Role of magnesium in heart diseases among elderly

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Abstract
Magnesium constitutes fourth most abundant cation in human body. It plays important role in the electrical stability of the conduction system of the heart. Measure of total serum magnesium correlates with ionized and intracellular levels of magnesium in human cells. Both low and high levels of magnesium are associated with cardiac disorders especially in older people. The hypomagnesemia contributes to atherosclerosis which in turn is a risk factor for Hypertension and cardiovascular diseases. The magnesium in diet is often not sufficient to meet the daily needs in older people hence they are prone for developing complication of cardiovascular events. This review relooks at the role of magnesium in causing cardiovascular diseases and its complications.

Keywords: Magnesium, Elderly, Heart Disease.

Introduction
In the earth crust, magnesium (Mg^{2+}) is the eighth common element.[1,2] The biologically available magnesium is present mainly in the water source, like ocean and rivers.[3]

In, humans it is the fourth most abundant cation and the second most abundant intracellular cation following potassium.[4-6] In human body, 99 percent of magnesium compound is within the bones, muscles and non-muscular soft tissues, mainly fat.[7] It acts as a cofactor for more than 300 enzymatic reactions.[8,9] It has been found that low serum magnesium levels are associated with type 2 Diabetes Mellitus, Hypertension, Insulin resistance, Asthma, Alzheimer's Disease.[10]

History
A farmer named Henry Wicker at Epsom in England in 1618, found that the cows owned by him refused to drink the water due to bitter taste. He also noticed that the same water instead helped in early healing of superficial wounds which was eventually recognized to be magnesium sulphate by Dr Nehemiah Grew in 1697 which is known as Epsom salts.

In 1920, Willey Glover Denis, showed that magnesium is present in blood plasma of human body. Magnesium deficiency in humans was first reported by Arthur Hirschfelder and Victor Haury in 1934.[11]

Metabolism
The concentration of Magnesium (Mg^{2+}) is maintained within normal limits by interaction between the Intestine, Kidney and Bone. As the blood concentration of Mg^{2+} falls, it is increased by increasing the absorption through gut and the Bone and when excess it is calibrated and excreted through kidney and faeces.[12]

In the gut, Magnesium is absorbed in small intestine mainly by jejunum and ileum by passive paracellular mechanism i.e, through small spaces between the cells which acts by electrochemical gradient and other pathway is Transcellular pathway, with Transcellular Transporter Transient Receptor Potassium Channel Melastatin Membrane (TRPM) 6 & 7 which contributes less but plays pivotal role.[13] The Mg^{2+} stores in body determine the rate of absorption and excretion and the content of magnesium in food is inversely proportional to absorption.[14,12]

The concentration of Mg^{2+} is mainly maintained by Kidney by filtration and reabsorption. The reabsorption from the filtrate produced by glomeruli occurs mainly at proximal convoluted tubule (PCT) which absorbs around 60-70% and partly by distal nephrons when the concentrations are low. Totally around 95% of Mg^{2+} is reabsorbed and only 3-5% is excreted through kidney.[12,15]

Diets rich in fibres, increased intake of calcium and phosphates hinders the absorption of magnesium through the gut.

Functions of magnesium
Magnesium has many physiological roles in different parts of the body like -

1. At Cellular Level – it acts as direct enzyme activator including the reactions which produce ATP.[16]
2. Metabolic – it has structural function in synthesis of DNA, RNA and many of the proteins.[16]
3. Muscular System – it acts as calcium antagonist, as it competes for the binding site and inhibits muscle contraction, its also competes for neurotransmitter release.[9]
4. Enzymes – hexokinase, Na^{+}-K^{+} ATPase, creatine kinase, protein kinase, and cyclase are important enzymes carrying out many of the important cellular functions which are dependent on magnesium.[9]

5. Structural functions – it helps in maintaining the structure of proteins, polyribosomes, nucleic acids, and the mitochondria.[9]

It also has role in nerve conduction, contraction of muscle and also acts in maintaining the rhythm of heart by active transport of calcium and potassium ions across the cell membrane. It plays an important role in production of glutathione, a potent intracellular antioxidant in human body, which is synthesized by Adenosine Triphosphate dependent pathway and this needs magnesium.[9,17-20]

Sources and daily requirements

Magnesium is a naturally available product, it is present mainly in water.[10,14] Green leafy vegetable, especially spinach has high content, Legumes, whole grains, Sea foods, Nuts and Fruits like banana and avocado.

