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Can Serotonin and Some other Biochemical Parameters be Manipulated by Some Nutritional Supplements in Patients with Migraine?

Ibrahim MA*

College of Pharmacy, University of Mosul, Iraq

***Corresponding author:** Manal Abdulmunem Ibrahim, College of Pharmacy, University of Mosul, Mosul, Iraq, Tel: +9647728430744; Email: alfarhamanal@uomosul.edu.iq

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Abstract

Background: Migraine is a "metaboloendocrine disorder" with serotonin dysregulation which lead to painful condition.

Aim: The study aims to find the effect of combined supplementation of omega-3, acetylcarnitine, and vitamin E on migraine headache frequency and their effect on different biochemical parameters including serum serotonin level.

Methods: Blood samples were collected from 21 migrainous men before and after one month of an intake of the combined supplement during a period free of migraine attacks. The blood samples are used to measure serum serotonin, liver enzymes, lipid profile, serum uric acid, serum bilirubin, serum magnesium, sodium, potassium, and chloride.

Results: Migraine men showed higher total serum cholesterol: HDL-c ratio, non-HDL-c, and total serum cholesterol than control men at p-values 0.012, 0.006 and 0.008 respectively. Upon supplement intake, migraine men showed a decrease in the number of headache attacks per month at a p-value of 0.001 with an insignificant decrease in the severity of migraine headaches. Also, total serum cholesterol and HDL-c showed a significant decrease at p-values 0.049 and 0.013 respectively.

Conclusion: Combined supplements of acetylcarnitine, omega-3, and vitamin E for one month may decrease migraine headache attacks. That may be related to the decrease in total serum cholesterol or to the possible effect of improving cholesterol transfer from HDL, which may explain the decrease in HDL-c. Other parameters are improved but insignificantly such as magnesium, uric acid and bilirubin.

Keywords: Migraine; Serotonin; Serum Lipid; Liver Enzymes; Electrolytes

Introduction

The Prevalence of migraine is 17-33% in women and 8-22% in men 1. Patients with migraine outside of the attack are in the interictal phase, while during the attack they are in the ictal phase [1]. Migraine occurs due to variation in blood flow in cerebral vessels due to activation of the trigeminovascular system, which increases the vasodilator neurotransmitter CGRP and decreases serotonin [2]. The low cellular energy of the brain at rest [3], with low mitochondrial phosphocreatinine [3], suggests a mitochondrial dysfunction in migraine [4]. As the abnormality in migraine mitochondrial oxidative phosphorylation leads to hypometabolism and low ATP [5], which lead to metabolic abnormality and increased oxidative stress [6]. It is thought that the altered neuronal excitability of migraine is due to abnormal energy

homeostasis such as mitochondrial phosphorylation, calcium channel dysfunction, and reduced magnesium level 4. Therefore, Migraine is a "metaboloendocrine disorder" where insulin resistance and impaired glucose homeostasis are the pivotal factors [7].

Serotonin (5-HT) is a monoamine that can be found in the CNS and the periphery [8], involved in sleep, mood, appetite and pain modulation [9]. Its dysregulation is related to painful conditions such as IBS and migraine [8]. serotonin can act as nociceptive (increase pain) or antinociceptive (decrease pain) according to the type of receptors and anatomical region [10]. It is thought that serotonin is low between migraine attacks and high during the attack. The low serotonin level may cause upregulation of serotonin receptors [11], which aggravates serotonin action in the ictal phase [12,13].

There are different studies including acetylcarnitine and neurodegenerative disorders, and the two enzymes in the "carnitine shuttle", carnitine palmitoyl transferase 1 and 2 are insufficient in migraine patients [14]. Moreover, depressive disorder, which has a high prevalence among migraine patients [15], showed a lower acetylcarnitine level [16]. Acetylcarnitine has an effective response in the treatment of depressive patients [17] and other neuropsychiatric dysregulation due to its effect on serotonin level in the cerebral cortex of the hippocampus [18], and prevent its decrease in several regions of the brain [19]. Moreover, acetylcarnitine is present in high concentrations in the brain, and its intake reduces brain damage and regulates mitochondrial function, by improving the expression of the respiratory chain component [19].

