RISK FACTORS OF HYPOMAGNESEMIA IN PATIENTS WITH ACUTE ISCHEMIC STROKE (AIS): A CROSS SECTIONAL STUDY OF A TERTIARY CARE HOSPITAL, LAHORE PAKISTAN DURING 2015.

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Abstract

Magnesium (Mg^{2+}) has a very important role in maintaining both normal cellular and various body functions. Therefore, magnesium deficiency can pose adverse health effects including strokes. This study was aimed to determine the frequency of hypomagnesaemia in patients with acute ischemic stroke (AIS). A cross-sectional study was carried out over a period of six months from during 2015 at the department of medicine, Services Hospital, Lahore. A total of 110 cases of AIS was included in the study and serum magnesium levels were determined including clinical information. The majority of the patients were between 61-70 years of age (43.6%). The 62 patients (56.4%) were male, and remaining 48 patients (43.6%) were female. The hypomagnesemia was found in 39 patients (35.5%). At the time of admission (at 24 hours) the mean serum Mg^{2+} concentration was found 1.5 mg/dl in acute ischemic patients. Among 39 hypomagnesemia patients, the majority (30%) were of age group 51-60 years. Among hypomagnesemia patients, the majority of the patients were male (38%) and nonsmokers (44%). The majority of hypomagnesemia patients was diagnosed with a history of diabetes (47%) and hypertension (44%). Most of the hypomagnesemia patients (53 %) were from middleclass. The hypomagnesemia patients (27%) were found malnutrition. There existed a significant difference in the following qualitative parameters: cigarette smoking, history of hypertension and malnutrition out of the total hypomagnesemia patients. The frequency of hypomagnesaemia in patients with stroke was 35.5%. Physicians should keep in mind that a high risk of hypomagnesemia exists and there is a need to recommend a Mg therapy.

Introduction

Stroke is a syndrome of rapid onset of focal cerebral deficit lasting greater than 24 hours (Kumar and Clark, 2009). A stroke episode occurs due to the interruption of blood supply in the brain, mostly because of the blockage of blood vessels or any blockage by a clot (Khan *et al.,* 2015). According to world health organization (WHO), it is a major disability worldwide and a 4th leading cause of deaths in U.S. (Lloyd-Jones *et al.,* 2010; Go *et al.,* 2013; Wasay *et al.,* 2014). South Asia has a high mortality rate > 40% (Khatri and Ismail, 2011). In Pakistan, the annual incidence is 250/100,000 with an estimate of 350,000 new cases per year (Mahmood *et al.,* 2013; Khan *et al.,* 2015). Incidence and case fatality are the two main determinants on which prevalence of stroke survivors depends. For example, in Nigeria, the prevalence is 58/100,000 to 400/100,000 and the crude annual mortality rate is 70/100,000 per year (Osuntokun, 1994). It is the second most common cause of mortality in developed countries like Germany (Warlow,1998). A Pakistani study reported that 64% of stroke cases caused by cerebral infarction, whereas, 36% occur by bleeding (Kamal *et al.,* 2010; in Khan *et al.,* 2015). Many metabolic abnormalities are associated with the stroke and the deficiency of Magnesium (Mg) is one of them. Magnesium has a neuroprotective role, as it acts on vascular supply, that is, increases blood flow to ischemic tissues. It promotes vasodilatation by blocking the function of vascular mediator like endothelin-1, neuropeptide-y and angiotensin-II. It also enhances vasodilator effect of prostacyclin. It also impends Ca^{2+} channel by competing with Ca^{2+} (Chang *et al.,* 2014). It also enhances the integrity of blood brain barrier (BBB) which reduces brain edema and increases formation of ATP (Cojocaru *et al.,* 2007). Being fourth most abundant mineral in the body, it is a potent vasodilator, nature's Ca^{++} antagonist and co-enzyme used in 300 biochemical reactions. According to the literature, in U.S., 64% males and 67% females are found with decreased Mg^{2+} levels due to poor Mg foods. Studies done in larger population with higher intake of Mg shows a decreased risk of hypertension, ischemic heart disease and strokes. Magnesium deficiency causes vasoconstriction, endothelial injury and increased rate of thrombosis, which are all risk factors for stroke. Hypomagnesemia promotes atherosclerosis three folds, thereby promoting coronary and carotid atherosclerosis (Chang *et al.,* 2014). The

non-modifiable risk factors are age, gender, race, ethnicity and family history of stroke (Stern *et al.*, 2003; Stern, 2003).

