CIUBA, Katarzyna, BORODZIUK, Barbara, BORODZIUK, Filip, DĄBROWSKA, Paulina, ŻUBER, Michał, BOCHYŃSKI, Karol, MOLENDA, Katarzyna, DACKA, Michał, GIŻEWSKA, Kamila and BIAŁOGŁOWSKI, Konrad. Caffeine and migraine – friends or enemies? Quality in Sport. 2024;18:53225. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.18.53225
https://apcz.umk.pl/QS/article/view/53225

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 06.07.2024. Revised: 22.07.2024. Accepted: 23.07.2024. Published: 25.07.2024.

Caffeine and migraine – friends or enemies?

Katarzyna Ciuba, Barbara Borodziuk, Filip Borodziuk, Paulina Dąbrowska, Michał Żuber, Karol Bochyński, Katarzyna Molenda, Michał Dacka, Kamila Giżewska, Konrad Białogłowski

Katarzyna Ciuba
katarzyna.ciuba@onet.eu
ORCID 0009-0007-8347-3282
Province Specialist Hospital named after Stefan Cardinal Wyszyński in Lublin,
Al. Kraśnicka 100, 20-718 Lublin, Poland

Barbara Borodziuk
basia.borodziuk@gmail.com
ORCID 0009-0009-2716-6653
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Filip Borodziuk
filipb899@gmail.com
ORCID 0009-0000-0394-1816
1 Military Clinical Hospital in Lublin,
al. Racławickie 23, 20-049 Lublin, Poland

Paulina Dąbrowska
paulina.dabrowska98@gmail.com
ORCID 0009-0004-6439-3357
Province Specialist Hospital named after Stefan Cardinal Wyszyński in Lublin
Al. Kraśnicka 100, 20-718 Lublin, Poland

Michał Żuber
michal.zuber10@gmail.com
ORCID: 0009-0000-2538-8556
4th Clinical University Hospital in Lublin,
ul. Kazimierza Jaczewskiego 8, 20-954 Lublin, Poland

Karol Bochyński
karolbochynski@gmail.com
ORCID 0009-0003-8309-2800
4th Clinical University Hospital in Lublin,
ul. Kazimierza Jaczewskiego 8, 20-954 Lublin, Poland

Katarzyna Molenda
zielinskakasia98@gmail.com
ORCID 0009-0005-1928-4220
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Michał Dacka
michal.dackaa@gmail.com
ORCID 0009-0005-8783-6517
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Kamila Giżewska
gizewska.kamila@gmail.com
ORCID: 0000-0003-1682-180X
1 Military Clinical Hospital in Lublin,
al. Racławickie 23,20-049 Lublin, Poland

Konrad Białogłowski
konrad.bialoglowski@gmail.com
ORCID: 0009-0001-1705-254X
University Clinical Hospital No. 1 in Lublin,
ul. Stanisława Staszica 16, 20-081 Lublin, Poland

ABSTRACT
Severe headaches or migraines are a common neurological disorder that can significantly affect people's daily lives and is serious problem for individuals and society. A migraine is intense headache lasting 4-72 hours, typically localized on one side of the head and accompanied by nausea, sensitivity to light (phonophobia), sound (photophobia), and smell (osmophobia). The pathophysiology of migraines is complex and involves neurovascular and biochemicals mechanisms. Understanding the mechanisms that trigger the transition from a headache-free state to the headache phase is important to understand the underlying causes of migraine attacks and developing effective treatment methods. Caffeine can have both positive and negative influence on individuals suffering from migraine. It is use as adjuvant component in migraine treatment, but it can also act as a trigger for migraines. The therapeutic mechanisms of caffeine in migraine headaches are multidirectional and include: vascular effects, modulation of NO production, adenosine antagonism, potential interactions with the gut-brain axis and inhibition of leukotrienes and prostaglandins' synthesis. On the other hand, the onset of migraine attack may be related to caffeine consumption or withdrawal. The purpose of this study is to review and systematize the available data about relation caffeine use to migraine.

1. Introduction

Severe headaches or migraines are a common neurological disorder that can significantly affect people's daily lives and is serious problem for individuals and society. According to Global Burden of Disease Study, headache disorders are second cause of years lived with disability [1]. A migraine is intense headache lasting 4-72 hours typically localized on one side of the head and accompanied by nausea, sensitivity to light (photophobia), sound (phonophobia), and smell (osmophobia) [2]. Many factors that can trigger migraine attack have been identified and one of them is caffeine. On the other hand caffeine is used in treatment as addition to analgesics. The coincidence between headache onset, migraine treatment and caffeine has been the subject of researches for many years. It is still unclear how migraines and caffeine are related. The purpose of this study is to review and systematize the available data about relation caffeine use to migraine.

