



Review Article

Migraine and zinc deficiency in women - A mini review

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ABSTRACT

Migraine is a frequently occurring multifactorial neurovascular disorder affecting over a billion people globally. Migraine load is distinctive concerning gender, i.e. it is more severe in women and has a prolonged healing period. People with migraine have a primary headache disorder, a public health concern in low and middle-income countries.

Studies have shown that brainstem regions and the trigeminovascular pathway are linked to the migraine attack's symptomatology. The episode is mediated by the release of Calcitonin Gene-Related Peptide (CGRP). It is a widely expressed neuropeptide with a sole role in sensory neurotransmission. Treatment of migraine remains underdiagnosed; its frequency and intensity are poorly understood. Although patients consume the antagonists of CGRP, migraine still prevails heavily in women. Dietary factors are often considered migraine triggers. One such dietary factor is Zinc deficiency. Zinc deficiency is mainly observed in women with poor dietary intake in rural and sub-rural areas of India. Recently Zinc has been shown to play a role in migraine disorders. This review briefly summarizes how supplementary Zinc may be a potential therapeutic strategy to overcome migraine pain.

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1. Introduction

Migraine is a neurovascular disorder constituting a substantial societal burden.¹ The Institute of health, metrics and evaluation estimates the Global prevalence of migraine to be 18.1% affecting 1.3 billion people globally. Migraine is reported to be two-three folds more prevalent in women. Yearly migraine attacks estimation indicates active migraine with 18% in females and 6% in males globally, the cumulative incidences in a lifetime is 43% and 18% in females and males respectively.²

Migraine is predominantly characterized by headache attacks and accompanying symptoms. General practitioners can be trained for migraine diagnosis skills based on medical history, excluding secondary causes. Evidence suggests that primary care can meet 90% of the needs

of patients for migraine and can be a primary setting for the migraine diagnosis.³ Readily available clinical tools can provide support to primary care centres. An easily translated headache diary is validated for diagnosis and treatment evaluation for new patients for at least one month. Migraine exists with (MA) or without aura (MO). An aura is a group of sensory, motor, and speech symptoms that warn the beginning of a migraine. Therefore, migraine exists in people with or without aura. In MO, the headache lasts for 4-72h with nausea, photophobia, and phonophobia symptoms. MA features headaches lasting for a few to several minutes with reversible aura symptoms. The events of female reproductive life greatly influence MO. A study in Italy revealed that menstrual triggered migraine was more frequent in MO than in MA patients. They also reported a favourable effect of pregnancy in patients, with MA patients having more improvement than MO patients. Besides this,

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a group of women consuming oral contraceptives showed worsening migraine in MA than MO patients, suggesting that migraine in women is significantly modulated by the reproductive life.⁴

2. Diagnosis and Treatments

International Headache Society has established Migraine as a clinical diagnosis. A neurological examination is done to avoid any other existing disorders. Anna et al. have listed a ten-step evaluating response and preventive treatment for the migraine.⁵ Acute migraine treatment is used to relieve the pain of the attack; these include simple analgesics such as acetaminophen, NSAIDs, combination analgesics including the over-the-counter aspirin/acetaminophen/caffeine combination and the prescription analgesics containing butalbital, serotonin receptor agonists (triptans), ergot derivatives (particularly dihydroergotamine), and antiemetics.⁶ Migraine treatment is also based on non-opioid analgesics as a primary treatment, followed by triptans if the therapy is unsatisfactory.⁷

2.1. Pathophysiology

Neurovascular events are involved in a migraine attack where the trigeminal pathway and its vasoactive neuropeptides play a crucial role. The trigeminal pathway later came into the picture as a common upstream headache initiation way and became a target for therapeutic leads. The vasoactive neuropeptides, i.e., Substance P, Calcitonin gene-related peptide (CGRP), and pituitary adenylate cyclase-activating polypeptide (PACAP), are substantial targets. Out of the three neuropeptides, the release of CGRP is directly connected to the rising intensity of migraine; a clinical trial reported CGRP blockage had reduced the effect of the migraine.⁸ CGRP is the most prevalent neuropeptide in the trigeminal system and plays a vital role in the pathophysiology of migraine. Chemical antagonists of CGRP are called gepants and have shown efficiency in migraine patients.

2.2. Reproductive life cycle and migraine in women

Reproductive life events are linked to hormonal changes that act as a trigger.

