Relation between serum magnesium level and migraine attacks

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ABSTRACT

الأهداف: تقييم مستويات المغنيسيوم في مصل الدم لدى المرضى المصابين بالشقيقة.

الطريقة: أُجريت هذه الدراسة المقارنة في جامعة تبريز للعلوم الطبية، تبريز، إيران، واستمرت خلال الفترة من يناير 2007م إلى ديسمبر 2007م. شملت الدراسة 140 مريضاً مصاباً بالشقيقة (مجموعة الدراسة)، و140 من الأصحاء الذين لم يكونوا يعانون من الصداع، أو أي من اضطرابات الكلى، أو الاضطرابات المعدية المعوية، أو لم يقوموا باستهلاك أي من مكملات المغنيسيوم. ولقد قمنا بفحص مستويات المغنيسيوم في كلتي المجموعتين، وعمل مقارنة فيما بينهما.

النتائج: لقد ضمت هذه الدراسة 140 مصاباً بالشقيقة (22 ذكراً، و118 أنثى) ويبلغ متوسط أعمارهم 33.82±10.31 عاماً، بالإضافة إلى 140 من الأصحاء (26 ذكراً، و114 أنثى) ويبلغ متوسط أعمارهم 34.19±9.95 عاماً. لقد كان 40 مريضاً في مجموعة الدراسة يعاني من الومضات، فيما لم يعاني 100 مريض من هذه الومضات. وأشارت نتائج الدراسة إلى أن مستويات المغنيسيوم لدى مجموعة الدراسة (26.14±4.3) كانت أقل بكثير من مستويات المغنيسيوم لدى مجموعة الشاهد (31.09±4.32) (p=0.000). ولم يكن هناك اختلافاً واضحاً في مستويات المغنيسيوم بين المرضى المصابين بالومضات والمرضى الغير مصابين بالومضات، غير أنه كان هناك علاقة خطية واضحة من الناحية الإحصائية بين نسبة المغنيسيوم في مصل الدم ونسبة تكرر الصداع.

خاتمة: أظهرت الدراسة تدني مستويات المغنيسيوم في مجموعة المرضى المصابين بالشقيقة مقارنةً مع مجموعة الأصحاء، بالإضافة إلى ارتباط تدني مستويات هذا العنصر بنسبة تكرر آلام المرض. ولهذا فإن موازنة مستويات هذا العنصر في الدم، والمحافظة على ثباتها يساعد على الوقاية من مرض الشقيقة، وعلاجه في حال الإصابة به.

Objectives: The determination of serum magnesium levels in migraine.

Methods: In a case control study performed between January 2007 and December 2007 at Tabriz University of Medical Sciences, Tabriz, Iran, 140 migraine patients were enrolled and their level of serum magnesium was determined and the results were compared with 140 healthy people who did not have any headache, kidney, or gastrointestinal disorders, and no consumption of magnesium complements.

Results: Migraine patients (22 male, 118 female) with a mean age of 33.82±10.31 and 140 healthy people (26 male, 114 female) with a mean age of (34.19±9.95) were enrolled. Forty patients had aura and 100 patients did not have aura. The average serum magnesium level in the patient group (26.14±4.3) was significantly lower than the control (31.09±4.32) group (p=0.000). There was no significant difference between the mean level of serum magnesium in patients with migraine with aura and without aura, however, there was a significant linear relationship between the amount of serum magnesium and the frequency of headache.

Conclusion: Serum magnesium in migraine patients was significantly lower than the normal population and related to the frequency of migraine attacks, supporting the use of magnesium in prevention and treatment of migraine.

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Migraine is a neurological syndrome that can be accompanied by functional disorders. The prevalence of this disease in women is 3-18%, and

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in men is 4-6%. Migraine attacks are of 2 types: migraine with aura and migraine without aura. The main pathogenesis of migraine is still not clear. Fifteen years of research results indicates that increasing irritability of the brain can cause a migraine. A wide spectrum of factors has been suggested for increased irritability including low magnesium levels of the brain, mitochondrial abnormalities, and dysfunction related to increasing nitric oxide or calcium channels.[1,2] Reducing the magnesium levels can lead to opening of calcium channels, increased intracellular calcium, release of glutamate, and increased extracellular potassium, which finally causes brain depression in migraine.[3] Magnesium deficiency can be associated with stimulation of excitatory neurotransmitters such as acetylcholine and serotonin.[4] This disorder can be primary or secondary to low intracellular free magnesium that is due to systemic free magnesium deficiency. This factor has lead to increased nervous irritability and supports that spreading depression of the brain cortex may explain neurologic manifestations of aura.[3-8] Lack of ionized magnesium can cause mitochondrial oxidative phosphorylation disorder and neuronal polarization instability, which is characteristic of migraine disease. Neurons may be more sensitive to the lack of ionized magnesium even if the mitochondrial metabolic defect is primary. In patients with migraine, low ionized magnesium has been reported in serum, saliva, erythrocytes, and blood mono nuclear cells (which have the highest tissue deposits of magnesium). It is also reported that in the occipital lobes of migraine patients cytosolic free magnesium ions and the free energy released by the reaction of adenosine triphosphate hydrolysis were significantly decreased.[8] There are numerous articles on the therapeutic role of magnesium in migraine, but there are few studies on serum magnesium levels in migraine patients.[9-11] Therefore, the purpose of this study was to determine serum magnesium levels in migraine patients in comparison with a healthy control group.

