Migraine and Fish Oil

Simin Mouodi¹ (b), Marjan Mouodi² (b), Shervin Rezaei Majd³ (b), Amirmohamad Rezaei Majd⁴ (b)

¹Social Determinants of Health Research Center, Babol University of Medical Sciences Health Research Institute, Babol, Iran ²Department of Endocrinology and Metabolism, Tehran University of Medical Sciences School of Medicine, Tehran, Iran ³Department of Research and Development, Scott Protein Products Company, Babol, Iran ⁴Department of General Practice, Babol University of Medical Sciences School of Medicine, Babol, Iran

ORCID IDs of the authors: S.M. 0000-0001-7868-9360; M.M. 0000-0002-5138-4855; S.R.M. 0000-0001-6900-5107; A.R.M. 0000-0002-1984-8795.

Cite this article as: Mouodi S, Mouodi M, Majd SR, Majd AR. Migraine and Fish Oil. Cyprus J Med Sci 2019; 4(3): 257-61.

Considering the importance of migraine as the seventh cause of disability globally, this study was conducted to evaluate the effectiveness of fish oil and omega-3 polyunsaturated fatty acids (PUFA) on migraine. In this review article, we included all clinical trials and review articles from four databases (Pubmed, the Cochrane database of systematic reviews, Scopus, and Clinicalkey), published from January I, 1990, to August 7, 2018, in which the treatment effects of fish oil or PUFA for the prevention or control of migraine attacks, either in basic science or clinical field, have been studied. At first, 54 articles or book chapters were found, and after reviewing their study design, 13 clinical trials and review articles were included in the study. Most of reviewed articles, including five clinical trials and four review articles, represented the positive impact of fish oil and omega-3 PUFA for improvement in frequency, intensity, or duration of migraine headache; however, a definite daily dosage and duration of treatment have not been defined. Although the evidence that supports the positive impact of fish oil on migraine. Furthermore, research is needed to define an appropriate daily dosage and treatment duration of fish oil on migraine. Furthermore, research is needed to define an appropriate daily dosage and treatment duration of fish oil and PUFA in migraine patients.

Keywords: Fish oil, migraine, omega-3 fatty acids

INTRODUCTION

Migraine manifests by recurrent, episodic headache attacks, which may or may not be preceded by a focal neurologic symptom (aura) (I-3). It is a debilitating disorder, affecting 2.6%–21.7% of general population, worldwide (4). Its lifetime prevalence has been reported to range between I3% and 33% (5). Self-reported prevalence rates of migraine and severe head-ache among US adult population were reported as I5.3% (9.7% for men and 20.7% for women) (6). Ninety percent of all headaches are either migraine, tension-type headache, or a mixture of them (7). The Global Burden of Disease Study 2015 represented migraine as the seventh cause of disability globally (8). A higher prevalence of this disorder has been reported in adults aged I8–44 years, the unemployed, people with lower family income, and the elderly and disabled individuals (6).

The mechanisms and contributing factors of a migraine attack are described in Figure I (2).

Migraine treatment includes both preventive therapy, for reducing the frequency and severity of migraine attacks, and acute therapy, for aborting acute symptoms. Treatment can be divided into pharmacological and psychological intervention approaches (9, 10), or specific and non-specific medications (II).

Fish and fish oils are rich in omega-3 polyunsaturated fatty acids (PUFA). They have several cellular and physiologic mechanisms of action, which produce the anti-inflammatory effects of this compound (I2).

Some previous studies demonstrated that the fish oil and PUFA intake could be effective in the prevention or control of migraine due to their anti-inflammatory properties, vascular relaxation effects, and inhibition of serotonin release from platelets (7); and some other did not confirm a positive impact of fish oil on migraine. The aim of this research was to review published scientific manuscripts in which the effectiveness of fish oil in the prevention or acute treatment of migraine attacks has been assessed.



Received: 24.11.2018 Accepted: 28.04.2019 We searched clinical trials and reviewed articles in four databases (Pubmed, the Cochrane database of systematic reviews, Scopus and Clinicalkey) from January I, 1990, to August 7, 2018. At first, all of clinical trials, systematic reviews, and review articles that used the entry terms ("Disorder, Migraine" OR "Disorders, Migraine" OR "Migraine Disorder" OR "Migraine" OR "Migraines" OR "Migraine Headache" OR "Headache, Migraine" OR "Headaches, Migraine" OR "Migraine Headaches" OR "Acute Confusional Migraine" OR "Acute Confusional Migraines" OR "Migraine, Acute Confusional" OR "Migraines, Acute Confusional" OR "Status Migrainosus" OR "Hemicrania Migraine" OR "Hemicrania Migraines" OR "Migraine, Hemicrania" OR "Migraines, Hemicrania" OR "Migraine Variant" OR "Migraine Variants" OR "Variant, Migraine" OR "Variants, Migraine" OR "Sick Headache" OR "Headache, Sick" OR "Headaches, Sick" OR "Sick Headaches" OR "Cervical Migraine Syndrome" OR "Cervical Migraine Syndromes" OR "Migraine Syndrome, Cervical" OR "Migraine Syndromes, Cervical") AND ("fish oil" OR "Omega 3 Fatty Acids") in title, abstract, or keywords were included. We also reviewed reference lists of included studies to identify the



FIGURE I. Mechanisms and contributing factors of a migraine attack (Adapted from: Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018;17:174-82-Figure courtesy of Andrew Charles – used with permission) articles related to search criteria. We searched published manuscripts in all languages. Two reviewers updated searches of the abstracts.