Hypomagnesaemia is taken into account when the serum magnesium level falls below 0.75 mmol/L (Gröber *et al.*, 2015). A firm balance of exchange between cells and the extracellular fluid maintains the constant Mg^{2+} level in interstitium and intracellularly. The uptake of peripherally administered Mg^{2+} is sluggish in normal brain as it is strictly regulated. It is seen that with only 3-4 times rise in Mg^{2+} levels, only 20% rise of it was seen in cerebrospinal fluid. (Oppelt *et al.*, 1963). Most common neuromuscular signs and symptoms reported from a magnesium deficiency are: Trousseau's sign (Kumar *et al.*, 2009), Chvostek's sign (Lloyd-Jones *et al.*, 2010), muscle fibrillations, muscle spasticity, tremor, and hyporeflexia. Gastrointestinal complications, diabetes, lethargy, weakness, alcoholism and renal disorders are mostly reported from depressed magnesium levels (Gröber *et al.*, 2015). Though, hypomagnesaemia has been reported as an etiological factor for an ischemic stroke (Khan *et al.*, 2015), but still its primary features of magnesium deficiency could be masked, because its deficiency usually comes with a secondary ailment (Shils, 1969). It is believed that a magnesium infusion could improve cerebral blood flow via. arteriolar vasodilation (Kurzepa *et al.*, 2008; Khan *et al.*, 2015). Depressed magnesium levels can induce pronounced neurological complications from cellular injury followed by the prognosis of ischemic stroke (Kurzepa *et al.*, 2008; Khan *et al.*, 2015). In Pakistan, the most common modifiable risk factors for stroke are as follows: 73% of hypertension, 42.5% of diabetes, 38% of coronary artery disease, 29% of smoking, 27% of obesity, 22% of atrial fibrillation and 12% of dyslipidemias (Khan *et al.*, 2015).

Because of increased hypomagnesemia related morbidity and mortality in strokes, there is a strong need to discuss and address its incidence and prevalence. Therefore, the current study was aimed to determine the frequency of hypomagnesaemia in patients with acute ischemic stroke (AIS). A total of 110 cases of AIS was included in the study and serum magnesium levels were determined including clinical information. A study reported 24 % of hypomagnesemia in acute ischemic stroke (ASI) patients (Romero *et al.*, 2012; Khan *et al.*, 2015). A research has been done to affirm the role of Mg therapy to achieve an improved neurological outcomes in patients after an onset of stroke (Westermaier *et al.*, 2013). Another research has also proved the correlation of hypomagnesemia with the stoke (Odom *et al*, 2013). A study done in Romania by Cojorcaru *et al.*, (2007), had measured serum Mg^{2+} levels of 40 ischemic stroke patients. A notable correlation between in first 48 hours and patients' disability was observed (Cojocaru *et al.*, 2007). But another study by Ovbiagele *et al.*, (2006) found that serum Mg^{2+} level at the time of admission was not a good prognostic factor.

Material and Methods

A cross-sectional study for a period of six months during year 2015 was conducted at the Department of Medicine, Services Hospital, Lahore. The sample size of 110 cases of acute ischemic stroke (AIS) was calculated with 95% confidence level, 8% margin of error. The sampling was non-probability purposive sampling.

Sample Selection Criteria

Inclusion Criteria

- Patient diagnosed with stroke.
- Age between 40-70 years.
- Patients of both genders.

Exclusion Criteria

- Current magnesium replacement in last three months (on history or medical record).
- Patients not willing for participation in the study.

Data Collection

The patients admitted in the medical ward of Services Hospital from emergency, were selected according to inclusion and exclusion criteria. The patient or relatives were informed that the information collected from him/her will be used in the study and the confidentiality and anonymity related issues will be taken care accordingly. After informed consents from patients or relatives, the serum venous blood samples for serum magnesium levels were taken and sent to SIMS (Services Institute of Medical Science) laboratory. The patients' information and results obtained from SIMS were recorded on patient Proforma. The Beckman-Coulter (AU480) an automated chemistry analyzer was used for the analysis of serum Mg^{2+} level concentration.

Data Analysis

The data was collected, compiled and analyzed statistically using SPSS version 22. The quantitative variable age expressed in mean and standard deviation (SD). The qualitative data like gender and hypomagnesemia was expressed in frequency and percentage. The stratification was done for age, gender, history of smoking, diabetes

mellitus (DM), hypertension, socioeconomic status and nutritional status. For post stratification, the Chi-Square (χ^2) test were applied. A p-value of $\leq$0.05 was taken as significant.

Results

A total of 110 patients of acute ischemic stroke (AIS) were included in the study and majority of the patients were between 61-70 years of age (43.6 %) and minimum patients were 40-50 years (17.3 %) old. Mean age of the patients was 60.47±7.78 years (**Table 1**). Out of 110 cases, 62 patients (56.4%) were male, while, remaining 48 patients (43.6%) were female (**Table 2**). The hypomagnesemia was found in 39 patients (35.5%) (**Table 3**). At the time of admission (at 24 hours) the mean serum Mg^{2+} concentration was found 1.5 mg/dL in acute ischemic patients.

The stratification with regard to age, gender, history of cigarette smoking, history of diabetes, history of hypertension, socioeconomic status and malnutrition was presented in **Tables 4-10.** Among 39 hypomagnesemia patients, the majority (30 %) were of age group 51-60 years. The AIS patients were found with the signs of body weakness, altered state of consciousness, increased blood pressure, difficulty in speech etc. Among hypomagnesemia patients, majority of the patients were male (38%) and nonsmokers (44 %). The hypomagnesemia patients were majority diagnosed with a history of DM (47 %) and hypertension (44 %). Most of the hypomagnesemia patients (53%) were from middle class having monthly income of 10,000-50,000 Rupees per month. The 27% hypomagnesemia patients were found malnutrition. It should be noted from Chi-Square test, that there existed a significant differences in the following qualitative parameters: history of cigarette smoking, history of hypertension and malnutrition with the following p-values: 0.009,0.002 and 0.001 respectively out of the total hypomagnesemia patients. Figure 1 (a-c) showing CT scans of an acute ischemic stroke patient.

