide a comprehensive overview of migraine as a neuroinflammatory disease, delving into its complex pathophysiology, current treatment modalities, and the often-underestimated impact of physical exercise. By synthesizing current knowledge, we aim to highlight the multifaceted nature of migraine and underscore the importance of a holistic approach to its treatment and prevention.

Methodology

This systematic review examines theoretical findings on the pathophysiology of migraine and explores potential management strategies. A comprehensive literature search was performed using the PubMed database to identify studies published between April 2005 and May 2025. The following keywords were used in various combinations: "migraine", "neuroinflammation", "pathophysiology", "cytokines", "treatment", "exercise", "physical activity", "diet", education". Original research articles, systematic reviews, and meta-analyses published in English were considered. Case reports, editorials, and studies unrelated to neuroinflammation,

migraine management, physical activity were excluded. All relevant titles and abstracts were screened. Data were extracted and synthesized narratively, with a focus on common findings related to inflammatory pathways, therapeutic mechanisms, and exercise-induced changes in migraine profiles. No statistical methods were applied, as this review did not involve quantitative synthesis of data.

Definition and course of the disease

Migraine can be described as a chronic paroxysmal neurological disease. Migraines typically present as recurring unilateral headaches that can persist for 4 to 72 hours and are characterised by severe, throbbing pain, accompanied by nausea, vomiting, photophobia, and phonophobia, which are exacerbated by everyday physical activity(Kursun et al., 2021). The Global Burden of Disease Study 2015 places migraine as the fourth leading cause of years lived with disability in women and the eighth in men, underscoring its significant influence on quality of life(Ramachandran, 2018).

Two primary forms are distinguished: migraine with aura, characterized by transient neurological symptoms preceding the headache, and migraine without aura(Kursun et al., 2021). Contemporary research emphasizes that beyond vascular disturbances, migraine is fundamentally driven by neuroinflammatory mechanisms and abnormal brain plasticity, underscoring its classification as a neuroinflammatory disorder.

Migraine is traditionally divided into four stages: premonitory, aura, headache, and postdrome. Although these stages are often presented as occurring in a clear, linear sequence, in reality, they frequently overlap, making this simple progression both appealing and misleading(Goadsby et al., 2017).

Many people experience nonspecific symptoms 24 to 48 hours before a headache. The premonitory stage is usually associated with appetite changes, thirst, or yawning(Goadsby et al., 2017; Peng & May, 2020).

Migraine aura is a unique phase that typically lasts 15-30 minutes and occurs just before the headache phase(Peng & May, 2020). More recent studies also reveal that, in certain instances, the duration can be prolonged by up to 4 hours(Goadsby et al., 2017; Qubty & Patniyot, 2020). However, it is not classified as a separate phase in the revised definition for several reasons: it occurs in only about one-third of migraine sufferers, many individuals with aura also have migraine attacks without it, aura can occur without any accompanying headache, and it does not always precede the headache(Goadsby et al., 2017; Peng & May, 2020).

Beginning slowly and gradually, the headache phase typically intensifies over the course of several hours. It is frequently unilateral and severe. The pain can be a dull, constant ache when mild to moderate, or it may be a throbbing pain if more severe. By definition, its duration ranges from 4 to 72 hours(Goadsby et al., 2017; Peng & May, 2020).

Even after the pain subsides, many people may still experience non-specific symptoms like cognitive deficits and fatigue. Most of these postdromal symptoms typically return to normal within 24 hours after the headache has completely gone away(Goadsby et al., 2017; Peng & May, 2020).

While we will attempt to explore the underlying mechanisms of the symptoms in a stage-by-stage manner, it is important to note that certain symptoms, such as fatigue or difficulty concentrating, can appear during any phase. In truth, the presence or absence of head pain is the only feature that distinctly defines each stage(Goadsby et al., 2017).

Pathophysiological Aspects of Neuroinflammation in Migraine

The pathophysiology of migraine is now understood as involving not only vascular factors, but also complex interactions among neurons, glial cells (supporting cells in the brain), the vascular system, and inflammatory pathways.

1. Role of the immune system in migraine

The immune system plays a crucial role in the development of migraines. Several cytokines - including tumor necrosis factor (TNF), interleukin-1 (IL-1), and adiponectin - have been implicated in promoting inflammation, modulating pain thresholds, sensitizing trigeminal nerve fibers, and ultimately triggering migraine attacks(Kursun et al., 2021).

