J Biochem Tech (2019) 10(1): 67-71
ISSN: 0974-2328

The Correlation between Migraine and some Biochemical Parameters in Saudi Females

Shouq A. Alshehri, Foziah A. Alshubaily*, Anbrah A. Alzubidi, Hala S. Sonbol, Sawsan A. Rahimuddin, Ebtihaj J. Jambi

Received: 14 November 2018 / Received in revised form: 05 March 2019, Accepted: 10 March 2019, Published online: 23 March 2019

Abstract

Migraine is a common disabling primary headache disorder. It affects 6% of men and 18% of women worldwide and 12.1% in Saudi Arabia. The lack of many nutrients like vitamin B_{12} and magnesium is associated with migraine. Migraine may be socicated with cardiovascular risk factors such as a high level of cholesterol. Ninety-one Saudi female patients with a mean age of 32.91±1.187 and fifty-four healthy Saudi females (control) with a mean age of 30.00±1.32 years participated in this study. Serum lipid profile, vitamin B_{12}, and magnesium levels were measured in both patients and controls. The results showed a significant increase in serum cholesterol and low-density lipoprotein (LDL), and lower levels of high-density lipoprotein (HDL) for migraine patients. However, no significant difference has been observed in triglyceride serum levels. No significant differences were found in vitamin B_{12} and magnesium (Mg) serum levels between the two groups (migraine patients and control). In conclusion, lipid profile was shown to be associated with Saudi female patients with migraine. Vitamin B_{12} serum levels and mg serum levels were not significantly correlated in migraine patientsand controls.

Keywords: Headache, migraine, vitamin B12, magnesium, lipid profile.

Introduction

Migraine is a common multifactorial brain disorder described by recurrent, disabling attacks of moderate to a severe headache lasting for 4–72 hours (Chua, Del Rio, and Silberstein, 2017) and is accompanied by nausea and hypersensitivity to light (photophobia) or sound (phonophobia) or odors (osmophobia) (Green, 2013; Dodick, 2018). The main types of migraine are: migraine with aura, migraine without aura and chronic migraine (Society, H.C.C.o.t.I.H, 2013). Migraine affects 12.1% in Saudi population (Rajeh et al., 1997; Benamer, Deleu and Grosset, 2010) and 11-12% of adults in the world population (Younger, 2016; Lipton et al., 2007). Females are about twice as likely to suffer from migraine as males because of hormonal effects (Lipton et al., 2001; Morillo, 2004). The prevalence of migraine is highest in ages from 25 - 55 years old (the most productive years) (Winter et al., 2012). Dietary and lifestyle habits, along with some biochemical parameters can affect the intensity of migraine such as: vitamin B_{12}, lipid profile and magnesium (Monastero et al., 2008; Reynolds, 2006; Bianchi et l., 2004; Nattagh-Eshtivani et al., 2018). Vitamin B_{12} is an important vitamin for many body functions including brain health and prevention of disorders of central nervous system (CNS) development (Reynolds, 2006). Vitamin B_{12} works as a coenzyme for a critical methyl transfer reaction that transforms homocysteine to methionine (Intakes, I.o.M.S.C.o.t.S.E.o.D.R, 1998). Vitamin B_{12} pathway dysfunction is related to migraine pathogenesis (Gabriel et al., 1992).

Increased cholesterol and free fatty acids blood levels are among the remarkable factors implicated in triggering migraine headache (Bic et al., 1999; Ferrara et al., 2015). Migraine is linked with high risk of cardiovascular disorders which are associated with cholesterol levels (Kurth et al., 2006; Linstra et al., 2017). High total cholesterol, low-density lipoprotein and triglyceride correlate with migraine with aura (Rist, Tzourio and Kurth, 2011).

Magnesium (Mg, the most abundant mineral in the body) works as a cofactor for many enzymatic reactions (Swaminathan, 2003). Lack of magnesium is more prevalent in migraine patients than in non-migraine patients (Mauskop and Varughese, 2012). Magnesium insufficiency may affect calcium channel and neuroinflammation, leading to an increased susceptibility to migraine (Taylor, 2011). There were many studies that showed the prevention of migraine by magnesium intake (Mauskop and Varughese, 2012; Grazzi et al., 2007; Wang et al., 2003).