2. Material and methods

Based on sources available on the Internet, we reviewed the literature covering topics connected with the connection between migraine and caffeine. We used the keywords: „migraine", "caffeine", "migraine treatment", "headache", "migraine triggers'' in medical research databases such as PubMed, Cochrane and Google Scholar. We focused on full-text articles that covered issues related to subject of this review. Approximately 100 papers were selected for analysis, of which 45 were used to compile this review.
Keywords: „Migraine", „Caffeine", „Migraine treatment''.

3. Migraine

According to the International Classification of Headache Disorders, 3rd edition migraine is characterized as a recurrent headache disorder, with attacks lasting between 4 and 72 hours. There are two major subtypes: migraine without aura and migraine with aura. A typical migraine headache is unilateral, pulsating and of moderate to severe intensity. Physical activity can intensify the pain. Additional symptoms include nausea, hypersensitivity for sensory stimulation (auditory, visual, olfactory) [3].

3.1. Pathophysiology

The pathophysiology of migraine is complex and involves neurovascular and biochemicals mechanisms.

3.1.1. Neurovascular changes

The trigeminovascular hypothesis of migraine was proposed in 1979 by Moskowitz et al. [4]. This theory suggests the potential role of released vasoactive neuropeptides from axonal projections of the trigeminal nerve. The action of these peptides leads to dilatation of blood vessels in the brain, resulting in pain and other symptoms [5].

3.1.2. Serotonin imbalance

Serotonin is a neurotransmitter involved in regulating mood, sleep, and pain. Imbalances in serotonin levels are thought to be associated with the onset of migraines [6-7].

3.1.3. Calcitonin Gene-Related Peptide (CGRP)

CGRP is a neuropeptide implicated in the dilation of blood vessels and the transmission of pain signals. Elevated levels of CGRP are observed during migraines [8].

3.1.4. Inflammatory responses

Neurogenic inflammatory processes may activate the development of migraine attack. The release of inflammatory substances can cause cascade of inflammation and provides to dilation of blood vessels, capillary leakage resulting in plasma extravasation, edema and mast cell degranulation. All these mechanisms may sensitize nerves and contribute to the pain experience [9].

3.1.5. Genetic factors

Certain genetic factors may influence an individual's predisposition to migraines. Mutations in genes related to ion channels, neurotransmitters, and vascular function have been associated with migraines [10].

3.2. Migraine attack phases

3.2.1. Prodromal phase

This phase occur 2-48 hours before the headache and present symptoms such as tiredness, mood change, yawning, sensitivity to light, noise, and smells. Patients can recognize these symptoms and predict the headache's onset.

3.2.2. Migraine aura

Transient neurological symptoms occur just before the actual headache starts and are observed in patients with migraine with aura.

3.2.3. Headache phase

An intense headache occurs. It is typically localized with additional symptoms, which were mentioned above

3.2.4. Postdrome phase

The phase follows the resolution of the headache. It characterized by fatigue and difficulty concentrating [11-12].

3.3. Migraine triggers

The most frequent reported triggers of migraine attacks include stress, lack of sleep [13], and exposure to bright light. Hormonal changes, especially in women, can trigger migraines. Fluctuations in estrogen levels, such as those occurring during the menstrual cycle, pregnancy, or menopause may play a significant role [14]. Alcohol consumption is indicated as one of possible cause of migraine occurrence [15]. Dietary habits can be reason for appearance of headaches. Food such as cheese, citrus fruit, chocolate, and also caffeine are listed as possible triggers [16-18]. Understanding the mechanisms that trigger the transition from a headache-free state to the headache phase is important to understand the underlying causes of migraine attacks and developing effective treatment methods [2].

3.4. Treatment

Acute migraine attack can be stopped using medication or nonpharmacological methods. Pharmacological treatment of acute episode of migraine includes non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, agonists or serotonin 5-HT receptors (triptans), calcitonin gene-related protein (CGRP) inhibitors, opioids, antiemetics, dihydroergotamine. These medications can be used in monotherapy or in combination, showing varying levels of effectiveness and associated risks [19]. The top three nonpharmacological treatment methods are hydration, beverages with caffeine and relaxation methods [20]. Hoy et al. observed that using caffeine itself in migraine treatment was effective and generally well-tolerated [21].

