

# Effect of Vitamin D supplementation on symptoms and C-reactive protein in migraine patients

Tayebeh Mottaghi, Gholamreza Askari<sup>1</sup>, Fariborz Khorvash<sup>2</sup>, Mohammad Reza Maracy<sup>3</sup>

Department of Community Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, <sup>1</sup>Food Security Research Center, Isfahan University of Medical Sciences, <sup>2</sup>Neuroscience Research Center, School of Medicine, Isfahan University of Medical Sciences, <sup>3</sup>Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

**Background:** Migraine is the most common headache around the world including Iran. In recent years, Vitamin D deficiency has been shown to be a global health problem. A few studies have been determined inverse association between serum levels of Vitamin D with a headache. So, in this study, we investigated the effect of Vitamin D supplementation on symptoms and C-reactive protein (CRP) among patients with migraine. **Materials and Methods:** This study was randomized, double-blind, and controlled-placebo clinical trial. Sixty-five migraine patients aged 10-61 years were included for analysis. Vitamin D was administered for 10 weeks with 50,000 IU dosage of Vitamin D per week. Multivariate analysis of covariate and univariate analysis of covariate were done to determine the effects of Vitamin D supplementation on symptoms, including severity, duration, frequency of headache, and the headache diary result (HDR). **Results:** Mean headache frequency and HDR had significant difference among two groups ( $5.9 \pm 7.0$  vs.  $7.0 \pm 6.0$ ,  $P = 0.06$  and  $85.0 \pm 134.2$  vs.  $132.1 \pm 147.1$ ,  $P = 0.04$ ). But, a mean difference of headache frequency was marginally significant ( $P = 0.06$ ). These values were lower among the intervention group compared to placebo group. The association was not observed between CRP with migraine disease. **Conclusion:** In this study, we shown Vitamin D supplementation may be useful in decreasing frequency of headache attacks and HDR among patients with migraine.

**Key words:** C-reactive protein, headache, migraine, Vitamin D

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## INTRODUCTION

Headache is prevalent among children and adolescents.<sup>[1]</sup> The most common types of primary headache disorders are migraine and tension headaches, which involves 80% of people in the world.<sup>[2]</sup>

Migraine is a neurological,<sup>[3]</sup> progressive, debilitating, and chronic disorder.<sup>[4]</sup> Migraine pains are caused by the release of pain-producing inflammatory materials around the nerves and blood vessels of the head.<sup>[5]</sup>

The main feature of the migraine attacks are headache,<sup>[6]</sup> last several hours to 2-3 days<sup>[5]</sup> and is often intense,<sup>[6]</sup> pulsatile, and unilateral.<sup>[5]</sup> Another related symptoms include nausea, sometimes vomiting, sensitivity to light and sound,<sup>[5]</sup> neck pain and muscle tension.<sup>[7]</sup> Migraine is associated with approximately 2-fold more risk of ischemic attacks.<sup>[8]</sup> Also, migraine in adults are related to seasonal allergies, asthma, epilepsy, continuous nightmares, atopic disorders, stroke, cardiovascular

disorders, sleep problems, motion sickness, epistaxis, and in reproductive age is associated with preeclampsia and uterine bleeding.<sup>[1]</sup> The most common reason of migraine is hunger or not eating adequate food, which is important specially among the young people.<sup>[6]</sup> Migraine is nineteenth cause of disability worldwide<sup>[9]</sup> that includes 10-20% of the population in the life.<sup>[10]</sup> Recent information demonstrate that 1 out of 4 American adults, suffer from frequent or severe headache including migraine.<sup>[1]</sup> The prevalence of migraine is more common in women compared with men.<sup>[6]</sup> Prevalence of migraine in Turkey 16.4%,<sup>[11]</sup> European adults 14.7%,<sup>[12]</sup> England (7.6% in men and 18.3% in women),<sup>[13]</sup> Germany 13.4%,<sup>[2]</sup> Africa (3-7%)<sup>[5]</sup> and in Asia (3% among men and 10% among women).<sup>[5]</sup>

Also, a migraine headache is one of the common types of headaches in Iran.<sup>[14]</sup>