Migraine is the most significant primary headache disorder because of its high occurrence and the inability that it causes (Chua, Del Rio, and Silberstein, 2017). Understanding the relationship among nutrients and migraine, lead to accurate diagnosis and decrease in the cost-effectiveness of migraine treatment (MacGregor, 2016). This study aims to investigate the correlation between migraine and some biochemical parameters in Saudi females, which could be an important factor that affect migraine as the previous studies on migraine were limited in Saudi Arabia population (Benamer, Deleu, and Grosset, 2010).

Shouq A. Alshehri, Foziah A. Alshubaily*, Anbrah A. Alzubidi, Hala S. Sonbol, Sawsan A. Rahimuddin, Ebtihaj J. Jambi

Biochemistry Department, Faculty of science, King Abdulaziz University, Saudi Arabia.

***Email:** falshibli @ kau.edu.sa

Materials and Methods

A. Study participants

Ninety-one adult Saudi females (19 - 65 years) suffering from migraine were enrolled in this study. This study was performed in Jeddah, Saudi Arabia, between January and May 2018. The participants were from the neurology clinic at King Abdulaziz University Hospital (KAUH) who have been diagnosed with migraine. The aim of the study was described to the participants and they joined the study conscious and with voluntary participation through signing of an informed consent. An interview with the patients was performed to evaluate the demographic factors including age, marital status, the common symptoms of headache and duration. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). For obesity, we considered BMI 30.0 kg/m^2 or above and below 25.0-29.9 kg/m^2 considered overweight according to World Health Organization (WHO). Control subjects consisted of 54 females with an average age ranging between 19-55 years. Most of the subjects were not taking any medication and did not suffer from any chronic diseases. This work was performed under the approval of the ethical committee of King Abdulaziz University Hospital in Jeddah (Reference number 453-16).

B. Blood collection

Blood samples were obtained after a 10-12 hour overnight fasting period. They were processed and centrifuged at 4500 rpm. Serum was stored at −80°C until analysis. Measurements of samples were done in the biochemical laboratory at King Abdulaziz University Hospital. Vitamin B_{12} was measured using Cobas machine (Roche Diagnostics GmbH; Mannheim, USA) while lipid profile and magnesium were assessed automatically in the chemistry lab of the hospital by using SIMENS (Dimension Vista 1500 System USA).

C. Statistical analysis

The analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 21. We used independent-sample t-test to compare between the two groups; patients and control. A p-value of < 0.05 was considered statistically significant.

Results

The study group consisted of 91 migraine patients and 54 subjects as control. The mean age of patients was (32.91 ± 1.187), the youngest being 19 years and the eldest 58 years; 46.7% were single, 46.7% were married and 6% were divorced. The clinical characteristics of the study population are presented in table 1. There is a significant difference in the body mass index (BMI) between the two groups (P < 0.05). The most common symptoms accompanying migraine headache were photophobia (71 people; 78.9%) and nausea (66 people; 73.3%) as shown in table 2. Each patient may have more than one accompanying symptom. The frequency of symptoms of migraine patients is presented in table 2.

The results of vitamin B_{12} serum measurements of migraine patients compared to control have no significant differences. Magnesium serum mean values show no significant difference between migraine patients and control. The patient group had significantly higher serum levels of cholesterol (4.91 ± 0.098 vs. 4.45 ± 0.092 mmol/L, p< 0.05) and LDL (2.88 ± 0.083 vs. 2.58 ± 0.077 mmol/L, p< 0.05). However, lower high-density lipoprotein (HDL) serum levels (1.43 ± 0.352 vs. 1.66 ± 0.055 mmol/L, p< 0.05) were observed in migraine patients. There was no significant difference in triglyceride (TG) levels in both groups. All parameter results are presented in table 3. The comparison of obese and normal weight migraine patients with obese and normal weight controls showed a significant difference in cholesterol, LDL and HDL. A significantly increase in cholesterol in normal weight group (BMI 18.6-24.9) was found as shown in Figure 1.