Discussion

The Mg^{2+} ions can hamper the NMDA (glutamatergic n-methyl-D-aspartate) receptors in CNS during the occurrence of ischemic stroke, i.e., a glutamate neurotoxicity. Low Mg^{2+} concentration at the onset of stroke, can escalate penumbral damage with some neurological deterioration which can adverse the stroke presentation, if sufficient magnesium levels do not settle (Cojocaru *et al.,* 2007; Cojocaru *et al.,* 2009; Siegler *et al.,* 2013). There is a growing interest in magnesium (Mg^{2+}) deficiency in nutrition and clinical medicine, because of the understanding that it has an important role in cellular functions, in signal transduction modulation, potassium and calcium ions transportation and energy metabolisms. It has been now observed that magnesium deficiency is getting very common in people due to either insufficient intake through natural sources or due to its excessive deprivation from different factors. Few studies have evaluated the impact of baseline Mg^{2+} on stroke outcome (Cojocaru *et al.,* 2007; Cojocaru *et al.,* 2009; Ovbiagele *et al.,* 2006; Lampl *et al.,* 2002; Siegler *et al.,* 2013). There is a special focus on magnesium deficiency in hypertension, diabetes, cardiac ailments, asthma, atherosclerosis and in eclampsia (Saris *et al.,* 2000; Dacey, 2001). Medicines such as proton-pump inhibitors can also disturb the gastrointestinal magnesium absorption (Palmer and Clegg., 2015; Perazella, 2013; Gröber *et al.,* 2015). The pronounced Mg^{2+} deficiency is observed with the symptoms of elevated neuromuscular excitability e.g., muscle cramps, tremors, carpopedal spasms and tetany and generalized seizures (Gröber *et al.,* 2015). Commonly, magnesium deficiency is ignored and it is not usually identified, may be because it is considered less specific as compared to other elements such as iron. In central nervous system, the magnesium homeostasis is regulated by an active transport of magnesium and so that its concentration in cerebrospinal fluid should be maintained (Mori *et al.,* 1992). But however, still mechanisms related to altered magnesium levels in ischemic stroke patients are not yet fully understood and there is a need to fully elucidate the associated risk factors. Therefore, the purpose of this study was to identify risk factors inducing ischemic stroke in connection with serum Mg^{2+} levels. Brain releases damaging chemicals such as glutamate in response to insufficient oxygen supply or nutrients in ischemic conditions (Izumi *et al.,* 1991). A magnesium deficiency links with a risk of thrombus formation (Shechter *et al.,* 2000). For example, the patients with coronary artery disease, suffer from elevated levels of platelet dependent thrombosis, along with depressed magnesium levels (Shechter *et al.,* 2000). In stroke, there is a release of excessive glutamate, which forms a pool of calcium into the cells of the brain leading them to die prematurely. The sufficient magnesium levels can prevent glutamate formation, thereby, saving brain cells to die prematurely (Lampl *et al.,* 2001; Van Swieten *et al.,* 1988).

In our study, the frequency of hypomagnesaemia in patients with thrombotic acute ischemic stroke (AIS) was 35.5 % with mean Mg^{2+} concentration 1.5 mg/dL. A study by Amighi *et al.,* (2004) reported depressed serum magnesium levels by which they had identified neurological statuses especially ischemic strokes. We found that there is a strong relationship between low magnesium level and severity of stroke. It is known that serum magnesium levels are inversely linked with the incidence of ischemic stroke (Ohira *et al.,* 2009). Ohira *et al.,* (2009) reported 577 cases of ischemic stroke cases with hypomagnesemia during 15 years. We found that the most prevalent age group was 51-60 years for ischemic stroke patients who were suffering from

hypomagnesemia. A Pakistani study has also found similar prevalence of hypomagnesaemia in stroke patients (Khan *et al.,* 2015). We found that the depressed levels of Mg^{2+} were more prevalent in male patients as compared to female patients. However, a recent study of Khan *et al.,* (2015) reported that male and female ASI patients were equally suffering from hypomagnesaemia. The overall frequency of hypomagnesaemia in ASI patients was 32% as reported by Khan *et al.,* (2015). A study by Cojocaru *et al.,* (2007) was conducted to analyze the link between serum magnesium levels and neurological deficits. They (Cojocaru *et al.,* 2007) included 40 cases of AIS with mean age 56 years. This study affirmed the association between low Mg^{2+} levels in serum at 48 hours after the onset of ischemic stroke and severity of neurological deficit. They (Cojocaru *et al.,* 2007) concluded that serum Mg^{2+} concentration can impact neurological states (Cojocaru *et al.,* 2007). Significant reduction in the risk of stroke was observed from magnesium intake in many prospective clinical trials. An 8% reduction in ischemic stroke was observed with 100 mg magnesium intake per day (Adebamowo *et al.,* 2015; Larsson *et al.,* 2012; Larsson *et al.,* 2011; Gröber *et al.,* 2015). In some cases of stroke, therapy of magnesium sulfate was recommended, because of its neuroprotective characteristics proved from preclinical models (Drew *et al.,* 2010; Gröber *et al.,* 2015). A prospective health professional follow-up study among 43,738 US men has demonstrated an inverse association between dietary Mg^{2+} intake and the stroke risks (Ascherio *et al.,* 1998; Saris *et al.,* 2000). The Mg^{2+} is a neuroprotective agent as proved from experimental models of brain injuries and strokes (Marinov *et al.,* 1996; Stys *et al.,* 1990; Izumi *et al.,* 1991; Saris *et al.,* 2000). The process of neuroprotection includes noncompetitive barrier of the NMDA receptor (Harrison and Simmonds, 1985; Saris *et al.,* 2000),increased cerebral blood flow to ischemic areas (Chi *et al.,* 1989; Saris *et al.,* 2000), inhibition of the Calcium into the cells, voltage & receptor operated channels, and recovery of cellular energy metabolism after the restoration of perfusion (Altura and Altura, 1994; Woods 1991; 85,101 Saris *et al.,* 2000). A large multicenter trial assessed the role of intravenous $MgSO_4$ treatment after acute stroke (Seelig and Rosanoff, 2003). It was recommended that clinicians should define properly that whether or not $MgSO_4$ should be included in the treatment of acute stroke (Saris *et al.,* 2000). The supplemental intake or intravenous infusion of Mg is found beneficial in various diseased states (Saris *et al.,* 2000). In China, Liang *et al.,* (2011) has reported that the dietary intake of Mg^{2+} was lower in ASI patients. It was found that with the increased dietary intake of Mg^{2+}, the risk of stroke was prevented (Liang *et al.,* 2011).

