Hypomagnesemia and cardiovascular system

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Abstract
Magnesium depletion in clinical practice is mainly related to loop diuretics and thiazides. Among patients treated with diuretics more than 1/3 exhibit hypomagnesa. Arrhythmias and sudden death attributed to magnesium depletion could be prevented by Mg administration. Magnesium deficiency in experimental animals promotes atherosclerotic lesions whereas this ion is involved in various stages of myocardial damage after experimental coronary artery occlusion. In humans magnesium administration in the first 24 hours of myocardial infarction was related to beneficial effects in first year mortality rate. Nevertheless more evidence from clinical investigation is needed for permanent conclutions. *Hippokratia 2006; 10 (4): 147-152*

Introduction

Magnesium is the second in abundance intracellular ion. The relationship between magnesium and cardiovascular system, arterial hypertension, central nervous system, skeletal muscles and pregnancy, is an already established knowledge.

The main part of total body magnesium is concentrated in the bones, only 1% is in the serum while the 31% is in the intracellular space diluted in the cytoplasm or conjuncted to enzymes or ATP.

The usual daily magnesium consumption is 200-300 mg but only 1/3 of this quantity is absorbed through small intestine. The magnesium renal excretion rate is approximately 100 mg per day. Normal values of serum magnesium are considered those between 0.75 and 1.5 mmol/L. Values below the threshold of 0.75 mmol/L are defined as hypomagnesemia.

Wide variety of methods have been used to measure magnesium in serum and intracellular space but none was reliable. During last decades by means of new techniques, the precise determination of magnesium concentration became possible. Magnesium depletion occurs when intracellular magnesium stores are depleted. Since there is no possibility to determine the levels of intracellular magnesium the physician is obliged to estimate the magnesium stores using the values of serum magnesium.

The main problem in diagnosis of intracellular magnesium depletion is that it can coexist even with normal serum values. This situation was confirmed with muscle biopsy in patients with normal serum magnesium values and evidence of magnesium stores depletion. However, the majority of patients with decreased total magnesium have low serum Mg as well. Thus, in clinical practice, patients with hypomagnesemia are considered as having intracellular magnesium depletion. The measurement of serum Mg is easy and considered as the main method of estimation the Mg stores. An other method for intracellular Mg estimation is measurement of Mg concentration in red blood cells or in monocytes or the 24 hour Mg renal excretion. Approximately 1/3 of serum Mg is in conjuction with albumin and during hypoalbuminemia false decreased values of Mg are encountered. Furthermore although the serum Mg level is normal there could be intracellular depletion of Mg that can cause symptoms. Unfortunately there is no quick and direct method of measuring the total Mg levels at the moment.

The most reliable method in diagnosis of Mg intracellular depletion is by measuring the Mg excretion through renal system following Mg loading. This method is indicated in patients exhibiting symptoms of hypomagnesemia from the cardiovascular and nervous systems while having normal serum values. The first step is the measurement of daily Mg excretion in 24-hour urine collection. If it is low (for example 1.1.mmol/d), sulphur magnesium is administered intravenously (0.1mmol/kg of body weight). Patients with intracellular Mg depletion excrete less than 50% of the administered drug, while patients with normal values excrete more than 60%. The procedure is recomended with caution in patients with renal insufficiency. Intravenous Mg administration is well tolerated whereas per os administration causes side effects such as diarrhoea. The problem has been overcome by using magnesium chloride in thin capsules. The main indication for

administering magnesium therapy is the presence of predisposing factors for hypomagnesemia.

Causes of hypomagnesemia

Hypomagnesemia as a side effect of diuretics is the most common cause of this disturbance. Loop diuretics and thiazides are involved in increased Mg excretion. An other common cause of hypomagnesemia is the decreased Mg consumption in the elderly and patients with disturbances in the intestinal absorption. In the developing countries Mg consumption is inadequate. Vegetables and fish are considered rich in Mg, while consumption of fatty food, salt, vitamin D, proteins and calcium increases the need for Mg. Patients with acute or chronic use of alcohol have Mg depletion due to osmotic diuresis by the alcohol. The same mechanism must be implicated in the development of Mg depletion in the diabetic patients.

Signs of Mg depletion

The main signs of Mg depletion concern neuromuscular and central nervous system, as well as electrolyte disturbances (Table 1).

Table 1. *Symptoms of Mg depletion*

Neuromuscular system	Central nervous system
Weakness	Depression
Tremor	Psychosis
Muscle contractions	Nystagmus
Positive Chvostek sign	Spasmus
Positive Trouseau sign	
Dysphagia	
	Metabolic disturbances
Cardiac arrythmias	Hypokalemia
ECG changes	Hypocalcemia

Pathophysiology
The role of Mg in the membrane potential

Changes in the concentration of serum potassium (K) affect the depolarization, repolarization and the automation of tissues such as the Purkinjie fiibres in the myocardium. The extracellular K is the main parameter determining the resting potential of the cytoplasmic membrane. Decrease of serum K concentration to the level of 2 meq/L causes hyperpolarization. Further decrease below the aforementioned value of 2 meq/L results in cytoplasmic membrane depolarization while the action potential that is generated lasts longer. Although it is unknown whether a slight elongation of the action potential and the subsequent decrease of the refractory period could cause arrythmias, in vitro experiments prove that the elongated action potential is connected to automatic firing of premature afterpotentials[1]. Decrease of extracellular K in the Purkinje fibers increases the phase 4 of the action potential causing increased automation

(Figure 1). During phase 4 of the action potential the inward flow of K ions is performed through channels depending on Mg. The action of this flow is disappeared when Mg is depleted[2,3].
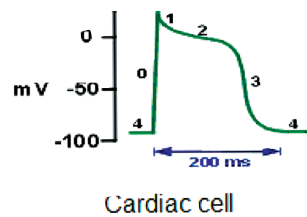
Figure 1. *Phases of myocardial cell depolarization*

Increase in serum K levels cause depolarization and reduces Na flow of Na during phase 1. Mg administration inhibits the results of hyperkalemia in the current of phase 1 and the slow calcium (Ca) inward flow of phase 2. Recent studies showed that a light increase in intracellular Mg resulted in an increase in the slow (L-type) Ca current, while greater increase in intracellular Mg decreased the Ca flow significantly. It appears that Mg influences the flow of Ca ions through the sarcoplasmic reticulum. In conclussion Mg has an action like the Ca-channel blockers[1]. Mg infusion in humans caused sinus bradycardia, longer propagation time through the atrioventricular node and longer refractory period. However with the current knowledge it is impossible to predict the exact impact of Mg depletion or its correction on heart electrophysiology. Theoretically Mg administration can help in controling arrythmias in certain cases.

The role of Mg in hypokalemia

It appears that Mg and K metabolism are closely linked. Observations in humans and animals show that Mg depletion renders the cell unable to retain K difference between intra- and extracellular space and results in intracellular K depletion. This phenomenon occurs because the Na/K pump action depends on Mg. The insufficient action of the Na/K pump results in K depletion and intracellular Na accumulation. Furthermore the kidney can not retain K[4]. Shils et al found that hypokalemia occured in experimentaly caused hypomagnesemia in volunteers. Whang et al concluded that in 46 hypokalemic patients with hypomagnesemia, hypokalemia could only be corrected when the Mg depletion was corrected[5]. In conclusion, Mg levels should be estimated in every patient with hypokalemia that can not be controled and the depleted amount of Mg should be administered[6].

Mg depletion and cardiac electrophysiology

In experimental animals when severe Mg depletion was established tachycardia was the prime manifestation followed by severe arrhythmia and consequently bradycardia. The ECG changes were: short PQ and

QRS, at a lesser degree shortening of the QT and negative T waves[1]. In less severe Mg depletion the ECG changes were: sinus tachycardia, high peak T waves and ST segment depression. Similar changes occured in hyperkalemia (Figure 2)[7].

Cardiovascular manifastations of Mg depletion

Hypomagnesemia in congestive heart failure(CHF)

In experimental models without organic cardiac disease hypomagnesemia caused signs of cardiac failure which was improved after Mg administration[8,9].

The main causes of hypomagnesemia in CHF include: administration of drugs such as furosemide, thiazides, digoxin, as well as activation of renin-aldosterone system or the arginine-vasopressin system and oedema of intestinal villi[10]. Although the prevalence of hypomagnesemia depends on dietary Mg intake as well as the standard values of each laboratory, it is estimated that it is about 7% among patients in coronary unit and 37% in patients using diuretics.
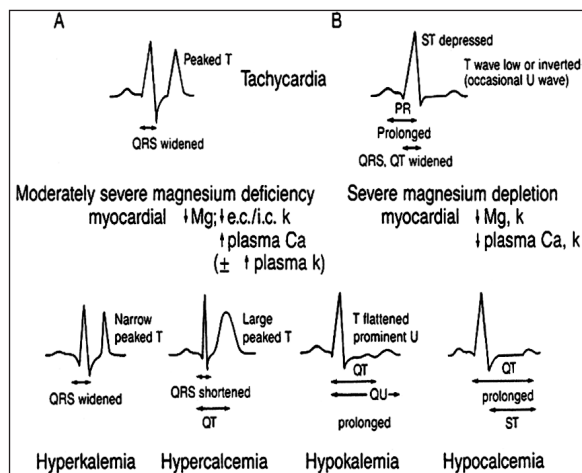
Figure 2. *ECG changes of severe and mild hypomagnesemia compared to hypo-hyper kalemia and hypo-hyper-calcemia (Seelig MS, Ann NY Acad Sci).*

Effects in blood flow

Mg depletion results in haemodynamic disturbances in the vast majority of organs. Endocrine tissues have increased blood flow while the rest tissues have vasoconstriction. These actions are due to the prostaglandin synthesis and the Ca entrance into the cells.

Pathology findings

In experimental animals receiving diet poor in Mg, lessions in small and subendocardial arteries causing myocardial ischemia were found. Mg regulates Ca entrance in the mitochondria and affects the degree of myocardial ischemia as well as the action of catecholamines. In experimental models of lethal ischemia in myocardial cells the primary disturbance was the Mg depletion[11].

Ventricular arrhythmias and hypomagnesemia

Arrhythmias caused by magnesium deficiency occur more frequently in patients with alcoholism in withdrawal state, in long term parenteral feeding, chronic diarrhea, short-bowel syndrome, surgical drainages of gastrointestinal tract and with anticoagulants binding drugs.

It is proven that the administration of magnesium salts reduces the incidence of arrhythmias and improves survival in patients with myocardial infarction. The impact of hypomagnesaemia on automatic triggered activity has drawn intense interest[5,8]. Given the increased incidence of sudden death among patients with chronic heart failure, even a minor decrease in arrythmiogenic deaths will lead to an important decrease of mortality (figure 3). A lot of investigation has to be done on this direction.

As a matter of fact the electrophysiological effects of magnesium are mediated through changes on Na/K ATPase activity. Magnesium is a necessary co-factor of Na/K ATPase. Since 3H houabain binding sites are already decreased in patients treated with diuretics, magnesium deficiency could lead to further elevation of intracellular sodium concentrations and reductions of potassium levels. Digoxin acts at the sodium potassium pump, and a low magnesium concentration may therefore be an important contributing factor in digitalis induced arrhythmias. All those results are overwhelming in coexistent magnesium deficiency. Even more, we know that hypomagnesaemia leads to hypokalemia, which is resistant to potassium administration as long as magnesium levels remain low.

Unfortunately, there are no controlled double blind studies evaluating the effects of magnesium supplementation on either ventricular arrhythmias or sudden death. On the contrary, in acute stages of a myocardial infarction, a randomized, double blind, placebo-controlled study demonstrated that magnesium supplementation could prevent arrhythmias.
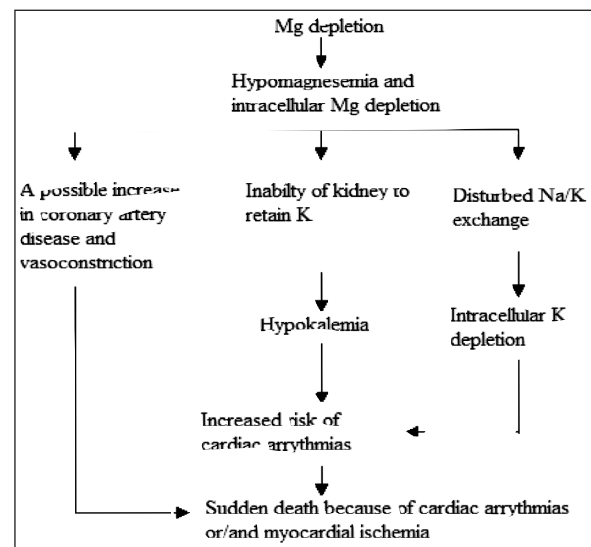
Figure 3. *Mechanisms of sudden death in Mg depletion*

Digitalis toxicity

The connection between magnesium and digoxin side effects is well known. Cardiac glycosides act by inhibiting Na/K pump, thus increasing intracellular sodium and through Na-Ca exchange they lead to Ca influx. Magnesium is a cofactor of Na/K pump and, as a result, deficiency of this cation plays a role in arrhythmias with the previous mechanism.