We included clinical trials and review articles that studied the treatment effects of fish oil or PUFA in the prevention or control of migraine attacks, either in basic science or clinical field. Relevant articles were selected using a two-phase process. Two researchers reviewed all identified abstracts for eligibility. Second, full text articles were revised to determine the mentioned treatment effects of fish oil or PUFA, including the prevention or improvement in frequency, duration, and intensity or characteristics of migraine headache. All the interventional studies and review articles regardless of the duration and the size of study population were included. The evidence published before 1990 was excluded.

Two authors, not blinded to data sources, summarized the included studies. Overall quality assessment was performed emphasizing the treatment effects of fish oil or PUFA on the prevention of migraine attack or control of its symptoms.

CONCLUSION

We found 54 articles or book chapters in the four mentioned databases in which the association between fish oil and migraine has been studied. After reviewing the study design of these manuscripts, there were I3 clinical trials and review articles included in the study. The included studies are summarized in Table I. This table shows that six clinical trials and five review articles studied the treatment effect of fish oil or omega-3 PUFA on clinical aspects of migraine, such as its frequency, severity, or duration; two clinical trials studied the treatment effect of PUFA on immunologic aspects of migraine. Seven of the included studies were published from 2016 to 2018.

Most of reviewed articles including five clinical trials (13-16) and four review articles (14, 17-19) represented the positive impact of fish oil and PUFA on the improvement in frequency, intensity, or duration of migraine headache; however, a definite daily dosage and duration of treatment have not been defined.

There were three clinical trials (20-22) that reported no significant statistical difference between the case and control groups regarding the treatment effects of fish oil in the prevention or control of migraine. In addition, Rajapakse in his review article reported non-adequate evidence to confirm the prophylactic effect of PUFA for migraine (23), and Maghsoumi-Norouzabad showed that omega-3 PUFA did not have a positive effect in the frequency and intensity of migraine headache, although it was effective in the reduction of migraine duration (14).

Soares evaluated 60 patients with chronic migraine undergoing prophylactic treatment with amitriptyline. The patients who received omega-3 PUFA for 2 months were compared to the control group receiving placebo, and they experienced a reduction in the number of days of headache. Furthermore, it was suggested that omega-3 PUFA could be useful in the prevention of migraine headache (I3). Ramsden (I5) and Tajmirriahi (I6) reported a similar positive effect of fish oil or PUFA in the prevention of headache attacks in their clinical trials conducted among the adult study population. Ramsden applied a combination of

ar Coun Brazi	try Study design Double- blinded, randomized, and	Description of intervention and control (if applicable) groups The case group: polyunsaturated omega-3 fatty acids	If the study is RCT Duration of intervention (days) 60	Participants (study sample size) Patients with chronic migraine (n=60)	Findings In the case group, 66.7% of participants had a reduction >80.0% per month in the number of
	acebo-controlled inical trial andomized inical trial	the control group: placebo Four groups: One group received omega-3 tatty acids, one group a combination nano-curcumin, one group a combination of both, and the last aroup a placebo	60	Patients with episodic migraine (n=72)	days with headache, while in the control group, the same improvement occurred in 33.3% of patients. The difference was significant. A significant reduction in attack frequency was observed in the combination group.
νοου	ystematic review nd meta-analysis f randomized ontrolled trials	-			Omega-3 intake had no effect on the frequency and severity of migraine, but it had a reduction effect on the duration of migraine attacks.
E O	candomized linical trial	Four groups: one group received omega-3 fatty acids, one group nano-curcumin, one group a combination of them, and the last group a placebo	60	Patients with episodic migraine (n=72)	A significant reduction in attack frequency was found in the combination group.
	Double-blinded randomized clinical trial	The case group: sodium valproate and I g of omega-3; the control group: sodium valproate and a placebo	60	Children aged 5–15 years with a diagnosis of migraine (n=25)	The average number of headache attacks per month and the severity of attacks decreased significantly in both groups; however, no significant difference was observed between the two groups.
ada	Narrative review article Review article				Low fat and high omega-3/low omega-6 fatty diets decrease the frequency of migraine attacks Inadequate evidence to support or refute the polyunsaturated fatty acids use in migraine prophylaxis.
	Randomized, ingle-blinded, parallel group	The case group: high n-3 plus low n-6 diet the control group: low n-6 diet	84	Ambulatory adult patients with chronic daily headache (headaches 24 hours per day and 215 days per month for at least 3 Months, and a headache history of 22 years) (n=67)	The combination of high n-3 with concurrent reduction in n-6 fatty acids diet produced significant improvements in headache hours per day, severe headache days, and headache-related quality of life compared to baseline, and compared to the n-6-lowering diet.
0, 2 0	Single-blind andomized clinical trial	The case group: sodium valproate 400 mg daily plus fish oil supplementation the control group: 400 mg/day sodium Valproate	06	Adult patients with migraine headache (n=67)	A significant decrease in the duration, monthly frequency, and severity of headache was observed after Months (2, and 3 in both groups There was a significant reduction in headache severity and frequency in the case group in comparison with the control group.
	teview article				Dietary supplementation with fish oils is effective in several inflammatory and autoimmune diseases in humans, such as migraine headaches
200	andomized, double-blind, cross-over study	2 months fish oil, I month washout period, and 2 months placebo (olive oil)	60	Adolescents with frequent migraines for at least I year (n=27)	A significant reduction in the headache frequency duration, and severity during fish oil and also during placebo treatment was observed, with no significant difference betweer treatments.
Φ	l6 weeks double-blinc clinical trial with 4 weeks single-blinded placebo run-in period	 The case group: omega-3 polyunsaturated fatty acid Gram per day the control group: placebo 	112	Migraine patients (96 individuals taking omega-3 polyunschurated fatty acid and 87 taking placebo)	The total number of migraine attacks was significantly lower in the case group. The mean intensity and duration of migraine were not significantly different between the two group Despite a run-in placebo period, a strong placeb effect was observed in this study.
	Review article				Fish oil can be safe and effective in migraine prevention due to its platelet-stabilizing and antivasospastic actions.