Methods. This case/control study performed between January 2007 to December 2007 was approved by the Local Ethics Committee of the Tabriz University of Medical Sciences. The patients were referred from the Sheykhorraeis Outpatient University Clinic, Tabriz, Iran. One hundred and forty migraine patients were randomly selected among those whose migraine was confirmed according to the International Headache Society criteria.[12] The study objectives were described to the patients and they entered the study consciously and voluntarily. Patients who simultaneously suffered from other types of headache were excluded from the study. The serum magnesium levels of patients were measured using the spectrophotometer atomic absorption technique, and were compared with 140 matched controls that had no headache and were referred for Lab studies for check up or other disease. In both patients and control groups, cases of renal or gastrointestinal disease and those taking magnesium supplements were excluded because of serum magnesium levels disturbance. We used the n = Z2 PQ/d2 formula to determine the study population. The study population was estimated at N=138 according to 10% incidence of migraine and d=0.05 with accuracy of 95%. Blood samples were taken in the migraine free phase. The serum obtained from each sample was diluted to 10 times of rate. Atomic absorption was performed by a spectrophotometer, and the serum magnesium level was measured by the flame chemtech method in ppm, and analyzed in both patients and controls. In the patient group, serum magnesium levels were evaluated according to the number of attacks, duration of headache, migraine type, and the time of headache onset.

The analysis was performed using the Statistical Package for Social Sciences version 12 (SPSS Inc., Chicago, IL, USA). We used T-test to compare between 2 groups, ANOVA and Chi-square for multiple comparisons, and Mann Whitney U-test to review the relationship between qualitative and ordinal variables. A p-value less than 0.05 was considered significant.

Results. One hundred and forty migraine patients including 22 men (15.7%, average age=35.09±8.73) and 118 women (84.3%, average age=33.58±10.59), and 140 individuals as the control group including 26 men (18.5%, average age=35.69±8.20) and 114 women (81.5%, average age=33.58±10.31) entered the study. The average duration of headache onset was 9.14±6.42 years in men, and 6.77±6.09 years in women (p=0.100). Duration of headache onset in migraine patients without aura was 6.11±7.11 years, and in migraine patients with aura was 6.44±7.21 years (p=0.934). The average duration of headache was 15.53±9.74 hours in men, and 13.43±9.79 hours in women (p=0.204). The average frequency of headache was 9.25±10.31 in men and 7.5±5.54 headaches per month in women (p=0.128). The average frequency of migraine headaches without aura was 6.03±6.15 per month, and migraine with aura was 5.5±5.54 headache per month (p=0.908). In 64 patients (9 males and 55 females), there was no specific time for the onset of headaches. The patients' complaints regarding the time of their headaches included: 5 female patients at night, 28 patients (3 men and 25 women) in the afternoon, 33 patients (6 males and 27 females) in the morning, 6 patients (2 males and 4 females) at noon, and 4 patients (2 male and 2 female) in both the morning and the afternoon.

The average magnesium levels were 26.14±4.3 (CI: 25.42-26.86) ppm in migraine patients, and 31.09±4.32 (CI: 30.38-31.82) ppm in the control group (p=0.000).

The changes in the level of serum magnesium in patients and controls are shown in **Figure 1**. There was no difference in mean magnesium levels between male patients (27.18±4.27) and female patients (25.94±4.29) (p=0.216). In the control group, the average magnesium level was 30.52±6.06 in men, and 31.23±3.83 in women (p=0.572). There was no significant difference in average magnesium levels between patients with aura (26.22±4.42), and patients without aura (26.1±4.27) (p=0.881). There was no statistically significant difference between magnesium levels and time of headache onset (p=0.442) and also place of headaches (p=0.150). There was no significant linear relationship between the mean serum magnesium level and age (p=0.656) and also start of headache history (p=0.287). There was a significant linear relationship between mean magnesium level and frequency of headaches (r=0.21, p=0.016) (**Figure 2**).