Long QT arrhythmias

Excluding congenital long QT syndromes, it is well known that electrolyte disorders induce polymorphic ventricular tachycardia. Although the reduction of extra cellular magnesium per se doesn't perturb the electrophysiology of myofibrils, in vitro models of early potentials have shown that adding magnesium blocks the automatic activity[1,8]. Magnesium administration is efficient in normomagnesemic patients with polymorphic ventricular tachycardia. In 12 patients with drug-induced torsades des points, Mg administration (1 gr in 20 min) was effective in 9 cases[12]. Consequently the role of magnesium in arrhythmias must be further elucidated[1,13].

Magnesium administration in therapy of ventricular arrhythmias

The relation between serious hypomagnesemia and digitalis-induced arrhythmias is well known. Recent recommendations suggest magnesium administration in normomagnesemic patients due to its anti-arrhythmic properties in three clinical settings 1) digitalis toxicity, 2) long QT 3) post-infractional arrhythmias.

Conclusions

Although the electrophysiological actions of magnesium are not fully understood, it is clear that the marked magnesium deficiency evokes arrhythmias and digitalis toxicity. Correction of Mg level in these cases is of paramount importance. Even in patients with normal serum magnesium further supplementation is beneficial in some cases[8].

Magnesium and coronary heart disease
Progression of atheromatosis

Atherosclerosis is consistently found in experimental models with high cholesterol diet. Magnesium deficiency promotes lesions in small and middle size arteries, characterized by eodema, intimal thickening, and deposition of calcium and lipids. In animals fed with a diet rich in lipids and calcium and low in magnesium, atherosclerosis accelerated in large size arteries.

Coronary heart disease and magnesium depletion

Magnesium depletion seems to be involved in onset, morbidity and mortality from myocardial infarction. In experimental animals the degree of atherosclerotic disease is inversely related with dietary magnesium intake. Deficiency causes endothelial disfunction, hypercoagulopathy and increases lipids concentration in atheromatic lesions. Further depletion seems to be related with hyperreactivity of coronary arteries to vasoconstrictive stimuli (neurohormonic, electrolytic), whereas Mg levels normalization plays a role in protection against angina and peripheral vasoconstriction[8].

On the other hand, magnesium is involved in various stages of myocardial damage after coronary artery occlusion. This is supported by various studies in magnesium deficient rats. In those animals a further derangement in metabolism of ischemic myocardium, is observed. During ischemia magnesium protects the cell from potassium loss and calcium influx[14]. In humans, epidemiological trials prove significant statistical correlation between atherosclerotic disease and low dietary intake of magnesium. Furthermore in experimental animals the extension of myocardial infarction is wider when magnesium deficiency coexists. There are recommendations that magnesium levels must be evaluated in all patients with vascular disease.

Magnesium in acute myocardial infarction (AMI)

Clinical trials have shown (Rasmussen et al, Abraham et al)[15] that magnesium administration in patients with AMI was associated with approximately 50% fewer arrhythmias than in placebo treated patients. In another study magnesium administration in the first 24 hours after coronary occlusion reduces the first year mortality indexes (p=0.02). Experimental models have shown that magnesium administration before, during or 15-20 min after coronary occlusion prevents the stunning of myocardium and reduces the ischemic area[16].

The mechanisms by which magnesium might exert a beneficial effect in myocardial infarction are obviously multiple, and include effects on both normal and abnormal automation, on intracellular calcium and, perhaps on factors such as coronary tone. It is not clear whether the frequent hypomagnesemia found in patients with acute myocardial infarction is the result of the increased cardiovascular risk or hypomagnesemia is an epiphenomenon of catecholamine release and subsequent lipolysis saponopoiesis[14]. However the low prevalence of cardiovascular diseases in areas with hard water in comparison with areas with soft water verifies that the preventive prescription of this element is beneficial.

Currently a large randomized double blind trial (magic) is in progress, which will evaluate the role of magnesium in acute myocardial infarction treatment. However it is imperative to measure the serum magnesium levels in all patients with AMI and if hypomagnesaemia is found, it should be corrected for the prevention of arrhythmias. On the other hand patients who are admitted after the critical point of six hours or those who are suffering from uncomplicated AMI seem to have no benefit from magnesium administration[17].

Coagulation and thrombosis

Animals with magnesium deficiency have significantly

shorter prothrombin time than healthy animals. Hypercoagulability caused by thrombogenic diet rich in fat was counteracted by oral supplements of magnesium. Most of the in vitro studies show that magnesium inhibits coagulation factors (protrombin, thrombin, V, VII, IX). The antithrombotic effect of high concentrations of magnesium has been investigated in animals receiving standard diets with artificially induced intimal lesions. The suppression of platelet aggregation by local application of a magnesium sulfate solution (6%) was demonstrated at areas of intimal injury. Repeated intravenous infusions of isotonic also suppressed the thrombus formation[18].

Magnesium and hypertension

The role of magnesium in hypertensive disease has been suggested since 19th century when it was introduced in the therapy of preeclampsia -eclampsia syndrome. Studies have verified the relation between magnesium levels and blood pressure. Vasoconstriction and subsequent high blood pressure is observed in patients with low magnesium intake, whereas the pharmacological administration of magnesium reduces the BP[19-23]. In general, hypertension seems to be related with low magnesium intracellular levels, which lead to intense muscle tone and over reactivity of middle layer. This is mediated through the increased concentration of inteacellular calcium, which activates the fibrin-myosin complex, and the contraction of arterioles. Whang et al have published studies revealing the increased demand for antihypertensive medication in patients with low magnesium levels. On the contrary with experimental studies, epidemiological trials did not confirm the correlation. In summary, results of clinical trials neither prove nor refute the hypothesis that oral Mg provides an effective means of reducing blood pressure. On the contrary in secondary hypertension e.g. eclapmsia, hypertension of alcohol withdrawal, the critical significance of hypomagnesaemia is well known.

Thiazide treatment of systemic hypertension and the risks of hypomagnesemia

Clinical and investigational evidence has proved an association between thiazide induced electrolyte imbalances and ventricular arrhythmias. Elderly hypertensive patients are at particular risk because of their tendency to have significantly reduced levels, which decrease further when treated with thiazide diuretics[2]. Therefore concomitant administration of potassium and magnesium supplementation appears to be an approach to reducing the risk of arrhythmias and deaths. Routine monitoring of potassium and magnesium is strongly recommended and co-administration of potassium sparing diuretics is indicated, especially in patients with left ventricular hypertrophy or coronary disease. Of the available formulations, magnesium chloride is particularly suitable for patients taking diuretics for the replenishment of Cl and the return of serum pH to normal levels.

Therapy of magnesium depletion

Individuals with reduced dietary intake of Mg must receive 350 mg for men and 280 mg for women in magnesium oxide formulations. Intravenous repletion of magnesium is justified in patients with cardiac diseases, convulsions, serious hypocalcaemia, hypokalemia, and hypomagnesemia <1.4 mg/dL[24-26]. In the inpatient setting, the intravenous route of administration favored because it is highly effective inexpensive and usually well tolerated. The standard preparation is $MgSO_4.7H_2O$. In patients who are actively seizing or who have cardiac arrhythmia, 8 to 16 mEq (1 to 2 gr) may be administrated intravenously over a 2-4 minute period. A slower rate of administration is safer (1 gr during 6 h). A simple regimen for not emergent magnesium repletion is to administer 64 mEq (8 g) of magnesium over the first 24 hours and then 32 mg (4 g) daily for the next 2 to 6 days. It is important to bear in mind that serum levels rise early whereas intracellular stores take longer to replete, so magnesium repletion should continue for at least 1 to 2 days.

In patients with a reduced glomerular filtration rate (GFR) the rate of repletion should be reduced by 25% to 50%, the patient should be carefully monitored for signs of hypomagnesemia (flushing, loss of deep tendon reflexes, hypotension, atrioventricular block, and respiratory depression). In addition over correction of magnesium depletion leads to decreased serum ionized Ca levels and to tetany[17]. In this case administration of calcium gluconate (2 amp in 10-15 min) prevents tetany. The physician must have in mind that the administration of anions, which are not absorbed in proximal convoluted tubules like SO4 favors the development of even greater negative electric voltage in the lumens of distal tubules and leads to kaliurisis. In case of hypokalemia salts formulations with not absorbable anions e.g. Cl are preferred.

In patients with inappropriate renal magnesium wasting, potassium-sparing diuretics that block the distal tubule epithelial Na channel, such as amiloride and triamterene, may reduce renal magnesium losses. There are recommendations that in patients with hypokaliemia caused by diuretics or in Gitelman-Barter syndrome, potassium sparing diuretic must be added to the regimen[27].

Referenses
1. Marsepoil T, Blin F, Hardy F et al. Torsades de pointes and hypomagnesemia. Ann Fr Anesth Reanim 1985; 4:524-526
2. Hollifield J. Electrolyte disarray and cardiovascular disease. Am J Cardiol 1989; 63:21-26
3. White RE, Hurtle HC. Magnesium ions in cardiac function: Regulator of ion channels and second messengers. Biochem Pharmacol 1989; 38: 859-867
4. Gennari FJ. Current Concepts: Hypokalemia. N Engl J Med 1998; 339:451-458
5. Whang R. Clinical disorders of magnesium metabolism. Compr Ther 1997; 23:168-173
6. Robert K. Rude Physiology of magnesium metabolism and

the important role of magnesium in potassium deficiency. Am J Cardiol 1989; 63:31-34

7. Salim Y, Govindarajan V, Koon T. Critical review of the approaches to the prevention of sudden death. Am J Cardiol 1993; 72:223-225

8. Nair RR, Nair P. Alteration of myocardial mechanics in marginal magnesium deficiency. Magnes Res 2002; 15:287-306

9. Stephen S. Gottlieb Importance of magnesium in congestive heart failure. Am J Cardiol; 63:39-42

10. Ohtsuka S, Yamaguchi I. Magnesium in congestive heart failure. Clin Calcium 2005; 15:181-186

11. Gums JG. Magnesium in cardiovascular and other disorders. Am J Health Syst Pharm 2004; 61:1569-1576

12. Sueta CA, Patterson JH, Adams KF Jr. Antiarrhythmic action of pharmacological administration of magnesiumin heart failure: a critical review of new data. Magnes Res 1995; 8:389-401

13. Dan Tzivoni, Andre Keren, Amos M et al. Magnesium therapy for torsades de pointes. Am J Cardiol 1984; 53:528-530

14. Mildred S. Magnesium in acute myocardial infarction (International Study of Infarct Survival). Am J Cardiol 1991; 68:1221-1222

15. Cooper HA, Domanski MJ, Rosenberg Y et al. Magnesium in Coronaries trial investigators. Acute ST-segment elevation myocardial infarction and prior stroke: an analysis from the Magnesium in Coronaries (MAGIC) trial. Am Heart J 2004; 148:1012-1019

16. Moens AL, Claeys MJ, Timmermans JP, Vrints CJ. Myocardial ischemia/reperfusion-injury, a clinical view on a complex pathophysiological process. Int J Cardiol 2005; 100:179-190

17. Hennekens CH, Albert CM, Godfried SL, Gaziano JM, Buring J E. Drug Therapy: Adjunctive Drug Therapy of Acute Myocardial Infarction - Evidence from Clinical Trials. N Engl J Med 1996; 335:1660-1668

18. Nigam S, Averdunk R, Guenther T. Alteration of prostanoid metabolism in rats with magnesium deficiency. Prostaglandins Leukotrienes Med 1986; 23:1-10

19. Bergman G, Daly K, Atkinson L, Rothman M, Richardson PJ, Jackson G, Jewett DE. Prostacyclin: haemodynamic and metabolic effects in patients with coronary artery disease. Lancet 1981; 1:569-572

20. David A, McCarron DA. Diuretic therapy for mild hypertension: The "real" cost of treatment. Am J Cardiol 1984; 53:A9-A11

21. Lichton IJ: Dietary intake levels of requirements of Mg and Ca for different segments of the U.S. population. Magnesium 1989; 8:117-123

22. Mc Carron DA: Calcium, magnesium, and phosphorus balance in human and experimental hypertension. Hypertension 1982; 4(suppl III):III27-III33

23. Marier JR: Magnesium content of the food supply in the modern-day world. Magnesium 1986; 5:1-8

24. Morton H, Maxwell G, Abraham U. Waks Cations in essential hypertension. Am J Cardiol 1987; 59:A108-A114

25. Chachashvily S, Averbukh Z, Golik A et al. Prognostic evaluation failure: pathophysiological correlates in (frusemide) treated patients with congestive heart failure. Serum magnesium aberrations in furosemide 2003; 89:411-416

26. Martinez-Riquelme A, Rawlings J, Morley S, Kendall J, Hosking D, Allison S. Self-administered subcutaneous fluid infusion at home in the management of fluid depletion and hypomagnesaemia in gastrointestinal disease. Clin Nutr 2005; 24:158-163

27. Ahsan SK. Magnesium in health and disease. J Pak Med Assoc 1998; 48:246-250