2. Involvement of Pro-inflammatory Cytokines

Several pro-inflammatory cytokines are implicated in migraine pathophysiology. Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) can modulate neuronal excitability, lower pain thresholds, and sensitize trigeminal nerve fibers, thereby contributing to the initiation and perpetuation of migraine pain(Edvinsson et al., 2019). Studies show changes in TNF levels in migraine patients, both during and between attacks, suggesting inflammation(Edvinsson et al., 2019). For example, TNF mRNA increased in an animal model of familial hemiplegic migraine, and elevated serum TNF in humans, even outside attacks,

points to its pathogenic role(Edvinsson et al., 2019). Despite these observed changes, the relevance of cytokines to migraine pathophysiology remains unclear(Edvinsson et al., 2019). Notably, etanercept, an anti-TNF antibody, has shown no benefit in migraine patients over millions of patient-years, casting doubt on TNF's direct role(Edvinsson et al., 2019).

3. Activation of microglia

The interplay between neurons and glial cells, specifically microglia, has a significant role in migraine. Microglia are immune cells of the central nervous system that can become activated in response to pain signals, contributing to neuroinflammation and the sensitization of pain pathways(Song et al., 2024). When activated, microglia can release various inflammatory mediators, including cytokines and chemokines, such as reactive oxygen species (ROS) and mediators like TNF-α, IL-7, and IL-1β, which can modulate neuronal activity and contribute to pain signaling(Song et al., 2024). NLRP3 activation in microglia induces microglial-neuronal communication, mediating inflammatory responses and leading to central sensitization(Song et al., 2024).

4. Neuron-Glia Crosstalk – Interactions and Impact on Pain Conduction

The pathophysiology of migraine is intricately linked to the dynamic interactions between neurons and glial cells, a phenomenon known as neuron-glia crosstalk(Amani et al., 2023). Neuron-glial interactions within the trigeminal ganglion (TG) are involved in peripheral sensitization(Song et al., 2024). Signaling between astrocytes, microglia, and neurons significantly contributes to the development of migraine(Song et al., 2024). This crosstalk plays a significant role in pain conduction and the overall sensitization processes that characterize migraine.

5. CGRP (Calcitonin Gene-Related Peptide) Pathway and its Significance

Calcitonin Gene-Related Peptide (CGRP) plays a central role in migraine pathophysiology, particularly through its interaction with dural afferent neurons and the immune system, establishing a strong link between neurogenic inflammation and peripheral sensitization(Edvinsson et al., 2019). It is a neuropeptide with potent vasodilatory properties, particularly affecting microvascular tone in the brain and peripheral systems, but vasodilation alone is not causative of migraine pain(Qubty & Patniyot, 2020; Ramachandran, 2018). Beyond vascular regulation, CGRP plays roles in nociception, glucose homeostasis, wound healing, and potentially in the phenomenon of cortical spreading depression (CSD) - a wave of neural excitation associated with migraine aura and pain(Qubty & Patniyot, 2020). CGRP is also emerging as a biomarker for migraine. Elevated CGRP levels have been found in patients, particularly those requiring preventive therapy(Qubty & Patniyot, 2020).

6. Mitochondria, Oxidative Stress, and Chronic Neuroinflammation

Furthermore, mitochondrial dysfunction and oxidative stress are implicated in chronic neuroinflammation, potentially contributing to the chronicity of migraine(Edvinsson et al., 2019; Goadsby et al., 2017; Kursun et al., 2021). Oxidative stress can lead to cellular damage and dysfunction, exacerbating inflammatory processes within the nervous system. Mitochondria are essential for cellular energy production, and their impairment leads to: elevated intracellular calcium (Ca^{2+}), excessive production of reactive oxygen species, deficient oxidative phosphorylation(Kursun et al., 2021). These disturbances result in neuronal and astrocytic energy failure, which may facilitate key migraine mechanisms like cortical spreading depression (CSD)(Kursun et al., 2021). Mitochondria also contribute to chronic neuroinflammation through the activation of the NLRP3 inflammasome(Kursun et al., 2021). The inflammasome connects metabolic stress to immune responses, solidifying migraine's classification as a neuroinflammatory disorder(Kursun et al., 2021). Targeting NLRP3 could represent a new therapeutic strategy.

Understanding these interconnected mechanisms is vital for developing targeted therapeutic strategies for migraine management.

