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Original Article

The Influence of Vitamin D3 Administration on the Levels of CGRP, Glutamate, and NLRP3 during the Ictal Phase in Chronic Migraine Patients

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ABSTRACT

Background: Migraine is a primary headache disorder that ranks as the third leading cause of disability. Various prophylactic therapies have been developed for migraine treatment, including vitamin D3 supplementation. The mechanism of action of vitamin D3 supplementation in the pathophysiology of migraine has not been extensively studied. **Objective:** This study assesses the impact of vitamin D3 administration on the levels of the biomarkers CGRP, Glutamate, and NLRP3 and its effect on reducing the frequency and intensity of migraine attacks in chronic migraine patients. **Methods:** This experimental study (single-blind clinical trial) observes two groups: a group given vitamin D3 at 2000 IU for 12 weeks and a placebo group. This study involved 61 chronic migraine subjects. At the end of the study, after excluded 31 subjects, there were 12 subjects in each of the two groups. **Results:** A significant relationship was found between vitamin D3 administration and the reduction in the frequency and duration of migraine attacks in both the vitamin D3 group ($p<0.001$) and the placebo group ($p=0.078$). No significant relationship was found between vitamin D3 administration and changes in CGRP levels ($p=0.633$), but there were significant changes in glutamate ($p<0.001$) and NLRP3 ($p=0.016$) levels following vitamin D3 administration. **Conclusion**: Vitamin D3 supplementation has an impact on reducing the frequency and duration of migraine attacks in chronic migraine patients, and there is a significant association with changes in glutamate and NLRP3 levels, but not with changes in CGRP levels.
Key words: Chronic Migraine, Vitamin D3, CGRP, Glutamate, NLRP3.

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INTRODUCTION

Migraine is a neurovascular disorder that affects more than one billion people worldwide, ranking as the third leading cause of disability. This condition has a negative impact on the quality of life of sufferers, affecting their ability to work and their daily social life.[1,2] Chronic migraine patients experience more significant adverse effects, as it has been proven to cause more disability in terms of workplace productivity compared to episodic migraines.[3]

Migraine attacks occur through neuroinflammatory and/or neurovascular processes. Several studies have shown that the levels of Calcitonin Gene Related Peptide (CGRP), glutamate, and IL-1β underlie the interaction between these two processes, making these biomarkers closely associated with migraine occurrence.[4-6] The relationship between migraine and inflammasomes has also drawn attention, with one relevant inflammasome being the NOD-Like Receptor Protein 3 (NLRP3). NLRP3 inflammasome is a crucial component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines IL-1β/IL-18[7,8]

The role of CGRP in the trigeminal system and migraine pathophysiology has been extensively studied. One approach is the use of selective monoclonal antibodies that can block CGRP transmission in migraine patients by binding to CGRP molecules or its receptors. These specific monoclonal antibodies have been recognized by the U.S. Food and Drug Administration (FDA).[9] However, the use of monoclonal antibodies is still rare in Indonesia due to their high cost and invasiveness in administration.

Various dietary supplements have been introduced for complementary migraine treatment. Vitamin D3, as an anti-inflammatory and antioxidant agent, has gained interest in recent years. Although the prevalence of vitamin D deficiency/insufficiency is higher in migraine patients compared to controls, there is no clinical consensus on vitamin D supplementation. Ghorbani *et al.* (2019) conducted a review compiling observational studies, case-control studies, and clinical trials on vitamin D3 and migraine. It was reported that 45-100% of migraine patients experience deficiency and insufficiency of vitamin D. Vitamin D levels negatively correlate with headache frequency. Further research is needed to elucidate the mechanism of action of vitamin D in migraines.[10]

Several studies have suggested the role of vitamin D in headache prophylaxis.11 A study conducted by Giovanni *et al.* (2021) on the consumption of Vitamin D 2000 IU/day for 12 weeks significantly showed a reduction in the frequency, duration of attacks, and analgesic usage.[12] The consumption of Vitamin D 2000 IU/day for 16 weeks also showed a significant decrease in CGRP levels. A randomized, concealed clinical trial conducted by Ghorbani *et*

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al. (2020) reported a significant reduction in CGRP levels in episodic migraine patients receiving daily vitamin D supplementation of 2,000 IU after 16 weeks.[11]