L-carnitine and acetylcarnitine are important for cellular energy production, by carrying long-chain fatty acid into the mitochondria for β-oxidation, but acetylcarnitine is a more effective dietary supplement than l-carnitine because it can decrease MDA, and nitrotyrosine in old rat brain [20]. However, the physiological roles of acetylcarnitine are to increase coenzyme A in mitochondria, increase B-oxidation of fatty acids, promote good mitochondrial function [21], remove oxidative product from mitochondria and increase acetyl group that is used for the synthesis of acetylcholine and GABA [22]. Neuroprotection involves (attenuating inflammation, preventing energy failure, preventing oxidative damage to cellular and mitochondrial proteins, and enhancing biosynthetic ability) and acetylcarnitine fulfil all these requirements [22].
there is a promising role of omega 3 PUFA in mitochondrial biogenesis in animal models with neurodegenerative disease [23]. Omega-3 PUFA can decrease nitric oxide and ROS in migrainous [24] and is considered in the treatment of inflammatory pain [25]. DHA (of omega 3 PUFA) is concentrated in the brain [26], and it is important for neurogenesis, neuron differentiation, membrane integrity and fluidity [27] and is involved in synaptic transmission and synaptogenesis [28]. Therefore, DHA can influence the function of the blood-brain barrier [29], and regulate the activity of membrane-bound enzyme Na/k dependent ATPase [30], ion channels and dopaminergic and serotoninergic neurotransmission [31]. The metabolite neuroprotectin 1 produced from DHA can inhibit cytokine production in microglia [32]. While resolvins produced from EPA(of omega 3 PUFA) can inhibit pain [25], by affecting certain channels called (TrpV1). Moreover, omega 3 PUFA improve ADP Kinetics in human mitochondria by alteration in mitochondrial membrane structure and ATP synthase [25], cell membrane and mitochondrial respiration kinetics [33,23]. While vitamin E is a fat-soluble antioxidant compound and a first line of defence against lipid peroxidation [34] has a beneficial effect on menstrual migraine headaches when given for five days during the menstrual cycle [35].

This study aims to find the effect of combined supplementation of acetyl-carnitine, omega 3 PUFA, and vitamin E on migraine headache frequency and their effect on serotonin serum levels as well as other biochemical parameters.

Subjects, Materials, and Methods

Overall 21 migraine men are included in this study, they did not take dietary supplements three months before the study. They agree to start supplements consisting of (Mera Omega-3 plus vitamin E)® soft gel contains omega-3 PUFA and vitamin E and (Adicarnit)® contains acetylcarnitine 500 mg once daily for each of 30 days. (Mera Omega-3 plus vitamin E)® softgel consists of fish oil including Eicosapentaenoic acid(EPA) 180mg, Docosahexaenoic acid(DHA) 120mg and DL-alpha-tocopherol(vitamin E) 3mg, manufactured by Starpharma Ltd/Poland for Mera Pharma GmbH/Switzerland, while (Adicarnit)® acetylcarnitine manufactured by dipharma EAD-Bulgaria EUA. The patients provide blood samples before and after the course of the supplement. Only three patients couldn't tolerate the supplement, one of them felt dizzy, and the two others did not give any reason. All the patients provided their blood samples in the period outside of the migraine attack. 13 healthy men provided blood samples to compare with the migrainous group.

The blood samples are used to measure serum serotonin, GPT, GOT, ALP, total cholesterol, serum triglyceride, LDL-c, HDL-c, non-HDL-c, total cholesterol: HDL-C ratio, uric acid, bilirubin, magnesium, ions of sodium, potassium, and chloride.

Serotonin is measured by using a kit (Human Serotonin(ST) Elisa Kit) Catalog No: YLA0836HU; Shanghai YL Biotech Co., Ltd. www.ylbiont.com. Lipid profile, GOT, GPT, ALP, and

uric acid are measured by Automatic Clinical Chemistry Analyzer "ACCENT-200" manufactured by P Z CORMAY S.A. **Headquarters:** Wiosenna 22 str.,05-092 Lomianki, Poland. The kits used are supplied from PZ CORMAY. S.A. While, direct bilirubin, total bilirubin, magnesium, sodium, potassium, and chloride are determined by dry chemistry analyzer Fujifilm nx 500i.