4. Caffeine

Caffeine is a methylxanthine that non-selectively antagonizes adenosine receptors [22].

4.1. Mechanism of action

After binding to adenosine receptors on the cell surface, caffeine induces cortical hyperexcitability and maintains stimulation of brain cells [23]. It is characterized by anti-oxidant, anti-inflammatory, anticholinesterase properties. Caffeine has an energizing effect and plays o role in learning and memorizing with a beneficial influence on cognitive abilities in older people [24-25].

4.2. Pharmacokinetics

After consumption, caffeine appears in the blood within minutes. The plasma concentration peak of caffeine after oral intake is reported to occur at times ranging from 30 to 120 min [26]. Caffeine metabolism is depended on the CYP1A2 isoform of cytochrome P450. Polymorphism of this isoform explains pharmacokinetic differences among people. Other factors that can affect metabolism of caffeine include age, gender, nutritional status, liver condition, hormones and diet [27].

4.3. Caffeine sources

Caffeine is commonly used legal, psychoactive drug worldwide. It is widely used as food ingredient and can be found in coffee, tea, soda, various types of nuts, sweets and energy drinks. Many people start their day with cup of coffee. Caffeine is also used as an adjuvant treatment and some over-the-counter (OTC) medications contains it as co-analgetic component [16, 28]. Combination of caffeine and commonly used analgesics (acetaminophen, ibuprofen, acetylsalicylic acid) is more effective in reducing pain than analgesics in monotherapy [29]. In combination with acetaminophen or aspirin, caffeine reduces the amount of analgesic needed to achieve the same effect by around 40% [16].

4.4. Negative effects

As adverse events caffeine can cause abdominal discomfort, nausea, nervousness, dizziness and worsening sleep quality. The maximum daily dose of caffeine is 400mg (around 4-5 cups of coffee) or a single dose of 200mg. Caffeine overdose can provide supraventricular and ventricular arrhythmias [24].

5. Caffeine in migraine treatment

The therapeutic mechanisms of caffeine in migraine headaches are multidirectional and include: vascular effects, modulation of NO production, adenosine antagonism, potential interactions with the gut-brain axis and inhibition of leukotrienes and prostaglandins' synthesis.

5.1. Vascular effects

The impact of caffeine on blood flow and arteries is still debated. Caffeine can pass the blood-brain barrier and act as a vasoconstrictor in the cerebral vascular system [30]. Studies using various methods, including transcranial Doppler, functional MRI and perfusion magnetic resonance imaging, have shown region-specific effects of caffeine on blood flow. Caffeine may increase blood flow speed through vasoconstriction, and its effects on arteries could be region-dependent [31]. Caffeine cause either vasoconstriction or vasodilation depending on binding strength and dose. While caffeine generally induces vasodilation, it can raise cerebrovascular resistance and reduce cerebral blood flow in the central nervous system [32].

5.2. Modulation of NO production

Caffeine's impact on nitric oxide (NO) production is another possible mechanism. Caffeine, by inhibiting phosphodiesterases, may modify NO production. As NO levels increase during a migraine attack, and NO synthase inhibitors are effective in migraine treatment, caffeine's ability to inhibit NO synthase production could potentially decrease the frequency of migraine attacks. On the other hand, some studies show increasing NO production after caffeine intake [33-34].

5.3. Adenosine receptors inhibition

There were observed some connections between adenosine and migraine attacks.

5.3.1. Elevated adenosine plasma levels during migraine attacks [35].

5.3.2. Migraine attacks after exogenous adenosine intake [36].

5.3.3. Increase of frequency of migraine attacks caused by dipyridamole, an adenosine uptake inhibitor [37].

5.3.4. More frequent occurrence migraine with aura in individuals with an adenosine gene haplotype [10].

Adenosine receptor antagonists may be useful in the treatment of migraine. Caffeine, a non-selective adenosine receptor antagonist, is already present in several over-the-counter anti-headache medications. The antimigraine potential of selective adenosine A2A receptor antagonists would be particularly relevant in those patients whose adenosine plasma levels are markedly increased during a migraine attack [38-39].