omega-3 PUFA intervention besides the reduction of omega-6 fatty acids in a daily food program (I5). Tajmirriahi compared the treatment effect of fish oil administration (I80 milligram/ day) plus sodium valproate 400 mg/day for 3 months in migraine patients with those who received only sodium valproate. In this research, a significant reduction in headache frequency was observed only during the 1st month of treatment; and this reduction was not significant during the 2nd and 3rd month of treatment (I6). Soveyd (24) and Abdolahi (25) evaluated the effect of omega-3 PUFA on immunologic aspects of migraine in their clinical trials, and headache frequency was the secondary outcome that they examined. They observed a significant reduction in migraine attacks in patients who received a combination of omega-3 PUFA and nano-curcumin.

Fayyazi examined the treatment effect of omega-3 PUFA in pediatric migraine. He observed that children aged 5–15 years treated with a combination of omega-3 PUFA (I gram per day) and sodium valproate for 2 months had a reduction in headache frequency and severity; however, the difference was not statistically significant between the case and control groups (22).

Although multiple factors and mechanisms have been described in the pathophysiology of migraine attacks (2), the origin of headache is not completely understood; recent evidence shows the effect of some vasomodulators, released by peripheral nerve endings on blood vessels in the scalp and meninges; furthermore, an inflammation and edema in blood vessels, with an increased sensitivity to mechanical stimulation are thought to be related to headache initiation. In addition, some receptors, such as nitric oxide, glutamate, and vanilloid, are also supposed to be involved in migraine (7). Some other evidence suggested that structural brain changes were more common in migraine patients, especially the patients with aura, than in control groups (26).

The exact mechanism of action of fish oil and omega-3 PUFAs in the prevention and control of migraine is still unclear, but it seems that their effect to inhibit multiple aspects of inflammation (27, 28); their effects on neuropeptides, neuro-receptors, and ion channels (29, 30); sympathetic nervous system (31); and also their vasomodulation impact (32) can justify their positive effect to improve migraine headache.

The most important limitation of this study was a non-specific quality assessment of included studies. It is suggested to future researchers to evaluate the treatment effect of fish oil and omega-3 PUFA with a different dosage and duration on the frequency, severity, and duration of migraine attacks.

Although the evidence supporting the positive impact of fish oil and PUFA in the prevention and control of migraine is more frequent, more evidence and longitudinal study designs need to confirm the positive impact of fish oil on migraine. Furthermore, research is needed to define an appropriate daily dosage and treatment duration of fish oil and PUFA in migraine patients.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – S.M., M.M., S.R.M.; Design – S.M., M.M., S.R.M.; Supervision – S.M., M.M., S.R.M.; Resource – S.M., M.M., S.R.M.; Materials – S.M., M.M., S.R.M., A.R.M.; Data Collection and/or Processing – S.M., M.M., S.R.M., A.R.M.; Analysis and/or Interpretation – S.M., M.M., S.R.M.; Literature Search – S.M., M.M., S.R.M., A.R.M.; Writing – S.M., M.M., S.R.M.; Critical Reviews – S.M., M.M., S.R.M.

Acknowledgements: Hereby, the support of the Vice-Chancellor for Research and Technology of Babol University of Medical Sciences for providing access to the mentioned data sources is appreciated.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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