The statistical analysis is done using SPSS version 26, using t-test, paired t-test and chi-square. Data expressed as mean, median, and standard deviation. P values of less than 0.05 are considered as significant.

Results

The basic data of all the study participants are presented in Table 1. Patients who participated in the study were found to be slightly older than the control group. All the biochemical data did not significantly differ from the control unless total cholesterol / HDL-c ratio, non-HDL and total cholesterol, at p-values 0.012, 0.006, and 0.008, respectively.

Variable	Control Gr.		Pt. Gr. Before supplement		P value
	Mean (SD)	Median	Mean (SD)	Median	
BMI	25.55 (2.18)	25.6	29.43 (5.313)	29.6	0.12
Age(years)	33.15 (6.02)	32	39.78 (9.65)	41.5	0.026
Number of attacks/month	N/P	N/P	4.78 (2.21)	4	N/P
Serotonin (ng/ml)	N/P	N/P	103.58 (26.85)	96.64	N/P
GPT (IU/L)	29.39 (13.05)	25.8	18.26 (11.83)	16.2	0.23
GOT (IU/L)	26.26 (9.45)	24.1	36.53 (32.07)	24.55	0.213
ALP(IU/L)	66.86 (71.3)	24.27	73.27 (19.38)	72.45	0.453
T. Cholesterol/HDL-c ratio	3.44 (0.71)	3.67	4.20 (0.85)	4.2	0.012
Non-HDL (mg/dl)	126.7 (36.98)	125.2	167.81(40.02)	170.85	0.006
Cholesterol (mg/dl)	179.1 (39.81)	172.5	220.90(39.98)	221.95	0.008
HDL-c (mg/dl)	52.39 (7.45)	53.2	53.08(6.15)	52.2	0.787
LDL (mg/dl)	105.39 (31.0)	100.4	116.42(35.98)	117.3	0.372
Non-fasting TG(mg/dl)	177.66 (75.84)	164.7	262.88(151.94	238.9	0.05
Uric acid(mg/dl)	5.98 (0.88)	6	5.83(1.78)	5.9	0.758
Total Bilirubin(mg/dl)	0.29 (0.11)	0.3	0.33(0.19)	0.3	0.473
Direct Bilirubin(mg/dl)	0.13 (0.08)	0.1	0.11(0.051)	0.1	0.43
Indirect Bilirubin(mg/dl)	0.15 (0.09)	0.1	0.21(0.179)	0.2	0.22
Mg(mg/dl)	2.32 (0.20)	2.3	2.18(0.19)	2.1	0.07
Na (mmol/l)	134.23 (6.9)	134	123.5(28.08)	124.5	0.135
K(mmol/l)	3.83(0.4)	3.7	4.18(0.64)	4.2	0.19
Cl (mmol/l)	100.07(6.39)	100	97.16(10.77)	93	0.356

Table 1: Basic results of the study participants' data.

With the addition of supplements to the ordinary treatment of patients with migraine, it was found that the number of attacks significantly reduced as shown in Table 2. In addition to that, the cholesterol level was also significantly reduced from the baseline before treatment. However, the level of HDL was also significantly reduced after treatment. In terms of the severity of migraine attack, the study showed that there was no significant association between the addition of supplements and the severity of the attack as shown in Table 3.