In recent years, Vitamin D deficiency has been identified as a global health issue.<sup>[15]</sup> Vitamin D deficiency has been

**Address for correspondence:** Dr. Gholamreza Askari, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.  
E-mail: askari@mui.ac.ir

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identified among 30-80% children and adults in the world.<sup>[16]</sup>

In Iran, the prevalence of Vitamin D deficiency is 75.1% in women and 72.1% in men.<sup>[17]</sup> Vitamin D deficiency is related to different kinds of disorders including musculoskeletal disorders, cancer, autoimmune disorders, cardiovascular disorders, kidney disorders, mental disorders, skin disorders, etc.<sup>[18]</sup> Previous studies have determined that lower levels of Vitamin D are associated with higher headache,<sup>[18-22]</sup> but a few evidence have been determined. No clinical trial study has been performed in this field.

According to the previous findings, Vitamin D supplementation can decrease inflammatory factors such as C-reactive protein (CRP).<sup>[23]</sup> Also according to theory of neurogenic inflammation in migraine pathogenesis<sup>[24,25]</sup> and because of increased CRP levels in response to inflammation among patients with migraine,<sup>[26,27]</sup> we assessed effect Vitamin D supplementation on CRP. So, the aim of present study is to investigate the effect of Vitamin D supplementation on symptoms and CRP among migraine patients.

## MATERIALS AND METHODS

The present study was randomized, double-blind clinical trial, and controlled with placebo. This study was performed among migraine patients in Isfahan city at Khorshid Clinic and Imam Mousa Sadr Clinic in autumn 2012. At baseline, 90 migraine patients aged 10-61 years participated. Confirmation of migraine disease was done by a neurologist. The informed consent form was taken from all participants. For ethical approval, the proposal was approved by the Ethics Committee of Isfahan University of Medical Sciences and was recorded in the website of Iranian Registry of Clinical Trials (IRCT2012122911763N4).

Data including age, gender, weight, height, waist circumference, body mass index (BMI), education, medical history, use of vitamin, and mineral supplements, migraine symptoms, serum levels of Vitamin D, calcium, phosphorus, albumin, and CRP were collected for all patients. BMI was calculated by the weight (kg) divided to squared height (m<sup>2</sup>).

Assessment form of migraine disease was completed by a neurologist for all participants.

Inclusion criteria were including confirmation of migraine disease by neurologist, tendency to participate in the study. And exclusion criteria contains cardiovascular, liver, kidney, primary hyperparathyroidism diseases, tension headache, and hypervitaminosis D, use of magnesium, calcium, B12, B9, B6, Vitamin D supplements, corticosteroids, and oral contraceptive in pregnancy.

All patients were referred for the laboratory to assess the serum levels of calcium, phosphorus, albumin, Vitamin D, CRP. Seventy-seven patients were placed in intervention and control groups. Thirty-nine patients in intervention group and 38 patients in the control group were located with simple randomization method. Patients were used supplementation or placebo of Vitamin D (50,000 IU/week) during 10 weeks (Zahravi company). The message was sent to all patients every week to remind participants for use of Vitamin D supplementation.

Also, 3-day food record were completed by patients every 2 weeks for dietary intakes. At the end, 65 patients were remained including 33 patients in intervention group and 32 patients in control group. At final, patients were examined for migraine symptoms (severity, mean duration of headache attacks, and frequency of attacks per month), and CRP.

Serum levels of Vitamin D were checked before and after the intervention. Food intakes of patients were analyzed using Nutritionist version 4 (N4) software to assess macronutrients and micronutrients.<sup>[28]</sup>

### Biochemical assessment

At the first and end of the study, serum levels of 25(OH) D were measured by enzyme-linked immunosorbent assay (ELISA) method. According to ELISA method in laboratory, serum Vitamin D levels were categorized as: Deficient (serum levels <12 ng/ml); insufficient (serum levels between 12 and 30 ng/ml) and sufficient (serum levels more than 30 ng/ml). At first and the end of the intervention, CRP was measured. Also, for the diagnosis of primary hyperparathyroidism was measured calcium, phosphorus, and albumin at the first study.

