A STUDY OF THE PREVALENCE OF SERUM MAGNESIUM DEFICIENCY IN PATIENTS WITH ACUTE ISCHEMIC CEREBROVASCULAR ACCIDENT

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BONAFIDE CERTIFICATE

This is to certify that dissertation named **"A STUDY OF THE PREVALENCE OF SERUM MAGNESIUM DEFICIENCY IN PATIENTS WITH ACUTE ISCHEMIC CEREBROVASCULAR ACCIDENTS"** is a bonafide work performed by Dr. S.T. Sakthi Suganya, post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfilment of regulations of the Tamilnadu Dr. M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2010 to April 2013.

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DECLARATION

I solemnly declare that this dissertation **"A STUDY ON THE PREVALENCE OF SERUM MAGNESIUM DEFICIENCY IN PATIENTS WITH ACUTE ISCHEMIC CEREBROVASCULAR ACCIDENTS"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr. S. Mayilvahanan M.D.**, Professor, Department of Internal Medicine, Government Royapettah Hospital, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfilment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

Place: Chennai

Date: (Dr. S.T.SAKTHI SUGANYA)

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ABSTRACT

Magnesium deficiency is described as the most under diagnosed electrolyte abnormality in current medical practice. Dietary magnesium deficiency is more prevalent than generally expected and remains to be one of the most common nutritional problems in the industrialized as well as the developing world. The chronic low magnesium diets are atherogenic and thrombogenic with association of a number of common chronic diseases like hypertension, diabetes and intensify the pre-existing cardiovascular diseases like stroke.

Aims and objectives:

To study the prevalence of serum magnesium deficiency in patients with acute ischemic cerebrovascular accidents. To assess the correlation between low magnesium levels and its association with diabetes mellitus, systemic hypertension, dyslipidemia and coronary heart disease.

Materials and methods:

60 patients who met the inclusion and exclusion criteria were selected. 30 patients who were admitted with a diagnosis of acute ischemic stroke were taken as cases. 30 patients were recruited from the outpatient department to participate in the study as controls. Serum magnesium levels were checked at the time of patients' admission.

Observation and results:

In our study, it was observed that 70% of the cases and 30% of the controls were deficient in magnesium. The mean serum magnesium levels were 1.39 and 1.76 in cases and controls respectively [$P<0.05$] which proved the association of ischemic stroke with the low magnesium levels. This study also showed a statistically significant relationship of association of systemic hypertension ($p<0.00$), dyslipidemia ($p<0.00$) with the serum magnesium deficiency.

Conclusion

In conclusion, the present study showed a statistically significant correlation between serum magnesium deficiency with the ischemic stroke and its risk factors diabetes, systemic hypertension and dyslipidemia.

CONTENTS

APPENDIX

AIM OF THE STUDY

1. To study the prevalence of serum magnesium deficiency in patients with acute ischemic cerebrovascular accidents.
2. To assess the correlation between low magnesium levels and its effect on serum cholesterol.
3. To study the relationship between serum magnesium deficiency and diabetes mellitus, systemic hypertension and coronary heart disease.
4. To assess the prognosis of acute ischemic stroke patients in accordance with the serum magnesium levels.

INTRODUCTION

Dietary magnesium deficiency is more prevalent than generally expected and remains to be one of the most common nutritional problems in the industrialized as well as the developing world. This is due to the result of current change in the dietary trends, agricultural practices and the food preparation techniques. World health organization and other health agencies say that more than 75-80% of the people do not consume the recommended daily intake of magnesium[(1)].

Magnesium depletion is described as the most under diagnosed electrolyte abnormality in current medical practice. Magnesium is gaining greater importance, as its deficiency is found to be a common problem and the prevalence of magnesium deficiency in hospital settings has been found to be 7 – 11 %. Its deficiency also coexists with other electrolyte abnormalities in 40% of the patients [(2)]. Due to the change in the dietary habits, an average human's diet is deficient in magnesium. This is more common in the alcoholics, young people, and people who receive certain medications. In otherwise normal people the chronic low magnesium diets are atherogenic and thrombogenic and disrupts the arterial and cardiac integrity and so, it is associated with a number of common chronic diseases like hypertension, diabetes, coronary, heart disease, stroke, osteoporosis, etc. [(3)]. It can also intensify the pre-existing cardiovascular

damage caused by the cardio-toxic drugs and other dietary factors like excess fat intake.

The National Institute of Health published in its website, “Magnesium is needed for the correct metabolic function of more than 350 enzymes in the human body. It helps in proper normal functioning of nerves and the muscles, maintains a strong immunity against infections, keeps the heart work in regular rhythm and supports the bone integrity. It regulates the blood sugar values, keeps the blood pressure under control, and also has a role in protein synthesis and energy metabolism. There’s a developing interest in the magnesium role in the prevention and treatment of diseases like diabetes, hypertension, cardiac and cerebral disorders.” It is thus magnesium deficiency is considered to be an epidemic deficiency. [(4)]

Magnesium is a natural antagonist of calcium and it helps in maintaining the tone and pressure in the blood vessels and the peripheral arterial blood flow. So, in its deficient state triggers vasoconstriction and enhances the injury to the vascular endothelial cells, thereby, promoting the progression in the process of atherogenesis. Virtually magnesium can affect every system of our body and is associated with every known disease.

For several hundred years, magnesium has been used as a therapeutic agent. A large number of benefits have been obtained from magnesium therapy, from antacid and laxative therapy to cytoprotection of transplanted organs.

In patients with acute ischemic stroke, for the majority of them, there is presently no widely applicable treatment, despite recent encouraging results with rt-PA. The results from various trials and preclinical studies have shown that, a number of agents that offer neuroprotection are in the developing stages of clinical advancement and have at last begun to change the treatment of ischemic stroke in everyday clinical practice.

In the pathogenesis of acute ischemic stroke, there are many factors that have an impact on the cellular injury and the extent of the area affected after ischemic damage or traumatic brain injury and subsequently on the patients function and prognosis. One among the factors is the neuroprotectant magnesium. Several studies have proved the hypothesis that in ischemic strokes, higher serum magnesium levels is accompanied by higher global function and better prognosis and administration of magnesium sulphate is associated with improvement in the neurological status and has effect on early recovery.

The present study was undertaken to evaluate whether there is correlation between serum magnesium levels of the patient with acute ischemics stroke and also on the other cardiovascular risk factors like hypertension, diabetes and dyslipidemia.

REVIEW OF LITERATURE

STROKE: A "BRAIN ATTACK" - NEGLECTED SILENT EPIDEMIC

DEFINITION

A stroke, or cerebrovascular accident, is defined by the abrupt onset of a neurologic deficit that is attributable to a focal vascular cause which lasts more than 24 hours. [5]

STROKE STATISTICS:

In the recent years, there is a shift in the diseases caused by poverty towards lifestyle-related chronic non communicable diseases in the developing countries due to the increase in the development of the economy and demography. In the developed as well as the developing countries, stroke remains to be the leading cause of serious long term neurological disability and also makes an important contribution to morbidity and mortality. In the world, stroke remains the third common most cause of death following coronary artery disease and cancer. It is also the fourth leading cause of disease burden. [6] The prevalence of stroke is nearly three-fourths more than the sixth decade. There is no age limit for the occurrence of stroke. One fourth of the overall incidences of strokes occur in young people less than the age of 65 years. [7] After the age of 55, the stroke risk is doubled for each decade. [8]

WORLDWIDE STATISTICS:

The incidence of stroke worldwide is 0.22 per 1000. Accordingly to the reports of the World Health Organization (WHO), every year worldwide, approximately around 15 million people are struck by stroke. Out of these strokes, 12.7 million are due to the higher systemic blood pressure. Of the 15 million people, around one third die and another one third have a permanent disability.[9] The number of people who are suffering from stroke is decreasing in the economically well developed countries, largely due to the fact that greater efforts are being taken to reduce hypertension and in reducing the smoking habit. However, due to ageing of the population, overall incidence of stroke remains to be high.

STROKE: THE SCENARIO IN INDIA

It is a major health problem in India. When compared to the developed countries, where it has reached plateau or has decreased, the burden of stroke has been rising in India. In India, of all the strokes, ischemic stroke contributes to around 80% and intracranial atherosclerosis appears to be commoner in Indian people.

It is estimated that approximately 1.6 million cases of stroke will be reported annually by the year 2015, out of which at least one third of them will have disability. By 2050, WHO has estimated that, 80% of all the strokes in the world would occur in the low and middle income countries, mainly India and

China [10]. It was found in Indian studies that about 10-15% of all the strokes that occur is found in the people below 40 years.

PROGNOSIS

Stroke remains the most common cause of neurological disability in the world. Patients who had suffered from stroke have a worse prognosis than for any type of cancer. Approximately after one year of the onset of stroke, half of all patients are dead or on survival becomes functionally dependent at one year. The Indian Council of Medical Research (ICMR) estimated that stroke contributes for 41 per cent of deaths and 72 per cent of disability adjusted life years (DALYS) among the non communicable diseases (NCDs).[11] Many other clinical problems like seizures, falls, fractures, depression and dementia secondary to stroke occur. So these patients are left with residual disabilities like physical dependence which leads to enormous socio-economic impact on individuals, families and health care institutions.

RISK FACTORS OF STROKE:

Various prospective epidemiological studies and the Framingham Heart Study identified hypertension, diabetes mellitus, hyperlipidemia, and smoking as the major atherogenic risk factors for stroke.

RECENT TRENDS IN THE MANGEMENT STRATEGY OF STROKE

In the recent time, there has been a dramatic improvement in the management of the ischemic stroke. Therapeutic management of acute ischemic stroke has been divided into the therapies that target the vasculature and those that target the nervous system. Current vascular strategies are limited to recanalization by clot removal (tPA thrombolysis, intraarterial fibrinolysis, mechanical removal), prevention of the clot propagation with aspirin and statins and by enhancement of the collaterals. These agents protect the brain are primarily through the hemodynamics rather than the metabolic mechanisms.[(12)]

INTRAVENOUS THROMBOLYSIS

The benefit of intravenous thrombolytic therapy in acute brain ischemia is strongly time dependent**.** Therapeutic yield is maximal in the first minutes after symptom onset and declines steadily during the first 3 hours. Patients who present to hospital within the first 60 minutes of onset (the "golden hour") have the greatest opportunity to benefit from recanalization therapy.[(13)] Target DTN (door to needle) $\leq$ 60 mins achieved in less than one fifth of golden hour-arriving patients. In a typical acute ischemic stroke, every minute the brain loses 1.9 million neurons, 14 billion synapses, 7.5 miles myelinated fibers. [(14)] Every 10 minute delay in delivery of TPA, 1 fewer patient has improved.

Every patient who reaches the medical setups within 4.5 hours of having had the event, there exists a possibility of thrombolysis. The time until the area becomes irreversibly damaged is the therapeutic window.[15] The window period for intravenous thrombolysis has recently been widened from three hours to 4.5 hours. [16] However, only a small proportion of stroke patients can avail of this therapy. So, the major target for stroke is in protecting the brain from ischemic damage.

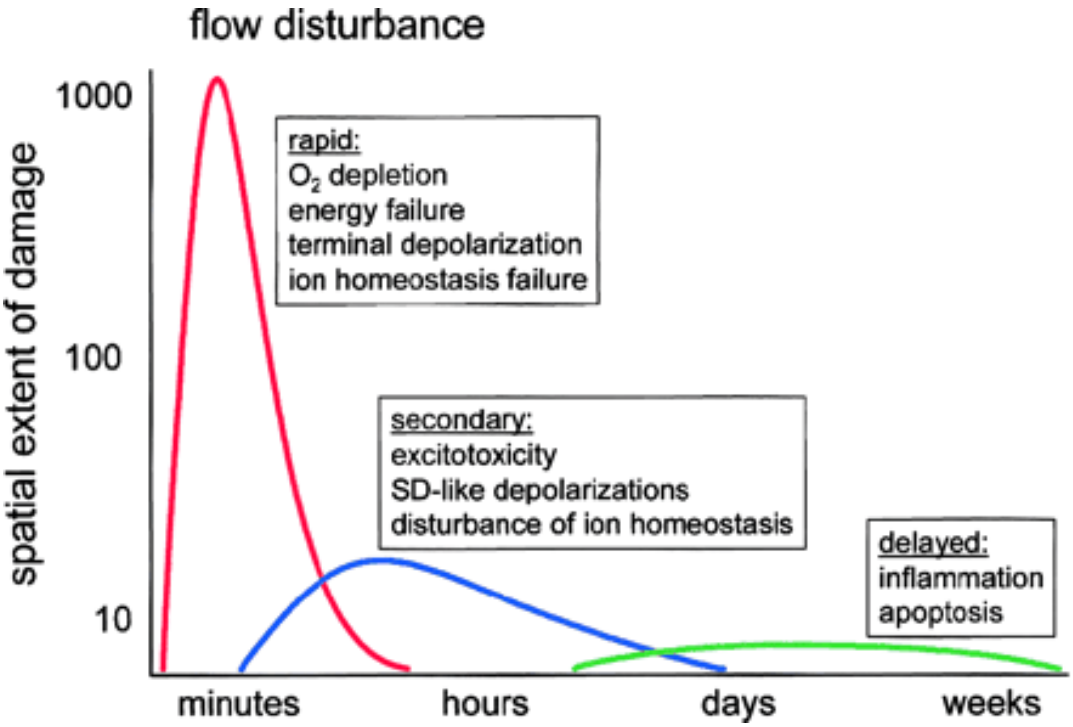
Current neural strategies for the treatment of ischemic stroke include acute neuroprotection and the sub acute promotion of brain plasticity. Various neuroprotective agents like glycine antagonists, calcium antagonists, free radical scavengers, etc., which are likely to intervene one of the various steps in the mechanisms of ischemic cell injury have been tried in the past as a part of the strategy for treating ischemic strokes. [17] But they were found to be either ineffective or too toxic to be used in humans.

In acute ischemic cerebrovascular accident, there has been a considerable progressive development in the understanding of its physiology and pathogenesis.

ISCHEMIC CASCADE IN THE PATHOGENESIS OF STROKE

After occlusion of the intracranial cerebral vessels, a series of time dependant neurochemical events takes place called the ischemic cascade which

results in energy failure.



ISCHEMIC CASCADE

The neuropathogenic processes (Fig 1) involved in this ischemic insult include,

1. The glutamate, an excitatory amino acid (EAA) is the most excessive excitatory neurotransmitter in the brain stored in the presynaptic vesicles. When it is released, it binds to the post synaptic glutamate NMDA (N- methyl D-aspartate) receptor. [(18)]
2. Once the reduction of cerebral blood flow commences, there is abundant release of excitatory neurotransmitters, especially glutamate and causes excess activation of the NMDA receptor.
3. Activation of these receptors leads to the influx of the calcium and the sodium ions through the ligand and voltage gated channels.

4. The intracellular enzyme systems which are dependent on calcium are activated and leads to the induction of

    i. free radical production[19]

    ii. membrane lipid breakdown proteolysis

    iii. initiation of an inflammatory response which stimulates apoptosis

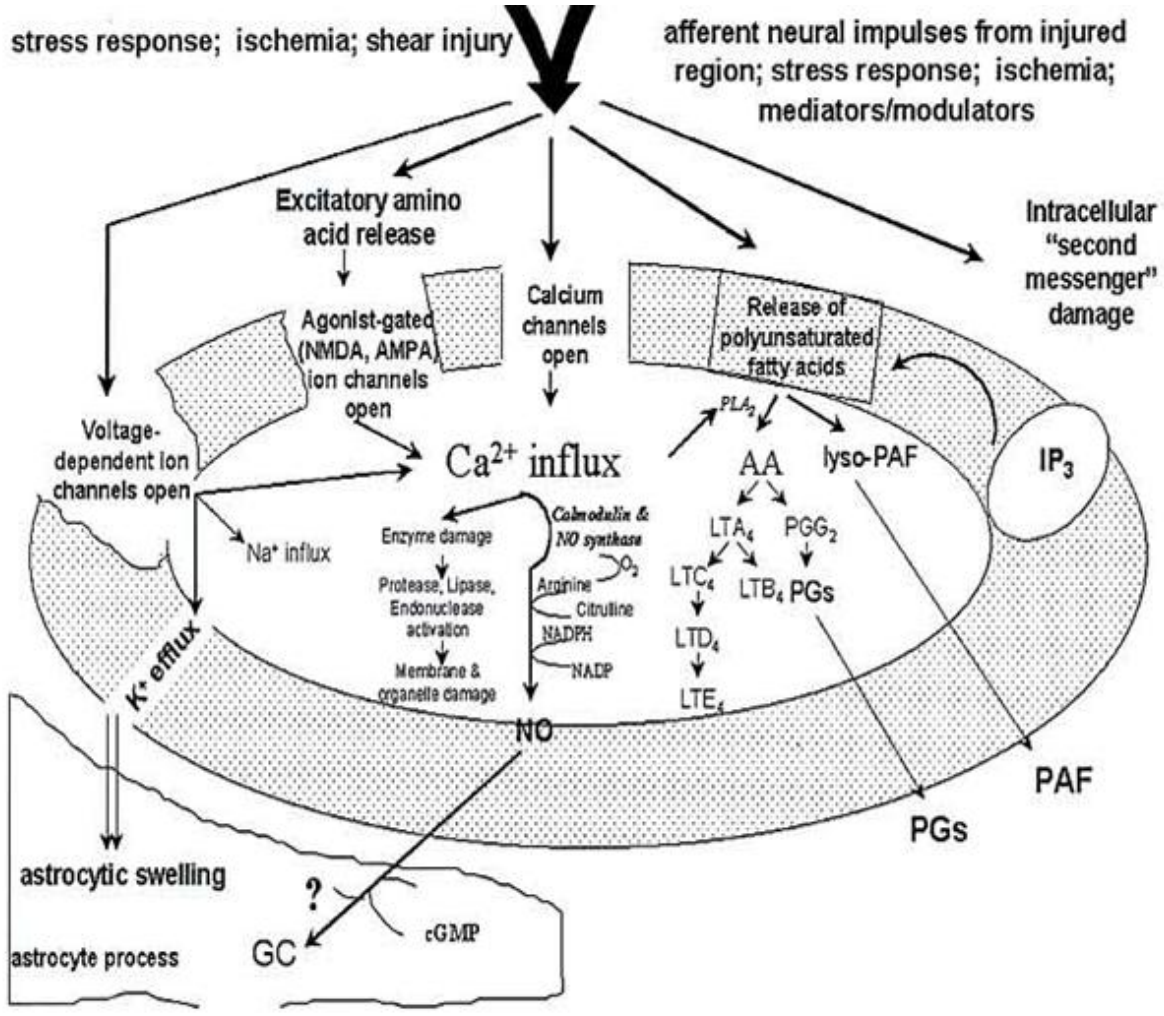


Fig 1: SCHEMATIC DIAGRAM OF SECONDARY CELLULAR RESPONSES IN RESPONSE TO DIRECT AND INDIRECT NEURONAL INJURY [28]

5. All of this contribute to compromise of the metabolic functions, expansion of the infarct volume and the development of neurotoxicity over a timescale of days or even weeks
6. The leucocyte and platelet activation cause direct micro vascular damage and worsen ischemia.[20]