Factors promoting neuroinflammatory aggravation in migraine

Many migraine patients report trigger factors preceding an attack. Studies estimate that 76% of migraineurs experience triggered attacks(Pavlovic et al., 2014). Common factors influencing or aggravating attacks include stress, sleep disorders, diet, the gut-brain axis, and lack of physical activity(Gazerani, 2020; Levis et al., 2024; On behalf of the School of Advanced Studies of the European Headache Federation (EHF-SAS) et al., 2020; Pavlovic et al., 2014; Peroutka, 2014).

1. Stress

Stress is a highly significant and consistently recognized trigger for migraine attacks. When a person experiences stress, the nervous system mounts a specific physiological response that involves a cascade of neuroendocrine events(Peroutka, 2014). These profound changes within the body and nervous system are believed to contribute to the neuroinflammatory processes underlying migraine(Peroutka, 2014).

2. Sleep

Migraine and sleep share a complex, bidirectional relationship('Therapeutic Role of Melatonin in Migraine Prophylaxis', 2020). While migraine is strongly associated with poor sleep, the exact mechanisms remain unclear(Mykland et al., 2022). Brain regions involved in migraine also regulate sleep, indicating shared pathways involving neurotransmitters and hormones('Therapeutic Role of Melatonin in Migraine Prophylaxis', 2020). Sleep disturbances can trigger migraine attacks, and poor sleep is linked to more frequent headaches(Mykland et al., 2022). Interestingly, coping strategies like going to bed early during an attack may worsen sleep quality, creating a cycle that reinforces both conditions(Ferini-Strambi et al., 2019). Understanding these connections may help differentiate migraine subtypes and improve treatment.

3. Gut-brain axis

An imbalance in the gut microbiome, known as dysbiosis, plays a significant role in migraine pathogenesis(Cavestro, 2025; Gazerani, 2020; Levis et al., 2024; On behalf of the School of Advanced Studies of the European Headache Federation (EHF-SAS) et al., 2020). Dysbiosis can increase intestinal permeability - commonly referred to as "leaky gut" - and trigger systemic inflammation(Levis et al., 2024). Pro-inflammatory cytokines may then reach the trigeminovascular system, activating pain pathways in the brain and ultimately provoking migraine attacks(Gazerani, 2020; Levis et al., 2024; On behalf of the School of Advanced Studies of the European Headache Federation (EHF-SAS) et al., 2020).

4. Diet

Dietary factors are widely recognized as potential migraine triggers, leading to the use of elimination diets in clinical practice. Foods such as chocolate, citrus fruits, dairy, alcohol, caffeine, aspartame, and gluten have been implicated, though evidence remains inconsistent(Cavestro, 2025; Gazerani, 2020). The effect of dietary triggers varies by individual and may depend on dose, timing, and biological sensitivity - such as food intolerances or immune responses (e.g., IgG antibodies or celiac disease)(Gazerani, 2020). Some ingredients may provoke migraines, while others can cause headaches upon withdrawal, like caffeine(Gazerani, 2020). Due to this variability, identifying dietary triggers can be challenging. It is commonly required to use a personalized approach in migraine dietary management.

Pharmacotherapy and biological treatment

Migraine treatment aims to manage acute attacks and prevent their recurrence, with the ultimate goal of improving the patient's quality of life. Management strategies include both pharmacological and non-pharmacological interventions. Early initiation of treatment is crucial for an effective response, and a hierarchical approach should be adopted, taking into account symptom severity, route of administration, and patient comorbidities.

1. Acute migraine treatment

Due to inconsistent and often suboptimal responses to therapy, migraine treatment frequently necessitates a personalized approach. For mild migraine attacks and aura, NSAIDs (such as aspirin, ibuprofen, diclofenac, or dexketoprofen) and acetaminophen are effective options(Aguilar-Shea et al., 2022). While acetaminophen is less potent, it is preferred in cases of NSAID or aspirin intolerance, and is considered safe during pregnancy, in children and adolescents, or when symptoms are not severely disabling(Aguilar-Shea et al., 2022).

Another common approach to managing migraine involves the use of triptans, typically prescribed for moderate to severe attacks. They act on 5-HT1B/1D receptors, reducing the release of neuropeptides like CGRP, which helps alleviate symptoms(Zobdeh et al., 2021). Their efficacy stems from their disease-specific mechanism, but due to vasoconstrictive effects, they are contraindicated in patients with cardiovascular, cerebrovascular, peripheral vascular disease, or uncontrolled hypertension(Aguilar-Shea et al., 2022; Zobdeh et al., 2021). Oftentimes, triptans are combined with acetaminophen or NSAIDs(Aguilar-Shea et al., 2022).