### Migraine assessment

Confirmation of migraine disease was done by a neurologist. For all patients, severity, mean duration of headache attacks and frequency of attacks per month was completed by a neurologist. Migraine severity was determined using Visual Analog Scale.<sup>[29,30]</sup> The headache diary result (HDR) was measured as: Duration of headache × frequency of headache.<sup>[29,30]</sup>

### Statistical analysis

Statistical analysis was performed by the SPSS version 18.0 software (SPSS, Inc., Chicago, IL, USA). The presence or absence of difference in mean food intakes among two groups were analyzed by independent *t*-test. Severity, frequency, and duration of headaches attacks and HDR variables were not normal, so this variables changed on the logarithm until to be normal. Multivariate analysis of covariate including MANCOVA was done to determine

the effects of Vitamin D supplementation on symptoms including severity, duration, and frequency of headache attacks. In addition, univariate analysis of covariate including ANCOVA was performed to investigate the effect of Vitamin D supplementation on HDR.

## RESULTS

In this study, 65 patients were enrolled in the intervention and control groups (33 patients in the intervention group and 32 patients in the control group). Twenty-five females and 8 males in the intervention group and 22 females and 10 males in the control group were enrolled. General and clinical information of patients are shown in Table 1. Thirty-three patients with mean age of  $32.7 \pm 10.6$  in the intervention group and 32 patients with mean age of  $33.9 \pm 11.6$  in the control group were enrolled. Mean BMI, waist circumference, and education levels were higher among control group in compared with the intervention group. The primary mean of migraine severity and frequency was higher in the intervention group in compared with control group. But, the primary average of migraine duration and HDR was higher in the control group compared to the intervention group. Also, secondary average of migraine severity, frequency, duration and HDR was higher in control group compared to intervention group, respectively, ( $5.9 \pm 1.5$  vs.  $5.0 \pm 2.0$ ), ( $7.0 \pm 6.0$  vs.  $5.9 \pm 7.0$ ), ( $21.7 \pm 17.0$  vs.  $13.6 \pm 4.0$ ), ( $132.1 \pm 147.1$  vs.  $85.0 \pm 134.2$ ).

Deficiency, insufficiency, and sufficiency of Vitamin D were reported among 15.4%, 66.1% and 18.5% patients, respectively.

Food intakes were analyzed with the software. These results are shown in Table 2. No significant difference was observed between mean dietary intakes of patients among the intervention and control groups.

Multivariate analysis of covariate was used to determine the mean difference of severity, frequency, and headache duration in intervention and control groups. But for a mean difference of HDR in two groups, we used from univariate analysis of covariate. Severity, frequency, and duration of headaches attacks and HDR variables were not normal, so this variables changed on the logarithm until to be normal.

Multivariate analysis of covariance for age, sex, waist circumference, education, BMI, primary Vitamin D levels, primary severity, primary frequency, and duration of headache were controlled. In univariate analysis of covariate were controlled previous variables and, in addition, primary HDR. Results of the average comparison of severity, frequency, duration and HDR among intervention and control groups are shown in Table 3.

**Table 1: General and clinical characteristics of patients with migraine**

Variables	Intervention group	Control group	P
Age (years)	32.7±10.6	33.9±11.6	0.67
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	25.0±4.0	27.0±5.7	0.1
Waist circumference (cm)	89.0±8.6	94.2±11.5	0.4
Education (years)	10.7±3.6	10.9±4.0	0.9
Serum Vitamin D (ng/ml)	16.0±5.4	20.2±2.5	0.1
Primary migraine severity	6.6±1.1	6.5±1.1	0.71
Primary frequency <sup>†††</sup>	8.4±7.6	8.0±6.4	0.85
Primary duration (h) <sup>‡</sup>	22.9±17.7	26.5±21.7	0.46
Primary HDR <sup>‡‡</sup>	169.6±193.6	172.7±166.8	0.94

The results are presented as mean ± SD; <sup>†</sup>BMI; <sup>†††</sup>Frequency of attacks per month; <sup>‡</sup>Average duration of migraine attacks; <sup>‡‡</sup>HDR = Duration of headache × frequency of headache; BMI = Body mass index; SD = Standard deviation; HDR = Headache diary result