ISCHEMIC PENUMBRA

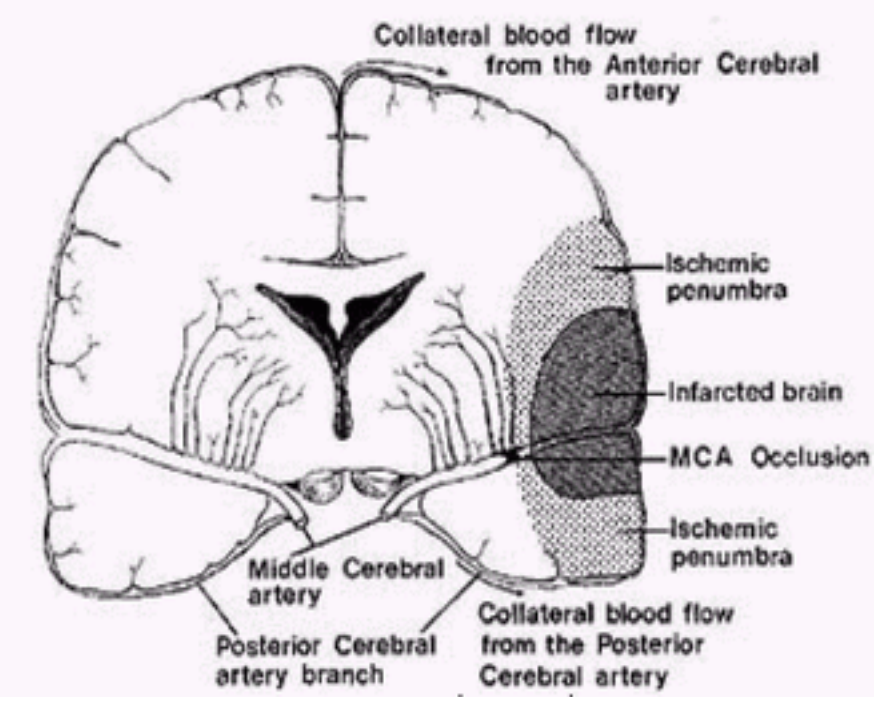


Fig 2: COLLATERALS AFTER MIDDLE CEREBRAL ARTERY OCCLUSION[29]

The ischemic penumbra can be broadly defined as that region of the ischemic zone that is potentially salvageable. [15] After the middle cerebral artery is occluded, (Fig 3) the blood flow of the core region decreases below

around 10 ml/100 g/min, which leads to rapid necrosis of this region. Surrounding the core region is the region of ischemic penumbra, where the collaterals support a blood supply of 10–20 ml/100 g/min.[19] Majority of the ischemic cascade occurs within this ischemic penumbra and many of the important biochemical reactions of this cascade occur within the first two hours of the onset of focal ischemia. [21]

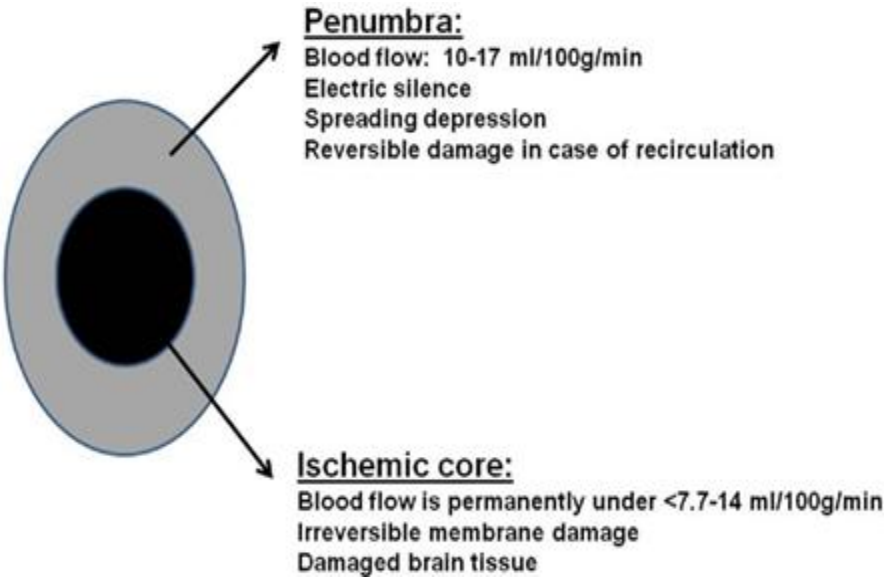


Fig 3: BLOOD FLOW IN THE ISCHEMIC CORE AND THE PENUMBRA [22]

The infarct core is surrounded by the ischemic penumbra which is functionally impaired but potentially viable tissue and can persist for upto 48 hours of the onset of the stroke. Unless an intervention occurs, either by promoting reperfusion with thrombolysis or by attenuating the ischemic cascade with neuroprotective agents, the penumbra is destined to necrosis due to the metabolic and neurochemical consequences of ischemia [23]

The main aim of treatment in acute stroke is in improving the disparity between the demand and the energy supply of the brain thereby minimizing the neuronal damage which can be done by restoring local blood flow, supplying alternative metabolic substrates, by reducing neuronal metabolism or by interfering with the complex mechanisms which can eventually lead to neuronal death after an ischemic insult thereby, protecting against the toxic effects of the ischemic cascade and improving the overall metabolic environment.[20]

There are only few specific treatments available for minimizing this acute injury of brain ischemia, which is a medical emergency. Current therapies are limited to clot removal (tPA thrombolysis, intraarterial fibrinolysis, mechanical removal), aspirin, and decompressive hemicraniectomy for ischemic stroke and moderate hypothermia (33°C) for cardiac arrest.

THE NEED FOR NEUROPROTECTION: WINDOW OF OPPORTUNITY

In humans, following an ischemic damage, the neurological insult produced spreads from the central core of the infarct. The excitotoxic injury continues beyond 48 hours to produce the maximal size of the infarct, and the local cerebral perfusion and the autoregulation are disturbed for the first 72 hours.[24] In most of the cases, within three to four days, the collateral vessels develop and reperfuse the damaged areas and the regional blood flow abnormalities tend to resolve.[25] The PET (Positron Emission Tomography)

imaging, which can distinguish ischemia from an infarct, cannot identify the areas of ischemia which will recover or transform into an infarct. It was found that blood flow was reduced locally in 100% of patients within 9 hours of the insult and it was reduced to 30% within 4 days. Following stroke, this ischemic but viable tissue was found for upto 48 hours. Because the hemorrhagic complications are high when reperfusion is done at later stages, the time window for thrombolysis is relatively short. So there is a rationale for need of initiating neuroprotective measures to prevent the continuing cerebral ischemia and to salvage the viable ischemic tissue during the time the cerebral autoregulation is deranged and the collateral circulation is developing (ie,3 to 4 days after the onset of stroke) when patient comes beyond the critical time allocated for thrombolysis.[26]

NEUROPROTECTION: TIME IS BRAIN

The main treatment strategies for therapeutic intervention in ischemic stroke are aspirin and thrombolysis. The concept of neuroprotection emerged only recently and is considered as an alternative additional intervention because of its relative safety, evidence of efficacy in animal models and potential to administer in the pre-hospital setting.[27] Thousands of experimental papers and more than 500 articles have been published on neuroprotection to emphasize its potential utility.

BASIC CONCEPTS OF NEUROPROTECTION:

Neuroprotection in ischemic stroke refers to the therapeutic interventions applied in single or in combination which will counteract, block, or slow the sequence of the injurious biochemical and molecular events that take place in the cascade of the irreversible ischemic brain injury. [28] Rigorously conducted experimental studies in animal models of brain ischemia provide incontrovertible proof of evidence that high grade protection of brain is an achievable goal.

A number of possible approaches have been suggested, considering the pathophysiological processes of neuroprotection.

Excitotoxicity can be attenuated [20] by

1. Decreasing the release of the excitatory neurotransmitters (especially glutamate) (Fig 4) or increasing its reuptake or its breakdown
2. Reducing their toxicity by blocking or down-regulating post-synaptic NMDA receptors
3. The release of inhibitory amino acids or the neurotransmitters like gamma-aminobutyric acid (GABA) can be stimulated.
4. By blocking the voltage-sensitive channels, the calcium influx is reduced by promoting its extrusion or sequestration there reducing the toxicity of excess intracellular calcium.
5. Modifying the other ‘downstream’ intracellular processes, such as the various nitric oxide-dependent pathways.

6. Other ways for neuronal salvage include the reduction of cerebral oedema, correcting acidosis and scavenging free radicals.

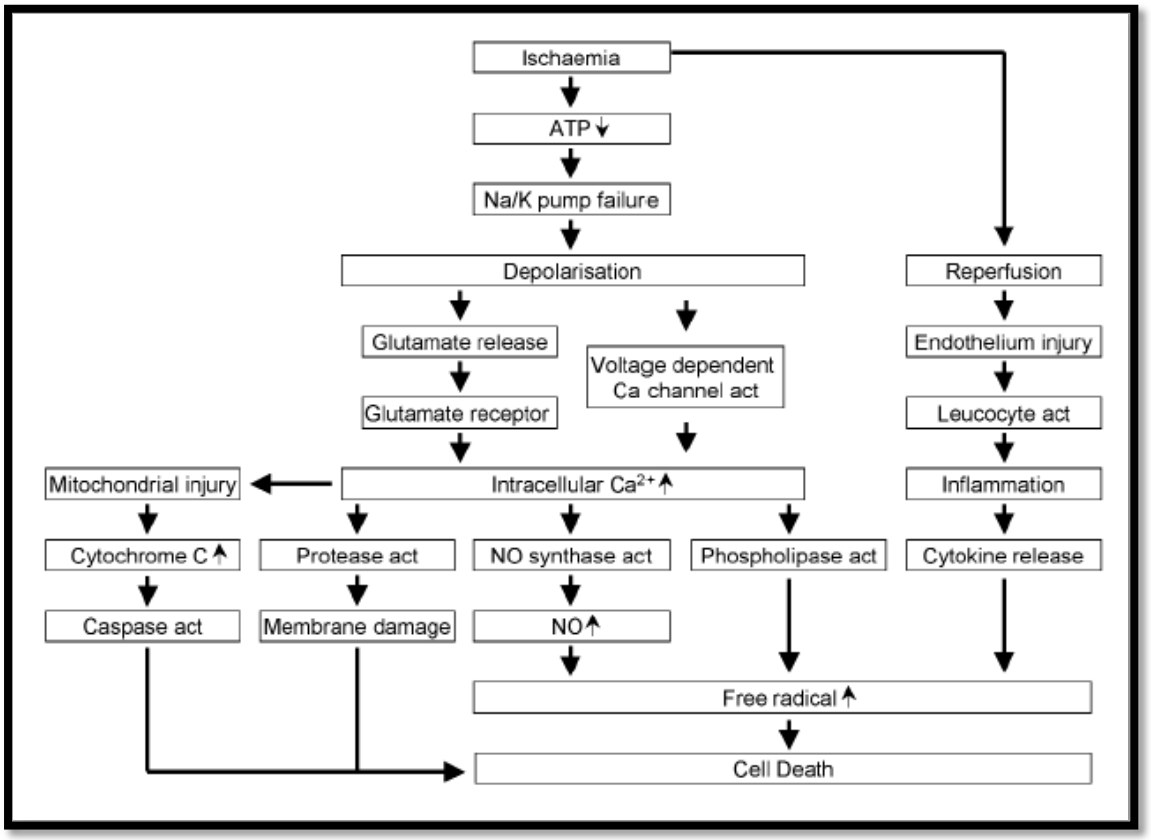


Fig 4: MAJOR STEPS IN THE CASCADE OF CEREBRAL ISCHEMIA

CLASSIFICATION OF NEUROPROTECTIVE AGENTS[18]

1. Modulators of Excitatory Amino Acids
2. Modulators of Calcium Influx
3. Metabolic Activators
4. Anti-edema Agents
5. Inhibitors of Leukocyte Adhesion
6. Free Radical Scavengers and Anti-Oxidants
7. Promotors of Membrane Repair

The most extensively studied and the promising neuroprotective agents are the hyperacute magnesium therapy, therapeutic hypothermia, high dose human albumin, calcium channel blockers, GABA agonists, glutamate antagonists, antioxidants, free radical scavengers, down-regulators of the nitric oxide signal transduction. [29]

Unlike the other majority neuroprotective agents, magnesium is used extensively for many clinical conditions like arrhythmias, myocardial infarction and pre-eclampsia/ eclampsia.[30] So these major clinical experiences confirm its tolerability, efficacy and safety. In recent times, many clinical trials conducted had proved the neuroprotection offered by magnesium and improvement in neurological outcome in patients with ischemic stroke.

THE VITAL MAGNESIUM – THE "FORGOTTEN CATION"

Magnesium is found in each and every cell of the body. The main source of energy in cells, ATP (adenosine triphosphate) is bound to the magnesium. It is vital for a normal biological function. So without it, there is no energy, no movement and no life. [31] It is the powerful calcium channel blocker and so it relaxes every muscle including the heart which is the vital muscle of our human body. Unlike the other medications which block the calcium channel, magnesium is a natural and nontoxic element which can be used safely.

The fourth most abundant mineral in our body is magnesium. Around 99% of the total body magnesium (Fig 5) is present in the bone, muscle and the soft tissue. Magnesium ion is present inside the cells at a concentration of 5 – 20mmol/L; present in the ionized form in around 1-5%, remaining is bound to the proteins, and adenosine tri phosphate (ATP). During states of acute deficiency, large amount of exchangeable pool for magnesium is from the bones. As age increases, the magnesium content of bone also decreases. Only 1% of the total intracellular magnesium is present extracellularly.[32] The primary extracellular concentration is present in the red blood cells (RBCs) and serum.

Tissue	Body weight (kg wet weight)	Concentration (mmol/kg wet weight)	Content (mmol)	% of total body magnesium
Serum	3.0	0.85	2.6	0.3
Red blood cells	2.0	2.5	5.0	0.5
Soft tissue	22.7	8.5	193.0	19.3
Muscle	30.0	9.0	270.0	27.0
Bone	12.3	43.2	530.1	52.9
Total	70.0	64.05	1000.7	100.0

Fig 5: MAGNESIUM DISTRIBUTION IN A NORMAL HUMAN ADULT [33]

Similar to calcium, magnesium is present in three forms (Fig 6) free/ionized, bound to proteins and anions like phosphate, bicarbonate, citrate or sulphate. The biological activity of magnesium is greater with the ionized form.

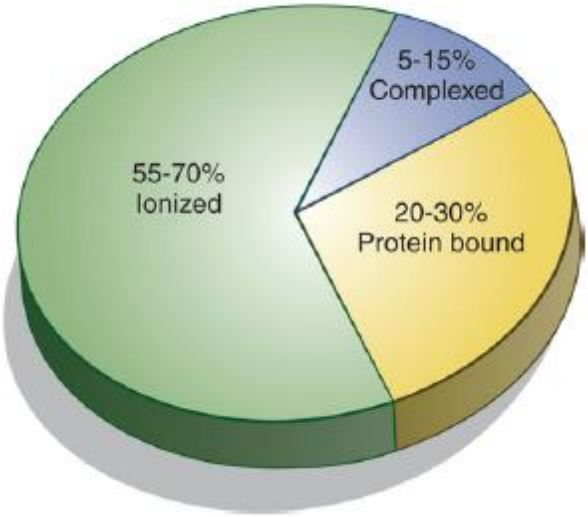


Fig 6: DISTRIBUTION OF THE TOTAL SERUM MAGNESIUM [34]

FOODS RICH IN MAGNESIUM (Fig 7)

Vegetables like pumpkin seeds, sesame seeds, sunflower seeds, spinach, legumes and green beans are very rich sources of the mineral. Refined grains are deficient in magnesium.

TABLE II High-Magnesium Content Foods

	Magnesium Content (mg %)
Cocoa and chocolate (bitter and sweet)	107-292
Nuts	132-411
Shellfish	34-414
Legumes	113-255
Grain and grain products	60-420
Dried fruit	59-92
Dark, leafy green vegetables	53-59

Fig 7: FOODS CONTAINING HIGHER MAGNESIUM

HARDNESS OF WATER AND MAGNESIUM [35]

"Hard water" which naturally contains abundant minerals is richer in magnesium than the "soft water." It is said that 12% of the total daily magnesium intake is derived from the drinking water. If the person consumes

only hard water, as much as 18% of the daily required magnesium can be obtained. For persons whose intake of magnesium from the food is marginal, these amounts might well be critical.

MAGNESIUM HOMEOSTASIS (Fig 8)

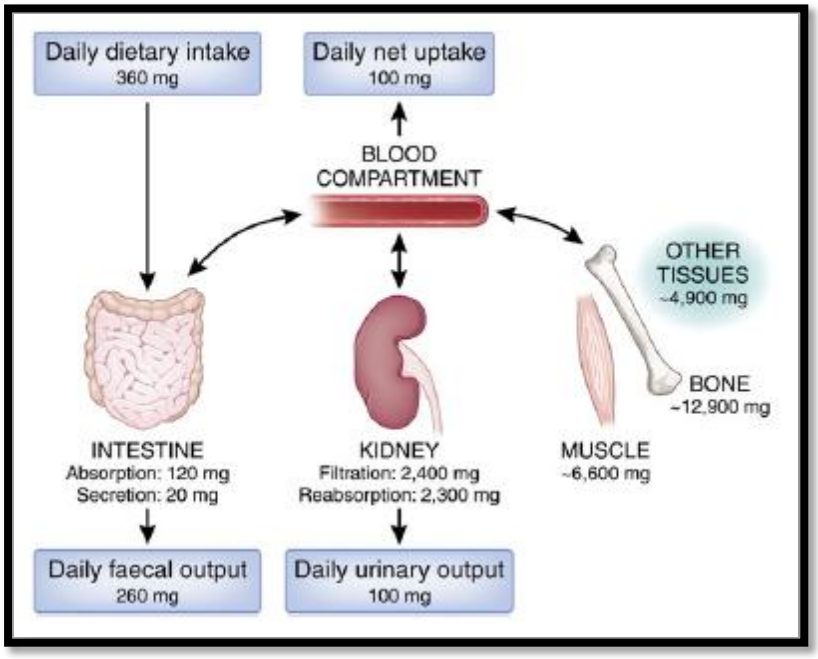


Fig 8: MAGNESIUM BALANCE

Magnesium homeostasis is achieved mainly through the bones, intestines and the kidneys. It is absorbed mainly in the small intestine by the passive transport. Only 25 – 75% of the total magnesium consumed is absorbed. The remaining is excreted in the faeces. The absorption of magnesium in the intestines depends not on the levels consumed, but on its status of the body. Lower the magnesium levels, higher the ion is absorbed. Serum magnesium levels are principally regulated by the kidneys. Around 95% of the filtered

magnesium is reabsorbed and only 3 -5% is excreted in the urine. The thick ascending limb of the loop of Henle is the primary site for reabsorption. [36]

MAGNESIUM – MEMBRANE STABILIZER

Magnesium provides critical cell membrane stability for the cellular and the sub- cellular (organelle) structures. When it binds to the phospholipids, it decreases the membranes permeability. In low level states, the stability of the membrane is deranged, resulting in increase in permeability and the damage of the whole structural cell. [37]

MAGNESIUM – NATURE'S PHYSIOLOGICAL CALCIUM CHANNEL BLOCKER (Fig 9)

Many calcium channels are found to be magnesium dependant. Higher levels of magnesium inhibit the flux of calcium from the sarcoplasmic reticulum and through the intra and extra cellular channels. So during deficiency state, there is unopposed influx of calcium and its levels increase intracellularly.