The significant risk factors of AIS were cigarette smoking, hypertension and malnutrition in the current study. A case report has correlated a heavy smoking and alcoholism with hypomagnesemia (Rolla and Bucca, 1989; Larsson *et al.,* 2008). A cigarette smoking is a potential risk of all types of stroke conditions (Shah and Cole, 2010). Magnesium levels can be depressed from low dietary Mg intake, poor ingestion and increased urinary loss (Peters *et al.,* 2013). Magnesium deficiency is also associated with malabsorption, endocrine disorders, alterations in blood lipid levels, myocardial infarction, premenstrual syndrome, kidney stones and psychiatric disorders. It is also associated with electrolytic imbalances such as hypocalcaemia or hypokalemia (Gröber *et al.,* 2015). Two medical conditions such as diabetes and hypertension are considered as causative agents of ischemic stroke, which can intervene serum magnesium levels as well. An oxidative response in endothelial cells could trigger from an inflammatory response, because of elevated circulatory cytokines induced by a magnesium deficiency (Ferre *et al.,* 2007; Peters *et al.,* 2013). In the current study, there was a marked increased risk of hypomagnesemia in AIS patients with the following: history of diabetes, hypertension, malnutrition and middle class status. Another Pakistani study by Shaikh *et al.,* (2012) identified hypomagnesemia (62%) in rural patients suffering from hypertension and among them, the 55% were having elevated fasting blood sugar levels. The stroke has been considered a significant gradient related to low levels of socioeconomic statuses (Grimaud *et al.,* 2011). A study by Saberi *et al.,* (2011) had also reported an inverse correlation between serum Mg^{2+} levels after ASI. Swaminathan *et al.,* (2003) observed in middle aged American women, that although the magnesium intake can reduce risk of ischemic stroke, but this can be insignificant with cardiovascular risk factors including hypertension condition. The magnesium is considered to have a function in the metabolism of carbohydrates along with insulin regulations, and therefore, diabetes is a key factor to reduce low magnesium levels. Hypomagnesemia has been diagnosed in the acute metabolic and extended complications of diabetes. Therefore, a routine magnesium supplement with increased natural intake are recommended in diabetes (Peters *et al.,* 2013). Because of inadequate magnesium dietary intake, there is an increased risk of forming glucose intolerance leading type-II diabetes (Ghose and Ide, 2014; Gröber *et al.* 2015), dyslipidemia and hypertension (Peters *et al.,* 2013). Diabetes, both type I &II, are among the most common origin of magnesium deficiency (Grober *et al.,* 2015). The incidence of hypomagnesemia in patients with type-II diabetes range from '13.5–47.7' % (Palmer and Clegg., 2015; Gröber *et al.,* 2015). A long term magnesium intake was investigated in adult patients suffering from systemic inflammation and diabetes and significant improvements were reported (Kim *et al.,* 2010; Gröber *et al.,* 2015). Magnesium is essential in regulating blood pressure. For stroke and heart diseases, hypertension is a major risk element. Alterations in arterial blood pressure are linked to the alterations of endogenous magnesium levels (Gröber *et al.* 2015). A research concluded that few weeks of supplemental magnesium intake can decrease systolic and diastolic blood pressure in hypertensive patients (Kass *et al.,* 2012; Gröber *et al.,* 2015).

Table 1. Distribution of cases by age.

Age (Year)	Number	Percentage %
40-50	19	17.3
51-60	43	39.1
61-70	48	43.6
Total	**110**	**100.0**
Mean±SD	60.47±7.78	

Table 2. Distribution of cases by gender.

Gender	Number	Percentage %
Male	62	56.4
Female	48	43.6
Total	**110**	**100.0**

Table 3. Distribution of cases by hypomagnesemia.

Hypomagnesemia	Number	Percentage %
Yes	39	35.5
No	71	64.5
Total	**110**	**100.0**

Table 4. Stratification with regard to age.

Age (Year)	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
40-50	07	12	19	0.886	0.642
51-60	13	30	43		
61-70	19	29	48		
Total	**39**	**71**	**110**		

Table 5. Stratification with regard to gender.