The mechanism of vitamin D supplementation in migraine pathophysiology has not been extensively studied. It is hypothesized that vitamin D plays a role in reducing excitotoxicity through modulation of NMDA (N-methyl-D-Aspartate) receptor.[6] NMDA is a glutamate receptor that binds and leads to increased calcium ion influx into postsynaptic neurons. Glutamate plays a crucial role in migraine pathophysiology as the most common excitatory mediator in the central nervous system. Glutamate increases in blood, cerebrospinal fluid, saliva, the occipital cortex, and thalamus during migraine attacks and between attacks.[13] An increase in blood glutamate levels is detected both during interictal (between migraine attacks) and ictal (during migraine attacks) periods in migraine patients.[14,15]

NLRP3 activation leads to the release of IL-1β, a cytokine known to directly sensitize nociceptors and cause pain. IL-1β-induced pro-inflammatory processes mediate the activation of trigeminal satellite cells and stimulate the excitation of satellite glial cells and neurons in the trigeminal ganglion, resulting in pain in migraine patients.[7,8] However, no study has directly outlined the relationship between vitamin D and NLRP3 in migraine patients.

Based on this background, the researchers are interested in demonstrating the role of Vitamin D3 in the biomarkers involved in migraines, namely CGRP, glutamate, and NLRP3.

METHODS

This study is an experimental research (single-blind clinical trial) that observed interventions in two groups. Data was collected through two observations, both before and after the intervention. The research was conducted in hospitals and health centers in the Padang city area from October 2022 to March 2023. Inclusion criteria included women with chronic migraines diagnosed by a neurology specialist based on the International Classification of Headache Disorders (ICHD-3 beta), aged 18-50 years, willing to participate in the study for 3 months, and signing informed consent. Exclusion criteria consisted of pregnancy and/or breastfeeding, mixed headache type, or medication overuse headache.

During the initial visit, demographic data such as age, marital status, education level, and migraine type were collected. At the beginning and end of the study, venous blood samples were taken to measure plasma levels of CGRP and glutamate, as well as serum levels of Vitamin D3 and NLRP3. Subsequently, blood samples were examined using ELISA at the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas, Padang, West Sumatra. Both measurements were taken during the ictal phase. Subjects were given treatment in the form of 2000 IU vitamin D3 tablets for 3 months, compared with a placebo group using the single-blind clinical trial method. During the research phase, research subjects could consume medications for acute or prophylactic management. The analysis of pre and post-treatment levels in each group was evaluated using the Paired Sample T-Test or Wilcoxon Test with SPSS V.26. Results were considered significant if $p < 0.05$.

This research has obtained approval from the Research Ethics Committee of the Faculty of Medicine, Andalas University, No. 968/UN.16.2/KEP-FK/2022.

RESULTS

In this study, a total of 61 individuals with chronic migraines were initially identified through screening by a neurology specialist. These subjects were provided with a headache diary, and MIGSEV and

Table 1: Basic characteristics of research subjects.

Characteristics		Vitamin D3 Group	Placebo Group	p value
Marital status	Not married yet	5 (41.67%)	5 (41.67%)	
	Marry	7 (58.33%)	7 (5833%)	
Level of education	Junior High School	2 (16.67%)		
	Senior High School	4 (33.33%)		
	Diploma/Bachelor	6 (50%)	12 (100%)	
Migraine Type	No aura	11 (91.67%)	7 (58.33%)	
	With Aura	1 (8.33%)	5 (41.67%)	
Age (years)	Mean ± SD	34.3 ± 11.8	33.5 ± 9.7	0.187*
BMI (kg/m2)	Mean ± SD	24.23 ± 3.28	22.92 ± 2.58	0.468*

Table 2: Frequency, duration and biomarker examination results before and after subgroup treatment.

Assessment Items		Vitamin D3 Group		Placebo Group	
		Baseline	After 12 weeks	Baseline	After 12 weeks
Headache Frequency (days/month)	Median (Min-Max)	16 (15-24)	5 (2-12)	15.5 (15-21)	12 (8-16)
	Pre-post paired test (p)	0.002[a]		0.002[a]	
Headache Duration (hours)	Median (Min-Max)	6 (4-24)	4 (2-10)	6 (6-12)	4 (2-6)
	Pre-post paired test (p)	0.002[a]		0.002[a]	
Vitamin D3 serum levels (ng/ml)	Mean ± SD	22.49 ± 2.75	30.35 ± 4.91	25.87 ± 3.42	26.16 ± 5.41
	Pre-post paired test (p)	<0.001[b]		0.078[b]	
CGRP plasma levels (pg/ml)	Mean ± SD	199.33 ± 30.24	193.74 ± 27.09	199.56 ± 27.16	180.15 ± 24.12
	Pre-post paired test (p)	0.633[b]		0.018[b]	
Glutamate plasma levels (microMoles/Liter)	Mean ± SD	49.83 ± 13.23	29.25 ± 10.77	27.08 ± 12.50	34 ± 5.41
	Pre-post paired test (p)	<0.001[b]		0.041[a]	
Serum NLRP3 Levels (ng/ml)	Mean ± SD	0.89 ± 0.42	0.81 ± 0.37	0.99 ± 0.68	0.75 ± 0.53
	Pre-post paired test (p)	0.016[b]		0.005[b]	