Table 1. Clinical characteristics of the study population

Parameters	Groups	Mean ± SEM	*P* value
Age (years)	Patients n=91) Control(n=54)	32.91 ± 1.187 30.00 ± 1.320	0.117
Height (cm)	Patients (n=91) Control (n=54)	156.57 ± 0.669 158.94 ± 0.729	0.035
Weight (kg)	Patients (n=91) Control (n=54)	65.34 ± 2.098 60.04 ± 1.417	0.113
BMI	Patients (n=91) Control (n=54)	25.62 ± 0.541 23.67 ± 0.527	0.019

Table 2. Frequency of symptoms of migraine patients

Symptoms	Number	Percentage
Photophobia	71	78.9%
Phonophobia	61	67.8%
Osmophobia	31	34.4%
Nausea	66	73.3%
Vomiting	27	30.0%

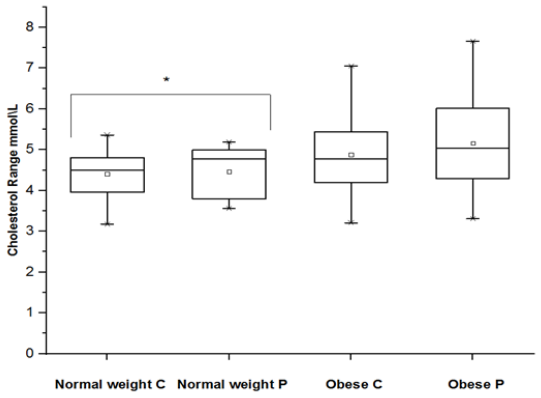

Figure 1. Comparison of cholesterol values between normal weight controls and patients, and between obese controls and patients. * P<0.05, C=control, P= patients.

Table 3. Mean levels of lipid profile, vitamin B_{12} and Mg in patients and control

Parameters	Patients	Control	*P* value

Vitamin B_{12} (156 – 672pmol/L) Mean± SEM	254.90 ± 13.140	258.46 ± 15.491	0.663
Mg (0.74 – 0.99mmol/L) Mean± SEM	0.834 ± 0.009	0.823 ± 0.010	0.736
Cholesterol (0.0 – 5.18mmol/L) Mean± SEM	4.91 ± 0.098	4.45 ± 0.092	0.003
TG (0.3 – 2.3mmol/L) Mean± SEM	0.94 ± 0.054	0.82± 0.048	0.165
LDL (0.0 – 3.57mmol/L) Mean± SEM	2.88 ± 0.083	2.58 ± 0.077	0.018
HDL (0.9 – 1.55mmol/L) Mean± SEM	1.43 ± 0.352	1.66 ± 0.055	0.000

*Mg: magnesium, TG: triglycerides, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

*values betweenbrackets indicates the normal range of the parameter.

Discussion

Migraine is a long-lasting and disabling disorder that has an effect on migraineurs and society (Leonardi et al., 2005). However, migraine pathophysiology is not completely clear (Faraji, Paknahad and Chitsaz 2018). Since migraine is a multifactorial disease (Kowalska et al., 2017), many modifying factors are involved in its progression. These factors include genes, lifestyle and biochemical markers (Dodick, 2018). Migraine is associated with high body mass index (BMI) (Bigal et al., 2006). In this study, the mean of BMI of the patients is higher than control, and was considered overweight (25 to 29.9). Bigal and Lipton (Bigal et al., 2006) found that increased BMI was linked to an increased prevalence of migraine about 1.2% in overweight subjects. This could be due to some preventive treatments of migraine, that are often linked with weight gain (Diener et al., 2003). In addition, there are many mechanisms that explain the connection between obesity and migraine (Hamed, 2009). The overweight subjects that consumed a higher fat diet, had a high secretion of Calcitonin Gene-Related Peptide (CGRP) (Zelissen et al., 1991). CGRP is a neuropeptide in the brain released from activated trigeminal sensory nerves. It is a postsynaptic mediator of trigeminovascular inflammation which increase headache susceptibility (Lassen et al., 2002).

In our study the migraine patients in the normal weight range showed significantly increased cholesterol, increased LDL and decreased HDL levels compared to controls with similar weight. Gruber et al. found similar results of normal weight patients and suggests that migraine is linked with an increased risk for cardiovascular disease (Gruber et al., 2010). There is a study which found a significant increased cholesterol and LDL levels of migraine patients compared with non-migraineurs controls (Gruber et al., 2010). Monastero et al, (2008) found a relationship between lipid levels in blood and migraine patients, specifically increased total cholesterol in subjects aged ≥50 years. Winsvold et al, (2011) found an association between migraine and low levels of total HDL. Studies show that HDL has anti-inflammatory properties that may probably alter the perception of pain (Bigal et al., 2009; Navab et al., 2007). Triglycerides levels were increased in obese migraineurs (Gruber et al., 2010). This study results were on line with above-mentioned studies. In our study a significant increase in cholesterol, LDL and a significant decrease in HDL were observed in migraine group comparing with control group.