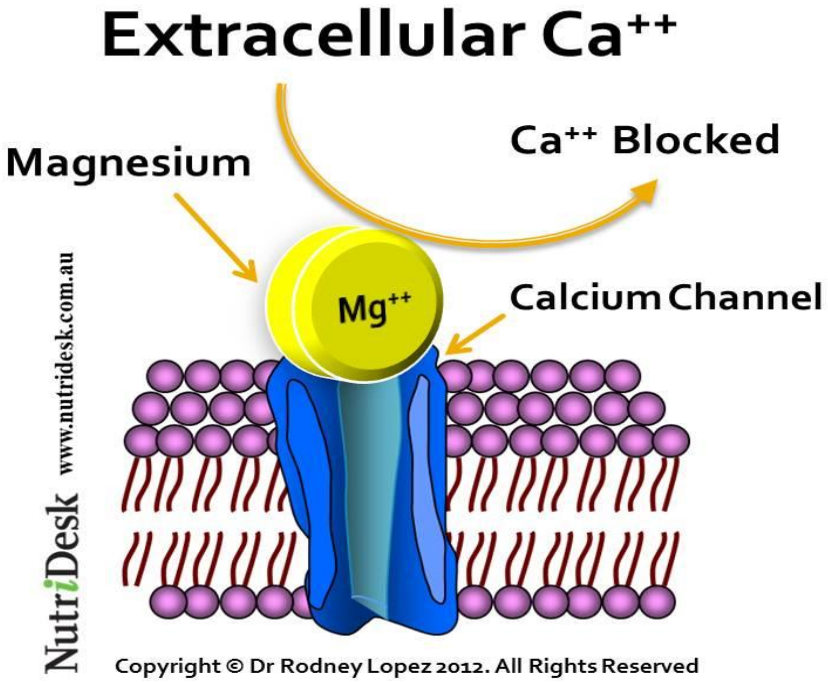


Fig 9: BLOCAKADE OF CALCIUM CHANNELS BY MAGNESIUM [38]

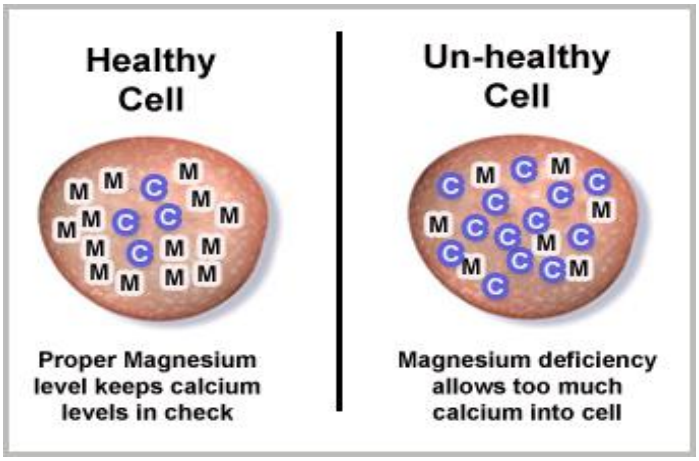


Fig 10: INTRACELLULAR CALCIUM LEVELS IN A NORMAL AND MAGNESIUM DEFICIENT CELL

Magnesium acts as a competitive antagonist of calcium as Mg^{2+} is a bivalent ion resembling Ca^{2+}. (Fig 12) Both calcium and magnesium have opposite effects on the vascular tone. So hypomagnesemia causes spasm of the blood vessels and increases resistance in the blood vessels.[39]

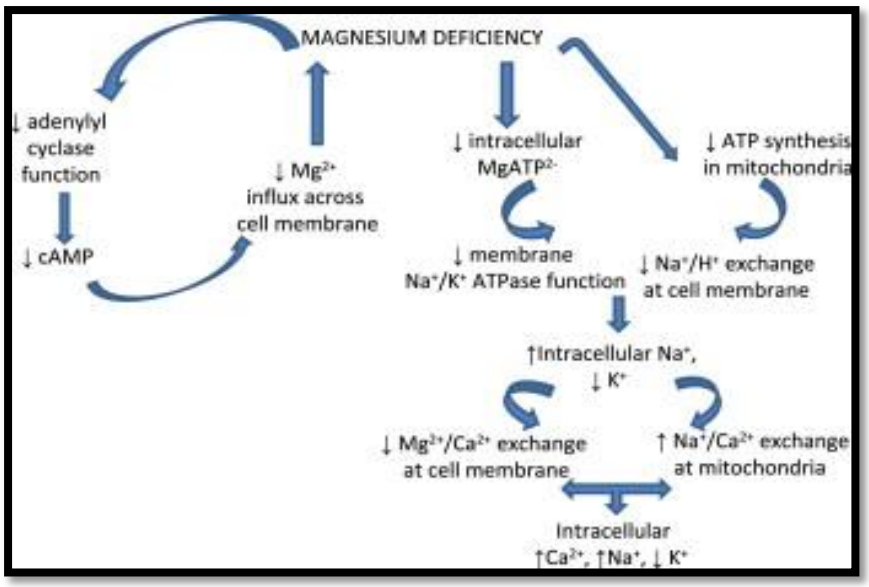


Fig 11: CELLULAR MECHANISMS INVOLVED IN HYPOMAGNESEMIA

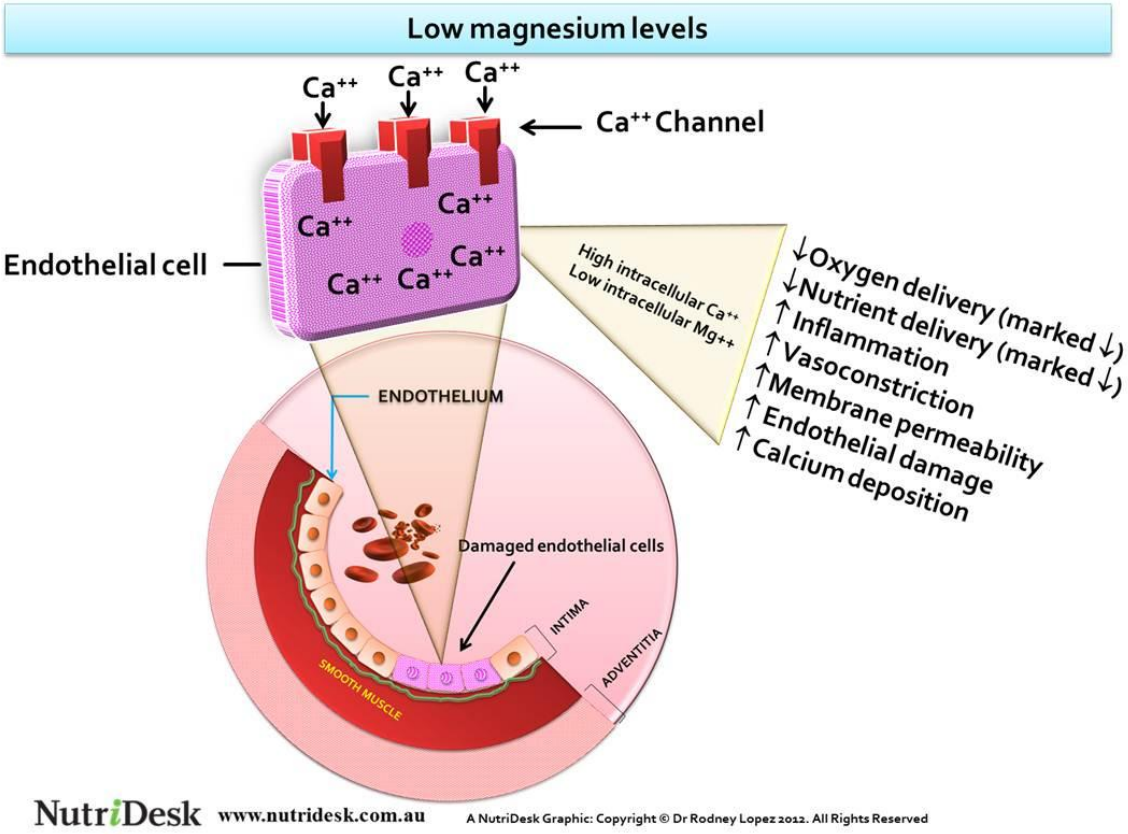


Fig 12: DELETERIOUS EFFECTS OF HIGH INTRACELLULAR CALCIUM DUE TO LOW MAGNESIUM [38]

An average 60 kg adult contains around 2000 mEq in the body. The normal serum magnesium values range between 1.5 – 2.5 mEq/L. (1 mEq = 0.5 mmol = 12 mg). [40]

DAILY REQUIREMENTS FOR MAGNESIUM (Fig 13)

Age (years)	Males (mg/day)	Females (mg/day)	Pregnancy (mg/day)	Lactation (mg/day)
1–3	80	80	N/A	N/A
4–8	130	130	N/A	N/A
9–13	240	240	N/A	N/A
14–18	410	360	400	360
19–30	400	310	350	310
31+	420	320	360	320

Fig 13: RECOMMENDED DAILY ALLOWANCES FOR MAGNESIUM [41]

(Published by the National Institute of Health (NIH))

MAGNESIUM DEFICIENCY

In the current westernization lifestyle of a calorie restricted diet, magnesium intake in the food and the drinking water has considerably reduced. Magnesium is almost missing in the bottled water which every healthy conscious people habituate to take in order to avoid the risk of contaminants particularly heavy metals and chlorine. From the bottled water only 30% of the recommended average daily intake of magnesium is obtained. The remaining

70% had to be taken through magnesium rich food sources. National health and nutritional examination survey conducted in the United States has found that considerable amount of adults have failed to get the recommended intake of magnesium. In every ethnic and racial group, it was found that magnesium intake was considerably lower in the older adults. The prevalence of magnesium deficiency is found in less than 2% of the general population, 10-20% of the hospitalized patients, 50- 60% of the intensive care unit patients and 30-80% of the alcoholics.

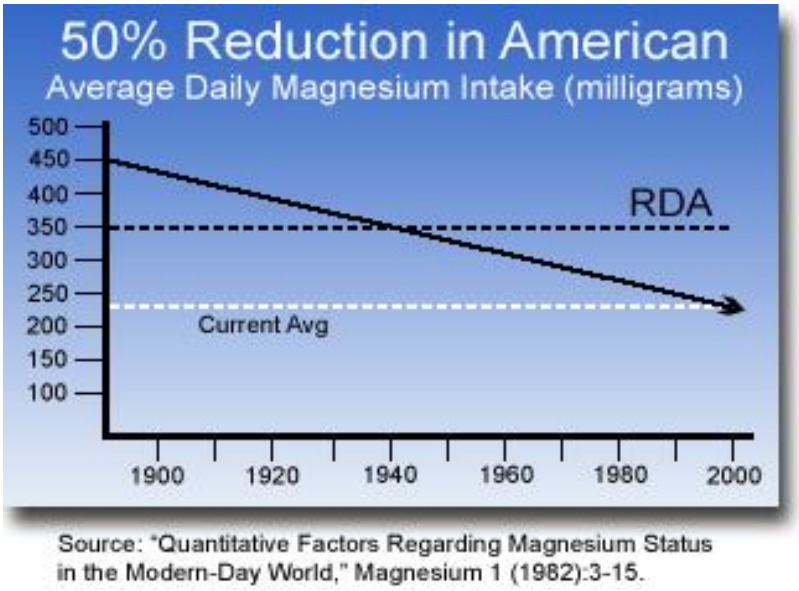


Fig 14: AVERAGE DAILY INTAKE OF MAGNESIUM (Mg) IN THE UNITED STATES [42]

(Reproduced from *"Magnesium in the Pathogenesis of the Disease"* Seeling, MS)

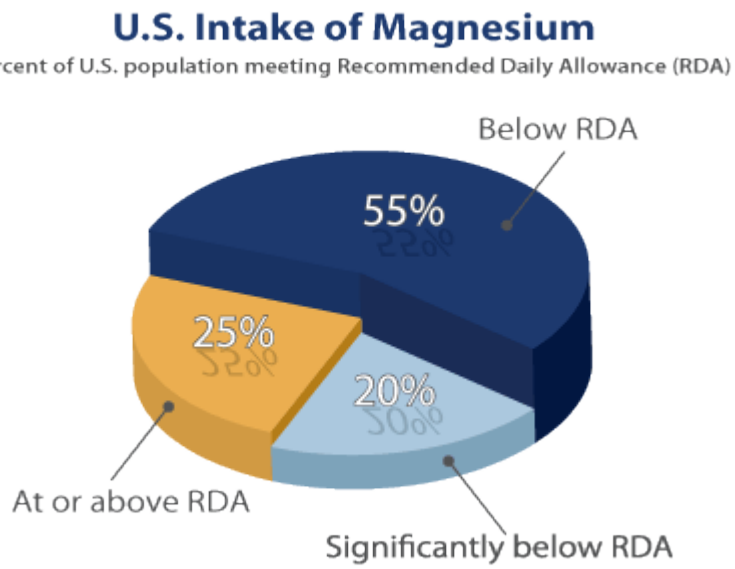


Fig 15: INTAKE OF MAGNESIUM IN THE UNITED STATES[42]

HYPOMAGNESEMIA

Serum magnesium levels less than 1.5 mEq/L is defined as hypomagnesemia. [36]

The factors that influence magnesium levels are

1. Inadequate dietary intake
2. Decrease in the absorption of magnesium in the gastrointestinal tract
    a. Diarrhoea, vomiting
    b. Gastro intestinal suction
    c. In chronic malabsorptive problems like Crohn's disease, regional enteritis, intestinal surgeries and gluten sensitive enteropathy.
    d. Steatorrhoea
    e. Acute pancreatitis

3. Increase in the renal excretion
    a. Renal tubular defect
    b. Alcoholism
    c. Diuretics- thiazides and loop diuretics
    d. Antimicrobials – aminoglycosides, amphotericin B
    e. Chemotherapeutic drugs – cisplatin, cyclosporine, tacrolimus

In terms of symptoms development the rate of development is more important than the absolute value. Cardiovascular and the nervous systems are the most affected in magnesium deficiency. The other systems are less commonly affected.

Cardiovascular manifestations [36]

Prolonged QT/QU interval, increased digitalis toxicity, torsades de pointes, ventricular fibrillation.

Neuromuscular manifestations:

Tremors, paresthesias, seizures, weakness of muscles, fasciculations tetany, letharginess, confusion, disorientation, irritability, agitation and psychosis.

Physical examination:

In patients with seum levels less than 1mEq/L develop muscular fibrillations, tremor, carpopedal spasms can progress to tetany, deep tendon

reflexes. Cardiac arrhythmias and respiratory failure can occur in patients with severe hypomagnesemia.

MEASUREMENT OF SERUM MAGNESIUM[36]

It can be assessed by measuring magnesium levels of

1. Total serum magnesium
2. Red blood cell
3. Mononuclear cell
4. 24-hour urinary excretion
5. Fractional excretion (FE) of magnesium
6. Intracellular content of skeletal muscle

Intracellular content of magnesium can be estimated using nuclear magnetic resonance spectroscopy or using fluorescent dye. Two things should be considered in estimation of serum magnesium. Firstly, most of the methods available estimate only the total serum magnesium. But only the free magnesium ion is functionally active. 30% of the magnesium is bound to albumin. So in hypoalbuminemic states, it can lead to falsely low values. So albumin levels should be considered in interpretation of magnesium. Secondly, the intracellular magnesium plays a major physiological role. Estimating in the serum assess the extracellular magnesium which constitutes only 2% of the total body levels. So a person can have normal serum magnesium level but depleted

at the intra cellular level. Unfortunately, no quick, simple, and accurate test is available to measure intracellular magnesium.

TREATMENT

Treatment is needed for patients with symptomatic hypomagnesemia with seizures or arrhythmias. Magnesium sulphate should be given intravenously in the dose of 2-4 grams given as 10% solution in 20 to 30 ml of 5% dextrose in water over 5 to 15 minutes. For repeated seizures, magnesium can be given to a total of 10 grams for the next 6 hours. [43]

THE EPIDEMIC OF MAGNESIUM DEFICIENCY

Magnesium is one of the most important electrolyte that is essential to the basic nucleic acid chemistry of life and so essential to all the known living organisms. It is a cofactor that is required for catalizing more than 350 enzymatic reactions in the body. So its deficiency can affect every aspect of our physiology. In numerous diseases, magnesium deficiency is found as either being a causative factor, or as expediting various disease processes.

MAGNESIUM DEFICIENCY: STATE OF LOW GRADE INFLAMMATION

There are various nutritional factors that affect the inflammatory response. Researches called out one particular common nutrient; magnesium in its deficient state is associated with a low grade inflammation. Magnesium has a role in regulating inflammation and decreasing the damage induced by the oxygen derived free radicals while deficiency increases oxidative stress and inflammation in humans. Various evidences from the studies prove that magnesium intake was inversely associated with the plasma concentrations of C- reactive protein (CRP), Interleukin- 6 and tumor necrosis factor-α. [44] Its deficiency is associated with conditions linked with chronic inflammation like heart disease, hypertension and diabetes.

ARTERIAL ENDOTHELIAL DAMAGE CAUSED BY "PURE" MAGNESIUM DEFICIENCY

The vascular changes caused by magnesium deficiency were studied in the animal experiments. The studies showed that the inflammatory changes (Fig 16) in the arterioles and the capillaries were extracellular edema with intimal thickening, thinning and disruption of the internal elastic membrane, and disorientation and hyperplasia of medial muscle cells.[45] Some arteries also had densely aggregated pyknotic cells in their enlarged tunica media, with narrowed lumina. Inspite of the low serum calcium levels, medial and intimal calcification was demonstrated in magnesium deficiency.

In magnesium deficiency, the endothelial cell is greatly injured by the free radical mediated oxidative stress and intracellular lipid peroxidation.

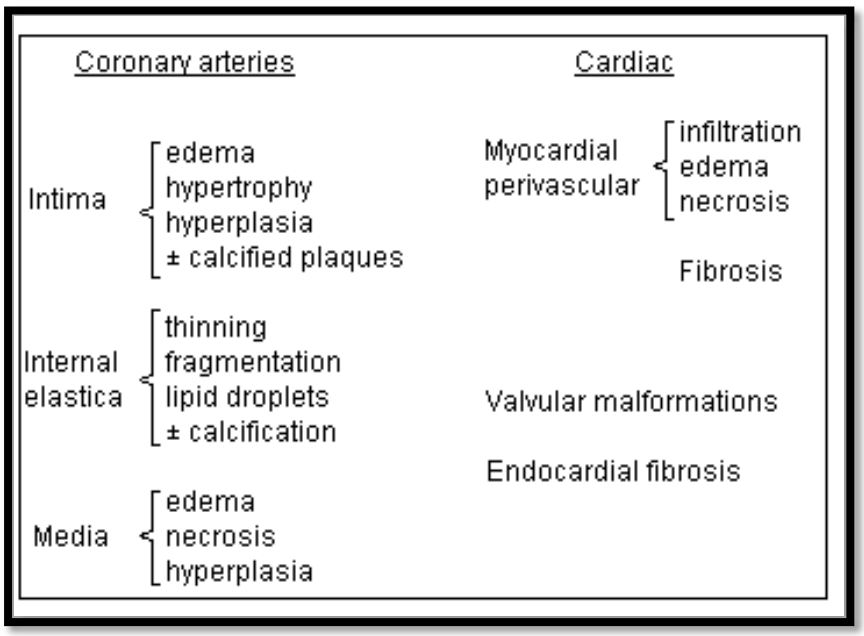


Fig 16: CORONARY ARTERIAL AND CARDIAC LESIONS CAUSE PURE MAGNESIUM DEFICIENCY

(Reproduced from *"Magnesium in the Pathogenesis of the Disease"* Seeling, MS.)