[a] = Wilcoxon Test
[b] = Paired Sample Test

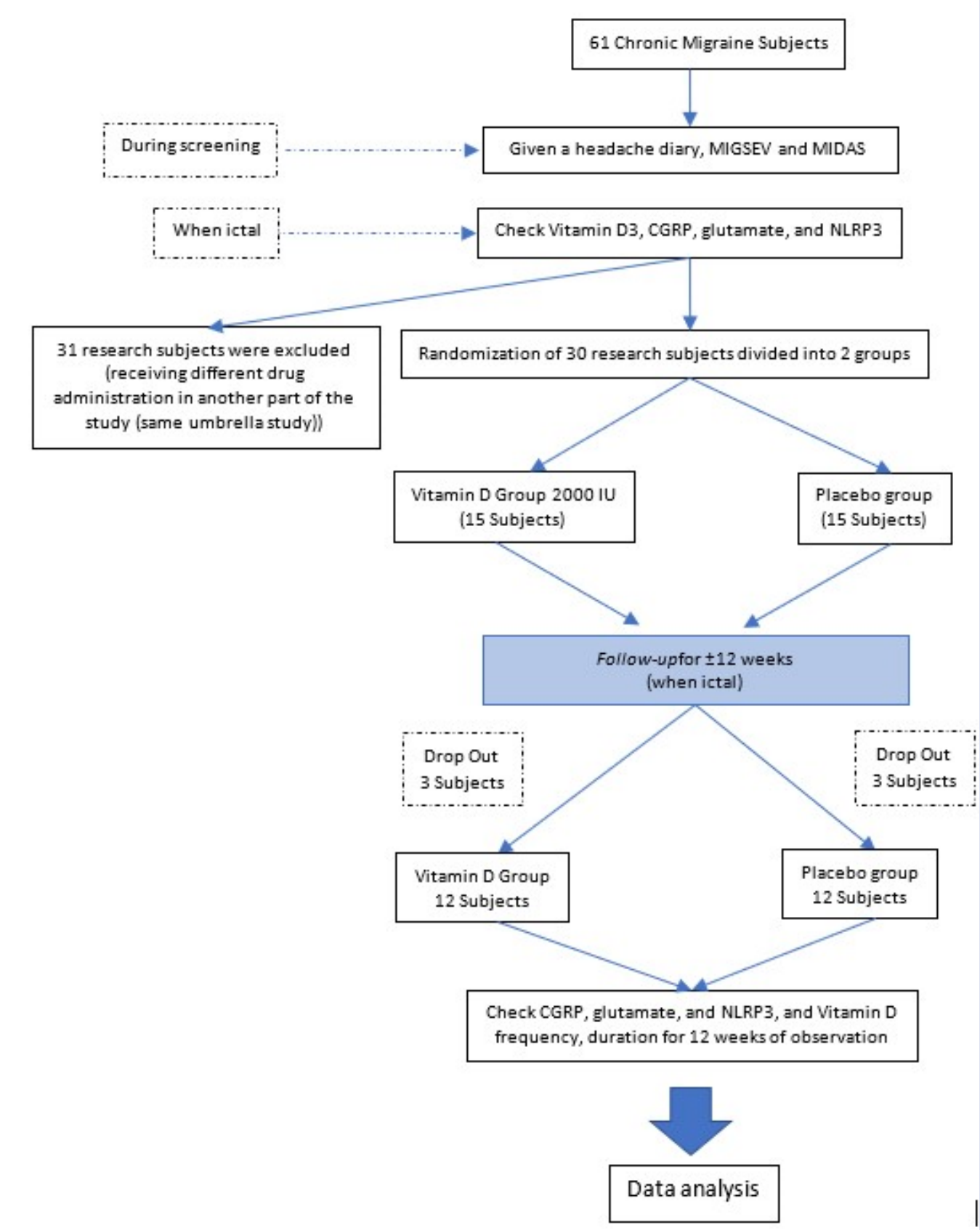

Figure 1: Flow-diagram of studied patients

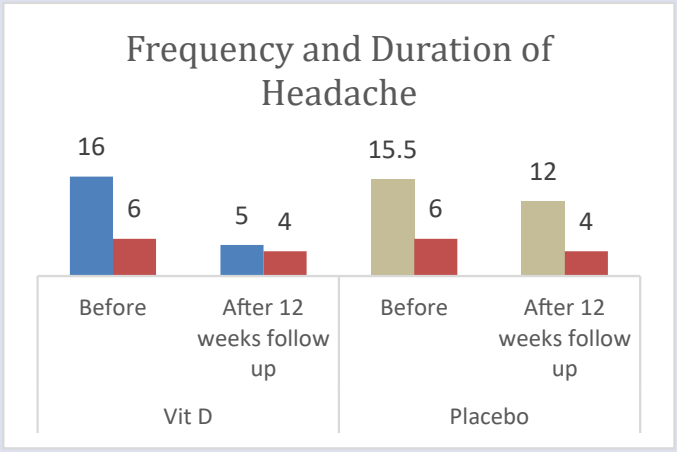

Figure 2: Comparison of headache frequency and duration in the Vitamin D3 and placebo groups after 12 weeks of observation

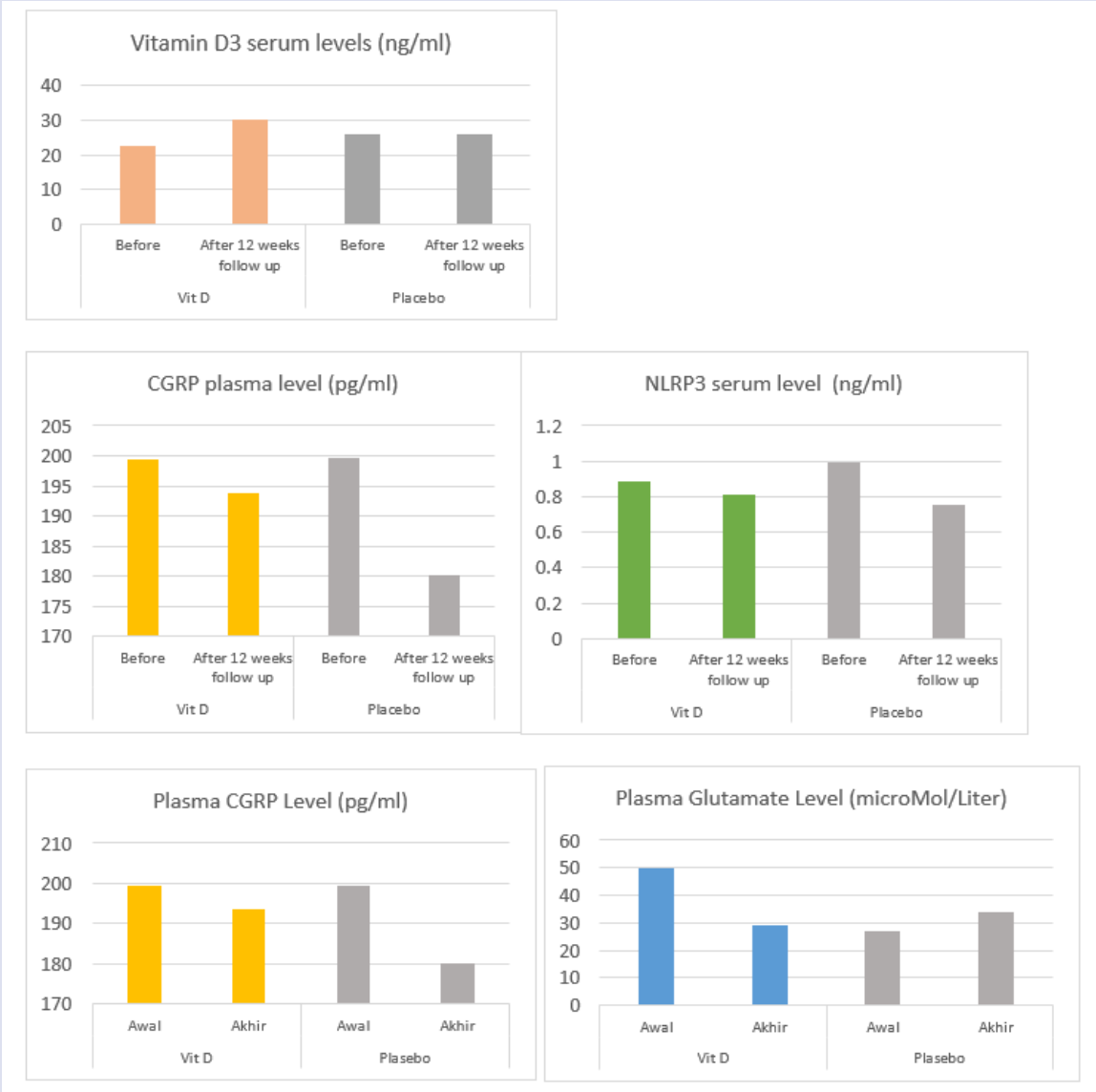

Figure 3: Comparison of each biomarker level in the Vitamin D3 and placebo groups after 12 weeks of observation.

MIDAS assessments were conducted. During the ictal phase, the levels of vitamin D3, CGRP, glutamate, and NLRP3 were examined. Out of the 61 migraine patients, 31 research subjects were excluded because they received different treatments in other research groups under the same research umbrella. Subsequently, 30 research subjects were randomly divided into 2 groups: a group receiving vitamin D3 2000 IU and a placebo group, each consisting of 15 subjects. During the 3-month follow-up period, there were dropouts of 3 individuals in each group, resulting in a final study population of 12 individuals in each group. This research is an experimental study conducted using the double-blind clinical trial method (Figure 1).

In this study, the characteristics of the selected samples were roughly equivalent in terms of age, BMI, and marital status (Table 1). The majority of the research patients had similar average ages in each treatment group: Vitamin D3 group (34.3 ± 11.8 years) and Placebo group (33.5 ± 9.7 years). Based on BMI, the subjects in both research groups had normal BMI averages. This study showed that migraine without aura dominated the research participants, with 11 individuals (91.7%) in the Vitamin D group and 7 individuals (58.3%) in the Placebo group (Table 1).

Significant differences were found in the frequency and duration of headache in migraine patients given Vitamin D and the placebo group. This is evident from the decrease in headache frequency with a median value of 16 (15-24) days/month to 5 (2-12) days/month with a p-value of 0.002 in the Vitamin D group and 15.5 (15-21) days/month to 12 (8-16) days/month. Similarly, the duration of headache decreased after vitamin D administration. Initial Vitamin D3 levels were higher on average among patients receiving the placebo than the vitamin D group. However, after 12 weeks of the study, serum vitamin levels increased significantly in the vitamin D group (from 22.49 ± 2.75 ng/ml to 30.35 ± 4.91 ng/ml; p-value <0.001). In contrast, the placebo group showed no significant changes (from 25.87 ± 3.42 ng/ml to 26.16 ± 5.41 ng/ml; p-value = 0.078) (Table 2).

In this study, there was an increase in CGRP levels during the ictal phase in chronic migraine patients, with an increased average concentration of plasma CGRP: 199.33 ± 30.24 pg/mL in the Vitamin D group and 199.56 ± 27.16 pg/mL in the Placebo group. After Vitamin D administration, a decrease in the average CGRP values was observed in both groups. However, after analysis, a significant decrease in CGRP levels was found in the placebo group (p = 0.018) compared to the Vitamin D3 group (p = 0.63) (Table 2).

This study also found an increase in glutamate levels during the ictal phase in chronic migraine patients, with an increased average concentration: 49.83 ± 13.23 µmol/L in the vitamin D3 group and 27.08 ± 12.50 µmol/L in the placebo group. In this study, there was a significant relationship between the administration of Vitamin D3 and glutamate levels (Vitamin D3 group p <0.001; placebo group p = 0.041). Meanwhile, there was a decrease in the average NLRP3 levels in both groups, from 0.89 ± 0.42 ng/ml to 0.81 ± 0.37 ng/ml in the Vitamin D3 group and from 0.99 ± 0.68 ng/ml to 0.75 ± 0.53 ng/ml in the placebo group, with p-values of 0.016 and 0.005, respectively (Table 2).

DISCUSSION

Migraine is a commonly reported primary headache disorder, with a higher prevalence and incidence rate in women compared to men, particularly in the age group of 18-55 years. This aligns with the findings of this study, which identified the average age of women with chronic migraines as 34.3 ± 11.8 years in the Vitamin D group and 33.5 ± 9.7 years in the Placebo group. In the literature, migraine without aura is mentioned as the most common form of migraine (80% of cases), which is consistent with this study where migraine without aura predominated in both groups, at 91.67% and 58.33%, respectively. This study also revealed that the nutritional status (Body Mass Index) of chronic migraine patients was normal. However, a meta-analysis of observational studies suggested an increased risk of chronic migraine in obese and pre-obese patients compared to those with normal weight.[16,17]

In recent years, vitamin D3 deficiency has been linked to global health issues, affecting 30-80% of children and adults. Vitamin D3 deficiency has also been associated with chronic migraines. In this study, the initial vitamin D3 levels in chronic migraine patients were 22.49 ± 2.75 in the Vitamin D3 group and 25.87 ± 3.42 in the Placebo group. This is consistent with the findings of Mottaghi T *et al.* (2013), where the average vitamin D3 level in female chronic migraine patients was 22.9±1.9 ng/ml. Furthermore, this study found a more significant reduction in headache frequency in the vitamin D3 supplementation group compared to the placebo group. This aligns with the study by Ghorbani Z et al. (2020), which reported that vitamin D3 supplementation at a dose of 2000 IU for 12 weeks improved headache characteristics and pro/anti-inflammatory biomarker levels in migraine patients.[11,18]

CGRP (Calcitonin Gene Related Peptide)

Calcitonin Gene-Related Peptide (CGRP) has emerged as a promising biomarker candidate in migraine cases.[19] CGRP is a potent vasodilator and has various other biological effects. The average plasma CGRP level has been reported to range from 3 pg/mL to 269 pg/mL in normal subjects. Clinical studies provide evidence that CGRP plays a crucial role in triggering migraines in some patients. CGRP levels increase in the plasma, saliva, and tears of patients during spontaneous migraine attacks.[20]

In this study, there was an increase in CGRP levels during the ictal phase in chronic migraine patients, with an increased average concentration of plasma CGRP: 199.33 ± 30.24 pg/mL in the Vitamin D group and 199.56 ± 27.16 pg/mL in the Placebo group. However, after treatment, there was a decrease in the average CGRP values in both groups. Further analysis revealed a significant decrease in CGRP levels in the placebo group (p=0.018) compared to the Vitamin D3 group (p=0.63). Based on the research by Ghorbani *et al.* (2020), vitamin D3 supplementation resulted in a significant increase in vitamin D3 levels and a decrease in plasma CGRP levels. Therefore, it is possible that the protective effects of vitamin D3 in improving migraine-related symptoms and reducing CGRP levels are associated with its anti-nociceptive properties and various indirect pathways.[11] However, the administration of vitamin D3 to migraine patients in this study did not show a significant relationship, which could be due to variations in the existing studies on CGRP, influenced by factors such as subject selection, blood sample source (cubital vein versus jugular vein), the timing of blood sample collection after the last headache, and other factors affecting CGRP levels, such as obesity, high-fat diet intake, and exercise. These factors were not mentioned in most of these studies.[21]

Glutamate

The mechanism underlying the increase in glutamate levels in migraines is still unclear. Under normal conditions, glutamate cannot cross the blood-brain barrier, except when there is an increase in blood-brain barrier permeability through the activation of NMDA receptors. Elevated levels of glutamate in neurons and platelets can affect plasma glutamate levels in migraine patients. Currently, various therapies target glutamate receptors. In the study by Taniura *et al.* (2016), it was explained that vitamin D3 therapy can protect neurons from glutamate toxicity. Glutamate is involved in the pathogenesis of migraines, particularly in cortical spreading depression, central sensitization, and pain transmission. In chronic migraines, there is a change in plasma glutamate levels, indicating higher levels of central sensitization and pain transmission compared to episodic migraines and control groups.[22,23]

In our study, there was an increase in glutamate levels during the ictal phase in chronic migraine patients. The average concentration of plasma glutamate in chronic migraine patients was 49.83 ± 13.23 µmol/L, while it was 27.08 ± 12.50 µmol/L in both experimental groups. Syafrita (2020) found that the normal glutamate level was 29.5 ± 79 µmol/L. In a study conducted by Park *et al.* (2022), when comparing episodic migraines, chronic migraines, and control groups, glutamate levels were found to be 49.73 µmol/L in episodic migraines, 58.70 µmol/L in chronic migraines, and 38.79 µmol/L in the control group. Therefore, it can be concluded that glutamate levels are higher in chronic migraine patients compared to other groups.[23,24]

In this study, significant differences were found in the frequency and duration of headaches in migraine patients who were given Vitamin D. Furthermore, the administration of vitamin D to migraine patients had a significant relationship with glutamate levels. This is evident from the reduction in headache frequency with a median value of 16 (15-24) days/month to 5 (2-12) days/month with a p-value of 0.002. Similarly, the duration of headaches decreased after vitamin D administration.

NLRP3

NLRP3 is one of the most studied inflammasomes. NLRP3 responds to various signals, including bacteria, fungi, and virus-associated molecular patterns; PAMPs (Pathogen-Associated Molecular Patterns), DAMPs (Damage-Associated Molecular Patterns) such as uric acid crystals, aggregated substances (asbestos, silica, α-synuclein fibrils, and amyloid-β), and intracellular homeostatic changes, such as increased potassium flux, mitochondrial dysfunction, lysosomal damage, and ROS (Reactive Oxygen Species) production.[25]

In the results of this study, a relationship was found in the group of migraine patients given vitamin D3. There was a decrease in serum NLRP3 levels in this group. Several studies have indicated that vitamin D3 inhibits the NLRP3 inflammasome, which protects against various inflammatory diseases. Duan *et al.* found that targeting the administration of vitamin D3 to the vitamin D receptor prevents the degradation of extracellular matrix cartilage by regulating macrophage NLRP3 activation and cytokine secretion, thereby reducing osteoarthritis. Dong *et al.* (2021) found that Vitamin D3 improved nitrogen-induced cutaneous inflammation by deactivating the NLRP3 inflammasome.[26,27]

Another study conducted by Ghorbani *et al.* (2020) assessed the effects of supplementation with vitamin D3 on headache characteristics and pro-/anti-inflammatory markers in patients with migraine, taking into consideration the anti-inflammatory effects of this vitamin.[11] The results of the study indicated that the group of patients receiving vitamin D3 supplementation experienced a decrease in the duration of attacks, fewer headache days per month, lower headache severity, and lower monthly consumption of pain relief medication compared to the placebo group.[25]

Vitamin D3 functions as a regulator of proliferation, differentiation, activation of inflammatory cells, and immune responses, such as macrophages, considering the expression of the vitamin D3 nuclear receptor in these cells. Stimulated macrophages can synthesize the major metabolite of vitamin D3 known as 1,25 $(OH)^2$ D. The anti-inflammatory effects of vitamin D3 can be applied by suppressing NF-κB activity through various mechanisms, one of which is stimulating the production of its inhibitory proteins (IκB). Therefore, the administration of vitamin D3 can reduce NLRP3 levels and inhibit neuroinflammation.[27]

Limitations of the study

Although our research presents some credible evidence, it has several limitations. Firstly, we only enrolled women to avoid potential gender-related differences in glutamate levels. Therefore, our findings may not reflect glutamate levels in male participants. Sex hormones influence glutamate levels, and while our study sampled women, menstrual cycles should still be considered regarding changes in glutamate levels. Secondly, this study did not include participants above 55 years of age. Although plasma glutamate levels did not significantly differ by age, the findings in this study do not reflect glutamate levels in different age groups. Therefore, measuring plasma glutamate levels in different age groups is necessary. Thirdly, despite enrolling a sample size based on previous research, the sample size in some subgroup analyses may be insufficient. Nevertheless, we present these results to provide further information on changes in some biomarkers, namely glutamate, CGRP, and NLRP3, in chronic migraine patients after vitamin D intake and their relationship with the reduction in headache frequency and intensity. Therefore, further research with a larger sample population is needed to compare biomarker levels in migraine participants based on these conditions.

CONCLUSION

There is a significant relationship between vitamin D3 supplementation and the reduction in the frequency and duration of headache attacks in chronic migraine patients concerning changes in glutamate and NLRP3 levels. However, there is no association with changes in CGRP levels.

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RECOMMENDATIONS

Further research is recommended on the relationship between vitamin D3 and changes in glutamate levels regarding the reduction in the frequency and duration of migraine attacks, with a larger population sample to allow for broader applicability.

REFERENCES

1. Ashina M, Katsarava Z, Do TP, Buse DC, Pozo-Rosich P, Özge A, *et al.* Migraine: epidemiology and systems of care. Lancet. 2021;397(10283):1485-95.
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
3. Serrano D, Manack AN, Reed ML, Buse DC, Varon SF, Lipton RB. Cost and Predictors of Lost Productive Time in Chronic Migraine and Episodic Migraine: Results from the American Migraine Prevalence and Prevention (AMPP) Study. Value Health. 2013;16(1):31-8.
4. Cernuda-Morollon E, Larrosa D, Ramon C, Vega J, Martinez-Camblor P, Pascual J. Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. Neurology. 2013;81(14):1191-6.
5. Hoffmann J, Charles A. Glutamate and Its Receptors as Therapeutic Targets for Migraine. Neurotherapeutics. 2018;15(2):361-70.
6. Holton KF. Micronutrients May Be a Unique Weapon Against the Neurotoxic Triad of Excitotoxicity, Oxidative Stress and Neuroinflammation: A Perspective. Front Neurosci. 2021;15.
7. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int J Mol Sci. 2019;20(13):3328.
8. Starobova H, Nadar EI, Vetter I. The NLRP3 Inflammasome: Role and Therapeutic Potential in Pain Treatment. Front Physiol. 2020;11.
9. Edvinsson L, Linde M. New drugs in migraine treatment and prophylaxis: telcagepant and topiramate. Lancet. 2010;376(9741):645-55.

10. Ghorbani Z, Togha M, Rafiee P, Ahmadi ZS, Rasekh Magham R, Haghighi S, *et al*. Vitamin D in migraine headache: a comprehensive review on literature. Neurol Sci. 2019;40(12):2459-77.
11. Ghorbani Z, Rafiee P, Fotouhi A, Haghighi S, Rasekh Magham R, Ahmadi ZS, *et al*. The effects of vitamin D supplementation on interictal serum levels of calcitonin gene-related peptide (CGRP) in episodic migraine patients: post hoc analysis of a randomized double-blind placebo-controlled trial. J Headache Pain. 2020;21(1).
12. Dell'Isola GB, Tulli E, Sica R, Vinti V, Mencaroni E, Di Cara G, *et al*. The Vitamin D Role in Preventing Primary Headache in Adult and Pediatric Population. J Clin Med. 2021;10(24):5983.
13. Mutlu B, Şiva Acar A, Erbaş O. Glutamate and Migraine. JEB Med Sci. 2021;2(2):253-60.
14. Peres M, Zukerman E, Soares CS, Alonso E, Santos B, Faulhaber M. Cerebrospinal Fluid Glutamate Levels in Chronic Migraine. Cephalalgia. 2004;24(9):735-9.
15. Ferrari A, Spaccalopelo L, Pinetti D, Tacchi R, Bertolini A. Effective Prophylactic Treatments of Migraine Lower Plasma Glutamate Levels. Cephalalgia. 2009;29(4):423-9.
16. Torres-Ferrús M, Ursitti F, Alpuente A, Brunello F, Chiappino D, de Vries T, *et al*. From transformation to chronification of migraine: Pathophysiological and clinical aspects. J Headache Pain. 2020;21(1).
17. Mungoven TJ, Henderson LA, Meylakh N. Chronic migraine pathophysiology and treatment: A review of current perspectives. Front Pain Res. 2021;2.
18. Mottaghi T, Khorvash F, Askari G, Maracy MR, Ghiasvand R, Maghsoudi Z, *et al*. The relationship between serum levels of vitamin D and migraine. J Res Med Sci. 2013;18(Suppl 1):S66-70.
19. Lee MJ, Lee S-Y, Cho S, Kang E-S, Chung C-S. Feasibility of serum CGRP measurement as a biomarker of chronic migraine: A critical reappraisal. J Headache Pain. 2018;19(1).
20. Wattiez A-S, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): Role in migraine pathophysiology and therapeutic targeting. Expert Opin Therap Targets. 2020;24(2):91-100.
21. Alemam AI, Alsheikh WM, Alahmar IA. Calcitonin Gene-Related Peptide as a Biomarker in Migraine. J Neurol Res. 2017;7(6):103-7.
22. Taniura H, Ito M, Sanada N, Kuramoto N, Ohno Y, Nakamichi N, *et al*. Chronic vitamin D3 treatment protects against neurotoxicity by glutamate in association with upregulation of vitamin D receptor mRNA expression in cultured rat cortical neurons. J Neurosci Res. 2006;83(7):1179-89.
23. Park CG, Chu MK. Interictal plasma glutamate levels are elevated in individuals with episodic and chronic migraine. Sci Rep. 2022;12(1).
24. Syafrita Y, Andy M, Rasyid HE. Analisa Kadar Glutamat pada Penderita Fibrilasi Atrium dengan Gangguan Fungsi Kognitif. Jurnal Kesehatan Andalas. 2021;9(4):407.
25. Salahi M, Parsa S, Nourmohammadi D, Razmkhah Z, Salimi O, Rahmani M, *et al*. Immunologic aspects of migraine: A review of literature. Front Neurol. 2022;13.
26. Dong X, He Y, Ye F, Zhao Y, Cheng J, Xiao J, *et al*. Vitamin D3 ameliorates nitrogen mustard-induced cutaneous inflammation by inactivating the NLRP3 inflammasome through the SIRT3-SOD2-mtROS signaling pathway. Clin Translat Med. 2021;11(2).
27. Jiang J, Huang X, Gao X, Yu S. Vitamin D3 Supplementation Attenuates Surgery-Induced Neuroinflammation and Cognitive Impairment by Regulating NLRP3 Inflammasome in Mice. Mediat Inflamm. 2022;2022:1-9.

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