As previously stated, studies show that CGRP plays a significant role in migraine pathophysiology. Hence, antagonism of the CGRP receptor has demonstrated efficacy in the acute treatment of migraine(Zobdeh et al., 2021). Gepants, small-molecule CGRP receptor antagonists such as ubrogepant and rimegepant, exert their therapeutic effect by inhibiting trigeminovascular and thalamic pain pathways. These agents are approved for the acute treatment of migraine and are being evaluated for preventive use, with the advantage of not causing vasoconstriction(Aguilar-Shea et al., 2022; Zobdeh et al., 2021).

2. Preventive treatments

The goal of preventive migraine therapy is to decrease the frequency, intensity, and duration of attacks. Prophylaxis is indicated in patients with frequent episodes (≥4 attacks or ≥8 headache days per month),

inadequate response or contraindications to acute treatments, prolonged aura, substantial impairment of daily functioning, menstrual-related migraine, or based on patient preference(Aguilar-Shea et al., 2022).

Topiramate and valproate are commonly used to prevent migraines(Aguilar-Shea et al., 2022; Zobdeh et al., 2021). Topiramate works by regulating brain excitability, blocking sodium channels, reducing excitatory glutamate activity, and limiting CGRP release from trigeminal neurons(Zobdeh et al., 2021). Among antiepileptics, topiramate is the most effective and widely prescribed, though it can cause side effects like cognitive issues, tingling sensations, kidney stones, mood shifts, and weight loss(Aguilar-Shea et al., 2022). Valproic acid tends to have more adverse effects, including weight gain, hair loss, and acne, and is generally not recommended as an initial treatment option(Aguilar-Shea et al., 2022).

Antidepressants, such as amitriptyline and venlafaxine, are another option and may be effective even if there is no depression(Aguilar-Shea et al., 2022).

Several antihypertensive agents are believed to be effective in migraine prevention. Beta-adrenoceptor antagonists such as propranolol and timolol are among the most recognized options, reducing attack frequency in approximately 50% of patients(Aguilar-Shea et al., 2022). Although their precise mechanism in migraine prophylaxis remains unclear, proposed actions include modulation of central excitability, inhibition of nitric oxide synthesis, reduction in noradrenaline release, and interaction with serotonergic pathways(Zobdeh et al., 2021). For patients with comorbid hypertension who are unsuitable for beta-blockers, alternatives such as the ACE inhibitor lisinopril or the angiotensin II receptor blocker candesartan may be considered(Aguilar-Shea et al., 2022). Flunarizine, a calcium channel blocker, has also demonstrated efficacy in the prophylactic treatment of episodic migraine(Aguilar-Shea et al., 2022).

Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor, such as erenumab, galcanezumab, fremanezumab, and eptinezumab, represent a significant advancement in migraine prophylaxis(Aguilar-Shea et al., 2022; Cohen et al., 2022; Zobdeh et al., 2021). These monoclonal antibodies act peripherally, as they do not cross the blood–brain barrier(Sevivas & Fresco, 2022). By neutralizing CGRP or blocking its receptor, they reduce trigeminal pathway activation and help lower headache frequency(Sevivas & Fresco, 2022). Approved between 2018 and 2020, these agents offer a targeted mechanism with favorable safety profiles(Zobdeh et al., 2021). Their long half-life enables infrequent dosing, and unlike many oral drugs(Sevivas & Fresco, 2022). They are administered either subcutaneously (monthly, or quarterly in the case of fremanezumab) or intravenously every 12 weeks (eptinezumab)(Aguilar-Shea et al., 2022). Adverse effects are generally mild, though potential cardiovascular risks warrant consideration(Aguilar-Shea et al., 2022; Cohen et al., 2022).

OnabotulinumtoxinA (Botox®) is approved for chronic migraine, typically in patients experiencing over 15 headache days per month(Aguilar-Shea et al., 2022). Administered every 12 weeks at standardized injection sites, it acts as a neuromodulator(Aguilar-Shea et al., 2022; Zobdeh et al., 2021).

Non-pharmacological interventions and lifestyle prevention

1. Physical activity as anti-inflammatory factor

Regular aerobic exercise is increasingly recognized as an effective non-pharmacological strategy for managing and preventing migraine. Its therapeutic potential is largely attributed to its systemic anti-inflammatory effects, neuromodulatory influence, and favorable impact on vascular and endocrine function(Barber & Pace, 2020; Flynn et al., 2007; Irby et al., 2016; Petersen & Pedersen, 2005).