5.4. The gut-brain axis interactions

Regular coffee consumption has influence on intestinal microbiota groups. The connection between migraines and the gut-brain axis provides another potential mechanism by which caffeine may influence migraines. [40]

5.5. Inhibition of leukotrienes and prostaglandins' synthesis

Caffeine can develop an analgesic effect by its ability to inhibit the synthesis of leukotrienes and prostaglandins. It can be consequence of two potential mechanisms which are receptor antagonism and a multi-site effect on eicosanoid pathways [41].

6. Caffeine as headache trigger

Contrary to concepts presented above, there are theories about potential role of caffeine as a trigger factor. Aladdin et al. conducted a study that revealed the migraine-triggering potential of caffeine [42]. The onset of migraine attack may be related to caffeine consumption or withdrawal.

6.1. Caffeine consumption

Caffeine can induce acute diuresis, which may lead to dehydration. Dehydration is also considered a possible cause of migraine attack [23]. Intensified diuresis can increase urinary loss of magnesium and lead to neuromuscular conduction disorders [16]. Shirlow et al. reported in their study that an increase in number of headache occurrences was related to the caffeine intake [43]. Also Zhang et al. conducted study showing that higher caffeine intake is positively associated with onset of migraines [23].

6.2. Caffeine withdrawal

There is a potential relation between caffeine withdrawal and migraine symptoms. The prodromal phase of migraines shares symptoms such as yawning, increased emotionality, concentration difficulties, fatigue, phonophobia, and nausea with caffeine withdrawal syndrome [44]. It suggests overlapping pathophysiological pathways between these two conditions. Caffeine withdrawal can induce headaches by itself, and individuals with a history of frequent headaches, including migraines, may be at an increased risk [45].

7. Summary

Migraine is one of the most quality-of-life-worsening disease. Despite knowledge about the connection between caffeine and migraine, the influence of caffeine on headaches remains unclear. Caffeine can have both positive and negative influence on individuals suffering from migraines. It is used as adjuvant component in migraine treatment, however, on the other hand it can act as a trigger for migraines. Migraine management should be highly individualized. It is advisable for individuals experiencing migraines to consult with healthcare professionals who can provide personalized advice based on their medical history and specific triggers. There is need for more clinical trials to fully understand mechanisms of caffeine's action, its role in migraine headaches, risk factors leading to migraine attacks, and to find safe and effective treatment methods.

Disclosure

Authors contribution:

Conceptualization: Katarzyna Ciuba, Paulina Dąbrowska, Katarzyna Molenda, Barbara Borodziuk

Methodology: Michał Żuber, Filip Borodziuk, Kamila Giżewska, Karol Bochyński

Formal analysis: Konrad Białogłowski, Kamila Giżewska, Katarzyna Ciuba, Paulina Dąbrowska

Investigation: Katarzyna Ciuba, Michał Żuber, Barbara Borodziuk, Michał Dacka

Writing – rough preparation: Michał Dacka, Karol Bochyński, Katarzyna Molenda, Filip Borodziuk

Writing – review and editing: Michał Żuber, Konrad Białogłowski, Filip Borodziuk, Kamila Giżewska

Visualization: Katarzyna Molenda, Katarzyna Ciuba, Barbara Borodziuk, Michał Dacka

Conflicts of interest: The authors declare no conflict of interest. All authors have read and agreed with the published version of the manuscript.

Funding statement: No external funding was received to perform this review.

Board statement: Not applicable – this review included analysis of the available literature.

Statement of informed consent: Not applicable.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 [published correction appears in Lancet. 2019 Jun 22;393(10190):e44]. Lancet. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7
2. Alstadhaug KB, Andreou AP. Caffeine and Primary (Migraine) Headaches-Friend or Foe?. Front Neurol. 2019;10:1275. Published 2019 Dec 3. doi:10.3389/fneur.2019.01275