Gender	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
Male	24	38	62	0.658	0.417
Female	15	33	48		
Total	**39**	**71**	**110**		

Table 6. Stratification with regard to history of cigarette smoking.

History of smoking	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
Yes	25	27	52	6.866	0.009*
No	14	44	58		
Total	**39**	**71**	**110**		

*significant value

Table 7. Stratification with regard to history of diabetes mellitus (Type 2).

History of diabetes mellitus	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
Yes	16	47	63	6.518	0.011
No	23	24	47		
Total	**39**	**71**	**110**		

Table 8. Stratification with regard to history of hypertension.

History of hypertension	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
Yes	35	44	79	9.593	0.002*
No	04	27	31		
Total	**39**	**71**	**110**		

*significant value

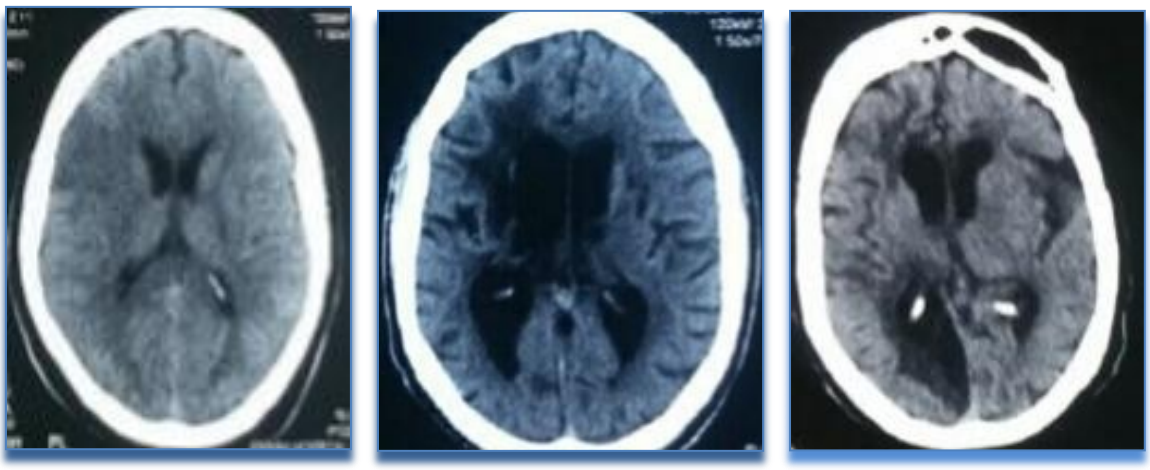
Table 9. Stratification with regard to socioeconomic status.

Socioeconomic status	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
Lower (Rs.<10,000/month)	10	18	28	0.001	0.973
Middle (Rs.10-50000/month)	29	53	82		
Total	**39**	**71**	**110**		

Table 10. Stratification with regard to malnutrition.

Malnutrition	Hypomagnesemia		Total	Chi Square	p-value
	Number	Percentage %			
Yes	28	27	55	11.481	0.001*
No	11	44	55		
Total	**39**	**71**	**110**		

*significant value



(a) (b) (c)

Fig. 1. ***(a) and (b)*** **Right Frontoparietal Infarct of a Patient of Acute Ischemic Stroke;** ***(c):*** **Right Posterior Cerebral Infarct of a Patient of Acute Ischemic Stroke.**

The daily intake of magnesium has substantially been declined for many years (Altura and Altura, 1995; Saris *et al.*, 2000). The body must have ample availability of magnesium concentration in order to protect neurological functions. There must be awareness regarding intake of natural dietary magnesium. The richest dietary sources of magnesium include: green leafy vegetables, raw grains, whole seeds, legumes and nuts. Processing of food items is responsible to decrease the nutritional value of magnesium. The RDA (recommended dietary allowance) for magnesium is 350 mg daily for male and 280 mg daily for a female

(National Research Concil US 1989; Saris *et al.*, 2000). It was recommended that increasing cereal fibers and magnesium rich foods, the diabetic risk can be reduced (Ghose and Ide, 2014). Various magnesium supplements are now available such as magnesium citrate, magnesium oxide, magnesium chloride, magnesium orotate, magnesium taurate and other as amino acid chelated forms. In order to treat magnesium deficiency the recommended form of magnesium is one with organic bound such as magnesium gluconate, magnesium citrate, magnesium aspartate or magnesium orotate (Kisters *et al.*, 2013; Gröber *et al.*, 2015). The physicians should keep in mind that a high risk of hypomagnesemia exists and they need to recommend a magnesium therapy. Magnesium supplements, though considered safe and well tolerated, but still they can cause gastrointestinal disturbances. Similarly, an overdose of intravenous magnesium can have side effects such as: muscle weakness, hypotension, drowsiness, cardiac arrhythmia, respiratory depression and comma (Gröber *et al.*, 2009; Gröber *et al.*, 2015).