Vitamin B_{12} has essential roles in CNS function, particularly the methionine-synthase mediated conversion of homocysteine to methionine (Reynolds, 2006). Many studies have shown an association between homocysteine level and migraine (Moschiano et al., 2008; Isobe and Terayama, 2010; Lippi et al., 2014). Decreased serum levels of vitamin B_{12}, folate and B_6 are associated with elevation of the homocysteine level in blood (Lippi et al., 2014). As a result, plasma homocysteine level may be decreased by folic acid supplementation (Pizza et al., 2013). Raised homocysteine level in the brain may increase negative electrophysiological hyperactivity, which may lead to migraine (Lippi et al., 2014). Also, homocysteine may increase oxidative stress by preventing the action of key antioxidant enzymes, like extracellular superoxide dismutase, which in turn is associated with migraine (Yamamoto, Hara, and Adachi, 2000). Lea et al, (Maizels, Blumenfeld, and Burchette, 2004) found that vitamin supplementations (2 mg of folic acid, 25 mg of vitamin B_6, and 400 μg of vitamin B_{12}) significantly reduce the prevalence of migraine disability. Another study conducted on Australian females suffering from migraine with aura showed that vitamins B_6, B_9, and B_{12} supplementation increase homocysteine levels and reduce the severity of migraine headache and disability among migraine patients and controls (Menon et al., 2012). In this study, there is a slight increase in vitamin B_{12} of control group (not significant) but is not compatible with the results of the previous studies. This may be due to that 10.9% of patients take B_{12} supplements and 16.7% of patients take multivitamins which may affect this study results, while in the above studies used to reduce the migraine attacks.

Magnesium has numerous functions in the human body. These functions are involved in intracellular energy storage, working as a cofactor in many enzymes, regulating ion channels and receptors as well as working in the transport system (Nattagh-Eshtivani et al., 2018). The importance of magnesium in the pathogenesis of migraine has been significant in several studies. Low levels of magnesium has been linked with cortical spreading depression (CSD) (Strong et al., 2002), neurotransmitter release (Coan and Collingridge, 1985), platelet cohesion (Baudouin-Legros, Dard and Guicheney, 1986), and vasoconstriction (Altura and Altura, 1980). Tarighat et al, (Esfanjani et al., 2012) found that magnesium supplementation minimize the severity and frequency of migraine attacks after consuming 500 mg/day of magnesium. Bigal et al, (2002) found that magnesium in 1g/day intravenous (IV) intake relieved pain and improved symptoms in 180 patients. In this study we did not find any statistically significant difference between patient and control groups regarding magnesium. We have measured the magnesium serum for patients while they were not having an active headache attack. A study showed decreased magnesium level during migraine attack in 50% of migraine patients (Mauskop and Altura, 1998). Masoud (2003) found a

significant difference between serum Mg levels during attacks, but after the migraine attack, the magnesium serum level was increased. Also, 16.7% of the patients were using multivitamins and 4.4% were taking magnesium supplementation which may affect this study results.

Conclusion

In conclusion, this study demonstrated elevated levels of serum cholesterol and LDL with low levels of HDL in Saudi females migraineurs. The monitoring of fat in diet and lipid profile may reduce the migraine attacks. Vitamin B_{12} serum levels and magnesium serum levels were not significantly different in migraineurs from those without migraine. Further investigations for a larger population sample may be required.

References

Altura, B.T. and B.M. Altura, Withdrawal of magnesium causes vasospasm while elevated magnesium produces relaxation of tone in cerebral arteries. Neuroscience letters, 1980. 20(3): p. 323-327.

Baudouin-Legros, M., B. Dard, and P. Guicheney, Hyperreactivity of platelets from spontaneously hypertensive rats. Role of external magnesium. Hypertension, 1986. 8(8): p. 694-699.

Benamer, H.T., D. Deleu, and D. Grosset, Epidemiology of headache in Arab countries. The journal of headache and pain, 2010. 11(1): p. 1.