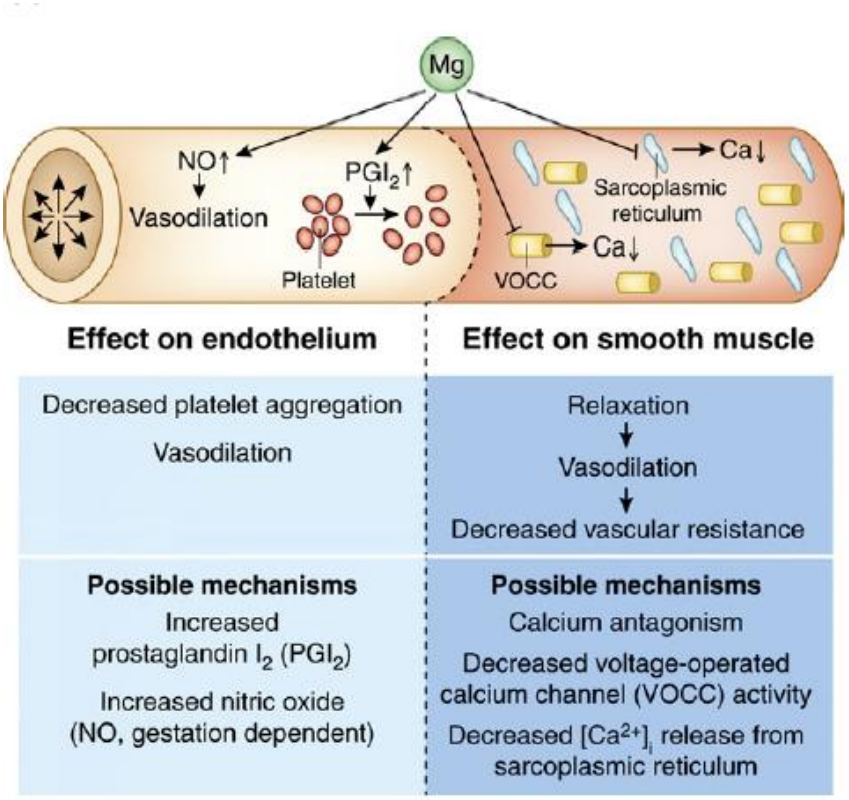


Fig 17: EFFECT OF MAGNESIUM ON THE VASCULAR SMOOTH MUSCLE AND THE ENDOTHELIUM

MAGNESIUM DEFICIENCY AND ATHEROSCLEROSIS

Atherosclerosis is the most important risk factor for the cardiovascular diseases mainly stroke and myocardial infarction. Large amount of evidence supports that the main causative factor responsible for the atherosclerotic burden in cardiovascular disease is the inflammation and the endothelial dysfunction. Various epidemiological studies from animal models suggest that magnesium deficiency at the cellular level accelerates the inflammation and intensifies the lipid deposition in the blood vessel wall and there is an inverse correlation cardiovascular incidence and the dietary magnesium. In the follow

up of the ARIC study, it was demonstrated that for every 0.1mm decline there was increase in the thickness of carotid intima- media thickness with the development of carotid plaques.[46]

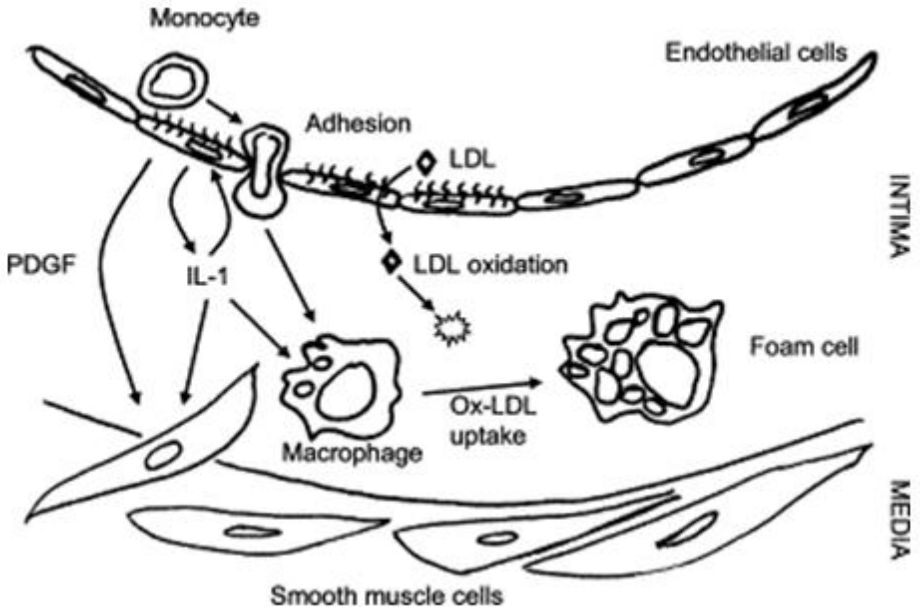


Fig 18: SCHEMATIC DIAGRAM OF THE ATHEROGENESIS [65]

In magnesium deficiency,

1. In the endothelium, (Fig 19) upregulation of the adhesion molecules like VCAM (vascular cell adhesion molecule), MCP-1(monocyte chemoattractant protein -1) and release of cytokines like platelet derived growth factor (PDGF), NFkβ (nuclear factor kappa- light chain- enhancer of activated B cells, interferons (IFs), interleukins (IL-1) etc are enhanced. [47]

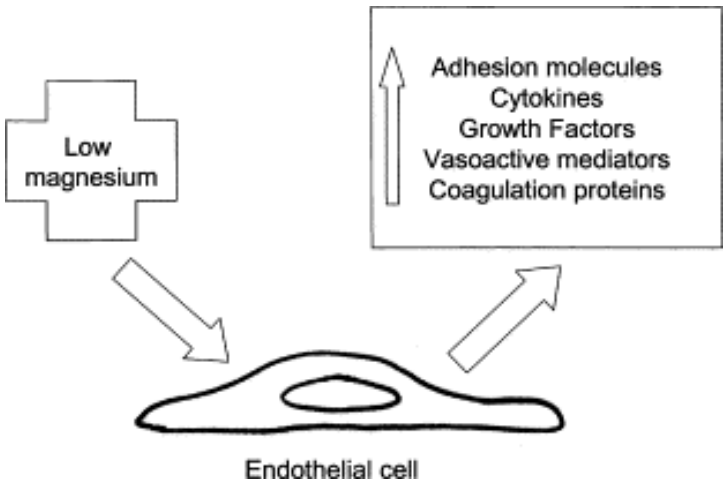


Fig 19: EFFECT OF LOW MAGNESIUM ON THE ENDOTHELIAL FUNCTION [48]

2. This leads to adhesion and migration (chemotaxis) of monocytes into the arterial wall and transformed into macrophages in the intimal layer.
3. It enhances the permeability of the LDL cholesterol and promotes the oxidation of LDL in the carotid intima. (Fig 20)

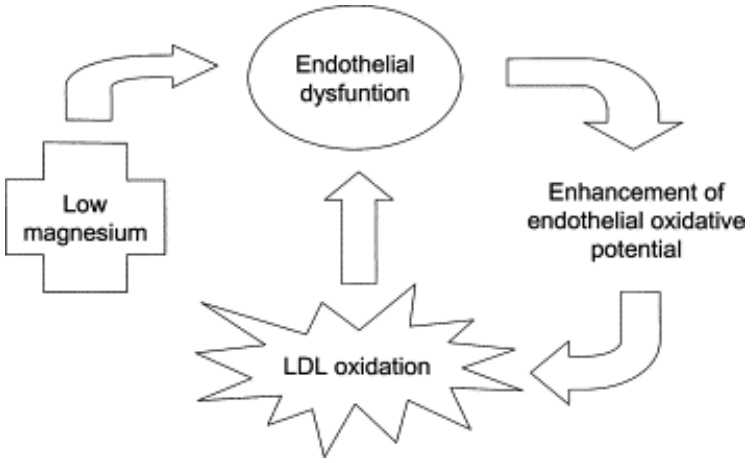


Fig 20: LOOP BETWEEN LOW MAGNESIUM, ENDOTHELIAL DYSFUNCTION AND LDL OXIDATION

4. In the carotid intima, there is increase in the uptake of oxidized LDL by the macrophages and the formation of foam cells thereby accelerating the inflammation and the atherogenic plaque formation which is the initiating event for all the cardiovascular diseases.

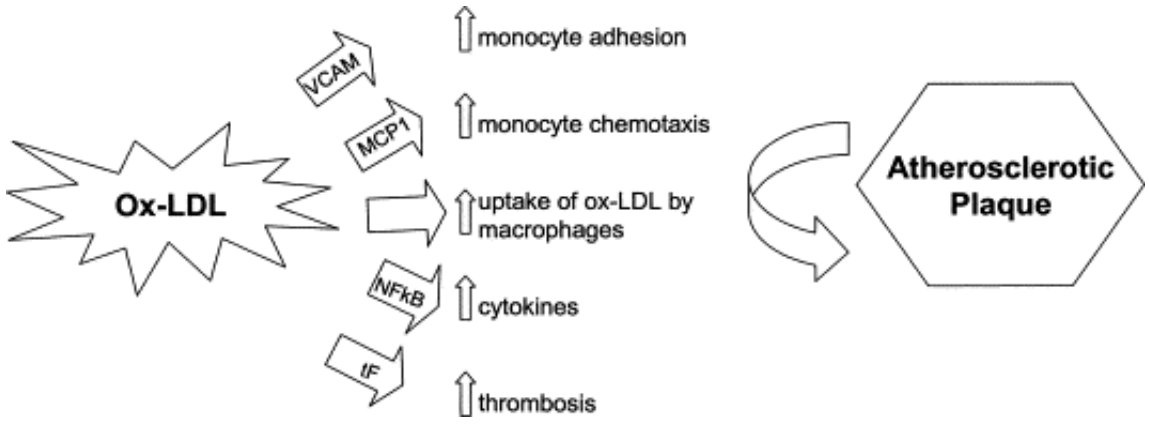


Fig 21: PROATHEROSCLEROTIC EFFECTS OF OXIDIZED LDL[48]

So magnesium which is a natural and a safe element can be used as an adjuvant therapy for the prevention of atherosclerosis.

MAGNESIUM - ANTITHROMBOTIC WITH CARDIOPROTECTIVE EFFECT [49]

The protective mechanisms of magnesium are

1. Reduction of the proinflammatory process
2. Stabilization of the membrane of platelets as magnesium is needed to maintain the shape of the platelets.

3. Inhibition of thrombogenesis through inhibition of ADP - platelet aggregation and adhesion.
4. The release of the platelets is dependent on the calcium and so magnesium physiologically inhibits its release.
5. The platelet dependant thrombosis was inversely correlated with the serum magnesium levels and its supplementation positively reduced the size and the number of platelet clumps and increased the number of discrete platelets.
6. Increase in the fibrinolytic activity.
7. By lowering the intracellular calcium concentrations, it decreases the tonicity of the blood vessels and also inhibits the vascular calcification.
8. Against oxidative stress, it helps to increase the protective enzymes.
9. Increases the nitric oxide (NO) release and enhances the endothelial dependant vasodilatation and inhibits the aggregation of platelets.

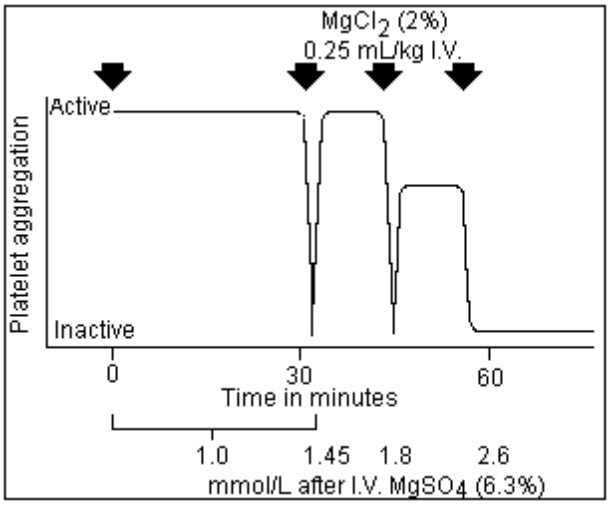


Fig 22: EFFECT OF INTRAVENOUS (i.v.) MAGNESIUM (Mg) ON THE PLATELET AGGREGATION [50]

(Adapted from Adams and Mitchell, *ThrombHaemost).*

LOW MAGNESIUM AND DYSLIPIDEMIA

Magnesium has an important role in control of the lipid metabolism. Dyslipidemia is found to be strongly associated with magnesium deficiency. The antiatherogenic effects of Mg2+ are due to the lipoprotein lipase, HMG CoA reductase, and lecithin acyltransferase enzyme modification of the lipid metabolism and turnover. It also modulates HMG-CoA reductase which is the main enzyme catalizing the rate limiting step in the cholesterol metabolism. So magnesium acts as a "physiological statin". [51] Clinicians from the British Commonwealth have reported that treatment with magnesium has resulted in the reduction of β- lipoproteins and increments in lecithin/cholesterol ratio and α- lipoproteins. Its deficient state is associated with decrease in HDL-C fraction, inhibition of the enzyme lipoprotein lipase and causes elevation in the levels of TGL associated lipoproteins and plasma apolipoprotein B. [52]

MAGNESIUM AND BLOOD PRESSURE

A clinical trial, DASH study (Dietary Approaches to Stop Hypertension) suggested that high intake of foods rich in magnesium, calcium and potassium

and low in sodium like fruits and vegetables had significantly lowered the high blood pressure. [53] In an observational study, the ARIC (Atherosclerosis Risk in Communities) study was conducted in 8000 men and women who were initially free of hypertension was followed up for six years. In this study, during follow up, the patients who consumed diet more in magnesium, potassium and dietary fibres were found to be at a lower risk of developing hypertension. [54] Joint National Committee stated that the diets that provide higher magnesium are positive lifestyle modifications for people with hypertension and there is a dose dependant improvement in blood pressure with magnesium supplementation.

MAGNESIUM DEFICIENCY IN TYPE 2DIABETES:

Magnesium has an important role in carbohydrate metabolism. Magnesium is required in the glucose metabolism for three critical enzymatic reactions namely pyruvate carboxylase, phosphoenol pyruvate carboxykinase, fructose 1,6 biphosphatase. It also plays key enzymatic roles in various hormones like insulin, glucagon, adrenaline and cortisol which have a regulatory effect on gluconeogenesis. Hypomagnesemia may worsen the insulin resistance. [31]

Diabetes and metabolic syndrome are strongly linked to magnesium deficiency. Type2 diabetics are always in an overactive dominant sympathetic state, which leads to elevated blood glucose and blood pressure. Magnesium

inhibits this excess activation of the sympathetic nervous system thereby preventing the development of hypertension and hyperglycemia. Researchers have found that people who had taken more magnesium from food and various vitamin supplements were half as less likely to develop type2 diabetes than people who took the least amount of magnesium.

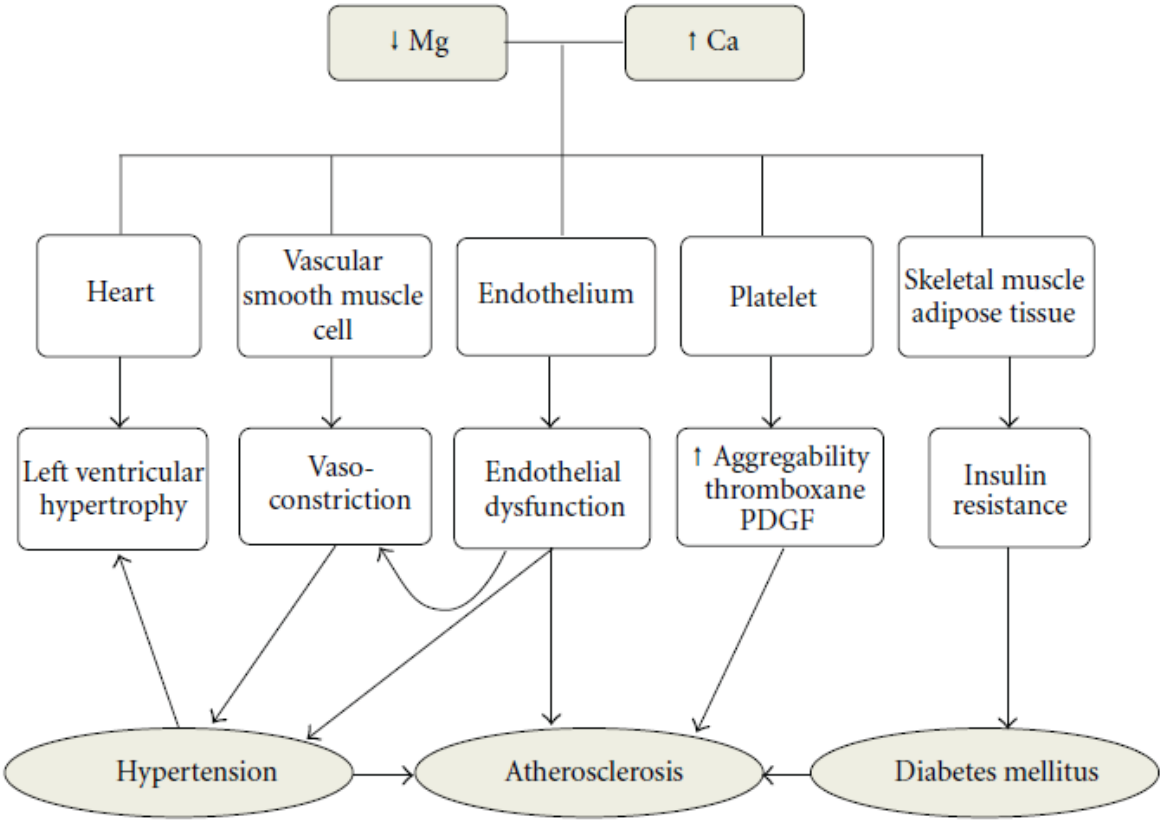


Fig 22: Role of magnesium and calcium in the pathophysiology of hypertension, diabetes mellitus, and atherosclerosis. [55]

MAGNESIUM AND CORONARY ARTERY DISEASE

Anderson *et al.* (1969) gave an hypothesis that there is an environmental factor magnesium, alters the excitability of the myocardium, which in deficient levels causes hyperexcitability of the myocardium and causes an increasing incidence in the cardiac arrhythmias like ventricular fibrillation leading on to sudden cardiac death and also noted that the decreasing hardness of water is associated with an acute and chronic coronary artery disease and an increase in the sudden death rate. [56] R. Parsons *et al.*, found that the hardness of water was due to the protective factor magnesium. Marier *et al.*, (1968) postulated that the higher serum magnesium levels provides protection for the myocardium against the ischemic injury and also resists the damage caused by the cardiotoxic agents. [57]

Magnesium deficiency causes high serum calcium concentration and causes spasm of the coronary arteries and also it potentiates the actions of norepinephrine, angiotensin, potassium, acetylcholine, and serotonin on the coronary arteries and can lead onto increased incidence in coronary artery disease and sudden cardiac deaths due to arrhythmias. [58]

MAGNESIUM DEFICIENCY IN CRITICALLY PATIENTS

In critically ill patients many factors contribute to magnesium deficiency like nasogastric tube suctioning, impairment in the gastrointestinal absorption,

poorly low content of magnesium in total parenteral nutrition and intravenous administration of drugs like diuretics, aminoglycosides, etc., the table gives us the information of various studies conducted on the magnesium levels in the critically ill patients. The prevalence of the magnesium deficiency varies from 15 to 70% in the ICU settings. [59] They also found that patients with the low magnesium levels had severe sepsis, frequently needed mechanical ventilation for a longer duration with increase in mortality rates.