Magnesium's neuroprotection role is though, is known still its specific therapy needs to be adjusted to achieve promising outcomes in patients with ischemic stroke. Singh *et al.*, (2012) evaluated the effect of IV $MgSO_4$ infusion to evaluate clinical outcome of patients with acute stroke. Singh *et al.*, (2012) was unsuccessful in documenting a remarkable stroke recovery, even with achieving a significant rise in serum magnesium level, with an intravenous $MgSO_4$ regime. A recent study by Saver *et al.*, (2015) has also reported that magnesium sulfate therapy was found safe and the entire therapy was recommended within 2 hours after stroke onset. However, the therapy was not much successful after 3 months time. Because of such views, it is very necessary to continuously monitor the levels of magnesium during episodes of stroke, because the levels may not always same. Moreover, which mode of magnesium therapy would be effective, needs a serious attention. Most of the hypomagnesemia cases are considered asymptomatic and the symptomatic conditions are observed when serum Mg^{2+} concentration declines less than 1.2 mg/dL (Assadi, 2010). There existed inconsistent results from several prospective studies and therefore there is a need to maintain and then test Mg^{2+} intake outcomes in AIS patients.

Conclusion and Recommendations: The hypomagnesemia in stroke is associated with risk factors such as hypertension, diabetes mellitus, poor nutritional conditions, and poverty. Physicians should keep in mind that a high risk of hypomagnesemia exists and there is a need to recommend a Mg therapy. The body must have ample availability of magnesium concentration in order to protect neurological functions. There must be awareness regarding intake of natural dietary magnesium. Magnesium supplementation in AIS patients can be of benefit in most cases. Moreover, there is a need to monitor those drugs or supplements which prone to reduce Mg^{2+} concentrations.

The authors report no conflict of interest.

Compliance with Ethical Standards Statement: Informed consents were obtained from all patients included in the study conformed to institutional ethical standards.

References

Adebamowo, S. N. Spiegelman, D. Willett, W. C. and Rexrode, K. M. (2015). Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. *The American journal of clinical nutrition*, ajcn100354.

Altura, B. M. (1994). Introduction: importance of Mg in physiology and medicine and the need for ion selective electrodes. *Scandinavian Journal of Clinical and Laboratory Investigation, 54*(sup217), 5-9.

Altura, B. M. and Altura, B. T. (1995). Magnesium in cardiovascular biology. *Sci. Am. Sci. Med, 2*(3), 28-37.

Amighi, J. Sabeti, S. Schlager, O. Mlekusch, W. Exner, M. Lalouschek, W. . . . Schillinger, M. (2004). Low serum magnesium predicts neurological events in patients with advanced atherosclerosis. *Stroke, 35*(1), 22-27.

Ascherio, A. Rimm, E. Hernan, M. Giovannucci, E. Kawachi, I. Stampfer, M. and Willett, W. (1998). Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation, 98*(12), 1198-1204.

Assadi, F. (2010). Hypomagnesemia: an evidence-based approach to clinical cases. *Iranian journal of kidney diseases, 4*(1), 13.

Chang, J. J. Mack, W. J. Saver, J. L. and Sanossian, N. (2014). Magnesium: potential roles in neurovascular disease. *Frontiers in neurology, 5*, 52.

Chi, O. Pollak, P. and Weiss, H. (1989). Effects of magnesium sulfate and nifedipine on regional cerebral blood flow during middle cerebral artery ligation in the rat. *Archives internationales de pharmacodynamie et de therapie, 304*, 196-205.

Cojocaru, I. M. Cojocaru, M. Burcin, C. and Atanasiu, N. (2007). Serum magnesium in patients with acute ischemic stroke. *Romanian journal of internal medicine= Revue roumaine de medecine interne, 45*(3), 269-273.

Cojocaru, I. M. Cojocaru, M. Tanasescu, R. Iacob, S. A. and Iliescu, I. (2009). Changes of magnesium serum levels in patients with acute ischemic stroke and acute infections. *Rom J Intern Med, 47*(2), 169-171.

Dacey, M. J. (2001). Hypomagnesemic disorders. *Critical care clinics, 17*(1), 155-173.

Drew, B. J. Ackerman, M. J. Funk, M., Gibler, W. B. Kligfield, P. Menon, V. . . . Zareba, W. (2010). Prevention of torsade de pointes in hospital settings. *Circulation, 121*(8), 1047-1060.

Ferrè, S. Mazur, A. and Maier, J. A. (2007). Low-magnesium induces senescent features in cultured human endothelial cells. *Magnesium research, 20*(1), 66-71.

Ghose, B. Ide, S. (2014). Hypomagnesemia and Type2 Diabetes Mellitus: A Review of the Literature. *Austin J Nutri Food Sci, 2*(4), 1025.

Go, A. S. ozaffarian, D. Roger, V. L. Benjamin, E. J. Berry, J. D. Borden, W. B. . . . Fox, C. S. (2013). Heart disease and stroke statistics-2013 update. *Circulation, 127*(1).

Grimaud, O. Dufouil, C. Alpérovitch, A. Pico, F. Ritchie, K. Helmer, C. . . . Chauvin, P. (2010). Incidence of ischaemic stroke according to income level among older people: the 3C study. *Age and ageing*, afq142.

Gröber, U. (2009). Magnesium. In *Micronutrients: Metabolic Tuning-Prevention-Therapy*, 1st ed.; Gröber, U., Ed.; MedPharm Scientific Publishers: Stuttgart, Germany, pp. 159–166.

Gröber, U. Schmidt, J. and Kisters, K. (2015). Magnesium in prevention and therapy. *Nutrients, 7*(9), 8199-8226.