3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202
4. Moskowitz MA, Reinhard JF Jr, Romero J, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine?. Lancet. 1979;2(8148):883-885. doi:10.1016/s0140-6736(79)92692-8
5. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol. 2019;18(8):795-804. doi:10.1016/S1474-4422(19)30185-1
6. Katalinic D, Vcev A, Smolic M, Aleric I. Serotonin Receptor Agonists in the Treatment of Migraine: A Meta-Analysis Considering Possible Connection with Paresthesia. Ann Indian Acad Neurol. 2022;25(3):332-333. doi:10.4103/aian.aian_266_22
7. Villar-Martinez MD, Goadsby PJ. Pathophysiology and Therapy of Associated Features of Migraine. Cells. 2022;11(17):2767. Published 2022 Sep 5. doi:10.3390/cells11172767
8. Santos-Lasaosa S, Belvís R, Cuadrado ML, et al. Calcitonin gene-related peptide in migraine: from pathophysiology to treatment. Neurologia (Engl Ed). 2022;37(5):390-402. doi:10.1016/j.nrleng.2019.03.025
9. Spekker E, Tanaka M, Szabó Á, Vécsei L. Neurogenic Inflammation: The Participant in Migraine and Recent Advancements in Translational Research. Biomedicines. 2021;10(1):76. Published 2021 Dec 30. doi:10.3390/biomedicines10010076
10. Hohoff C, Marziniak M, Lesch KP, Deckert J, Sommer C, Mössner R. An adenosine A2A receptor gene haplotype is associated with migraine with aura. Cephalalgia. 2007;27(2):177-181. doi:10.1111/j.1468-2982.2007.01254.x
11. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. J Headache Pain. 2019;20(1):117. Published 2019 Dec 23. doi:10.1186/s10194-019-1066-0
12. Puledda F, Silva EM, Suwanlaong K, Goadsby PJ. Migraine: from pathophysiology to treatment. *J Neurol*. 2023;270(7):3654-3666. doi:10.1007/s00415-023-11706-1
13. Boardman HF, Thomas E, Millson DS, Croft PR. Psychological, sleep, lifestyle, and comorbid associations with headache. Headache. 2005;45(6):657-669. doi:10.1111/j.1526-4610.2005.05133.x
14. Reddy N, Desai MN, Schoenbrunner A, Schneeberger S, Janis JE. The complex relationship between estrogen and migraines: a scoping review. Syst Rev. 2021;10(1):72. Published 2021 Mar 10. doi:10.1186/s13643-021-01618-4
15. Hindiyeh NA, Zhang N, Farrar M, Banerjee P, Lombard L, Aurora SK. The Role of Diet and Nutrition in Migraine Triggers and Treatment: A Systematic Literature Review. Headache. 2020;60(7):1300-1316. doi:10.1111/head.13836
16. Nowaczewska M, Wiciński M, Kaźmierczak W. The Ambiguous Role of Caffeine in Migraine Headache: From Trigger to Treatment. Nutrients. 2020;12(8):2259. Published 2020 Jul 28. doi:10.3390/nu12082259
17. Peroutka SJ. What turns on a migraine? A systematic review of migraine precipitating factors. Curr Pain Headache Rep. 2014;18(10):454. doi:10.1007/s11916-014-0454-z

18. Mollaoğlu M. Trigger factors in migraine patients. J Health Psychol. 2013;18(7):984-994. doi:10.1177/1359105312446773
19. Singh RBH, VanderPluym JH, Morrow AS, et al. Acute Treatments for Episodic Migraine. Rockville (MD): Agency for Healthcare Research and Quality (US); December 2020
20. Goadsby P, Ruiz de la Torre E, Constantin L, Amand C. Social Media Listening and Digital Profiling Study of People With Headache and Migraine: Retrospective Infodemiology Study. J Med Internet Res. 2023;25:e40461. Published 2023 May 5. doi:10.2196/40461
21. Hoy SM, Scott LJ. Indomethacin/prochlorperazine/caffeine: a review of its use in the acute treatment of migraine and in the treatment of episodic tension-type headache. CNS Drugs. 2011;25(4):343-358. doi:10.2165/11206740-000000000-00000
22. Chen JF, Eltzschig HK, Fredholm BB. Adenosine receptors as drug targets--what are the challenges?. Nat Rev Drug Discov. 2013;12(4):265-286. doi:10.1038/nrd3955
23. Zhang L, Yin J, Li J, Sun H, Liu Y, Yang J. Association between dietary caffeine intake and severe headache or migraine in US adults [published correction appears in Sci Rep. 2023 Sep 29;13(1):16391]. Sci Rep. 2023;13(1):10220. Published 2023 Jun 23. doi:10.1038/s41598-023-36325-8
24. Altabakhi IW, Anderson J, Zito PM. Acetaminophen/Aspirin/Caffeine. In: StatPearls. Treasure Island (FL): StatPearls Publishing; November 12, 2023.
25. Dong X, Li S, Sun J, Li Y, Zhang D. Association of Coffee, Decaffeinated Coffee and Caffeine Intake from Coffee with Cognitive Performance in Older Adults: National Health and Nutrition Examination Survey (NHANES) 2011-2014. Nutrients. 2020;12(3):840. Published 2020 Mar 20.
26. Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci. 2010;75(3):R77-R87. doi:10.1111/j.1750-3841.2010.01561.x
27. Guest NS, VanDusseldorp TA, Nelson MT, et al. International society of sports nutrition position stand: caffeine and exercise performance. J Int Soc Sports Nutr. 2021;18(1):1. Published 2021 Jan 2. doi:10.1186/s12970-020-00383-4
28. Baratloo A, Rouhipour A, Forouzanfar MM, Safari S, Amiri M, Negida A. The Role of Caffeine in Pain Management: A Brief Literature Review. Anesth Pain Med. 2016;6(3):e33193. Published 2016 Mar 26. doi:10.5812/aapm.33193
29. Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. Cochrane Database Syst Rev. 2014;2014(12):CD009281. Published 2014 Dec 11. doi:10.1002/14651858.CD009281.pub3
30. Boppana SH, Peterson M, Du AL, Kutikuppala LVS, Gabriel RA. Caffeine: What Is Its Role in Pain Medicine?. Cureus. 2022;14(6):e25603. Published 2022 Jun 2. doi:10.7759/cureus.25603
31. Xu F, Liu P, Pekar JJ, Lu H. Does acute caffeine ingestion alter brain metabolism in young adults?. Neuroimage. 2015;110:39-47. doi:10.1016/j.neuroimage.2015.01.046
32. Higashi Y. Coffee and Endothelial Function: A Coffee Paradox?. Nutrients. 2019;11(9):2104. Published 2019 Sep 4. doi:10.3390/nu11092104