Fig 23: PREVALENCE OF HYPOMAGNESEMIA IN CRITICALLY ILL PATIENTS IN VARIOUS STUDIES [59]

Study	Year	No. of patients	Magnesium measured	Low magnesium	High magnesium	Normal magnesium
INTERNATIONAL STUDIES						
Ryzen et al[7]	1985	94	Total	51%	-	-
Chernow et al[8]	1989	193	Total	61%	5%	34%
Reinhart et al[9]	1989	102	Total	20%	9%	71%
Rubeiz et al[10]	1993	197	Total	20%	7%	73%
Guerin et al[11]	1996	179	Total and erythrocyte	44% 66%	6% 4%	50% 30%
Huijigen et al[12]	2000	115	Ionized	14%	12%	74%
Deheinzelin et al[13]	2000	226	Total	45.6%	-	54.4%
Soliman et al[14]	2003	422	Ionized	18%	14%	68%
Safavi et al[15]	2007	100	Total	51%	-	49%

.

MAGNESIUM DEFICIENCY AND OSTEOPOROSIS:

Around 50% of the total magnesium is found in the bones. Therapy with magnesium in osteoporotic patients results in osteoblastic activity (bone formation). It does so by keeping the calcium in ionized state and also increases the availability of vitamin D. Adequate intake of magnesium is associated with increased calcium utilization and retention. Several studies of older adults proved that supplementation with magnesium improved the bone mineral density (BMD).

MAGNESIUM DEFICIENCY AND PSYCHIATRIC ILLNESS

Depression is considered as a sign of magnesium deficiency as reported by National Institute of Health in 2000. Earlier symptoms include anxiety, insomnia, poor attention and memory, confusion Obsessive Compulsion disorder (OCD). Delirium, depression, hallucinations and dementia (Alzheimer's disease) are associated with very severe magnesium deficiency[60]

EFFECTS OF MAGNESIUM IN OTHER DISEASES

Magnesium protects the cell from aluminum, mercury, lead, cadmium, beryllium and nickel. Low levels of total body magnesium results in deposition of heavy metals in the brain which leads to a predisposition for the development of diseases like multiple sclerosis, Parkinson's and Alzheimer's disease. In children, magnesium deficiency leads in heavy metal toxicity which contributes to learning disorders. [61]

MAGNESIUM AS A THERAPEUTIC AGENT

1. For decades, magnesium sulphate has been used safely and successfully to prevent eclamptic seizures in the management of pre- eclampsia and eclampsia (62).
2. In the management of arrhythmias like digoxin induced arrhythmias and torsades de pointes with long QT syndrome.
3. The role of magnesium in atrial fibrillation needs further studies for evaluation.

INTRAVENOUS MAGNESIUM SULFATE

The ideal neuroprotective agent for stroke would be inexpensive, readily available, easy to administer and have no significant adverse side effects. Intravenous Magnesium sulphate offers promise as just such an agent. Multiple randomized controlled trials had suggested that magnesium has a demonstrable neuroprotective potential in acute ischemic strokes, head trauma, spinal cord damage and any excitotoxic injury. The readily available source of ionized magnesium is the Magnesium sulfate which has an established safety and efficacy profile in myocardial infarction, eclampsia and cardiac resuscitation.

EFFECTS OF MAGNESIUM IN ISCHEMIC STROKE

ANTAGONISM OF INTRACELLULAR CALCIUM IN THE ISCHEMIC CASCADE[63]

Cerebral ischemia by lowering the transmembrane potential opens up the calcium channels causing the release of calcium from the sarcoplasmic reticulum and the mitochondria. This released calcium hydrolyze the membrane phospholipids by the activation of the phospholipases. The damaged membrane further increases the influx of calcium producing a positive feedback mechanism, by which ischemia produces higher calcium levels. The high levels of calcium inside the cell disturb the mitochondrial phosphorylation and increase the calcium dependant processes which utilize large amounts of ATP. This along with decreased ATP production causes depletion of ATP reserves thereby resulting in irreversible cell death. During ischemia, calcium entry into the cell is through the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor.

Many calcium channel blockers were used in the setting of ischemia mainly to prevent the vasospasm. They have effect mainly on the calcium channels and do not affect the intracellular release of calcium in the damaged membranes. Thus magnesium has an advantage in that it has effect on antagonizing the intracellular calcium and preventing the positive feedback mechanisms.

MAGNESIUM: A HIGHLY PROMISING NEUROPROTECTIVE THERAPY FOR STROKE

NEUROPROTECTANT EFFECTS (Fig 24)

1. VASCULAR EFFECTS

Magnesium stimulates the release of prostacyclin from the endothelium. Prostacyclin causes vasodilatation and inhibition of the aggregation of the platelets. So in deficient states increases the thromboxane/ prostacyclin ratio induces platelet aggregation and vasoconstriction. Also magnesium increases the endothelial dependant cerebral vasodilatation by stimulating the release of NO (nitric oxide) and inhibiting the potent vasoconstrictors mainly calcium and $PGF_{2\alpha}$.[64] This decreases the cerebral vascular resistance thereby increasing the cerebral blood flow. It inhibits the aggregation of platelets and prevents the propagation of thrombus and re-occlusion of the thrombosed vessels after recanalization.

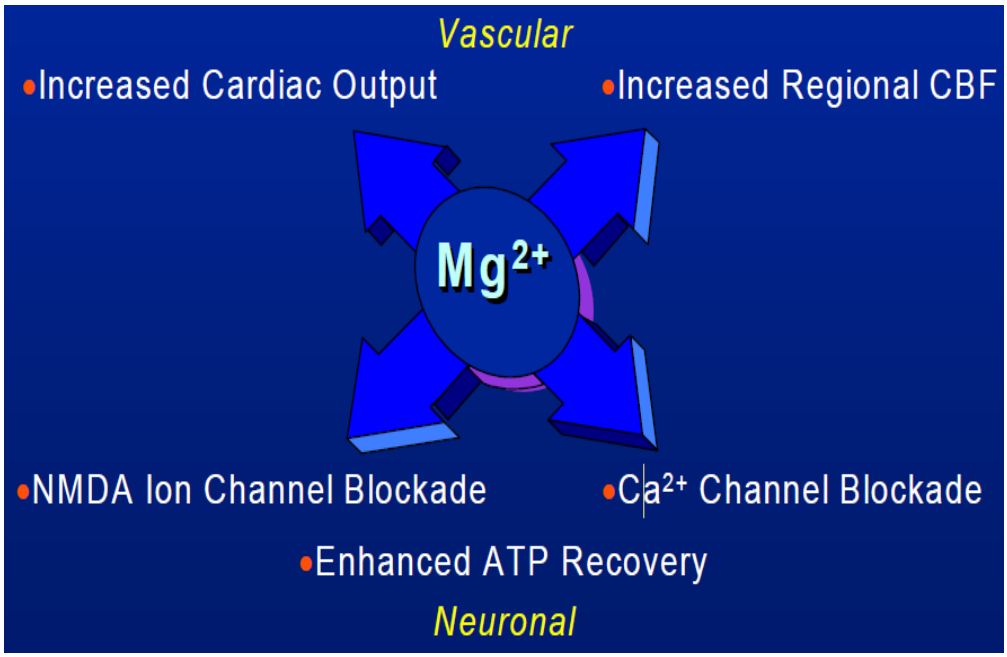


Fig 24: **POSSIBLE EFFECTS OF MAGNESIUM IN ISCHEMIC STROKE**

2. NEURONAL EFFECTS: ANTIEXCITOTOXIC

In the process of ischemic cascade, magnesium prevents the various excitatory events leading to ischemic neuronal death which are as follows.

1. Magnesium is an anti-excitotoxic agent, as it provides a voltage dependent block, through which it causes the inhibition of ischemia induced glutamate release.
2. Magnesium binds with ATP and blocks the voltage dependant ion channel of the NMDA receptor complex (Fig 25) and in higher doses acts as a non competitive N-methyl-D-aspartate (NMDA) receptor antagonist.

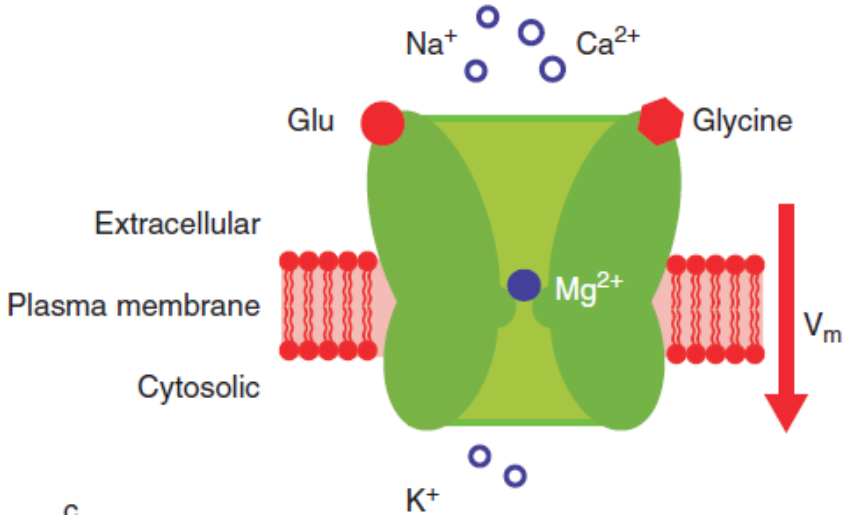


Fig 25: **NMDA RECEPTOR INHIBITION BY MAGNESIUM**

3. By the inhibition of NMDA receptor, the release of the major excitatory neurotransmitter, glutamate is inhibited, which is released excessively from the presynaptic neurons by the ischemic damage thereby causing a reduction in the post synaptic neurotoxicity.
4. Magnesium at the presynaptic level prevents the release of excitatory neurotransmitters thereby inhibiting the entry of calcium through the voltage gated channels. Intracellular magnesium concentrations are sufficiently high to antagonise a number of voltage gated ion channels including calcium, sodium and potassium, all implicated in cerebral ischemia.[19]
5. After an ischemic event, it enhances the recovery of cellular energy metabolism.
6. By preventing the cortical spreading depression and by suppression of anoxic depolarization, magnesium has the most effective potential neuroprotection.
7. There is a considerable reduction in the volume of the cerebral infarct.

8. The reasons for this improvement are due to the effects of increasing regional cerebral blood flow to the ischemic areas, or primarily neuronal actions, or a combination of these effects.

   Thus magnesium provides neuroprotection by boosting the tolerance to the ischemic insult such that the tissue retains the viability till other defence mechanisms come into play.

METHODS AND STUDY DESIGN

This was a cross sectional study, done in patients admitted in the medicine wards in Government Royapettah Hospital, conducted from July 2012 to December 2012. This study protocol was approved for research studies by the Ethical committee Government Kilpauk Medical College Hospital, Chennai.

INCLUSION CRITERIA

30 patients who were admitted in the medicine wards and intensive care unit with a diagnosis of acute ischemic stroke were taken as cases. Acute

ischemic stroke was diagnosed based on the clinical grounds and was later confirmed with either the initial CT scan or the delayed CT when the initial CT scans were normal. 30 patients were recruited from the outpatient department to participate in the study as controls. The age group included in the study was > 40 years. Patients with history of diabetes, hypertension and coronary artery disease were also included in the study. Written informed consent was obtained from the controls and the relatives of the cases and the blood was withdrawn at the time of admission to determine the serum magnesium levels. Patients (study and control population) were subjected to analysis of serum magnesium using colorimetric method. On each patient, complete clinical examination was done during the time of admission. Neurological status of the patients suffered from stroke was assessed at the time of admission by Glasgow coma scale and during discharge using Modified Rankin scale. From all the patients, information on medical histories regarding hypertension, diabetes mellitus, coronary heart disease, smoking and use of any medications were obtained through questionnaire and the patient's medical records.

Around 2 ml of venous blood was collected from the patients. Blood was allowed to clot and serum was separated by centrifugation and serum magnesium was estimated. Similarly blood was collected to check for random blood sugar, serum lipid levels. Serum magnesium was estimated by the colorimetric method. The normal levels of magnesium are 1.5 – 2.5 mEq/L.

Patients whose serum magnesium levels were found to be significantly lower were treated with intravenous magnesium sulphate.

EXCLUSION CRITERIA

1. Chronic kidney disease
2. Alcoholic liver disease
3. Thyroid disorders – hypo/hyperthyroidism
4. Chronic diarrhea
5. Patients on drugs that affect serum magnesium levels like diuretics, digoxin and antibiotics like amphotericin B, amino glycosides.

STATISTICAL ANALYSIS

Statistical analysis was done to identify significance and correlation between serum magnesium levels and acute ischemic strokes. Statistical analysis was done using Statistics Products Services Solutions (SPSS 15) software. Univariate analysis was done with paired t test and Pearson product moment correlation coefficient. A chi squared test was used to analyze the probability of differences in frequency distributions between the groups and $p<0.05$ was taken to be statistically significant in all calculations.

VARIABLES MEASURED IN THE STUDY

The important variables measured in the study are the serum magnesium levels compared with the age, sex, systolic and diastolic blood pressure, random blood sugar values, HDL, LDL cholesterol and the neurological outcomes of the acute ischemic stroke patients using Glascow coma scale and Modified Rankin scale. (Fig 26,27).

Table 1. Glasgow Coma Score

Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4=opens spontaneously	5=normal conversation	6=normal
3=opens to voice	4=disoriented conversation	5=localizes pain
2=opens to pain	3=words, incoherent	4=withdraws from pain
1=none	2=incomprehensible sounds	3=decorticate posturing
	1=none	2=decerebrate posturing
		1=none

Adapted from ACS ATLS[6]

Fig 26: **GLASCOW COMA SCALE**

Table 14. Modified Rankin Scale (MRS)

0 No symptoms
1 No significant disability, despite symptoms; able to perform all usual duties and activities
2 Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3 Moderate disability; requires some help, but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6 Death

Fig 27: **MODIFIED RANKIN SCALE**

OBSERVATIONS AND RESULTS OF THE STUDY

COMPARISON OF THE MAGNESIUM DEFICIENCY WITH THE VARIABLES

VARIABLES:

1. AGE AND SEX OF THE PATIENT

Among the study population, 30 patients of stroke patients, in the age group 45 – 80 years. Maximum incidence of stroke in the study was in the age group of 61 -70 years. Maximum incidence of age group in the control is 51 – 60 years. The percentage of smokers in both the case and control population was approximately 40%. So smoking as a confounding variable is removed. In both the cases and the controls, male (60%) to female ratio (40%) was 3:2. In the study, it was found that the cases were above the age of 45 years and below 80 years with the majority of cases were within the sixth decade.

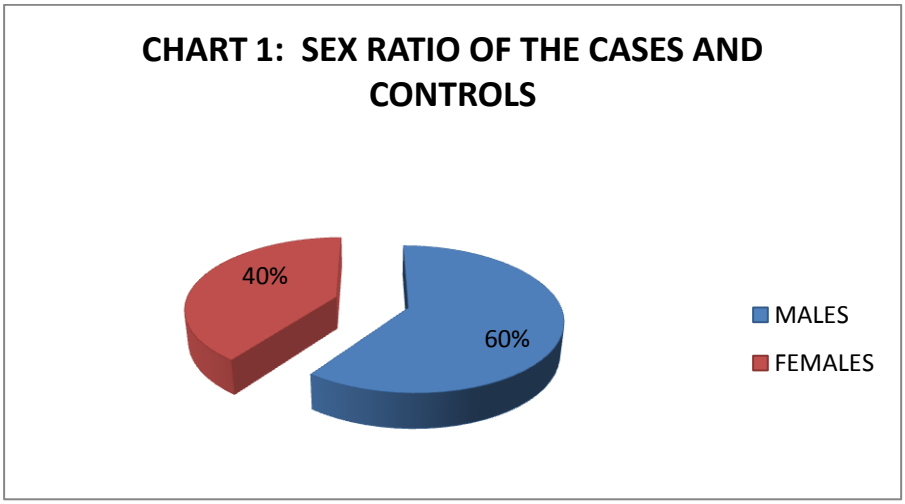


TABLE 1: PERCENTAGE OF MALES AND FEMALES IN THE CASES AND CONTROLS

			SEX		
			Male	Female	Total
Group	Case	Count	18	12	30
		% within Group	60.0%	40.0%	100.0%
	Control	Count	18	12	30
		% within Group	60.0%	40.0%	100.0%
Total		Count	36	24	60
		% within Group	60.0%	40.0%	100.0%

P=1.000

3. MAGNESIUM

In the study, serum magnesium was below the normal range in 70% of the cases and 26.6% of the controls. Male distribution: 43.33% and female distribution: 26.67%. The maximum incidence of magnesium deficiency for

both males and females in the stroke population were in the age group of 61 – 70 years which contributed to around 50% of the study population. Patients who were severely deficient were also in the age group of 61 – 70 years. The mean serum magnesium levels were significantly lower in the stroke patients (1.46) compared to the controls (1.83).