Migraine attacks are higher in women and are believed so due to the ovarian steroid hormones- estrogen and progesterone.⁹ A study on the Caucasian population revealed that a woman with early age of menarche (early puberty) showed 7% lower chances of migraine at early adulthood. Migraine before and after menstruation has been classified separately as menstrual migraine (MM) by the International Classification of headache (ICHD). In female migraineurs without aura, the progesterone levels are seen significantly higher. Women in their early pregnancy and

postpartum have reported the MM self-report to be higher compared to women without self-reported MM. However, as Menopause commences, early menopause transition links serum oestrogen fluctuations which stabilize in the late menopause transition period followed by the varying migraine attacks, i.e., remain unchanged, improve, worsen.² Besides triggers such as stress, fasting, menstruation and weather change,¹⁰ one such factor related to diet has been identified as zinc deficiency.¹¹

2.3. Zinc deficiency as a trigger of migraine women

Zinc is one of the essential nutrients for humans and is involved in several metabolisms in the body. Approximately 57% and 29% of Zinc exist in skeletal muscle and bones, respectively. Despite being one of the most abundant micronutrients, Zinc cannot be stored in significant amounts and therefore requires regular intake. Inadequate intake, low absorption or higher loss of Zinc result in lowering optimum zinc quantity in the body. This phenomenon was called Zinc deficiency and was discovered in 1961. An estimated 17% of the global population is at risk for Zinc deficiency.¹² Among the people, women and children are the most vulnerable group. The Zinc concentration in Plasma of Indian origin women was less than white women in South Africa due to lower dietary intake.¹³ About 49% of adult girls and 52% of non-pregnant women of central India suffers from Zinc deficiency.¹⁴ About 64.6% of the pregnant women suffer from zinc deficiency in the state of Haryana in India due to low dietary intake; in addition, 41% of the high prevalence of Zinc deficiency has been reported in Non- pregnant women in India.¹⁵ An observational study reported a moderate rate of zinc deficiency in patients with migraine and revealed low serum concentrations of Zinc associated with migraine attacks.¹¹ Zinc is an essential trace element that plays a significant role in neuronal signalling.¹⁶ In addition, it also has anti-inflammatory properties. Given the inflammatory nature of migraine, Zinc may have a favourable effect on migraine. Dietary factors have shown their action in migraine symptoms.¹⁷ In a study, zinc administration improved cold-related headaches.¹⁸ An investigation revealed that a lower quality diet could be a factor for migraine and a high-quality diet contains a good amount of Zinc.¹⁹ However, the mechanism is unclear, but one factor may be hormones in females that fluctuate in their entire reproductive life. The hormones may contribute to the homeostasis of minerals to play a significant role in the pathobiology of migraine, i.e., from Hypothalamus to hypophysis to endocrine glands to neurotransmitters to minerals.²⁰ Relevant mechanisms involve estrogen, Prolactin, Cortisol, progesterone, Thyroxine, Melatonin Parathyroid hormone.²¹ Recently a study used a randomized clinical trial where patients were assigned 220mg/d Zinc sulfate or placebo for 8 weeks. Zinc supplementation showed a beneficial effect on the frequency of migraine

attacks in migraine patients.²² This study was also supported by an assessment study of the effect of Zinc in adult women for 12 weeks and revealed similar results as Zinc supplementation have promising effects on migraine frequency and severity.²³ Although these studies are preliminary with a limited number of patients and duration, an investigation with varying dosage and a more extended period of Zinc intervention may reveal a robust understanding of dietary Zinc for migraineurs.

A study in the US population of males and females showed higher prevalence in women, specifically during reproductive years, during menstrual cycles. Also, the prevalence of migraine in women was double folded higher beyond 42yrs of age.²⁴ In India, however, a single migraine prevalence study reported a higher incidence of migraine post surgeries such as hysterectomy and caesarean section.²⁵ Antionette suggests that the rise and fall of oestrogen drive the impact of migraine attacks.²⁶ CGRP also has a clear sex-specific difference, where CGRP elicited potent pain response in females than males, suggesting that CGRP may work in low concentration in women.²⁷ Therefore, the prevalence of Migraine in women is based on several aspects of their reproductive life. It is crucial to understand the rise of migraine and their risk triggers in women. The role of hormones is complicated in women, and further exploration of studies and interventions is required to improve personalized medicine. Knowing that hormonal fluctuations contribute to CGRP regulations and affect pregnant and lactating women more, an intervention study of prescribed drugs by a physician and dietary habits may lead to fundamental insights into migraine and establish possible therapeutic options to treat the disease. Together these studies indicate an urgent regime to rescue patients suffering from migraine. A specific intervention study is required to understand the lifestyle effects on the intensity of migraine.

3. Conclusion

Migraine is considered one of the highest prevailing neuro disorders globally. There exist a sexual dimorphism in migraine prevalence i.e., it affects women largely. The female hormones are one firm contributor to migraine. The reproductive cycles in women's lives are coupled with migraine frequency and severity. Available drugs for the treatment of migraine have severe side effects for long-term usage. The development of new drugs is continuously under research. Dietary factors have been shown to be critical risk factors. One such factor in women is Zinc deficiency. Zinc deficiency in women is prevailing for a decade, and very few improvements is seen in the past few years. Zinc supplementation is one crucial step that must be taken into account for the women population. Simultaneously, there is a lack of randomized control trial studies of migraine in Indian women. Zinc supplementation can therefore play

a therapeutic role to improve migraine. The doses and duration need more investigation to decipher the role of Zinc in migraine and headaches.

4. Conflict of Interest

The researcher claims no conflict of interest.

5. Source of Funding

None.

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