**Table 2: Food intakes of patients according to intervention and control groups**

Nutrients	Intervention group	Control group	P
Energy (kcal)	1480.0±450.8	1680.5±459.5	0.32
Carbohydrate (g)	214.3±75.9	245.5±83.9	0.37
Protein (g)	48.3±20.3	50.4±13.1	0.78
Fat (g)	46.9±22.0	59.1±12.7	0.14
Cholesterol (mg)	129.3±115.7	106.6±30.3	0.51
Fiber (g)	9.7±6.4	6.7±2.7	0.20
Sodium (mg)	2079.6±1372.9	1792.2±461.5	0.55
Potassium (mg)	1469.0±627.4	1625.3±626.9	0.57
Calcium (mg)	651.4±555.7	572.0±139.9	0.68
Magnesium (mg)	197.2±100.7	249.2±85.6	0.22
Zinc (mg)	7.2±3.9	6.6±2.0	0.69
Riboflavin (mg)	1.3±0.8	1.3±0.5	0.87
Folic acid (µg)	185.2±125.3	232.2±119.9	0.39
Phosphorus (mg)	861.6±426.6	897.4±206.3	0.81
Vitamin D (µg)	0.6±0.9	0.6±0.7	0.89
Vitamin B <sub>6</sub> (mg)	0.7±0.5	1.0±0.5	0.35

The results are shown as mean ± SD; SD = Standard deviation

**Table 3: Comparison of severity, frequency, duration and HDR in intervention group and control group**

Variables	F-test	df	P
Migraine severity <sup>†</sup>	1.4	1.51	0.24
Frequency <sup>†</sup>	3.6	1.51	0.06
Duration (h) <sup>†</sup>	1.1	1.51	0.30
HDR <sup>‡</sup>	4.2	1.53	0.04

<sup>†</sup>Adjusted for age, sex, BMI, waist circumference, education, primary serum levels of Vitamin D, primary severity of headache, primary frequency, and duration of headache attacks; <sup>‡</sup>Adjusted for previous variables and plus primary HDR; BMI = Body mass index; HDR = Headache diary result

No significant difference was observed for mean severity and duration headache attacks among two groups. But, a mean difference of headache frequency was marginally significant ( $P = 0.06$ ) and mean frequency of migraine was lower among intervention group to compared with control group ( $5.9 \pm 7.0$  vs.  $7.0 \pm 6.0$ ). Mean HDR had significant difference among two groups ( $P = 0.04$ ) that mean HDR was

lower in the intervention group and compared to control group ( $85.0 \pm 134.2$  vs.  $132.1 \pm 147.1$ ).

Two patients had positive CRP, however, other patients were negative CRP. One of two patients with positive CRP refused to continue. Thus, we can conclude that there were not a relationship between CRP with migraine.

## DISCUSSION

In the present study, there was a significant difference in the mean daily headache among the intervention and control groups. Also, the mean difference in headache frequency was significance threshold between two groups. But, no association was shown in migraine with CRP.

In three case-report studies have been shown the role of Vitamin D in headache, including migraine.<sup>[18,20,21]</sup> Thys-Jacobs performed two case-reports on this issue in 1994.<sup>[20,21]</sup> A case-report study was performed in two female patients with migraine headache related to menstruation and premenstrual syndrome. In these two patients with low Vitamin D levels and with use of Vitamin D and calcium supplements (1600-1200 IU/day) were found significant decrease in migraine attacks and premenstrual symptoms in 2 months treatment.<sup>[20]</sup> Next study, was conducted among postmenopausal patients with migraine headache and low Vitamin D levels which with use of Vitamin D and calcium supplementations decreased the frequency and duration of migraine attacks, but the study was case-report study.<sup>[21]</sup> Prakash and Shah have been reported that use of Vitamin D and calcium supplementations (1500 IU Vitamin D3 and 1000 mg calcium per day) can be effective in headache improvement during 4-6 weeks. Although, Vitamin D was probably more important than compared with calcium in headache improvement.<sup>[18]</sup>

Two studies have found an inverse relationship between the serum Vitamin D levels with a headache.<sup>[19,22]</sup>

In 2008, Turner *et al.* reported that the prevalence of Vitamin D deficiency were 26% in 267 patients with chronic pain (25 patients with a headache).<sup>[31]</sup>

In a study performed in Norway, an inverse association was determined between headache with Vitamin D and also, the association was observed with adjustment for different variables such as age, sex, season, and geographical region.<sup>[22]</sup>

Wheeler have found that migraine patients have low levels of Vitamin D.<sup>[32]</sup> Prevalence and frequency of headaches was reported greater in Northern regions

and areas with mean low temperature than in Southern regions in Greece.<sup>[33]</sup>

Serum levels of Vitamin D are higher among people in the lower latitudes that is a main factor for the low headache prevalence.<sup>[15]</sup>

In the else study, a significant association was not shown between serum Vitamin D levels and migraine headache, but significant relationship between nonmigraine headache with serum levels of Vitamin D was determined among nonsmokers group.<sup>[19]</sup>

In a study performed in Isfahan in autumn 2012 by Mottaghi *et al.*, positive weak association was seen between serum levels of Vitamin D with HDR ( $P = 0.04$ ,  $r = 0.19$ ) and this relationship remained significant after adjusting confounding variables.<sup>[30]</sup>

One theory of migraine pathogenesis is neurogenic inflammation.<sup>[24,25]</sup> The CRP level, a marker of inflammation<sup>[26]</sup> and an acute-phase protein in blood, increases in response to inflammation.<sup>[24]</sup> CRP level has been described to be abnormal among patients with migraine, probably through vascular inflammation.<sup>[26,27]</sup>

Welch *et al.* reported a clinical report of 60 patients with migraine.<sup>[27]</sup> Findings demonstrated that 43% of the patients had increased CRP (defined as  $>3$  mg/l), with a higher ratio in the patients without aura than in the patients with aura.<sup>[27]</sup>

A case-control study of 50 patients with migraine and 50 controls reported CRP level among migraineurs was higher (1.42 mg/l) compared to controls (0.90 mg/l) ( $P = 0.03$ ).<sup>[34]</sup> CRP level was higher in patients without aura compared to controls, 2.11 mg/l versus 0.90 mg/l ( $P = 0.0002$ ).<sup>[34]</sup>

Also, a Cohort study showed that CRP level was higher among patients with a history of migraine than in the women with no migraine history.<sup>[35]</sup> serum CRP levels were higher in the women without aura compared to women with aura.<sup>[35]</sup>

So, findings from these studies, suggest that CRP is modestly elevated among patients with migraine compared to controls.<sup>[26]</sup> But in our study, we didn't observe the relationship between CRP with migraine.

Amer and Qayyum reported a statistically significant inverse relationship between 25(OH)D at serum levels lower than 21 ng/ml with CRP. But described that 25(OH) D at serum level  $\geq 21$  ng/ml is associated with an increase

in serum CRP. So, the role of Vitamin D supplementation to decrease inflammation is useful only among adults with lower serum 25(OH)D.<sup>[23]</sup>

The role of Vitamin D deficiency in the cause of headache is unfamiliar.<sup>[15]</sup>

The presence of alpha 1-hydroxylase enzyme, Vitamin D receptors and Vitamin D binding protein in the brain, especially hypothalamus<sup>[15]</sup> and low levels of magnesium<sup>[18]</sup> are the mechanism about the association between Vitamin D deficiency and headache. Because intestinal absorption of magnesium is dependent on Vitamin D.<sup>[18]</sup>

The strength of this study is the first clinical trial study in the world about the effect of Vitamin D supplementation on symptoms and CRP in patients with migraine. Sunlight exposure assessment was not measured in this study and was one limitation of our studies.

## CONCLUSION

In summary, the present study showed that Vitamin D supplementation on the frequency and headaches diary result can be effective, although the effect on migraine frequency was significance threshold. But, no association was seen between migraine with CRP levels. Thus, it is required to do further clinical trial studies with larger sample size.

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## AUTHOR'S CONTRIBUTIONS

TM, FK, GA, RG designed, conducted and edited the manuscript. MM analyzed and interpreted data. All authors read and approved the final manuscript.

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