Hard water constitutes more magnesium than the soft water, and thus hard water fulfills the requirement better than soft water.[21-23] Water accounts for around 10 percent of daily magnesium intake.[24] With time, the essence of calcium consumption has increased leading to increased calcium intake, which has produced relative magnesium deficiency.[25]

It has been found that vitamin-D deficiency or its altered metabolism occurring in the renal diseases like chronic renal disease, decreases serum calcium levels, which has direct effect on magnesium absorption leading to decreased serum magnesium.[26,27]

Recommended dietary allowance

Intake of up to 5 mg/kg/day is insufficient to maintain the equilibrium hence, 6 mg/kg/day in normal status (300 – 360 mg/day)[23] and 7-10 mg/kg/day is considered to be adequate when the person is under physical or emotional stress.[28,29]

Methods of assessment of magnesium levels

Magnesium is present in various tissues and its measurement in respective tissues is possible by different methods. It is measured in following tissues:

1. Serum: The total body magnesium is not represented by the serum magnesium, instead it reflects the concentration in interstitial fluid and bone,[8,30] as the serum magnesium forms 0.3 percent of total body magnesium.[31]

   The serum magnesium levels are affected by heamolysis, concentration of bilirubin, exertion, third trimester of pregnancy and also there is intra individual variability found in healthy adults.[32-34]

   The normal serum magnesium levels in healthy adults lies between 1.70 and 2.55 mg/dl, done by using Calmagite method.[35]
2. Red Blood Cells: the magnesium in RBC's doesn't correlate well with the status of total serum magnesium.
3. Leucocytes: magnesium content within leucocytes correlates more better with the skeletal and cardiac magnesium content.[36]
4. Muscle: the assessment of magnesium levels in muscles is most expensive and is also an invasive procedure, hence not preferred.[37]

Renal excretion of magnesium – magnesium excretion through the kidney act as a circadian rhythm. It is helpful to measure the renal loss of magnesium which may be due to drugs (loop diuretics) or congenital anomalies (Bartter's Syndrome).[38] Normal excretion range is 60 - 210 mg/24 hours.[35]

Free magnesium levels in body is measured by using following methods,

1. Fluorescent Probes: This method uses Mag-Fura 2 as fluorescent, not useful as it also binds to calcium.[10]
2. Ion-Selective Electrodes, and Nuclear magnetic Resonance Spectroscopy which uses atomic absorption spectroscopy (AAS) and Metallochrome Dyes are used to measure the free magnesium levels.[10]

Serum magnesium levels in elderly

The serum magnesium levels in elderly has been studied widely and found to be marginally low and not clearly deficient when compared to adult where serum magnesium levels are above the lower margin of normal levels.

The exact magnesium requirement per day still has to be systematically investigated and hence fixed magnesium consumptions could not be made in elderly.[39,40]

The main reason for low serum magnesium levels in elderly[41] in comparison to adults is postulated to be due to

1. Low magnesium intake, which accounts for major portion for low levels.
2. Decreased intestinal absorption
3. Increased urinary loss
4. Stress, the add on factor for low levels of serum magnesium among elderly, which acts as a predisposing factor.

The availability of magnesium in bone decreases with age and hence may not be available during magnesium deficiency in elderly.[41]

Hypomagnesemia

It seems easy to define hypomagnesemia, but primarily accurate tests for the assessment of Mg^{2+} status are still lacking.[42] Patients with serum Mg^{2+} levels less than 1.7 mg/dl were considered to be hypomagnesemia.[35] Chronic Mg^{2+} deficiency, where in plasma Mg^{2+} levels may be in borderline or with in normal range, but total body Mg^{2+} are low and have increased risk of Atherosclerosis, Hypertension and Myocardial Infarction.[43] The clinical features of

hypomagnesaemia develops, when serum magnesium levels fall below 1.2 mg/dl.

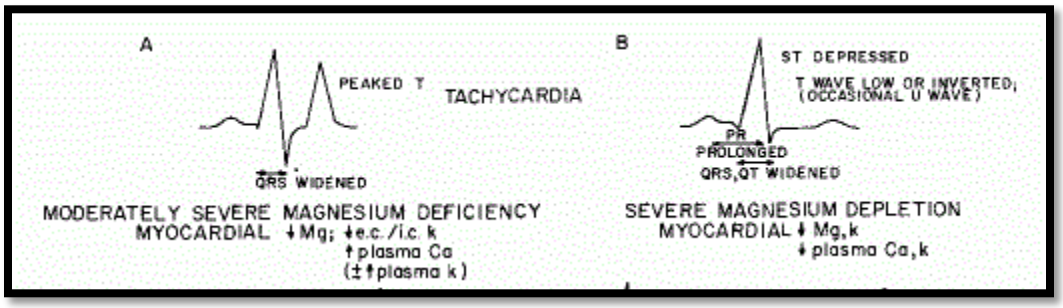
As the homeostasis of serum magnesium is maintained by intestinal absorption, bone stores and renal excretion, any alteration in these parameters causes hypomagnesaemia and it is also produced due to redistribution of serum magnesium.

Clinical features

CARDAIC- the changes produced here are mainly recorded in the ECG which shows arrhythmias; Atrial Fibrillation and ventricular tachy-arrythmia being more common.[38]

ECG changes

Minimal deficiency - short PR interval, little shortening of QT interval, short QRS and negative T waves.
Severe deficiency – sinus T wave, peak T wave and ST depressions.



Treatment

Magnesium supplementation is given as magnesium sulphate ($MgSO_4$).Magnesium Sulphate is available as powder and also as 10% and 50% solutions.

In mild hypomagnesemia, treatment is by giving oral Magnesium Sulphate 2gm thrice a day. And in severe hypomagnesemia i.e, less than 1.2 mg/dl, treatment with 2gm of magnesium sulphate intravenously slow over ten minutes and then followed by 10ml of 50% magnesium sulphate in 500ml normal saline for 3 days.

Along with this, underlying cause and associated hypokalaemia, hypocalcaemia if present, need to be corrected.

Hypermagnesemia

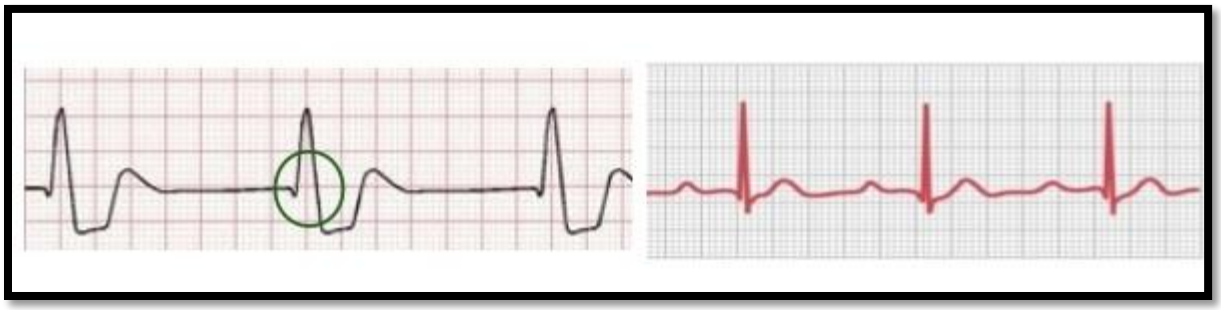
As mentioned earlier Kidney plays a vital role in Magnesium homeostasis, hence in renal impairment the kidneys are unable to excrete the excess magnesium leading to Hypermagnesemia.[44] Serum magnesium levels more than 3.0 mg/dl is considered to be hypermagnesemia.

Clinical features

Cardiac manifestations like hypotension which is due to peripheral vasodilation, bradyarrhythmia and in severe cases cardiac asystole is seen.[45]

ECG changes

Bradycardia or prolonged PR interval, QRS and QT intervals, complete heart blocks and AF which are all not specific to hypermagnesemia.[45]



Treatment

Eliminating the source of magnesium is first mode of treatment.

When the renal function is intact, injection furosemide can be used and when its impaired dialysis is the treatment of choice.

To correct acute manifestations like hypotension or cardiac bradyarrhythmias, intravenous calcium gluconate 10- 20 ml slowly over 10 minutes is effective.

Role of magensium in myocardial infarction

It has been studied since long years and found that magnesium has a role in the pathogenesis of atherosclerosis and myocardial infarction.

Abraham et al, presented a pioneering paper showing association between low magnesium and myocardial infarction in 1970.[46]

The increased risk of myocardial infarction due to low serum magnesium is proposed to be due to strong anti-inflammatory role of magnesium which indirectly inhibits initiation of atherosclerosis, lowers the lipid levels, and also reduces free reactive oxygen species (ROS), which all together initiate atherosclerosis.[47,48]

It also prevents blood clotting by reducing platelet aggregation and is a strong vasodilator.[49]

Low magnesium levels directly affect the endothelial behaviour, the effects of it are due to decreased endothelial proliferation, decreased CDC 25B and increased Interleukin-1 (IL-1) and vascular cell adhesion molecule 1 (VCAM-1), which leads to atherosclerosis. This effect adds to pro-inflammatory, pro-thrombotic and pro-atherogenic environment.[50]

In, many experiments it has been found that early treatment with magnesium intravenously limits the infarct size and the possible mechanisms are as proposed.[51]

1. It decreases the vulnerability of injured myocardium to the oxygen derived free radicals.
2. Decreases intracellular calcium levels by inhibiting influx of calcium ions.
3. The balancing of increased oxygen demand by reducing the sinus rate and also by lowering the arterial pressure
4. Coronary vasodilatation
5. Inhibiting platelet aggregation and thus thrombus formation.

High magnesium dietary consumption has been found to reduce the coronary artery calcification and thus can be considered as protective in preventing acute myocardial infarction.

Atherosclerosis is produced due to endothelial dysfunctioning which results in increased adherence of leucocytes, excessive secretion of chemokines and increase permeability to lipids into the cells and enhanced oxidation of low density lipoprotiens (LDL), and stimulation and proliferation of smooth muscle cells into the intima and also activation of platelets which all together leads to atherosclerosis.[51]

Thus, the deficiency of magnesium is involved in dysfunctioning of endothelium and also acts as an important add on factor for increase in lipid concentration in the atheromatous plaque.[52]

Magnesium contributes to the synthesis of nitric oxide within the endothelial cells and reduce the vascular tone and prevent the occurrence of hypertension, which is a known risk factor for atherosclerosis and thus myocardial infarction.[53]

Magnesium deficiency found to increase the free radicals which are toxic to endothelial cells.[54]

The small and medium sized arteries are affected by hypomagnesemia, by producing lesions like thickening of intima, localised edema and depolarisation of calcium and lipids which contribute the formation of atherosclerosis.[55]

The hypercoaguability secondary to hypomagnesemia is due to the fact that magnesium inhibits prothrombin, thrombin, coagulation factors like 5, 7 and 9 which are must for the initiation and progression of clot formation.[56]

It has also been found that the oxidative stress produced in the endothelial cells leading to increase in reactive oxygen species (ROS) and thus cytotoxicity of the endothelial cells is enhanced by the deficiency of magnesium.[57,58]

The ROS which act on the endothelial cells produce a permanent inflammation which is shown by increased Nuclear Factor-kB (NF-kB) activity. As Nuclear Factor-kB (NF-kB) regulates Interleukin-1 (IL-1), tumour necrosing factor-alpha transcription, which acts as a pro-inflammatory cytokine, triggering the localised inflammation resulting in recruitment of monocytes and proliferation of smooth muscle cells which is further exacerbated by increase in matrix metalloproteases 2 and 9, which is markedly influenced by low magnesium.[59,60]

Thus, the hypomagnesaemia produces atherosclerosis, vascular thrombosis and/or vascular calcification.[1]

Magnesium helps in prevention of myocardial infarction and the possible action predicted is magnesium induced relaxation of endothelial and smooth muscle cells of heart and vasculature.[61-63]

The vasodilatation property of magnesium also helps in reducing the blood pressure which is a known risk factor for Myocardial Infarction and thus indirectly reduce the risk of myocardial infarction, it does so by reducing the expression of endothelin-1 which is most potent vasoconstrictor, and magnesium also increases Prostaglandin I_2 (PGI_2) which is a well-known vasodilator.[64-67]

It has also been postulated by Iseli et al**[68]** that decrease in magnesium increases intracellular calcium levels and thus increases the duration of contraction of heart and vascular smooth muscle cells and there by leading to ischaemia and hypertension respectively.-

Role of magnesium in arrhythmias

In 1935, Dr Zevillinger, first reported that Mg^{2+} has anti-arrhythmic effects.[69] Magnesium doesn't inhibit arrhythmias by itself *per se*, but it does by altering the cardiac potentials by interfering with the calcium and potassium channels, as magnesium, regulates their activity.[70,71]

The myocardial cells and other cell action potential is determined by the electrical activity acting across the

cell membrane which in turn is regulated by electrochemical gradient across the cell membrane.[72]

The depolarisation and repolarisation are brought by the transmembrane movement of electrolytes like sodium, potassium, and calcium, which monitor the action potential.[73]

The resting action potential of cell membrane is maintained by the Na^+/K^+ ATPase pump, which causes efflux of sodium and influx of potassium against the concentration gradient, utilising adenosine triphosphate (ATP) by phosphorylation and Magnesium acts as a co factor for this reaction, and without which the reaction cannot be taken place.[74-78]

Hence, reduction in magnesium or hypomagnesaemia alters/hinders the activity of Na+/K+ ATPase pump leading to accumulation of sodium within the cell and potassium out of the cell. The accumulated sodium is exchanged with the calcium within the cell, resulting in transient depolarisation of cell membrane and repetitive arrhythmias.[74-78]

Serum potassium mainly regulates the depolarisation, repolarisation of cellular membrane and also the automation of myocardial conducting cells like the purkinje fibre cells.[79]

Decrease in the extracellular potassium in the conductive cells of purkinje fibres results in prolongation of phase 4 of action potential and thus increasing the automation and occurrence of arrhythmias. And the flow of potassium into the cell during phase 4 of action potential is dependent on serum magnesium. Decrease in magnesium results in decreased influx of potassium.

Similarly, the inward flow of calcium during the second phase if action potential occurring through the L-type of calcium channels is dependent on serum magnesium. Increase in serum magnesium acts on the slow L-type of calcium channels and decrease the flow of calcium into cells, and there by producing longer refractory period and increased propagation through the AV Node, thus magnesium acts a calcium channel blocker, producing bradycardia.[62]

With this it is predicted that magnesium has rate limiting activity and hypomagnesaemia can cause increase in heart rate and severe hypomagnesaemia can cause arrhythmias.[62]

Decrease in serum magnesium has been found to be associated, as a risk factor for occurance of prolongation of QTc interval and supplementation of magnesium even in patients with normal serum magnesium levels has found to decrease the QTc interval.[80]

QTc is produced due to low resting membrane potential which is produced by the low serum magnesium levels, which not directly but indirectly decreases the potassium concentration within the cell and thus the resting membrane potential leading to QTc prolongation, which can be initiation for arrhythmia.[81]

Magnesium in heart failure

Heart failure is hypothesised to be produced mainly due to endothelial dysfunctioning which acts as the main initiating and propagating factor for heart failure.[82]

It has been observed that removal of magnesium from the disrupted endothelium produces vasoconstriction and this was confirmed by restoration of vascular tone on replacement of magnesium into the endothelium[83]

Magnesium is thus implicated to reduce the systemic vascular resistance, mean arterial pressure, and also found to reduce coronary vasoconstriction and thus increase the coronary blood flow, and increases the cardiac index.[84-86]

It has been found that treatment with 400 mg of oral Magnesium Sulphate twice daily for 3 months improved the outcome in patients with heart failure.[87]

Screening for serum magnesium levels

Magnesium is a micronutrient, with the dietary allowance that can be met by the daily food we consume. The magnesium in body is still found to be low, which is due to the factors which interfere with its absorption from the gut like the drugs and in elderly the main reason being decreased consumption and which is added up by stress.

Magnesium has been implicated as a contributing factor in many diseases and the identification and correction of low magnesium has improved the outcome (evidenced by LIMIT-2 study). As it is also evidenced that patients admitted in Intensive Care Unit (ICU) and having low serum magnesium levels had poor outcome with increased mortality.

Hence, screening in all elderly with acute coronary syndrome and treated accordingly with intravenous magnesium in severe hypomagnesaemia and with oral supplementation in mild to moderate hypomagnesaemia has beneficial effects.[88]

Conclusion

Magnesium being a trace element, forms an important cation in human body, as it has a major contribution in many of the physiological functions occurring in human body.

It has also been proposed that serum magnesium levels decrease with increasing age and the elderly (>60 years) are at high risk for hypomagnesemia, due to the decreased intake and second factor being stress and others like chronic medications.

The beneficial effects were seen in LIMIT-2 study, favouring magnesium supplementation. The studies namely ISIS-4, MAGIC showed no additional benefits mean time also noted no adverse outcomes. There were wide variations noted in study designs.

Hence, in all elderly patients with myocardial infarction who are at higher risk than adults should always undergo for screening of serum magnesium

levels irrespective of clinical features and ECG changes.

In patients with low serum magnesium levels, correction with oral supplementation in mild to moderate hypomagnesaemia and in with intravenous magnesium in severe hypomagnesaemia should be done. It may be followed by oral supplementation as a long-term treatment.

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