Discussion. Generally, several factors have been known as the creators of migraine headaches, including emotional factors, environmental factors, and biochemical markers. In recent decades, the decreased serum magnesium levels in patients with migraine and using magnesium in the prevention and treatment of patients has been noticed.[9-11] Several studies have shown the relationship between magnesium metabolism and migraine,[13-15] or premenstrual syndrome[16,17] and the role of magnesium in migraine prophylaxis.[18-26] Magnesium administration has reduced clinical symptoms of migraine in many clinical studies.[27-29] The study by Masoud[9] showed low serum magnesium levels during attacks. However, our study showed an increase of attacks in low serum magnesium level patients, and there was a significant reduction in serum magnesium levels in migraine patients in comparison with healthy subjects (p=0.000). The relationship between frequency of headaches and reduction of serum magnesium level was so evident that when the number of headache attacks was more than 3 times per month the level of serum magnesium showed further reduction in comparison with the number of attacks less than 3 times a month. However, there was no significant relation between the serum magnesium levels and patients' gender, duration of headache, and time of headache onset.

In 2005, Cete et al[27] treated acute migraine attacks with magnesium sulphate and placebo in a double blind study, and the patients treated with magnesium sulphate showed more improvement compared with the control group. There are some studies on the positive role of magnesium in the treatment of children and pregnant women.[21,30] Trauninger et al[30] showed low magnesium levels in 20 migraine patients. Bigal et al[29] treated 180 migraine patients by using magnesium sulphate and concluded that the treatment in patients without aura was not helpful but in patients with aura, it decreased symptoms such as vomiting and photophobia. Rios et al[22] and Durlach et al[31] also reported the positive role of magnesium in the treatment of migraine. In an article on lifestyle changes and nutrition, Taylor[24] pointed out the positive role of magnesium in preventing migraine attacks. In study by Koseoglu et al,[25] oral magnesium citrate supplementation significantly reduced the frequency of migraine attacks in comparison with placebo. Mauskop et al,[17] and Boska et al[14] both reported low levels of magnesium in migraine patients. Prevention of migraine with magnesium is listed in the US headache consortium.[32]

In a study in National Institute of Neurology, Italy, Bussone[15] reported low magnesium levels in migraine patients. Mukherjee et al[10] measured serum magnesium in 116 migraine patients, and the results showed low serum magnesium in a considerable number of these patients. In the present study, the number of migraine

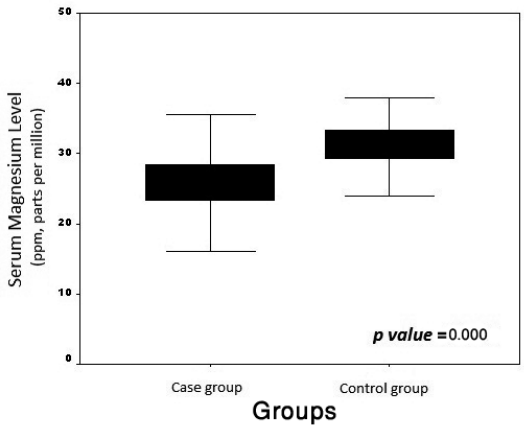

Figure 1 - Serum magnesium level in migraine patients and controls.

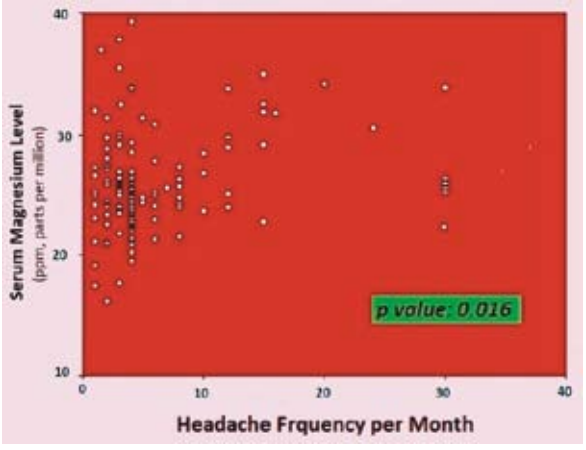

Figure 2 - Relationship between serum magnesium level and frequency of headache.

patients was more than previous studies and we studied patients in 2 groups of migraine, with and without aura. We also considered parameters such as frequency and duration of headache attacks and gender of patients. In the present study, the magnesium serum level was measured only in the headache free period and limited to middle aged patients with female dominance. We would recommend further study of the relation of magnesium in childhood and elderly migraine patients. It would also be interesting to research magnesium fluctuation during the menstrual periods of patients with migraine.

In conclusion, according to the results of the present study and other mentioned studies, the mean serum magnesium levels in migraine patients are significantly less than in normal people, and this demonstrates the role of magnesium deficiency in occurring migraine attacks. In our study, the highest relationship was between low magnesium level and frequency of headaches. Therefore, magnesium is recommended as a prophylactic treatment for patients with migraine. Also, we recommend measuring the magnesium levels in other primary headaches and during active migraine attacks.

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