Harrison, N. L. and Simmonds, M. A. (1985). Quantitative studies on some antagonists of N-methyl D-aspartate in slices of rat cerebral cortex. *British journal of pharmacology, 84*(2), 381-391.

Izumi, Y. Roussel, S. Pinard, E. and Seylaz, J. (1991). Reduction of infarct volume by magnesium after middle cerebral artery occlusion in rats. *Journal of Cerebral Blood Flow & Metabolism, 11*(6), 1025-1030.

Kamal, A. Aslam, S. and Khattak, S. (2010). Frequency of Risk Factors in Stroke Patients admitted to DHQ Teaching Hospital, DI Khan. *Gomal Journal of Medical Sciences, 8*(2).

Kass, L. Weekes, J. and Carpenter, L. (2012). Effect of magnesium supplementation on blood pressure: a meta-analysis. *European journal of clinical nutrition, 66*(4), 411-418.

Khan, K. M. Naeem, F. and Iqbal, R. (2015) To Determine the Frequency of Hypomagnesemia among patients with Acute Ischemic Stroke and to Study the Correlation of Serum Magnesium with Modified Rankin Scale After Acute Ischemic Stroke. *Pakistan Journal of Medical and Health Sciences*, Vol. 9, No. 4, 1240-1243.

Kim, D. J. Xun, P. Liu, K. Loria, C. Yokota, K. Jacobs, D. R. and He, K. (2010). Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. *Diabetes care,* 33**,** 2604-2610.

Khatri, I. A. and Wasay, M. (2011). Can we stop the stroke epidemic in Pakistan? *Journal of the College of Physicians and Surgeons Pakistan, 21*(4), 195-196.

Kisters, K. (2013). What is the correct magnesium supplement? *Magnesium Research, 26*(1), 41-42.

Kumar ,P. Clark, M. (2009). Kumar and Clark's clinical medicine. 7th ed. WB Saunders Elsevier, P. 1126-36.

Kurzepa, J. Bielewicz, J. Bartosik-Psujek, H. Szczepañska-Szerej, A. and Stelmasiak, Z. (2008). Simvastatin inhibits the increase in serum tau protein levels in the acute phase of ischemic stroke. *Pharmacological Reports, 60*(6), 1014.

Lampl, Y. Gilad, R. Geva, D. Eshel, Y. and Sadeh, M. (2001). Intravenous administration of magnesium sulfate in acute stroke: a randomized double-blind study. *Clinical neuropharmacology, 24*(1), 11-15.

Larsson, S. C. Orsini, N. and Wolk, A. (2012). Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. *The American journal of clinical nutrition, 95*(2), 362-366.

Larsson, S. C. Virtamo, J. and Wolk, A. (2011). Potassium, calcium, and magnesium intakes and risk of stroke in women. *American journal of epidemiology, 174*(1), 35-43.

Larsson, S. C. Virtanen, M. J. Mars, M., Männistö, S. Pietinen, P. Albanes, D. and Virtamo, J. (2008). Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. *Archives of internal medicine, 168*(5), 459-465.

Liang, W. Lee, A. H. and Binns, C. W. (2011). Dietary intake of minerals and the risk of ischemic stroke in Guangdong Province, China, 2007-2008. *Prev Chronic Dis, 8*(2), A38.

Lloyd-Jones, D. Adams, R. J. Brown, T. M. Carnethon, M., Dai, S. De Simone, G. . . . Gillespie, C. (2010). Heart disease and stroke statistics—2010 update. *Circulation, 121*(7), e46-e215.

Mahmood, T. Anjum, M. S. Iqbal, S. Kalsoom, N. and Manzoor, H. (2013). Evaluation of Risk Factors in Ischemic Stroke. *Journal of Rawalpindi Medical College (JRMC), 17*(1), 138-139.

Marinov, M. B. Harbaugh, K. S. Hoopes, P. J. Pikus, H. J. and Harbaugh, R. E. (1996). Neuroprotective effects of preischemia intraarterial magnesium sulfate in reversible focal cerebral ischemia. *Journal of neurosurgery, 85*(1), 117-124.

McKee, J. A. Brewer, R. P. Macy, G. E. Phillips-Bute, B. Campbell, K. A. Borel, C. O. . . . Warner, D. S. (2005). Analysis of the brain bioavailability of peripherally administered magnesium sulfate: A study in humans with acute brain injury undergoing prolonged induced hypermagnesemia. *Critical care medicine, 33*(3), 661-666.

Mori, H. Masaki, H. Yamakura, T. and Mishina, M. (1992). Identification by mutagenesis of a Mg2+-block site of the NMDA receptor channel.

National Research Council (US). (1989) Recommended dietary allowances, 10th ed, Washington, DC: National Academy Press, 1989.

Odom, M. J. Zuckerman, S. L. and Mocco, J. (2013). The role of magnesium in the management of cerebral vasospasm. *Neurology research international, 2013*.

Ohira, T. Peacock, J. M. Iso, H. Chambless, L. E. Rosamond, W. D. and Folsom, A. R. (2009). Serum and dietary magnesium and risk of ischemic stroke the atherosclerosis risk in communities study. *American journal of epidemiology, 169*(12), 1437-1444.

Oppelt, W. MacIntyre, I. and Rall, D. (1963). Magnesium exchange between blood and cerebrospinal fluid. *American Journal of Physiology--Legacy Content, 205*(5), 959-962.