Bianchi, A., et al., Role of magnesium, coenzyme Q10, riboflavin, and vitamin B12 in migraine prophylaxis. 2004.

Bic, Z., et al., The influence of a low-fat diet on incidence and severity of migraine headaches. Journal of women's health & gender-based medicine, 1999. 8(5): p. 623-630.

Bigal, M., et al., Headache Prevention Outcome and Body Mass Index. Cephalalgia, 2006. 26(4): p. 445-450.

Bigal, M., et al., Intravenous Magnesium Sulphate in the Acute Treatment of Migraine Without Aura and Migraine with Aura. A Randomized, Double-Blind, Placebo-Controlled Study. Cephalalgia, 2002. 22(5): p. 345-353.

Bigal, M.E., et al., Migraine and cardiovascular disease. Possible mechanisms of interaction, 2009. 72(21): p. 1864-1871.

Chua, A.L., M.S. Del Rio, and S. Silberstein, Migraine☆, in Reference Module in Neuroscience and Biobehavioral Psychology. 2017, Elsevier.

Coan, E. and G. Collingridge, Magnesium ions block an N-methyl-D-aspartate receptor-mediated component of synaptic transmission in rat hippocampus. Neuroscience letters, 1985. 53(1): p. 21-26.

Diener, H.-c., et al., Topiramate in migraine prophylaxis: results from a placebo-controlled trial including an active comparator-propranolol. Cephalalgia, 2003. 23(7): p. 691.

Dodick, D.W., Migraine. The Lancet, 2018.

Esfanjani, A.T., et al., The effects of magnesium, l-carnitine, and concurrent magnesium–l-carnitine supplementation in migraine prophylaxis. Biological trace element research, 2012. 150(1-3): p. 42-48.

Faraji, H., Z. Paknahad, and A. Chitsaz, Dietary intake of thiamine in migraine patients and healthy subjects: a case-control study. Clinical nutrition research, 2018. 7(1): p. 40-47.

Ferrara, L.A., et al., Low-lipid diet reduces frequency and severity of acute migraine attacks. Nutrition, Metabolism and Cardiovascular Diseases, 2015. 25(4): p. 370-375.

Gabriel, S., et al., Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Commentary. Annals of internal medicine, 1992. 116.

Grazzi, L., et al., Magnesium as a preventive treatment for paediatric episodic tension-type headache: results at 1-year follow-up. Neurological Sciences, 2007. 28(3): p. 148-150.

Green, M.W., Migraine, in The Neuropsychiatry of Headache: M.W. Green and P.R. Muskin, Editors. 2013, Cambridge University Press: Cambridge.

Gruber, H.J., et al., Lipid profile in normal weight migraineurs–evidence for cardiovascular risk. European journal of neurology, 2010. 17(3): p. 419-425.

Hamed, S.A., The vascular risk associations with migraine: relation to migraine susceptibility and progression. Atherosclerosis, 2009. 205(1): p. 15-22.

Intakes, I.o.M.S.C.o.t.S.E.o.D.R., Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. 1998: National Academies Press (US).

Isobe, C. and Y. Terayama, A remarkable increase in total homocysteine concentrations in the CSF of migraine patients with aura. Headache: The Journal of Head and Face Pain, 2010. 50(10): p. 1561-1569.

Jabbar, M.A. and A. Ogunniyi, Sociodemographic factors and primary headache syndromes in a Saudi community. Neuroepidemiology, 1997. 16(1): p. 48-52.

Kowalska, M., et al., Migraine and Risk Factors of Vascular Diseases, in Ischemic Stroke of Brain. 2017, IntechOpen.

Kurth, T., et al., Migraine and risk of cardiovascular disease in women. Jama, 2006. 296(3): p. 283-291.

Lassen, L., et al., CGRP may play a causative role in migraine. Cephalalgia, 2002. 22(1): p. 54-61.

Leonardi, M., et al., The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). The journal of headache and pain, 2005. 6(6): p. 429.

Linstra, K.M., et al., Migraine and cardiovascular disease in women. Maturitas, 2017. 97: p. 28-31.

Lippi, G., et al., Homocysteine and migraine. A narrative review. Clinica Chimica Acta, 2014. 433: p. 5-11.

Lipton, R.B., et al., Migraine prevalence, disease burden, and the need for preventive therapy. Neurology, 2007. 68(5): p. 343-349.

Lipton, R.B., et al., Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache: The Journal of Head and Face Pain, 2001. 41(7): p. 646-657.

MacGregor, E.A., Diagnosing migraine. J Fam Plann Reprod Health Care, 2016. 42(4): p. 280-286.

Maizels, M., A. Blumenfeld, and R. Burchette, A combination of riboflavin, magnesium, and feverfew for migraine

prophylaxis: a randomized trial. Headache: The Journal of Head and Face Pain, 2004. 44(9): p. 885-890.

Masoud, A., A study on relation between attacks of migraine headache and serum-magnesium level. Iranian Journal of Public Health, 2003. 32(4): p. 27-30.

Mauskop, A. and B.M. Altura, Role of magnesium in the pathogenesis and treatment of migraines. Clin Neurosci, 1998. 5(1): p. 24-7.

Mauskop, A. and J. Varughese, Why all migraine patients should be treated with magnesium. Journal of neural transmission, 2012. 119(5): p. 575-579.

Menon, S., et al., Genotypes of the MTHFR C677T and MTRR A66G genes act independently to reduce migraine disability in response to vitamin supplementation. Pharmacogenetics and genomics, 2012. 22(10): p. 741-749.

Monastero, R., et al., Association between plasma lipid levels and migraine in subjects aged ≥50 years: preliminary data from the Zabùt Aging Project. Neurological Sciences, 2008. 29(1): p. 179-181.

Monastero, R., et al., Association between plasma lipid levels and migraine in subjects aged≥ 50 years: preliminary data from the Zabùt Aging Project. Neurological Sciences, 2008. 29(1): p. 179-181.

Morillo, L.E., Migraine headache in adults. Clinical evidence, 2004. 2004.

Moschiano, F., et al., Homocysteine plasma levels in patients with migraine with aura. Neurological Sciences, 2008. 29(1): p. 173-175.

Nattagh-Eshtivani, E., et al., The role of nutrients in the pathogenesis and treatment of migraine headaches: Review. Biomedicine & Pharmacotherapy, 2018. 102: p. 317-325.

Navab, M., et al., High-density lipoprotein: Antioxidant and anti-inflammatory properties. Current Atherosclerosis Reports, 2007. 9(3): p. 244-248.

Pizza, V., et al., The role of homocysteine in the pathogenesis of migrane. Curr Nerubiol, 2013. 4: p. 19-24.

Rajeh, S.A., et al., The prevalence of migraine and tension headache in Saudi Arabia: a community-based study. European Journal of Neurology, 1997. 4(5): p. 502-506.

Reynolds, E., Vitamin B12, folic acid, and the nervous system. The lancet neurology, 2006. 5(11): p. 949-960.

Rist, P.M., C. Tzourio, and T. Kurth, Associations between lipid levels and migraine: cross-sectional analysis in the epidemiology of vascular ageing study. Cephalalgia, 2011. 31(14): p. 1459-1465.

Society, H.C.C.o.t.I.H., The international classification of headache disorders, (beta version). Cephalalgia, 2013. 33(9): p. 629-808.

Strong, A.J., et al., Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke, 2002. 33(12): p. 2738-2743.

Swaminathan, R., Magnesium metabolism and its disorders. Clin Biochem Rev, 2003. 24(2): p. 47-66.

Taylor, F.R., Nutraceuticals and Headache: The Biological Basis. Headache: The Journal of Head and Face Pain, 2011. 51(3): p. 484-501.

Wang, F., et al., Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache: The Journal of Head and Face Pain, 2003. 43(6): p. 601-610.

Winsvold, B., et al., Headache, migraine and cardiovascular risk factors: the HUNT study. European journal of neurology, 2011. 18(3): p. 504-511.

Winter, A.C., et al., Associations of socioeconomic status with migraine and non-migraine headache. Cephalalgia, 2012. 32(2): p. 159-170.

Yamamoto, M., H. Hara, and T. Adachi, Effects of homocysteine on the binding of extracellular-superoxide dismutase to the endothelial cell surface. FEBS Letters, 2000. 486(2): p. 159-162.

Younger, D.S., Epidemiology of Migraine. Neurologic Clinics, 2016. 34(4): p. 849-861.

Zelissen, P.M., et al., Calcitonin gene-related peptide in human obesity. Peptides, 1991. 12(4): p. 861-863.