Physical activity lowers pro-inflammatory cytokines such as TNF-α and inflammatory markers like C-reactive protein, while enhancing anti-inflammatory mediators including IL-10 and adiponectin(Barber & Pace, 2020; Flynn et al., 2007; Irby et al., 2016; Petersen & Pedersen, 2005). Muscle contractions stimulate the release of myokines, such as IL-6, which promote anti-inflammatory responses and support lipid metabolism independently of TNF-α(Petersen & Pedersen, 2005). Exercise also activates regulatory T cells within muscle tissue, which help reduce chronic inflammation and improve muscle metabolism and endurance(Flynn et al., 2007). These anti-inflammatory and immunomodulatory effects may explain the observed improvements in migraine frequency, intensity, and duration(La Touche et al., 2023). A neuroinflammatory model suggests that suppression of inflammatory and stress-related mediators, including CGRP, substance P, cortisol, and ACTH, contributes to reduced migraine burden(Barber & Pace, 2020). Additionally, exercise enhances microvascular function, which may help counteract cortical spreading depression, a proposed mechanism in migraine pathophysiology(Barber & Pace, 2020). Higher-intensity training has been associated with improved cerebral perfusion and fewer migraine days, possibly through retinal arteriolar dilation(Barber & Pace, 2020). Long-

term aerobic exercise may also increase pain thresholds via modulation of stress hormones such as growth hormone and prolactin(Barber & Pace, 2020).

Beyond its migraine-specific effects, exercise offers broad health benefits that support its inclusion in treatment protocols. It can aid in weight control, improve sleep, stabilize mood, and benefit cardiovascular health(Irby et al., 2016). These advantages are particularly relevant in migraine patients with comorbid conditions such as obesity, hypertension, anxiety, and depression(Irby et al., 2016).

Despite the need for further research, aerobic exercise is frequently recommended due to its favorable safety profile and wide-ranging physiological benefits. Randomized controlled trials have shown that aerobic exercise alone can lead to meaningful reductions in headache frequency, duration, and intensity, often comparable to pharmacologic agents like topiramate(Barber & Pace, 2020; Irby et al., 2016). In some cases, exercise has demonstrated similar effectiveness with fewer side effects and better adherence than medication or relaxation techniques(Irby et al., 2016).

While intense or prolonged exercise may acutely elevate both pro- and anti-inflammatory markers, potentially leading to temporary immune disruption, regular moderate-intensity activity remains the preferred approach to achieving sustained anti-inflammatory effects and migraine relief(Cerqueira et al., 2020).

2. The impact of diet and supplementation

Emerging research suggests that dietary interventions and targeted supplementation can play a significant role in preventing and alleviating migraines by addressing the underlying neuroinflammatory and metabolic dysfunctions. One promising approach involves modulating the gut microbiota, particularly through the use of probiotics and synbiotics(Gazerani, 2020; Ghavami et al., 2021; On behalf of the School of Advanced Studies of the European Headache Federation (EHF-SAS) et al., 2020). Strains such as Lactobacillus and Bifidobacterium may help strengthen the gut barrier, reduce the release of inflammatory cytokines, and support immune balance(Gazerani, 2020; Ghavami et al., 2021). Combining probiotics with prebiotics (synbiotics) appears to enhance these effects, improving gut permeability and decreasing markers of systemic inflammation(Cavestro, 2025; Ghavami et al., 2021). Specific compounds like fructooligosaccharides (FOS) also promote the production of short-chain fatty acids, which offer neuroprotective and anti-inflammatory benefits(Ghavami et al., 2021). Dietary patterns that support gut health and reduce inflammation may further impact migraine occurrence. Approaches such as high-fiber intake, low-glycemic-index diets, and the inclusion of anti-inflammatory nutrients like omega-3 fatty acids and vitamin D have been linked to improvements in migraine symptoms(Gazerani, 2020; On behalf of the School of Advanced Studies of the European Headache Federation (EHF-SAS) et al., 2020). For some individuals, eliminating gluten or adopting weight loss strategies may reduce the inflammatory burden and improve outcomes, particularly in patients with obesity or gluten sensitivity(Cavestro, 2025; Gazerani, 2020). More structured diets, such as ketogenic, Mediterranean, and low-fat vegan regimens, have shown potential in reducing migraine frequency and intensity(Cavestro, 2025). The ketogenic diet may exert its benefits through metabolic shifts that stabilize neuronal function and reduce oxidative stress(Cavestro, 2025). Plant-based diets, on the other hand, may influence hormone levels and reduce menstrual-related migraine episodes(Nguyen & Schytz, 2024). Incorporating specific nutrients, such as magnesium, riboflavin, coenzyme Q10, curcumin, zinc, folate, tryptophan, and vitamin B1, may also support mitochondrial health, reduce oxidative stress, and modulate inflammatory pathways, all of which are implicated in migraine pathophysiology(Cavestro, 2025). Additionally, personalized approaches that account for individual metabolic profiles, such as insulin resistance or food sensitivities, can enhance treatment efficacy(Cavestro, 2025). Identifying dietary triggers, for instance via immunological testing, and implementing exclusion diets can offer symptom relief for some patients(Nguyen & Schytz, 2024). While the evidence base is growing, further well-designed clinical trials are needed to validate these strategies. Nonetheless, nutrition-based interventions and supplementation represent a promising, safe addition to standard migraine treatments, with the potential to reduce both symptom burden and reliance on medication.

3. The importance of patient education

Patient education represents a foundation of non-pharmacological migraine management. By improving patients' understanding of migraine as a chronic, neuroinflammatory disease, education allows patients to actively participate in their own care. Crucial educational interventions include providing information about the chronic nature of migraine, identifying and managing triggers, understanding comorbidities, and differentiating between abortive and prophylactic treatments. Non-pharmacological interventions such as behavioral therapy, biofeedback, relaxation, and mindfulness are recommended alongside education(Haghdoost & Togha, 2022). A combined approach of pharmacological and educational strategies

enhances treatment effectiveness and improves patient adherence(Haghdoost & Togha, 2022). The importance of health education in migraine therapy research demonstrates that therapeutic patient education significantly improves quality of life, reduces disability, and decreases the frequency of migraine attacks(Smith et al., 2010). Well-structured educational programs boost one's abilities for headache management and decrease anxiety and emergency room visits related to migraine(Smith et al., 2010). Ongoing education also raises patient satisfaction with their care and enhances long-term outcomes(Smith et al., 2010). The biopsychosocial model is increasingly recognized as critical for comprehensive migraine management. This model integrates biological, psychological, and social factors that influence the onset, severity, and chronicity of migraine(Rosignoli et al., 2022). Factors such as stress, mood disorders, social support, and coping strategies play important roles in modulating migraine risk(Inan, 2024; Rosignoli et al., 2022). The biopsychosocial approach encourages individualized, patient-centered care and supports the integration of non-pharmacological strategies, such as cognitive-behavioral therapy and social support, into conventional treatments(Inan, 2024; Persson et al., 2023; Rosignoli et al., 2022).

Conclusions

Migraine is more than a vascular or episodic pain disorder. It is a chronic neuroinflammatory condition involving diverse physiological and environmental factors. Understanding the role of cytokines, glial activation, CGRP, mitochondrial dysfunction, and oxidative stress sheds light on the biological foundation of migraine and opens new directions for targeted therapy. While pharmacological treatments remain essential for many patients, the growing body of evidence supports the use of lifestyle interventions, particularly regular aerobic exercise, as effective tools in migraine prevention and management. Exercise not only reduces neuroinflammatory markers but also improves mental health, sleep, and cardiovascular function, all of which are critical in migraine pathogenesis. Future therapeutic strategies should adopt a comprehensive and individualized approach, integrating pharmacological treatments with physical activity, dietary adjustments, gut health optimization, and patient education. This multifaceted model aligns with the biopsychosocial pattern and holds the potential to significantly improve patient outcomes while reducing dependency on medication.

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Author's contribution:
Conceptualization: Agnieszka Floriańczyk, Ewa Romanowicz
Methodology: Aleksandra Kołdyj, Agnieszka Ozdarska
Software: Adrian Krzysztof Biernat, Marcin Lampart
Check: Anna Rupińska, Hanna Skarakhodava
Formal analysis: Kamila Krzewska, Hanna Skarakhodava
Investigation: Agnieszka Floriańczyk, Agnieszka Ozdarska
Resources: Aleksandra Kołdyj, Ewa Romanowicz
Data curation: Adrian Krzysztof Biernat, Hanna Skarakhodava
Writing—rough preparation: Agnieszka Floriańczyk, Kamila Krzewska
Writing—review and editing: Anna Rupińska, Hanna Skarakhodava
Supervision: Aleksandra Kołdyj, Marcin Lampart
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