Variable	Pt. Gr. Before supplement		Pt. Gr. After supplement		P value
	Mean (SD)	Median	Mean (SD)	Median	
BMI	29.43 (5.313)	29.6	29.43 (5.313)	29.6	N/P
Age(years)	39.78 (9.65)	41.5	39.78 (9.65)	41.5	N/P
Number of attacks /month	4.78 (2.21)	4	2 (1.45)	2	<0.001
Serotonin (ng/ml)	103.58 (26.85)	96.64	92.34 (42.1)	78.09	0.361
GPT (IU/L)	18.26 (11.83)	16.2	25.14 (18.66)	20.4	0.197
GOT (IU/L)	36.53 (32.07)	24.55	32.99 (20.42)	28.6	0.695
ALP (IU/L)	73.27 (19.38)	72.45	68.07 (17.32)	63.6	0.403
T. Cholesterol /HDL-c ratio	4.20 (0.85)	4.2	4.16(0.83)	4.16	0.887
Non-HDL (mg/dl)	167.81(40.02)	170.85	148.54(32.73)	151.3	0.123
Cholesterol (mg/dl)	220.90(39.98)	221.95	196.35(31.56)	200.95	0.049
HDL-c(mg/dl)	53.08(6.15)	52.2	47.81(5.84)	46.4	0.013
LDL (mg/dl)	116.42(35.98)	117.3	116.88(23.756)	116.15	0.965
Non fasting TG(mg/dl)	262.88(151.94	238.9	291.7(111.92)	279.95	0.522
Uric Acid (mg/dl)	5.83(1.78)	5.9	5.88(1.68)	6	0.924
Total Bilirubin(mg/dl)	0.33(0.19)	0.3	0.36(0.2)	0.3	0.678
Direct Bilirubin(mg/dl)	0.11(0.051)	0.1	0.15(0.11)	0.1	0.273
Indirect Bilirubin (mg/dl)	0.21(0.179)	0.2	0.21(0.1)	0.2	0.911
Mg (mg/dl)	2.18(0.19)	2.1	2.23(0.17)	2.3	0.379
Na (mmol/l)	123.5(28.08)	124.5	127.22(4.58)	126	0.586
K (mmol/l)	4.18(0.64)	4.2	3.96(0.58)	4.2	0.516
Cl (mmol/l)	97.16(10.77)	93	91.05(7.27)	92	0.055

Table 2: Biochemical results before and after supplement use.

Supplement use	Severity of Pain			
	Not at all	Mild	Moderate	Severe
Before use	0.0 (0.0)	1 (33.3)	4 (50)	12 (57.1)
After use	3 (100)	2 (66.7)	4 (50)	9 (42.9)
Data presented as n(%), Fisher exact test = 3.736, P=0.291				

Table 3: Effect of the supplement on the severity of migraine headache.

Discussion

This study showed a decrease in the number of migraine attacks per month from 4.78 on average to 2 per month (Table 2). which may be attributed to the effect of acetylcarnitine and /or Omega 3 PUFA. However, the severity of headaches showed no significant difference in Table 3, although of that the patients with severe headaches were 12 before supplements and became 9 after supplements and those with no attacks became 3, while before supplements were 0 (Table 3). The result of this study is in agreement with another study that involved supplementation of omega 3 PUFA for one month and exhibited a decrease in the frequency of headaches in patients with chronic migraine [36]. This result may be due to the effect of omega 3 PUFA in decreasing prostaglandin and Leukotrienes or to changes in serotonin release or synthesis by platelets. Another opinion is that the inhibitory effect of omega 3 PUFA on cyclo-oxygenase enzyme and nitric oxide may prevent migraine progression [37]. Concerning acetylcarnitine, one study found that it has no effect on migraine pain in patients with lower episodic headache frequency [38], but a study involving the administration of l-carnitine and coenzyme Q10 showed an improvement in migraine symptoms [39].

In this study, serotonin is measured in migraine patients before and after supplement intake, but not in control healthy men. However, migrainous brain serotonin levels when compared to control in other studies showed either an increase or a decrease [11]. This study reveals that the supplement for one month showed no significant changes in serum serotonin level in a period of free migraine attack (Table 2), suggesting that these supplements do not affect serum serotonin in migrainous. The higher standard deviation after supplement combination intake may be attributed to that one of the patients showed a paradoxical increase in serotonin level from 167 to 206.7 ng/ml, but still not significant when compared to migrainous before supplement combination intake.

It is found that serum serotonin is low during periods free of migraine attacks, but during the attack, plasma serotonin is increased [40,41]. The high serotonin vasoconstricts the nerve endings and blood vessels and activate the pain receptors [42], while the low serotonin levels dilate blood vessels and initiate migraine [43]. The low serotonin level during the period of free migraine attack may be attributed to an increase in serotonin turnover [41], which decreases tryptophan metabolites and leads to increased glutamate and neuroinflammation [44].

Acetylcarnitin is reported to modulate serotonin levels in the cerebral cortex of the hippocampus [18]. Moreover, acetylcarnitine improves respiratory chain components and prevents a decrease of 5-HT in the brains of rats after long-term amphetamine intake [19]. It was found that acetylcarnitine is effective in central and peripheral neuron protection [22,45] has an effect on acetylcholine neurotransmitters and increases glucose utilization in brain tissues [46], in addition to its analgesic effect [47]. One study showed that l-carnitine combined with coenzyme Q10 can improve migraine symptoms [39]. Two studies involved the administration of acetyl-carnitine for migrainous, one of them revealed that acetylcarnitine does not affect headache [38], while the other study revealed that acetylcarnitine can be used as migraine prophylaxis in children [48].

GOT, GPT, and ALP are measured in this study to show if these enzymes have a relation to migraine pathophysiology, especially since GOT and GPT elevations are markers of hepatocellular injury, while, intrahepatic and extrahepatic biliary obstruction are marked by an increase of ALP [49]. One study found a high prevalence of non-alcoholic fatty liver in migrainous of long duration and highly frequent attacks [50]. while another study revealed that migrainous have an involvement of biliary stasis manifested by an increase in ALP [51]. However, the present study showed no differences in these three enzymes before and after intake of supplements or between control and migrainous, suggesting no liver or biliary injury in migrainous involved in the study.

This study showed higher total cholesterol: HDL-c ratio, non-HDL-c, total serum cholesterol in migrainous when compared to control at p-values 0.012, 0.006 and 0.008 respectively, while non-fasting triglyceride is higher at p-value 0.05 (Table 1). This study is in agreement with other studies,[52-54] which found that total cholesterol is higher in migrainous and Assarzadegan F, et al. [52] found that triglyceride and HDL-c don't differ in migrainous when compared to control groups. While Gruber HJ, et al. [53] showed that triglyceride-rich lipoprotein cholesterol is higher in migrainous. Other studies showed controversial results such as Monastero et al. who found a strong association between LDL-c and total cholesterol in migrainous [54], while Pamela MR, et al. [55] and Saberi A, et al. [56] showed a strong association between total cholesterol, and triglyceride in patients with migraine [55,56]. However, Saberi A, et al. [56], Scher AI, et al. [57], and Winsvold BS, et al. [58] showed lower HDL-c in migrainous. A cohort study of 5087 women showed a significant increase in total cholesterol and non-HDL-c in migrainous when compared to control [59].

It is believed nowadays that migraine is a neurometabolic disorder [4]. The abnormal lipid metabolism in migrainous may be attributed to abnormal carnitine shuttle [14], or the low omega 3 fatty acids in migraine men [14]. It has been suggested that carnitine palmitoyl transferase 1 and 2 are insufficient in migraine patients [14], and four lipid metabolites from four lipid classes significantly differed between migrainous and control [14]. While Gocke N, et al. [60] showed that hypertriglyceridemia is associated with peripheral arterial vasodilatation. The mitochondrial dysfunction in migraine men may lead to the loss of energy production, fatty acid accumulation, excess reactive oxygen species, and shift in glucose metabolism [61], therefore, a high-fat diet and low-carbohydrate ketogenic diet have been proposed for migraine patients [62] to overcome the low cellular energy in the brain of migraine patients [3].

Upon supplement intake serum total cholesterol and HDL-c are significantly decreased with a concomitant decrease in the frequency of the numbers of migraine attacks at p-values 0.049, 0.013 and < 0.001 respectively (Table 2). It has been found that acetyl-l-carnitine regulates blood lipids and reduces total cholesterol, triglyceride, and LDL in rats fed on a high-fat diet, while normal rats showed no effects on total cholesterol, triglyceride, and LDL-c after acetyl-carnitine administration [63]. On the other hand, omega 3 PUFA can increase large HDL-c, reduce small HDL-c, and improve HDL-c functionality by changing lipid antioxidant and enzyme composition [64]. The review of Khorshidi M, et al. [65] revealed that omega 3 PUFA has no effect on total cholesterol, HDL-c and LDL-c but can decrease triglyceride in

hypertriglyceridemic individuals [65] and the effect of omega 3 PUFA on HDL-c requires a longer duration.

A recent study suggested that the intensity and frequency of migraine attacks may be related to blood lipids [52], which is in agreement with the result of this study that the number of migraine attacks has decreased with the decrease of total cholesterol. There are major differences in lipid metabolism in migraine patients when compared to healthy control [14,66], especially since 29 metabolites of lipid significantly differed in migrainous, and a large-scale plasma metabolic analysis reveals that there is a big alteration in HDL metabolism in migrainous [67]. The specific HDL function is altered in migrainous with decreased free cholesterol to total lipid ratio in small HDL [67]. the function of HDL in atheroprotection is not reflected by the amount of cholesterol in HDL [67]. The HDL-c in migrainous showed a decrease in lipoprotein A1 and free cholesterol to lipid ratio in the small HDL-c [61] and there is a change in HDL-c metabolism in migrainous [39]. The decrease of HDL-c after supplement combination intake in this study (Table 2) may be related to the effect of omega 3 PUFA on HDL. It is reported that omega 3 PUFA increase the functionality of HDL, increases large HDL, and decreases small HDL and non-esterified fatty acid in HDL [64]. Also, omega 3 may improve cholesterol transfer from HDL [64], which may explain the decrease in HDL-c in this study. However, small and large HDL have not been measured in this study.

This study revealed that total bilirubin, direct bilirubin and indirect bilirubin showed no significant differences between the control group and migrainous before supplement intake (Table 1) and no significant differences between migrainous before and after supplement intake (Table 2). It is reported that migrainous have elevated total bilirubin [51], while other studies showed that total, direct and indirect bilirubin are lower in migrainous children and adolescents than non-migrainous [68,69]. The higher bilirubin studies considered that biliary tract disorders are accompanied by toxic metabolite formation that precipitates in the brain of migrainous [51], while the studies involved lower bilirubin in migrainous considered that bilirubin is an antioxidant substance [70,71] and the decreased level is related to its overconsumption in neurogenic inflammation [68]. This study showed insignificant differences in total, direct, and indirect bilirubin which may be related to the small sample size of migrainous and control groups.

This study revealed that uric acid showed no significant differences (Table1, and Table 2), although the mean was lower in migrainous than control (Table 1), and tended to increase in migrainous after supplement intake (Table 2). Uric acid is a powerful antioxidant and the increase of serum uric acid within normal levels is related to decreased neuroinflammation and tissue damage [72,73]. The result of this study is consistent with the result of Altunkaynak Y, et al. [74] who found no significant difference in uric acid levels between migrainous in a period of free migraine attack and control but the value of uric acid in control was lower than migrainous. While the study of Yang Z, et al. [75] showed that serum uric acid is significantly lower in migrainous when compared to control. The insignificant difference may related to the low sample size in this study. However, the migrainous after the supplement showed an increase in the mean uric acid level but remained insignificant; this may be due to the effect of omega 3 PUFA and vitamin E in decreasing oxidative stress and decreasing utilization of uric acid as an antioxidant substance.

Concerning electrolytes, sodium and potassium ion homeostasis may have a role in migraine pathophysiology [76]. As sodium level in cerebrospinal fluid is increased during a migraine attack [77], while thirst symptom is highly found before migraine attack in patients with highly frequent attack [78]. In addition, comorbidities such as hypertension, and chronic kidney disease are frequently found in migraine patients [79]. The altered brain electrolyte homeostasis in migraine patients is due to disturbances of Na-K-ATPase [80].

The sodium level in this study showed that migraine males before the intake of the supplement had insignificant lower plasma sodium than the control group (Table 1). This may be attributed to the lower intake of dietary sodium in migraine males than control group. Pogoda et al. found that migrainous exhibit less dietary sodium intake [81]. Another explanation for lower though not significant sodium levels is that those patients exhibit natriuresis after an attack [82]. However, supplement intake did not affect serum sodium significantly (Table 2).

In this study, migraine patients showed insignificant higher potassium levels than the control group (Table 1), but upon intake of the supplement, the potassium level insignificantly decreased (Table 2). This result may be related to that; when intestinal luminal sodium is decreased, potassium intestinal absorption is increased [83], or the increase of potassium level may be attributed to the possible mitochondrial dysfunction found in migraine [84], which results in a decrease of ADP/ATP ratio activating certain channels that increase intracellular calcium and increase extracellular potassium [85]. It has been found that elevated extracellular potassium lead to different disorders including migraine [86,87]. Once cortical potassium concentration reaches 20Mm, will result in the depolarization of neurons and the release of more potassium, vascular tension and a decrease in oxygen supply [88].

Supplement effects in decreasing potassium plasma levels though not significant may not be attributed to the vitamin E effect, as it is reported that vitamin E has no effect on potassium levels in hypercholestemic individuals [89], but omega 3 PUFA can decrease potassium levels [90,91]. The proposed mechanism may be related to omega 3 PUFA's effect on mitochondrial function through increased mitochondrial respiration and increased ADP sensitivity [92].

Moreover, migraine patients in this study showed no difference in chloride plasma level when compared to the control group (Table 1), but upon intake of omega-3 PUFA, vitamin E, and acetylcarnitine supplement, migrainous showed chloride decrease at a p-value of 0.055 (Table 2). This decrease may be attributed to the effect of vitamin E [89] or to the effect of polyunsaturated fatty acid on muscarinic activity which leads to increased secretion of chloride to the intestinal lumen [93].

The study revealed that serum magnesium is lower in migrainous patients before supplement intake when compared to the control (Table 1). The average serum magnesium in control was 2.32 mg/dl, while the in the migraine was 2.18, the difference was insignificant at a p-value of 0.07. upon supplement intake, the serum magnesium level increases in migrainous to reach an average level of 2.23 mg/dl, this increase is insignificant at a p-value of 0.379. magnesium is very important for migraines, Karim MR, et al. [94] found that serum magnesium is lower in migrainous [94], while Talebi M, et al. [95] revealed that serum magnesium is related to the frequency of migraine attacks.[95] Salvin et al. showed that magnesium intake is associated with lower magnesium attack [96].

The low serum magnesium may enhance glutamic neurotransmission, excitotoxicity, and oxidative stress [97], moreover, reduce nociceptive sensation and increase headache. The increase in magnesium improves mitochondrial dysfunction, reduces oxidative stress and increases brain energy production [98]. The insignificant lower magnesium level in migrainous may be related to the small sample size. However, serum magnesium does not reflect its concentration inside cells [99]. The suggested increase in serum magnesium level after supplement intake in migrainous though not significant may be related to the effect of omega 3 PUFA, and acetylcarnitine in enhancing mitochondrial respiration and increasing ATP production, which increases magnesium extrusion from cells [100].

Conclusion

Combined supplementation of acetylcarnitine, omega-3 PUFA, and vitamin E to migraine men may have the ability to decrease the number of migraine attacks due to their effect on mitochondrial and cellular metabolism and increased energy production. Also, it is found that these supplements decrease total serum cholesterol and HDL-c. However, the metabolism of lipids is different in migrainous from healthy individuals according to different studies, and the effect of this supplement may affect the functionality of HDL lipoprotein as the measurement of cholesterol in HDL is not a measurement of HDL functionality. Also, this study revealed that migrainous have abnormal lipids when compared to control concerning total serum cholesterol, non-HDL-cholesterol and total cholesterol/HDL-c ratio. Serotonin and other parameters showed insignificant changes after supplement intake.

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Conflict of Interest

The author declares there is no conflict of interest.

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