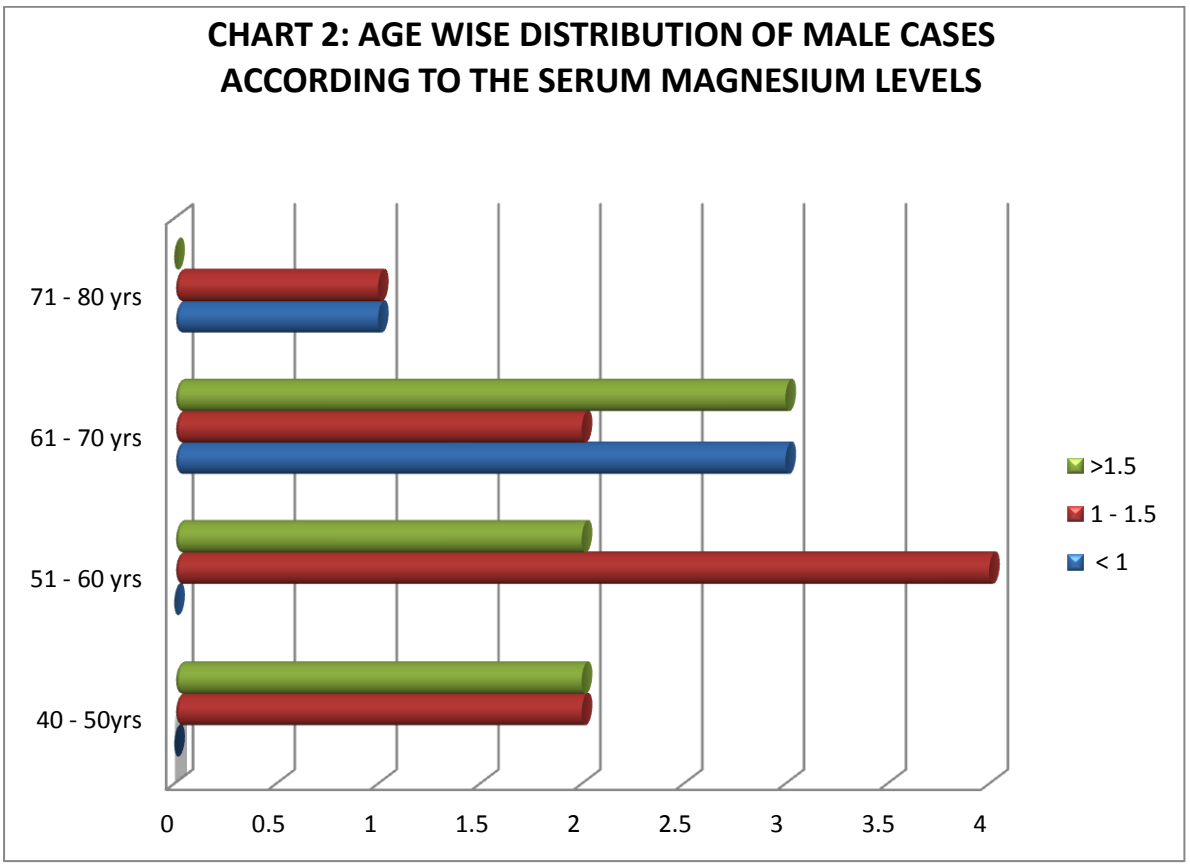


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CHART 3: AGEWISE DISTRIBUTION OF FEMALE CASES ACCORDING TO THE SERUM MAGNESIUM LEVELS

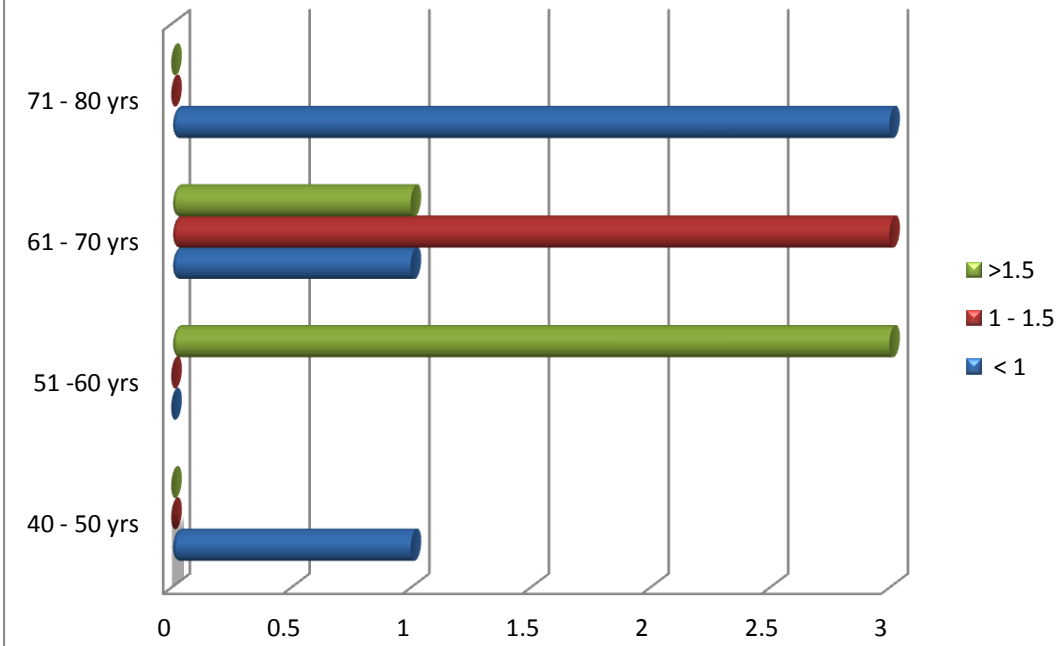


CHART 4: MEAN SERUM MAGNESIUM LEVELS IN CASES

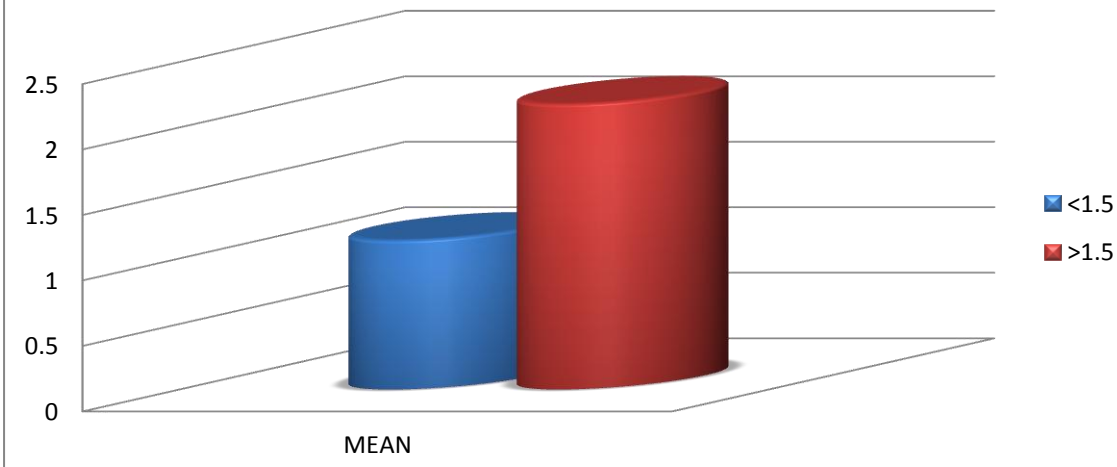


TABLE 2: AGE AND SEX DISTRIBUTION OF STROKE PATIENTS ACCORDING TO THE SERUM MAGNESIUM LEVELS

AGE	SEX	SERUM MAGNESIUM < 1.0 mg/dl	SERUM MAGNESIUM 1.0 – 1.5 mg/dl	SERUM MAGNESIUM >1.5 mg/dl
40 – 50 YEARS	MALE	0	2	3
	FEMALE	1	0	0
51 – 60YRS	MALE	0	4	2
	FEMALE	0	0	3
61 – 70 YRS	MALE	3	2	0
	FEMALES	1	3	1
71 – 80 YEARS	MALES	1	1	0
	FEMALES	0	0	3
TOTAL	MALES	4	9	5
	FEMALES	5	3	4
RESULT		MAGNESIUM DEFICIENT - 70% MALES: 43.33% FEMALES : 26.67%		SUFFICIENT – 30%

TABLE 3: PREVALENCE OF SERUM MAGNESIUM DEFICIENCY IN CASES AND CONTROLS

			Serum magnesium			
			Severe <1.0	Mild 1 – 1.5	Normal >1.5	Total
Group	Case	Count	8	13	9	30
		% within Group	26.7%	43.3%	30.0%	100.0%
	Control	Count	4	4	22	30
		% within Group	13.3%	13.3%	73.3%	100.0%
Total		Count	12	17	31	60
		% within Group	20.0%	28.3%	51.7%	100.0%

P=0.003

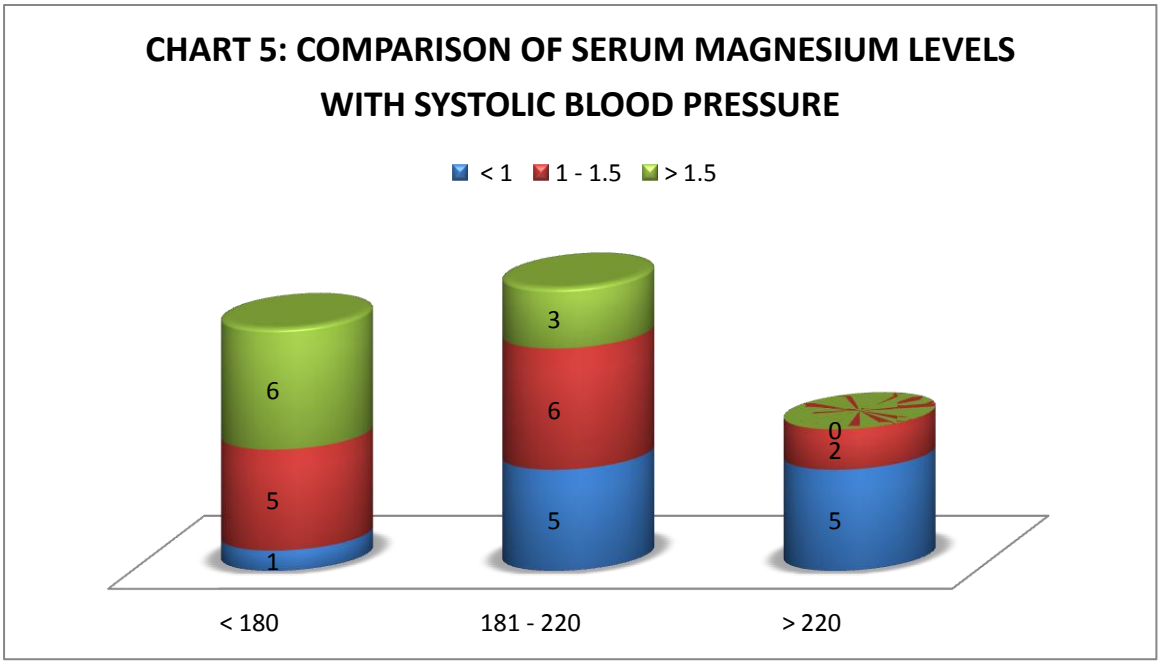
4. SYSTEMIC HYPERTENSION

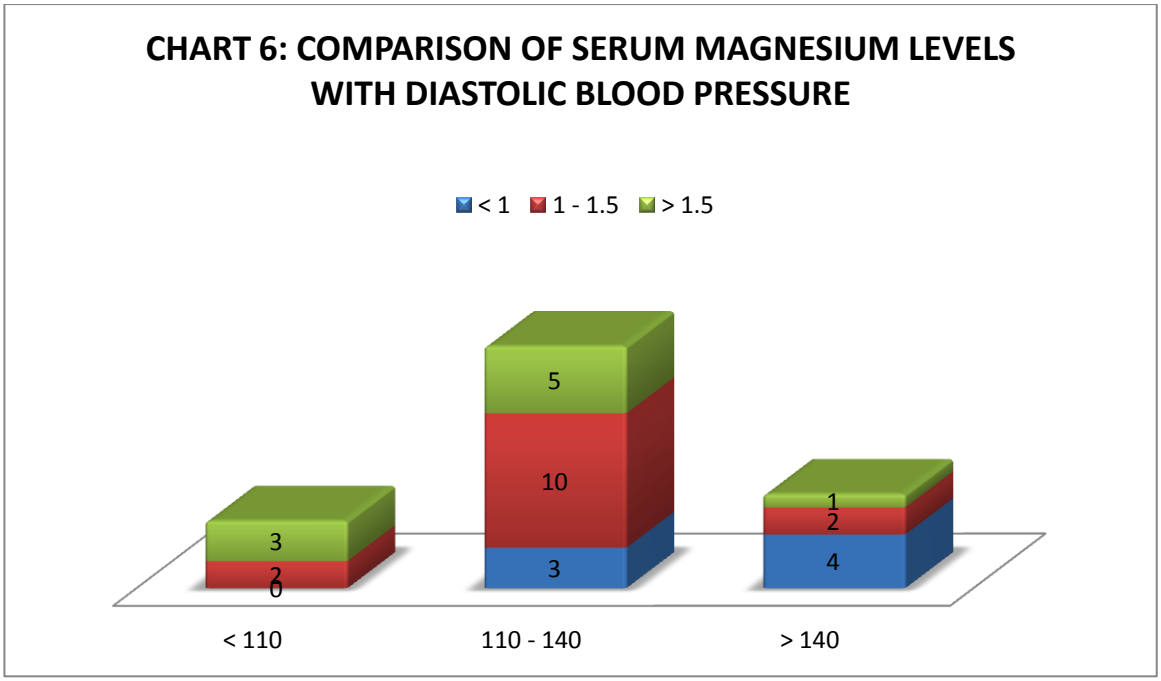
Hypertension was present in 60% of the cases and 40% of the controls. In the stroke patients and the controls, the mean systolic and diastolic blood pressure was significantly higher in the patients with magnesium deficiency compared to the patients with the normal magnesium levels.

TABLE 4: PERCENTAGE OF HYPERTENSION IN THE CASES AND CONTROLS

			SHT		
			Yes	No	Total
Group	Case	Count	18	12	30
		% within Group	60.0%	40.0%	100.0%
	Control	Count	12	18	30
		% within Group	40.0%	60.0%	100.0%
Total		Count	30	30	60
		% within Group	50.0%	50.0%	100.0%

P=0.196





In the cases, from this table we see that, lower the serum magnesium levels, higher the systolic and the diastolic blood pressure during presentation.

T-Test

TABLE 5: MEAN VALUE OF SERUM MAGNESIUM IN PATIENTS WITH AND WITHOUT HYPERTENSION IN THE TOTAL POPULATION

	SHT	N	Mean	Std. Deviation	P-value
SERUM MAGNESIUM	Yes	30	1.4133	.55319	0.031
	No	30	1.7400	.58933	

5. DIABETES MELLITUS

TABLE 6: PERCENTAGE OF DIABETES MELLITUS IN THE CASES AND CONTROLS

			DM		
			Yes	No	Total
Group	Case	Count	17	13	30
		% within Group	56.7%	43.3%	100.0%
	Control	Count	12	18	30
		% within Group	40.0%	60.0%	100.0%
Total		Count	29	31	60
		% within Group	48.3%	51.7%	100.0%

P=0.301

Diabetes mellitus was present in 57% of the cases and 40% of the controls. The mean random blood sugar values in the cases were higher when compared to the controls. The random blood sugar values were comparatively higher at the time of admission in the magnesium deficient compared to the patients with the normal levels in patients with the stroke.

T-Test

TABLE 7: MEAN VALUE OF SERUM MAGNESIUM IN PATIENTS WITH AND WITHOUT DIABETES IN THE TOTAL POPULATION

	DM	N	Mean	Std. Deviation	P-value
SERUM MAGNESIUM	Yes	29	1.3759	.66475	0.011
	No	31	1.7645	.44388	

6. CORONARY HEART DISEASE

TABLE 8: PERCENTAGE OF CORONARY HEART DISEASE IN THE CASES AND CONTROLS

			CAD		
			Yes	No	Total
Group	Case	Count	14	16	30
		% within Group	46.7%	53.3%	100.0%
	Control	Count	12	18	30
		% within Group	40.0%	60.0%	100.0%
Total		Count	26	34	60
		% within Group	43.3%	56.7%	100.0%

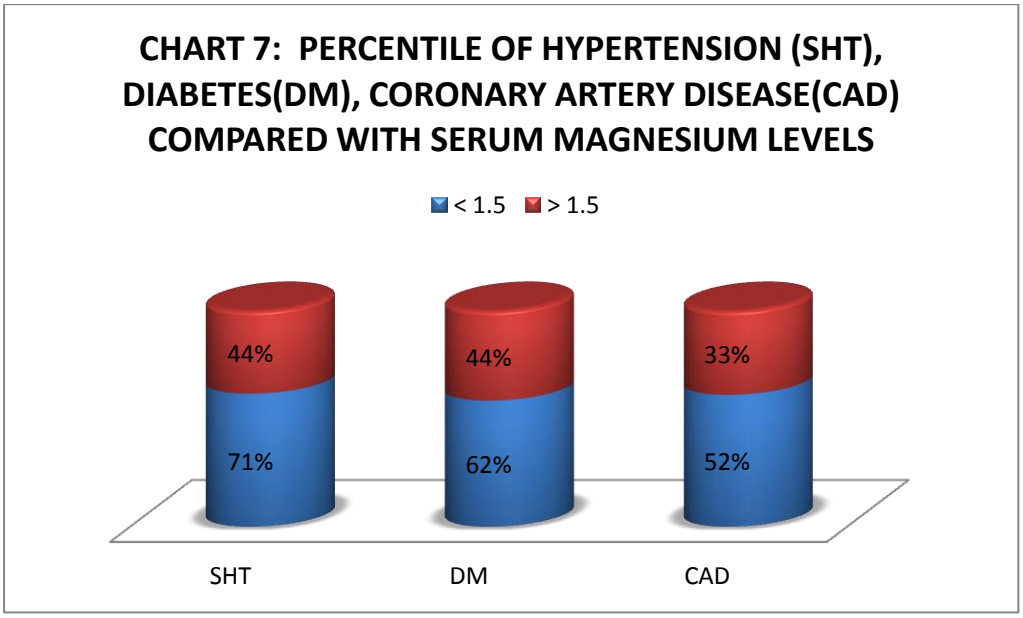
P=0.795

The coronary heart disease was present in 47% of the cases and 40% of the controls. In both the case and the control population, patients with systemic hypertension, diabetes mellitus and coronary heart disease considerably found to have significantly lower levels of serum magnesium than those who don't have.

T-Test

TABLE 9: MEAN VALUE OF SERUM MAGNESIUM IN PATIENTS WITH AND WITHOUT CORONARY HEART DISEASE IN THE TOTAL POPULATION

	CAD	N	Mean	Std. Deviation	P-value
SERUM MAGNESIUM	Yes	26	1.3923	.61834	0.033
	No	34	1.7176	.53455	



From this chart, we infer that percentage of stroke patients with the risk factors namely systemic hypertension, diabetes and coronary artery disease are deficient in serum magnesium which evidences that the development of the these risk factors can be secondarily due to magnesium deficiency.