Osuntokun, B. O. (1994). Epidemiology of stroke in Blacks in Africa. *Hypertension Research, 17*(SupplementI), S1-S9.

Ovbiagele, B. Liebeskind, D. Starkman, S. Sanossian, N. Kim, D. Razinia, T. and Saver, J. (2006). Are elevated admission calcium levels associated with better outcomes after ischemic stroke? *Neurology, 67*(1), 170-173.

Palmer, B. F. and Clegg, D. J. (2015). Electrolyte and acid–base disturbances in patients with diabetes mellitus. *New England Journal of Medicine, 373*(6), 548-559.

Perazella, M. A. (2013). Proton pump inhibitors and hypomagnesemia: a rare but serious complication. *Kidney international, 83*(4), 553-556.

Peters, K. E. Chubb, S. P. Davis, W. A. and Davis, T. M. (2013). The relationship between hypomagnesemia, metformin therapy and cardiovascular disease complicating type 2 diabetes: the Fremantle Diabetes Study. *PloS one, 8*(9), e74355.

Rolla, G. and Bucca, C. (1989). Hypomagnesemia and bronchial hyperreactivity. *Allergy, 44*(7), 519-521.

Romero, F. R. de Moraes Neto, B. G. Araújo, G., and Munhoz, E. G. (2012). Serum Magnesium Levels and Neurological Outcome After Acute Ischemic Stroke. *Rev Neurocience, 20*(3), 468-472.

Saberi, A. Hatamian, H. R. Esmaeilzadeh, K. and Heydarzadeh, A. (2011). The relationship between magnesium level and first 72 hours Rankin score and Rankin score in 1 week after an ischemic stroke. *Iranian journal of neurology, 10*(1-2), 26.

Saris, N.-E. L. Mervaala, E. Karppanen, H. Khawaja, J. A. and Lewenstam, A. (2000). Magnesium: an update on physiological, clinical and analytical aspects. *Clinica Chimica Acta, 294*(1), 1-26.

Saver, J. L. Starkman, S. Eckstein, M. Stratton, S. J. Pratt, F. D. Hamilton, S., . . . Kramer, I. (2015). Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *New England Journal of Medicine, 372*(6), 528-536.

Seelig, M. S. and Rosanoff, A. (2003). *The magnesium factor*: Penguin.

Shah, R. S. and Cole, J. W. (2010). Smoking and stroke: the more you smoke the more you stroke. *Expert review of cardiovascular therapy, 8*(7), 917-932.

Singh, H. Jalodia, S. Gupta, M. Talapatra, P. Gupta, V. and Singh, I. (2012). Role of magnesium sulfate in neuroprotection in acute ischemic stroke. *Annals of Indian Academy of Neurology,* 15**,** 177.

Shaikh, M. K. Samo, J. A. and Mangrio, G. M. (2012). Fasting Blood Glucose and Serum Magnesium Levels in Patients with Hypertension. *World Applied Sciences Journal, 17*(10), 1261-1264.

Shechter, M. Merz, C. N. B. Rude, R. K. Labrador, M. J. P. Meisel, S. R. Shah, P. K. and Kaul, S. (2000). Low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease. *American Heart Journal, 140*(2), 212-218.

Shils, M.E. (1998). Magnesium. In Modern nutrition in health & disease. ME Shils, JE Olson, M Shike and AC Ross, editors. Baltimore: Williams & Wilkins,. p. 169-92.

Siegler, J. E. Boehme, A. K. Albright, K. C. Bdeir, S. Kar, A. K. Myers, L. . . . Martin-Schild, S. (2013). Acute decrease in serum magnesium level after ischemic stroke may not predict decrease in neurologic function. *Journal of Stroke and Cerebrovascular Diseases, 22*(8), e516-e521.

Stern, B. (2003). Ischemic Brain Injury And Vascular Biology. *CONTINUUM: Lifelong Learning in Neurology, 9*(2, Acute Stroke Management), 11-18.

Stern, B. Wityk, R. J. Pullicino, P. and Chan, R. (2003). Vasculitis, arterial dissection, and other causes of stroke. *Continuum: Lifelong Learning in Neurology, 9*(2, Acute Stroke Management), 131-140.

Stys, P. K. Ransom, B. R. and Waxman, S. G. (1990). Effects of polyvalent cations and dihydropyridine calcium channel blockers on recovery of CNS white matter from anoxia. *Neuroscience letters, 115*(2), 293-299.

Swaminathan, R. (2003). Magnesium metabolism and its disorders. *The Clinical Biochemist Reviews, 24*(2), 47.

Van Swieten, J. Koudstaal, P. Visser, M. Schouten, H. and Van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke, 19*(5), 604-607.

Warlow, C. (1998). Epidemiology of stroke. *The Lancet, 352*, SM1.

Wasay, M. Khatri, I. A. and Kaul, S. (2014). Stroke in south Asian countries. *Nature Reviews Neurology, 10*(3), 135-143.

Westermaier, T. Stetter, C. Kunze, E. Willner, N. Raslan, F. Vince, G. H. and Ernestus, R.-I. (2013). Magnesium treatment for neuroprotection in ischemic diseases of the brain. *Experimental & translational stroke medicine*, *5*(1), 6.

Woods, K. L. (1991). Possible pharmacological actions of magnesium in acute myocardial infarction. *British journal of clinical pharmacology*, *32*(1), 3-10.