33. Bruce C, Yates DH, Thomas PS. Caffeine decreases exhaled nitric oxide. Thorax. 2002;57(4):361-363. doi:10.1136/thorax.57.4.361
34. Umemura T, Ueda K, Nishioka K, et al. Effects of acute administration of caffeine on vascular function. Am J Cardiol. 2006;98(11):1538-1541. doi:10.1016/j.amjcard.2006.06.058
35. Guieu R, Devaux C, Henry H, et al. Adenosine and migraine. Can J Neurol Sci. 1998;25(1):55-58. doi:10.1017/s0317167100033497
36. Brown SG, Waterer GW. Migraine precipitated by adenosine. Med J Aust. 1995;162(7):389-391. doi:10.5694/j.1326-5377.1995.tb139957.x
37. Hawkes CH. Dipyridamole in migraine. Lancet. 1978;2(8081):153. doi:10.1016/s0140-6736(78)91534-9
38. Haanes KA, Labastida-Ramírez A, Chan KY, et al. Characterization of the trigeminovascular actions of several adenosine A2A receptor antagonists in an in vivo rat model of migraine. J Headache Pain. 2018;19(1):41. Published 2018 May 25. doi:10.1186/s10194-018-0867-x
39. Thuraiaiyah J, Kokoti L, Al-Karagholi MA, Ashina M. Involvement of adenosine signaling pathway in migraine pathophysiology: a systematic review of preclinical studies. J Headache Pain. 2022;23(1):43. Published 2022 Apr 5. doi:10.1186/s10194-022-01412-0
40. Gazerani P. Migraine and Diet. Nutrients. 2020;12(6):1658. Published 2020 Jun 3. doi:10.3390/nu12061658
41. Zduńska A, Cegielska J, Zduński S, Domitrz I. Caffeine for Headaches: Helpful or Harmful? A Brief Review of the Literature. Nutrients. 2023;15(14):3170. Published 2023 Jul 17. doi:10.3390/nu15143170
42. Aladdin YS, Alsharif R, Mattar W, et al. Migraine Prevalence and Analysis of Dietary Habits in Relation to Headache in the Female Population: A Single-Center Study From Jeddah, Saudi Arabia. Cureus. 2022;14(5):e24848. Published 2022 May 9. doi:10.7759/cureus.24848
43. Shirlow MJ, Mathers CD. A study of caffeine consumption and symptoms; indigestion, palpitations, tremor, headache and insomnia. Int J Epidemiol. 1985;14(2):239-248. doi:10.1093/ije/14.2.239
44. Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. Psychopharmacology (Berl). 2004;176(1):1-29. doi:10.1007/s00213-004-2000-x
45. Alstadhaug KB, Ofte HK, Müller KI, Andreou AP. Sudden Caffeine Withdrawal Triggers Migraine-A Randomized Controlled Trial. Front Neurol. 2020;11:1002. Published 2020 Sep 10. doi:10.3389/fneur.2020.01002