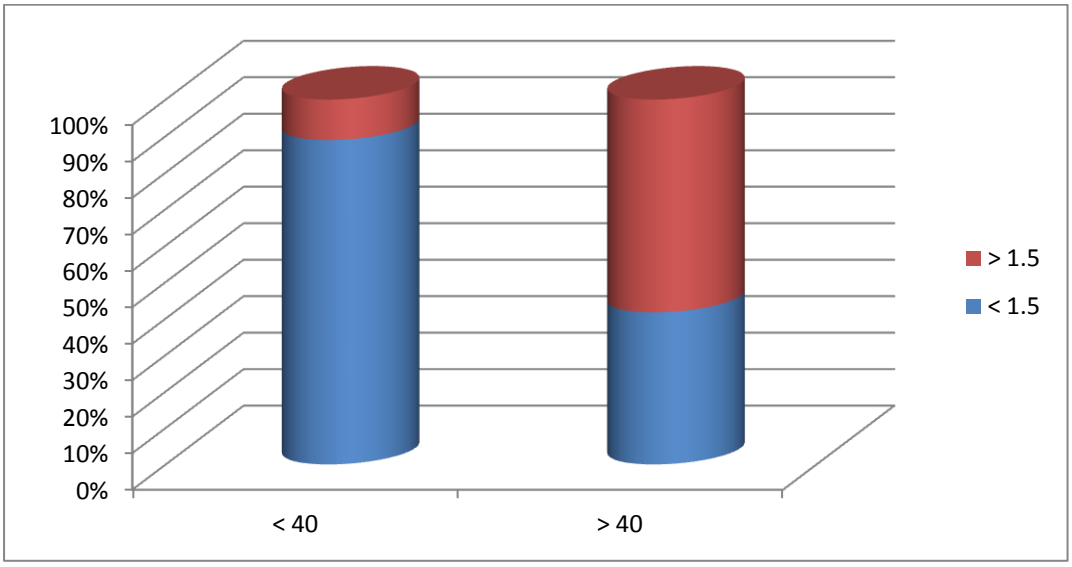
7. HDL CHOLESTEROL

TABLE 10: PERCENTAGE OF HDL CHOLESTROL IN THE CASES AND CONTROLS

			HDL_GP		Total
			<40	>=40	
Group	Case	Count	18	12	30
		% within Group	60.0%	40.0%	100.0%
	Control	Count	10	20	30
		% within Group	33.3%	66.7%	100.0%
Total		Count	28	32	60
		% within Group	46.7%	53.3%	100.0%

P=0.070

CHART 8: CORRELATION OF HDL LEVELS WITH THE SERUM MAGNESIUM LEVELS



8. LDL CHOLESTEROL

TABLE 11:PERCENTAGE OF LDL CHOLESTROL IN THE CASES AND CONTROLS

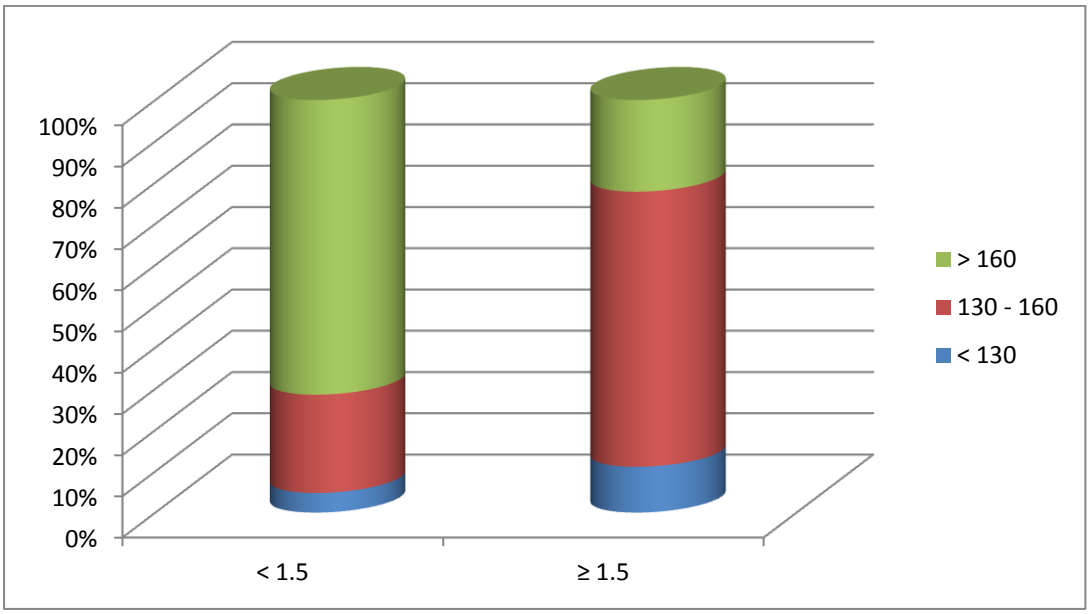
			LDL_GP			Total
			<=130	131-160	>160	
Group	Case	Count	2	10	18	30
		% within Group	6.7%	33.3%	60.0%	100.0%
	Control	Count	16	6	8	30
		% within Group	53.3%	20.0%	26.7%	100.0%
Total		Count	18	16	26	60

TABLE 11:PERCENTAGE OF LDL CHOLESTROL IN THE CASES AND CONTROLS

			LDL_GP			Total
			<=130	131-160	>160	
Group	Case	Count	2	10	18	30
		% within Group	6.7%	33.3%	60.0%	100.0%
	Control	Count	16	6	8	30
		% within Group	53.3%	20.0%	26.7%	100.0%
Total		Count	18	16	26	60
		% within Group	30.0%	26.7%	43.3%	100.0%

P=0.000

CHART 9: CORRELATION OF LDL LEVELS WITH THE SERUM MAGNESIUM LEVELS



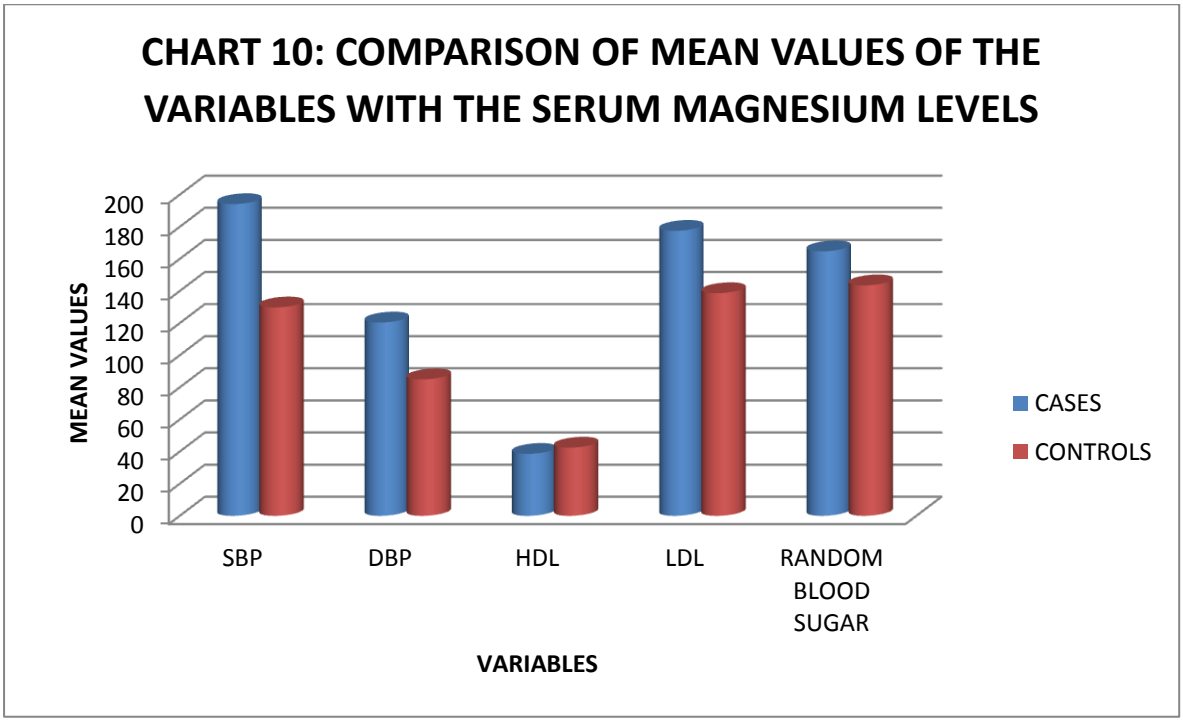
From these tables it can be found that that levels of HDL cholesterol were lower < 40 mg/dl and LDL cholesterol were comparatively higher > 130 mg/dl in magnesium deficient patients for both the cases and the controls. In the stroke patients compared to the controls, HDL cholesterol was lower and LDL cholesterol was higher.

From this graph chart, it can be identified that from the study, the mean values of systolic and diastolic blood pressure and LDL cholesterol were significantly higher in the magnesium deficient and HDL cholesterol was lower compared to the cases with the normal magnesium levels.

TABLE 12: COMPARISON OF MEAN VALUES OF THE VARIABLES IN THE CASE AND CONTROL POPULATION

Group		AGE	SBP	DBP	GCS	HDL	LDL	Serum magnesium	Blood sugar
Case	Mean	60.17	194.13	120.40	10.43	38.57	177.50	1.390000	164.73
	N	30	30	30	30	30	30	30	30
	Std. Deviation	9.377	34.224	16.786	3.411	10.647	37.175	.5944282	63.725
Control	Mean	61.17	129.80	85.00		42.47	138.67	1.763333	143.53
	N	30	30	30		30	30	30	30

	Std. Deviation	9.370	26.368	16.348		8.241	33.365	.5320639	53.402
Total	Mean	60.67	161.97	102.70	10.43	40.52	158.08	1.576667	154.13
	N	60	60	60	30	60	60	60	60
	Std. Deviation	9.308	44.381	24.258	3.411	9.642	40.123	.5901355	59.262



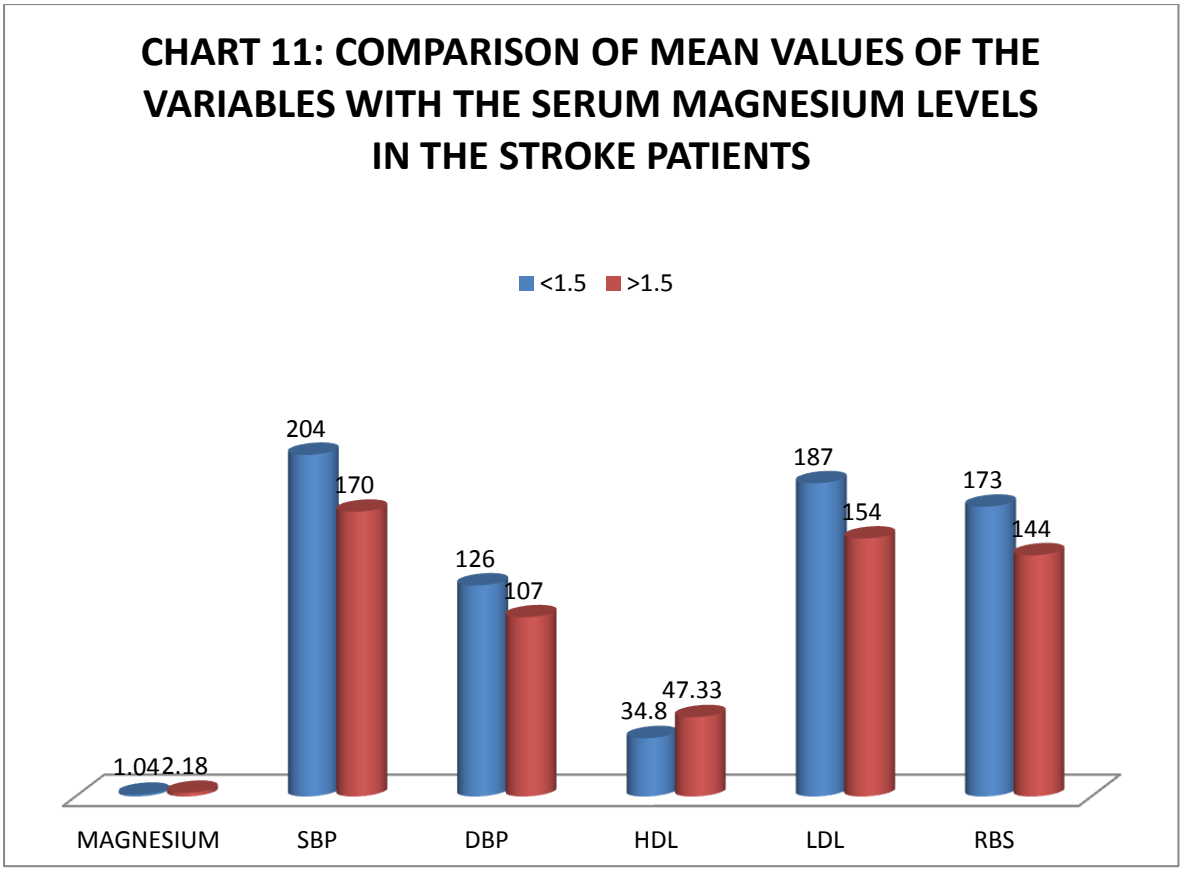


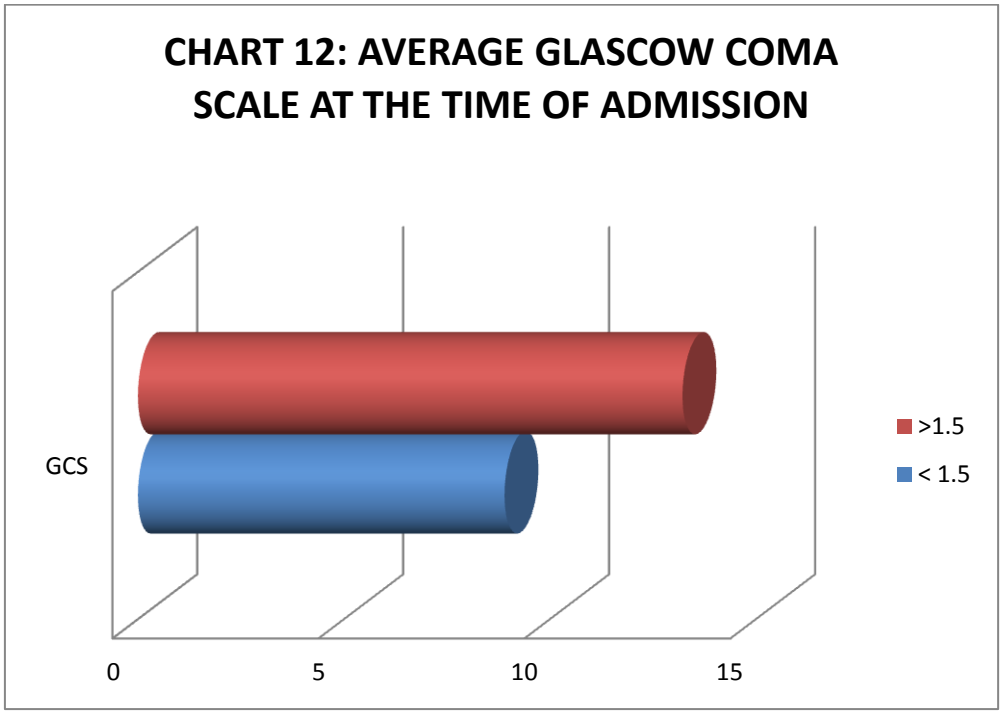
TABLE 13: p VALUE OF THE DIFFERENT VARIABLES

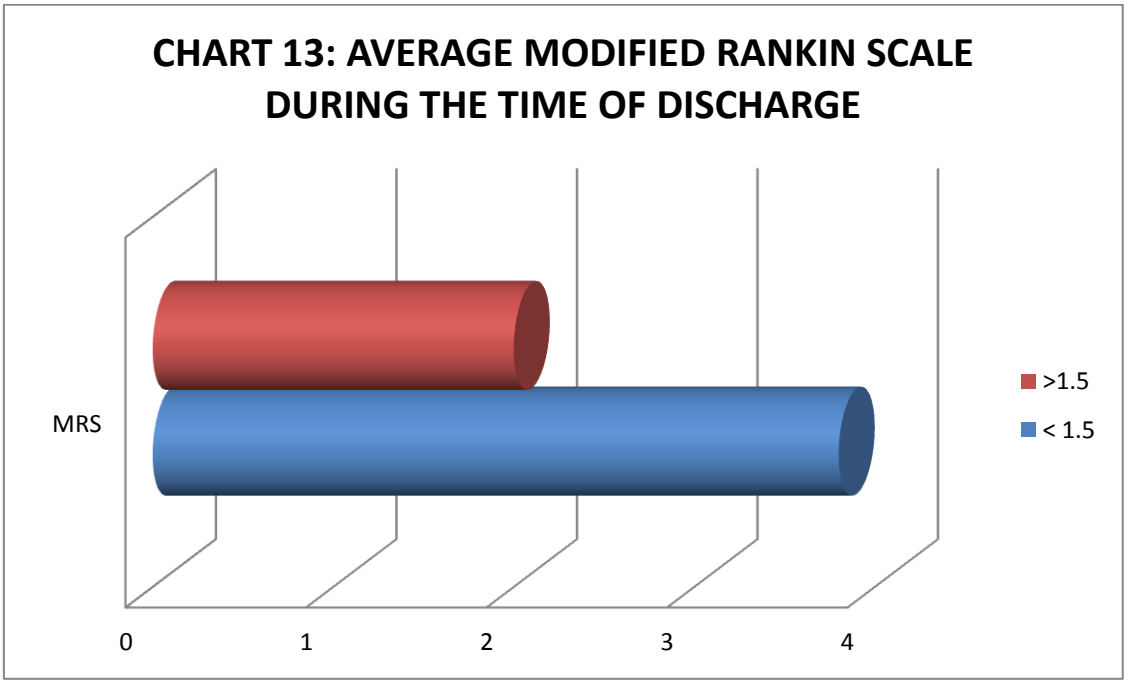
	Group	N	Mean	Std. Deviation	P-value
AGE	Case	30	60.17	9.377	0.681
	Control	30	61.17	9.370	
SBP	Case	30	194.13	34.224	0.000
	Control	30	129.80	26.368	
DBP	Case	30	120.40	16.786	0.000
	Control	30	85.00	16.348	

HDL	**Case**	**30**	**38.57**	**10.647**	**0.118**
	Control	**30**	**42.47**	**8.241**	
LDL	**Case**	**30**	**177.50**	**37.175**	**0.000**
	Control	**30**	**138.67**	**33.365**	
Serum magnesium	**Case**	**30**	**1.390000E0**	**.5944282**	**0.013**
	Control	**30**	**1.763333E0**	**.5320639**	
Blood sugar	**Case**	**30**	**164.73**	**63.725**	**0.168**
	Control	**30**	**143.53**	**53.402**	

From this table, we can find that p value was significant (<0.05) for serum magnesium (p = 0.013), systolic and diastolic blood pressure (p = 0.00), LDL cholesterol (p = 0.00) which proves the association of these variables with the serum magnesium.

9. NEUROLOGICAL OUTCOME OF THE STROKE PATIENTS





In the study population of stroke patients, the neurological outcome was assessed. The Glascow coma scale was lower at the time of admission and the Modified Rankin scale was higher during discharge in the patients with the low serum magnesium levels compared to the patients with normal levels. This showed that the severely magnesium deficient patients have a poor neurological outcome in patients suffered from stroke.

LIMITATIONS OF THE STUDY

1. The study was conducted in a sample size of only 30. Further studies need to be carried in a larger study population to verify the results and to show that there is a significant relationship between the serum magnesium and ischemic stroke.
2. The study was conducted only in the patients with acute ischemic cerebrovascular accidents. The haemorrhagic strokes and transient ischemic attacks were not considered in the study. So further studies trials have to be

conducted on all the three types of strokes to verify the relationship between these.

DISCUSSION

The prevalence of serum magnesium deficiency in acute ischemic cerebrovascular accidents was studied and found that there was a significant correlation between serum magnesium levels and the stroke. The mean serum magnesium levels were significantly lower in the cases (1.39) than the controls (1.76) (p=0.00) among the 30 patients with stroke, 70% (21) of them had magnesium levels below 1.5 and only 30% (9) of them had normal magnesium levels. The maximum incidence of deficiency in the cases occurred in the sixth decade. Overall, most of them who had lower magnesium levels also had

multiple risk factors for stroke in both the cases and the controls. Thus magnesium deficiency is also associated with these risk factors for cardiovascular diseases like systemic hypertension, (p=0.00) diabetes, coronary artery disease and dyslipidemia (p=0.00).

According to a case – control pilot study conducted by the University College of Medical Sciences (UCMS), New Delhi in the north Indian population, and serum magnesium was measured in 50 diagnosed cases of acute stroke which included transient ischemic attacks, ischemic and hemorrhagic strokes. It was a similar type of our study and the results were that the patients who had suffered ischemic stroke had significantly lower magnesium levels than the controls and also in patients who had suffered hemorrhagic strokes and transient ischemic attacks. Our study did not include strokes other than ischemic and the study population included only thirty cases and controls, but the observation was similar to theirs and was statistically significant. Their study did not include the diabetic population. Our study found that significant population of magnesium deficient patients were also diabetics, had dyslipidemia and hypertension. Hence in our study, hypertension and diabetes mellitus were found to be the important mediating factors associating serum magnesium with the ischemic stroke.

Many epidemiological studies reported that there was inverse relationship between the cardiovascular risk factors like hypertension, diabetes and the metabolic syndrome. In the Atherosclerosis Risk in Communities (ARIC) Study, they studied the relationship of the serum magnesium levels and the dietary intake in 14,221 males and females aged 45 – 64 years. They were followed up for fifteen years and 577 strokes occurred. It was observed that the incidence of stroke was higher in patients with low magnesium level and also the prevalence of hypertension and diabetes is lower in the population with the higher magnesium levels. They reported that the increased risk is mainly through the primary effects of magnesium on diabetes and hypertension. But in contrary, they also noted that dietary magnesium intake had only a marginal inverse association with the ischemic strokes.

There are ample amount of mounting evidence to prove that magnesium play a critical role in causing stroke and also in the healing process that take place during and also after the event of stroke.

After conducting various clinical trials, the American Journal of Clinical Nutrition and Reuters published that for every extra 100 milligrams of magnesium intake per day decreased the risk of an ischemic stroke by 9%.

A meaningful study was conducted in New York in the emergency department of three hospitals in 100 patients who had suffered from stroke. It established that in a significant number of patients there was a demonstrable deficiency of magnesium. It also exhibited these patients also had high calcium to magnesium ratio which are signs of increased vascular tone and vasospasm.

Magnesium in drinking water exists in a hydrated form and thus is easily more absorbed. In Taiwan, it was identified that the increase in hardness of water which is determined by the mineral content of calcium and magnesium was associated with a decrease in morbidity and mortality from cardiovascular and cerebrovascular diseases. A study compared all deaths due to stroke among their residents (17,133 cases) of Taiwan compared with all deaths from other causes (17,133 controls) conducted from 1989 till 1993. It was found that in the drinking water consumed by the Taiwan residents, higher the magnesium levels, the lower the incidence of stroke. This showed that magnesium had a significant protective effect from the drinking water on the risk of cerebrovascular diseases.

In the Journal of the American Academy of Nurse Practitioners published in 2009 by the Brigham Young University that from population based studies, the clinical evidence suggests that people are in greater risk for stroke who consumed low magnesium in their diet.

Every moment in stroke is crucial to outcome. In any untreated stroke, ischemic cascade injury process kills 12 million brain cells in a minute. Experimental studies had proved that magnesium slows this injurious process. Eight of the nine preclinical trials had demonstrated a significant decrease in sizes of the infarct volume treated with magnesium sulphate in animal acute ischemic stroke models. So magnesium has the ability to limit the area of infarct that is permanently lost as a result of stroke.

The IMAGES (Intravenous Magnesium Efficacy in Stroke) trial is an international RCT that was conducted on 2,386 patients treated with IV magnesium sulfate started within 12 hours after the onset of stroke (16 millimoles over 15 minutes, then 65 millimoles over 24 hours). The 90-day survival and disability data was followed on these patients. It showed a positive trend in protecting the patients with noncortical stroke.

Field Administration of Stroke Therapy- Magnesium (FAST-MAG) trial is a large trial sponsored by NIH-NINDS, conducted in Los Angeles, California to find the effects of intravenous magnesium for very early stroke. This trial found that there was a dramatic early recovery in 42 percent of patients infused with magnesium within two hours onset of stroke onset. In about 69% of all the patients and in 75% of patients infused with magnesium within two hours of stroke onset, good global function was achieved at 90 days after the onset of stroke. This trial was conducted primarily in the field, where magnesium

sulphate can be easily given, efficacious and can be given over a wide range of dose.

This unique trial hopes to demonstrate “pre-hospital initiation” whether magnesium infusion therapy, mostly via paramedics, can be effective in halting or slowing the ischemic cascade in most patients within those first crucial two hours. If this bold field trial proves to improve stroke outcome, it could usher in a new era of acute stroke management since rtPA cannot realistically be administered in the field.

Stroke remains the leading cause of disability worldwide. Unfortunately, the current therapies used in acute ischemic strokes are of extremely limited utility. The ideal neuroprotective agent for stroke should be inexpensive, readily available, easy to administer, have no significant adverse side effects with the added advantage of earlier administration even prior to obtaining a CT or a MRI brain scan. Magnesium offers promise as such an agent. The present study provided some evidence that serum magnesium can be considered as a modifiable risk factor in the development of acute ischemic stroke primarily by preventing the endothelial dysfunction which is the initiating event in the development of atherosclerotic plaque. So, if therapeutically intervened early in the course of the disease using magnesium as an adjuvant therapy for patients with the risk factors for stroke, it can prevent or modify the subsequent risk of

developing cardiovascular events. Further studies, with larger populations, are needed to prove our findings.

IMPLICATIONS FOR THE FUTURE

1. Serum magnesium levels should be done as a screening for patients who have the risk factors for stroke like diabetes mellitus, hypertension, dyslipidemia and coronary artery disease.
2. If they are found to be deficient, even if they are asymptomatic, they can be benefitted by advising the patient to increase the daily intake of magnesium in food or by supplementing with drugs.
3. Most of the available experimental trials and studies on magnesium have been conducted in countries outside India.
4. In India, there is not much study done on serum magnesium. To highlight its association with systemic hypertension, diabetes, coronary artery disease and

cerebrovascular accidents, further trials with a larger population need to be carried out in our country to document the prevalence of serum magnesium deficiency and its association with cardiovascular risk factors.

CONCLUSION

In conclusion, the present study showed a statistically significant correlation between the serum magnesium deficiency with the ischemic stroke. It is also associated with its risk factors diabetes, systemic hypertension and dyslipidemia which are important factors mediating association of serum magnesium with the incidence of ischemic stroke. Higher serum magnesium levels are accompanied by higher function and better prognosis after a stroke. So if a patient with the risk factors for stroke is found to have low levels of magnesium during screening, prophylactic supplementation with magnesium can prevent the more disability in the persons that will be involved by stroke in future and can reduce the social, emotional and economical losses among them.

Disclosure

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ABBREVIATIONS

rt- PA – recombinant tissue plasminogen activator

WHO - World Health Organization

ICMR - Indian Council of Medical Research

DALYS - Disability adjusted life years

NCD - Non communicable diseases

DTN - door to needle

EAA - Excitatory Amino Acid

NMDA – N- methyl D- aspartate

PET – Positron Emission Tomography

ATP - adenosine tri phosphate

NO – Nitric oxide

RBC – Red blood cell

Mg^{2+} - magnesium

Ca^{2+} - calcium

mEq/L – milli equivalents per litre

NIH - National Institute of Health

RDA – Recommended daily allowance

FE - Fractional excretion

CRP - C- reactive protein

ARIC – Atherosclerosis Risk in Communities

VCAM - vascular cell adhesion molecule

MCP-1 - monocyte chemoattractant protein -1

PDGF - platelet derived growth factor

NFkβ - nuclear factor kappa- light chain- enhancer of activated B cells

IF – interferons

IL – interleukins

LDL – Low density lipoprotein

HDL – High density lipoprotein

HMG-CoA – 3-hydroxy-3-methyl-glutaryl-CoA reductase

TGL - Triglyceride

DASH - Dietary Approaches to Stop Hypertension

BMD - bone mineral density

CT – Computed tomography

GCS – Glascow coma score

MRS – Modified Rankin scale

QUESTIONNAIRE

Name / Age / Sex / Occupation / Address/IP/OP Number.

HISTORY

Unilateral weakness of limbs, loss of consciousness, seizures, giddiness, syncope, headache, vomiting - duration, onset, progression

PAST HISTORY

Diabetes Mellitus, Systemic Hypertension, Dyslipidemia, Cardiovascular Disease, Cerebrovascular Disease, Peripheral Vascular Disease, Thyroid Disorders, Liver Diseases, Renal Failure, Chronic diarrhoea

PERSONAL HISTORY

Alcohol - amount, frequency, duration

Smoking - beedi/cigarette, number/day, duration

DRUG HISTORY

- Magnesium supplementation
- Anti Diabetic , Anti Hypertensive Medications , Cardiac Drugs (Diuretics)
- Drugs affecting Serum Magnesium Levels

ON EXAMINATION

- General Examination
- Vital Signs - Pulse Rate, Blood Pressure, Respiratory Rate
- Systemic Examination - CVS , RS , Abdomen , CNS

INVESTIGATIONS

- Serum magnesium

- Blood Sugar – FBS, PPBS
- Lipid Profile
- Renal Function Tests
- Liver Function Tests
- Thyroid Function Tests
- ECG
- CXR
- CT Brain

சுய ஒப்புதல் படிவம்

பங்கு பெறுபவரின் பெயர்:

முகவரி:

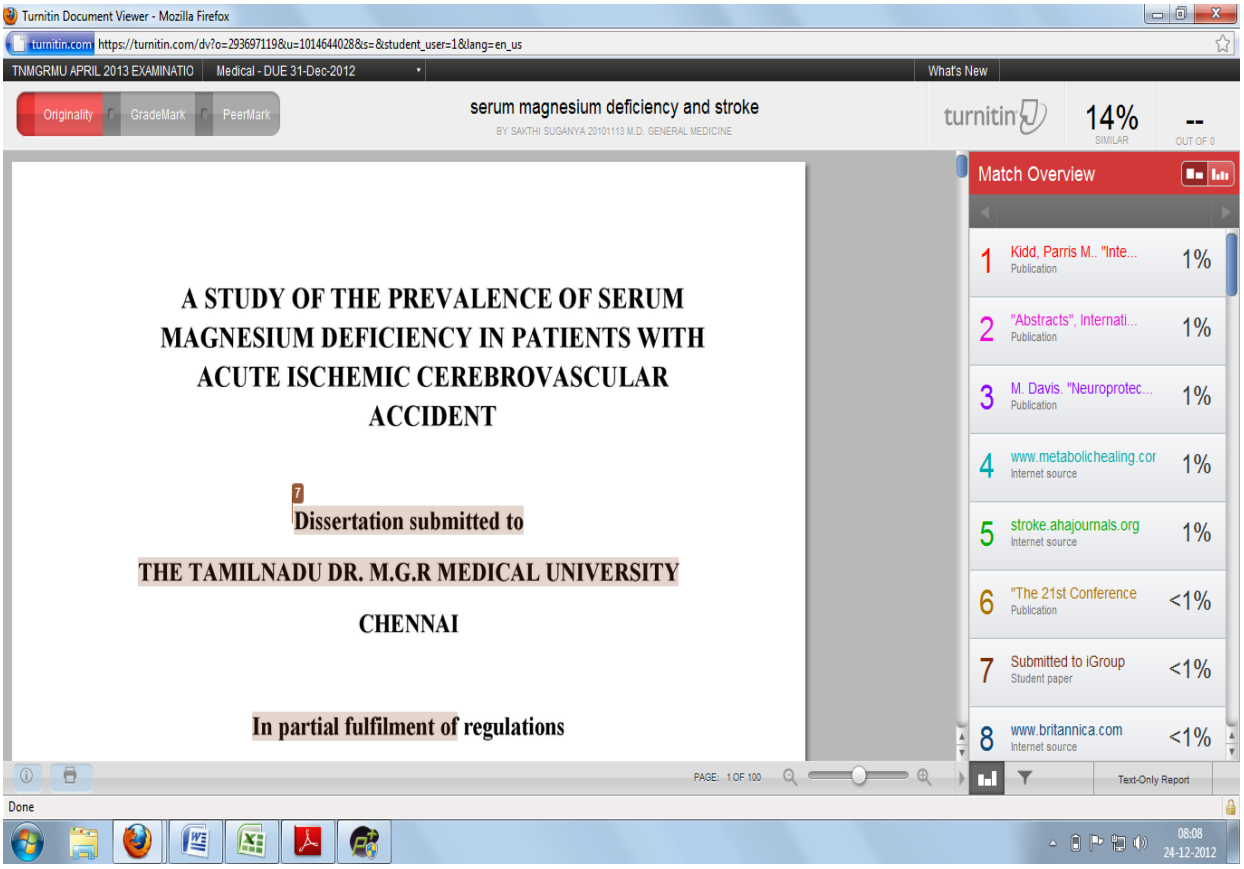
திட்டத்தின் தலைப்பு: நீரிழிவு மற்றும் இரத்த அழுத்தத்தால் விழித்திரை பாதிப்பும், விரல் நுனி இரத்த தந்துகிகளின் தொடர்பும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன். நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரத்தினாலோ, எந்த சட்டசிக்கலுக்கும் உட்படாமல், நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலுமாய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மருக்கமடேன். இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம்: _____

தேதி: _____

PLAGIARISM REPORT



TURNITIN ORIGINALITY REPORT

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MASTER CHART

CASES

NAME	AGE	SEX	TERRITORY	SBP	DBP	GCS	HDL	LDL	SMOKER	SERUM MAGNESIUM	BLOOD SUGAR	DM	SHT	CAD	MRS
BABU	56	M	MCA	190	118	10	38	158	YES	1.3	144	NO	YES	NO	3
RANI	65	F	MCA	244	146	8	34	178	NO	1.1	162	YES	YES	NO	5
RAHMATH BEE	68	F	PCA	170	98	13	46	154	NO	2	138	NO	NO	YES	2
RAMDOSS	45	M	MCA	160	96	15	48	148	NO	2.2	132	YES	YES	NO	1
ANNAMALAI	78	M	MCA	250	146	6	24	224	NO	0.8	312	YES	NO	YES	6
VADIVEL	60	M	PCA	150	106	11	38	164	YES	1.4	108	YES	YES	YES	4
KURSHITH BEE	73	F	MCA	246	138	7	34	180	NO	0.9	264	YES	NO	NO	5
PALANI	54	M	ACA	142	84	12	39	152	YES	2.1	164	NO	YES	YES	4
NARAYANAN	63	M	MCA	260	150	8	32	168	NO	0.9	148	YES	YES	NO	5
KALAIYARASI	58	F	PCA	168	114	13	37	140	NO	1.8	126	NO	NO	NO	3
SUMATHI	48	F	MCA	174	112	14	44	154	NO	0.9	182	YES	NO	YES	2
SAKTHIVEL	58	M	MCA	180	100	11	49	168	YES	1.4	102	NO	YES	NO	2
RAMAYEE	70	F	MCA	256	144	3	20	268	NO	0.9	134	YES	YES	YES	6
DHANDAPANI	47	M	MCA	174	110	13	36	234	NO	1.3	154	NO	YES	NO	2
VENKATESH	64	M	MCA	198	126	9	37	208	YES	1.3	204	YES	YES	NO	5
MURUGESAN	49	M	PCA	166	110	14	41	186	YES	2.5	140	NO	NO	YES	1
MANJU	55	F	MCA	192	126	13	62	130	NO	2.3	148	YES	YES	NO	2
DEVI	62	F	MCA	220	110	13	54	136	NO	1.4	116	NO	YES	YES	2
SUBRAMANI	59	M	PCA	178	142	14	42	148	NO	1.4	140	YES	NO	NO	1
BALAJI	75	M	MCA	250	134	7	25	190	YES	1.2	122	YES	NO	YES	6
SARASWATHI	63	F	MCA	180	118	12	38	196	NO	1.3	158	NO	YES	YES	3
PATTAMAL	80	F	MCA	198	124	5	24	264	NO	0.8	402	NO	YES	YES	6
MUNIYAN	53	M	MCA	170	116	12	40	188	YES	2.4	184	YES	YES	NO	2
KUMAR	47	M	PCA	166	116	13	43	176	YES	1.4	166	NO	YES	YES	3
KRISHNAN	64	M	MCA	188	118	7	29	197	NO	0.9	172	YES	YES	NO	4
KANCHANA	56	F	PCA	178	110	13	58	146	NO	2.5	138	YES	NO	NO	2
NOORNISHA	63	F	MCA	180	124	11	38	172	NO	1.3	98	NO	NO	YES	2
DAVID	57	M	MCA	174	118	9	32	124	YES	1.2	136	YES	YES	NO	3
MOHAMED	48	M	PCA	184	112	14	55	146	YES	2.3	132	NO	NO	NO	1
FAZIL	67	M	MCA	238	146	3	20	228	NO	0.8	216	YES	NO	YES	5

CONTROLS

NAME	SEX	AGE	SERUM MAGNESIUM	HDL	LDL	PPBS	SBP	DBP	DM	SHT	CAD	SMOKER
BANUMATHI	F	58	2.1	48	126	102	138	80	NO	YES	NO	NO
PADMAVATHI	F	70	0.9	38	158	136	178	110	YES	YES	YES	NO
RANGAN	M	65	2.3	50	182	116	96	60	NO	NO	YES	YES
PANDIYAN	M	59	1.7	42	108	148	130	82	NO	YES	NO	YES
KAMALA	F	64	2.1	40	146	98	100	70	NO	NO	YES	NO
SRIDHAR	M	55	2.3	36	112	176	120	80	YES	YES	NO	YES
THOMAS	M	47	1.7	54	104	100	114	78	NO	NO	NO	NO
RAHIMA	F	74	1.4	30	166	124	106	82	YES	NO	NO	NO
SURESH	M	57	2	49	124	280	140	90	NO	NO	NO	NO
KANCHANA	F	80	1.4	48	144	140	156	100	NO	YES	YES	NO
BALARAMAN	M	61	2.2	29	162	322	160	100	YES	YES	YES	YES
RAMESH	M	65	1.8	56	96	116	110	64	YES	NO	NO	NO
KANNAGI	F	63	1.9	46	154	124	90	60	NO	NO	NO	YES
MUTHAMMA	F	64	1.3	53	182	150	134	94	NO	NO	YES	YES
SEKAR	M	50	1.1	28	224	186	190	124	YES	NO	YES	YES
JAYARAMAN	M	69	2.3	44	102	148	106	80	NO	NO	NO	NO
GOPAL	M	78	1.7	52	136	104	92	64	NO	YES	NO	YES
JANAKI	F	45	2.3	31	128	94	128	90	YES	YES	NO	NO
THANGAM	F	78	1.3	30	192	136	148	94	YES	YES	YES	YES
NAWAZ	M	68	1.7	48	188	150	140	76	NO	YES	YES	NO
SUMATHY	F	60	2.4	40	122	134	100	72	NO	NO	YES	NO
KUMAR	M	59	1.8	37	114	134	120	80	YES	NO	NO	NO
DANIEL	M	58	1.9	42	98	128	116	70	NO	NO	NO	NO
JAFFER	M	55	2.6	48	106	118	120	76	NO	NO	NO	YES
MANGAI	F	45	1.4	45	126	148	168	116	NO	YES	NO	NO
VELMURUGAN	M	66	2.4	45	110	104	132	88	YES	NO	NO	NO
BALAN	M	56	2	42	102	98	128	80	NO	NO	NO	NO
MUTHIAH	M	63	1.9	36	144	146	130	90	YES	NO	YES	YES
VASUDEVAN	M	49	1.8	54	128	100	126	86	NO	NO	NO	NO
CHITHRA	F	54	1.3	33	176	246	178	114	YES	YES	YES	YES

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.6206/ME-1/Ethics/2012 Dt:05.07.2012.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on Serum magnesium deficiency in acute cerebrovascular accidents" submitted by Dr.S.T.Sakthi Suganya, MD (General Medicine), PG Student, Govt. Royapettah Hospital, Chennai.

The Proposal is APPROVED

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
12 OCT 2012
Kilpauk, Chennai-10.

12/10/12
CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai