"SERUM MAGNESIUM LEVEL AND ITS CORRELATION WITH PRIMARY HYPERTENSION - ONE YEAR CROSS SECTIONAL STUDY"

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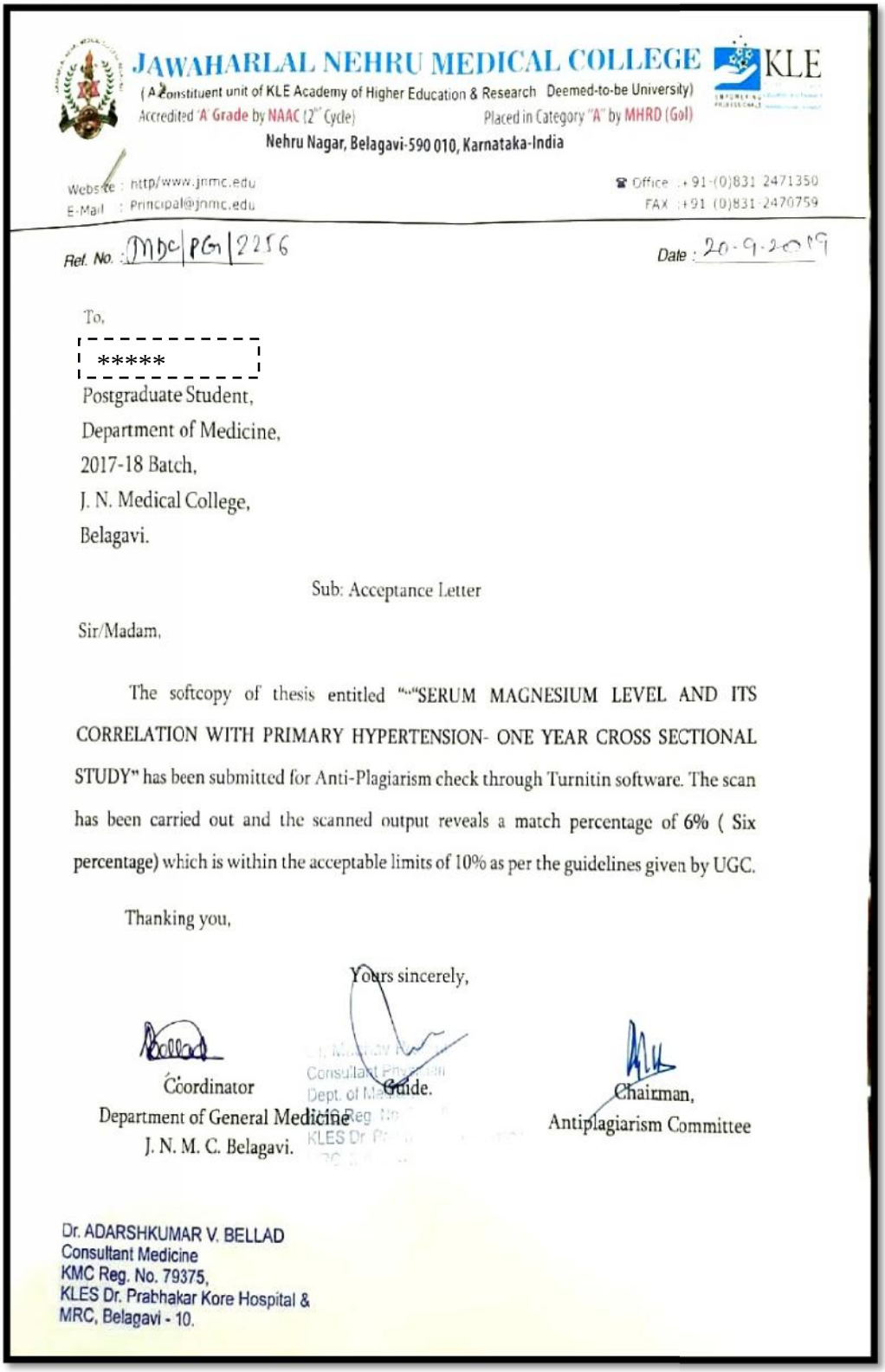

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LIST OF ABBREVIATIONS USED

$1,25(OH)_2D$	1, 25-dihydroxyvitamin D
ATP	Adenosine triphosphate
BP	Blood Pressure
Ca^{2+}	calcium
CKD	Chronic kidney disease
CO	Cardiac Output
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
DCT	Distal convoluted tubule
DGLA	dihomo-gamma-linoleic acid
DM	Diabetes mellitus
g	Grams
GLA	gamma-linoleic acid
HTN	Hypertension
LA	linoleic acid (LA)
LOH	Loop of Henle
mg	milligrams
Mg^{2+}	Magnesium
mL	Millilitre
mmol	milimoles
n	Total number
NO	nitric oxide
OPD	Outpatient department
PCT	Proximal Convoluted Tubule

PGE1	prostaglandin E1
PGI2	prostacyclin
PPIs	proton pump inhibitors
SBP	Systolic blood pressure
SD	Standard deviation
SVR	Systemic Vascular Resistance
T2DM	Type 2 diabetes mellitus
TAL	Thick ascending limb of loop of Henle
TRPM6	Transient Receptor potential cation channel subfamily M member 6
TRPM7	Transient Receptor potential cation channel subfamily M member 7
CNNM3	Cyclin and CBS domain divalent metal cation transport mediator 3
SLC41A1	The human solute carrier family 41
MagT1	Magnesium Transporter1
MRS2	Mitochondrial RNA slicing 2 protein

ABSTRACT

Background and objectives

The etiology of primary hypertension are multifactorial, magnesium status in human body is thought to be a crucial factor in pathogenesis of primary hypertension This study was aimed at finding the association between the serum magnesium level and blood pressure in patients with primary hypertension.

Methodology

The present one year hospital based cross-sectional study was done on 100 patients with primary hypertension from January 2018 to December 2018 in Department of Medicine, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Results

In the present study, 61.00% of the patients were males while 39.00% of the patients were females. The male to female ratio was 1.6:1. Youngest participant in the study was 30 years of age and oldest was 91years. The mean age was 59.30 years with SD $\pm$ 14.79. out of 100 cases ,11% of patients had serum magnesium less than 1.6mg/dl , 82% of patients had serum magnesium between 1.6 mg/dl to 2.5mg/dl,7 % of patient had magnesium above 2.5 mg/dl. The patients were divided into grade 1 and grade2, where grade 1 patients had systolic BP from 140 to 159 or diastolic 90 to 99 & grade 2 patients had systolic BP more than or equal to 160 or diastolic BP more than or equal to 100 mmHg. The mean serum magnesium level in the study population was 1.99 mg/dl. The mean serum magnesium levels in subjects with grade 1 hypertension was 2.1mg/dl compared to mean value of 1.87 mg/dl in grade 2

hypertension. Comparison between serum magnesium levels and blood pressure revealed statistically significant association with a p-value of 0.0073. study showed inverse association of serum magnesium levels with both systolic and diastolic blood pressure recordings.

Conclusion and interpretation

The present study showed a significant inverse association between serum magnesium level and blood pressure in patients with primary hypertension.

Keywords:

Serum magnesium, primary hypertension,

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INTRODUCTION

The prevalence hypertension is more than 1 billion individuals, with estimated death related to hypertension is as high as 9.4 millions/year globally. The prevalence is increasing, forcing us to adopt newer strategies in primary prevention and effective treatment to prevent complications arising out of hypertension. The etiology for primary hypertension is multifactorial and include environmental, genetic, racial variation , lifestyle which includes physical activity and diet and stress. Pathogenesis of primary hypertension includes changes in the nervous system(sympathetic activity), the renin-angiotensin-aldosterone system, and the plasma volume.[1]

Clinical studies correlating magnesium status in patients with primary hypertension have shown that both serum magnesium, tissue magnesium levels have an inverse correlation with blood pressure levels.[2] Magnesium being a major intracellular cation has important physiological role in various functions.[3] Magnesium is necessary for the synthetic functions and for regulation of essential biochemical reactions , cell replication and metabolism.[4,5]

Even after extensive research work the cause for hypomagnesaemia is not known. The deficiency is either due to low intake or defective metabolism which can lead to endothelial damage and vasospasm.[6,7,8] In magnesium deficiency and secreted catecholamine along with oxidative stress increase calcium entry into cells of vascular smooth muscles, which will increase tone of arterioles and cause coronary spasm. Hypertension and its complications are due to increased entry of calcium into arterial smooth muscle cells causing contractions.[9,10]Low serum magnesium levels plays vital role in pre-hypertension in healthy subjects. Higher blood pressure was seen in women with low serum magnesium levels treated using diuretics. Also, it was

observed that diabetes mellitus, dyslipidaemia, and hypertension correlated negatively with serum magnesium levels. Apart from blood pressure, magnesium regulates intracellular level of sodium, potassium and more importantly calcium and pH . Studies have shown that low magnesium can lead to increase in mass of left ventricle, reduce sensitivity to insulin, and decrease compliance of arteries.[11] Multiple other studies have shown that low serum magnesium concentration irrespective of other cardiovascular risks were related to the gain in mass of left ventricle.[12]

Magnesium depletion is connected to thiazides and loop diuretics. Among patients on treatment with diuretics more than one third exhibit hypomagnesaemia. Arrhythmias and sudden death due to low magnesium could be prevented by magnesium administration. Studies have shown a correlation between electrolyte disturbance due to thiazide use with ventricular arrhythmias. Therefore supplementation with potassium and magnesium will reduce arrhythmias and sudden deaths[12] . Magnesium will help in synthesis of prostacyclin and its release by the endothelium, which is a strong vasodilator, it also inhibits platelet aggregation.[13]

Importance of magnesium is being increasingly recognized and constantly rediscovered and correlated with many medical conditions but still remains overlooked and undertreated in clinical practice. There is no comprehensive understanding about relation of magnesium with development of hypertension. Various studies have yielded contradicting results, hence there is a need to fill these gaps in knowledge. Therefore this topic was chosen to study association of serum magnesium level with blood pressure in primary hypertension.

OBJECTIVE

The objectives of this study were to,

1. To determine the serum magnesium levels in patients with primary hypertension.
2. To study correlation between serum magnesium level and blood pressure in patient with primary hypertension.

REVIEW OF LITERATURE

Magnesium is an important cation responsible for various functions, it is found in large quantity inside the cell compared to its plasma concentration. Magnesium is needed for synthesis of building blocks of the cells like protein, nucleotides, it also catalyzes many biochemical reactions inside the cells to maintain the normal physiology. Intracellular magnesium forms a key complex with the ATP and has a role in process such as synthesis of protein, cell division & metabolism.[3,4,5]

Total human body content of magnesium is about 1,000 milimoles (22-26g) out of this 67% is present in bones & hard tissue, 31% is found inside cells & ~2% in serum.[14] The process of intracellular regulation of magnesium is still poorly understood & the levels are well maintained except in some situations like hypoxia & prolonged magnesium depletion. The recommended dietary allowance (RDA) for magnesium in adults is 4.5 mg/kg/day. The daily requirement is higher in pregnancy & lactation & after critical illnesses.[15]Amount of magnesium consumed depends on the Mg^{2+} concentration in food, water and supplements (if taking). Magnesium is abundant in almonds, nuts, cashews, dark chocolates, avocados, legumes, green leafy vegetables, whole grains, bananas, meat & fish etc. milk is a poor source of Mg^{2+}.[15,16]

Biochemical importance of Magnesium

Magnesium activates the host enzyme system that are crucial for cellular metabolism. Most essential are the enzymes that hydrolyze & transfer phosphate group, especially those seen in reactions involving ATP. ATP is needed for glucose utilization, protein, nucleic acid, fat & co-enzyme synthesis, muscle contraction & other reaction .[17] About 30-40% of magnesium is absorbed in small intestine. Absorption is related to dietary consumption i.e., up to 65% is absorbed when

consumed in small quantity and 11% at high intake. Large amount is absorbed in jejunum, ileum & colon. Absorption is both active and passive but is mainly passive during normal intake.[18] Research have shown that parathyroid hormone plays an important role in absorption. Mg^{2+} absorption in intestine is increased by vitamin D, up to 70% absorption can be seen during magnesium deficiency, but this role is still controversial.[19]

Kidneys are most important in maintenance of serum Mg^{2+} levels. Amount excreted in urine is nearly similar to the amount absorbed through the gut which is ~100mg/day (~4mmol/day) . Serum Mg^{2+} is regulated by controlling the reabsorption of Mg^{2+} through kidneys. Major part of the serum Mg^{2+} is filtered & more than 95% of the filtered Mg^{2+} is reabsorbed, leaving only a small quantity to be excreted in the urine. To be more precise 20% is reabsorbed in PCT, 60% in LOH & 5-10% in DCT.[20.21] Magnesium reabsorption in PCT is passive, which depends on the sodium water reabsorption & magnesium levels, magnesium reabsorption in TAL is dependent on voltage gradient and Nacl absorption. Similarly tubular absorption is determined by serum magnesium levels, total body magnesium states, GFR, hormones (PTH, ADH, Insulin), volume status & diuretic use.

There are no simple laboratory tests to estimate the total body Mg^{2+} levels, most widely used tests for estimation of Mg^{2+} level is the serum magnesium levels. This method may not be the best to access the magnesium status in human body because changes in serum protein levels will affect the magnesium levels without altering the total magnesium levels in the body & importantly magnesium levels may not always reflect the intracellular magnesium concentration.[15,22]

Measurement of Mg^{2+} excreted may be helpful to estimate the Mg^{2+} levels in body but routine tests are not available for use. Recently ion electrodes have been used for magnesium estimation which are available for commercial users and give accurate measure of ionized magnesium. It is useful in may clinical scenarios but it is not available for use in most of the health care systems, so no lab tests is good enough for estimation of Mg^{2+} status but studies over years have proved that serum Mg^{2+} levels are one of the easiest, reliable and readily available tests of Mg^{2+} levels in human body . MR spectroscopy, fluorescent probes, all the newer modalities which have been developed recently but they are not easily available tests for routine assessment.[14,15]

Hypomagnesaemia manifests when there is significant deficiency of Mg^{2+} stores in the body (0.5 to 1mol/kg).[15] The word hypomagnesaemia is sometimes interchangeably used for magnesium deficiency. However there can be significant reduced Mg^{2+} stores in body with normal serum Mg^{2+} & normal Mg^{2+} stores with low serum Mg^{2+}. [19] In routine clinical practice magnesium deficiency is missed or under diagnosed, therefore routine assessment of serum Mg^{2+} in patient with critical illness & diseases like T_2DM, HTN & other diseases predisposing to Mg^{2+} deficiency is justified.[3] The causes for low Mg^{2+} levels may be due to impaired absorption of magnesium in intestine, increased loss from intestines, reduced absorption from kidneys and due to drugs causing Mg^{2+} deficiency like ethanol, diuretics, amphotericin B, aminoglycosides, cisplatin, cyclosporine etc. Hypomagnesaemia with hypocalcaemia is seen in patient with history of chronic use of omeprazole or PPIs (for >1year duration).[17]

Magnesium and Hypertension

The abnormality in hemodynamic seen in patients with hypertension is the increase in peripheral vascular resistance due to the increase in the size of lumen in resistance arteries. Since resistance is inversely related to the radius (4^{th} power of radius). Small changes in size of arterial lumen will cause significant changes in vascular resistance. Development of hypertension includes alterations in structure and functions of smaller arteries. These changes occurring in tunica media due to increased cell growth, intracellular matrix deposits, change the tone of vessels. Decreased vasodilatation or increased vasoconstriction will reduce the size of the lumen & enhances the resistance to flow of blood in periphery. [22,23] Movement of magnesium across the membrane takes place by two mechanisms they are, sodium-dependent transport & sodium-independent transport across cell membrane. Magnesium has important role in regulation of Ca^{2+} levels in the cells of myocardium, kidneys, smooth muscles of vessels & endocrine system.

Magnesium plays a vital role in various functions and biochemical reactions at cellular level and tissue level. Inside the cells magnesium controls the contractile proteins, regulates transport of calcium, sodium and potassium across the cell membrane and also acts as co-factor in activation of ATPase, Mg^{2+} also manages the energy dependent processes in cytoplasm and mitochondria, it has a part in oxidative phosphorylation and a major role in DNA synthesis & protein production.[24,25] Mechanism by which Mg^{2+} decreases blood pressure is by regulating the intracellular level of calcium by acting similar to a calcium channel blocker. The competition by magnesium to bind on the cells in vessels reduces the binding of Na^{+}, increases the production of prostaglandin E. Magnesium also regulates the movement of K^{+} across

the cell membrane and causes vasodilatation by the action of endothelial cells. Magnesium also improves endothelial dysfunction is patients with hypertension, diabetes and decreases calcium & sodium levels inside the cells resulting in reduction of blood pressure.[26,27,28]

Magnesium is necessary for the enzyme delta-6-desaturase enzyme action, which is the rate-limiting step for the synthesis of GLA(gamma linoleic acid) from LA(linoleic acid). After the above step DGLA(dihomo-gamma-linoleic acid) is formed from GLA(gamma linoleic acid). DGLA is the precursor for the synthesis of PGE 1 (prostaglandin E1). Low levels of the magnesium will result in low levels of PGE1 production which will cause vasoconstriction and result in higher blood pressure.[29-31] Minute changes in magnesium levels will have great effect on excitability of cells and on vascular tone along with contractility.

Even after large amount of research the actual cause for development of low Mg^{2+} state in an individual is unclear. It is thought that consumption of lesser quantity of magnesium in diet or malfunctions in metabolism of magnesium may lead to lesser levels of serum magnesium in body. Low magnesium, stress, excess catecholamine secreted can increase the intracellular calcium concentration in the smooth muscle cells of vessels which will cause increased arterial tone and coronary spasm. The pathogenesis of hypertension and complications inside the smooth muscle cells leading to enhanced vascular tone.[9,10]

Large quantity of magnesium in body is intracellular which is either attached to ribosome or polynucleotide or ATP, therefore the amount of magnesium found in extracellular space is only a fraction of total body magnesium content which is roughly 0.5-1.2 milimoles.[32]Inspite of this huge difference in the gradient across the

membrane ,the free magnesium inside the cell and in plasma is nearly equivalent. Magnesium has hydration shells which makes its radius 400 times bigger than other ions like sodium, potassium and calcium.[33] So to facilitate transport of magnesium across cell membranes, its radius or size has to be reduced, which requires removal of water from the ion. This process of removing water from magnesium requires energy.

Many studies have shown inverse relation between magnesium level and hypertension.[34,35,36] Magnesium acts on the vascular smooth muscles which in turn controls compliance of the vasculature, this process is mediated my altering concentration inside the smooth muscle cells causing vasodilatation which reduces the blood pressure. High level of magnesium in plasma decreases the expression of endothelin-1 and increases the release of prostacyclin causing vasodilatation .Apart from the above mentioned mechanism Mg^{2+} also regulates the production of nitric oxide in the vasculature .[37,38.39] The use of Mg^{2+} began in 1925 when magnesium salts were given for preeclampsia and eclampsia, where infusion of magnesium resulted in decrease in peripheral vascular resistance causing reduction in blood pressure.[40]Many epidemiological studies have shown that infusion or supplementation through preparations or diet rich in magnesium have an effect related to both systolic blood pressure and diastolic blood pressure.[41,42,43] But "Systemic review of the Cochrane hypertension group reports a small reduction of diastolic blood pressure(DBP by 2.2mmHg) but not of the systolic blood pressure (SBP by 1.3mmHg)".[44] A meta-analysis was able to find a dose dependent effect of magnesium on blood pressure, In contrast, another meta-analysis of a subset of studies which includes patients on antihypertensive drugs with high blood pressure (SBP>155 mmHg) reports much stronger effects of oral magnesium treatment on systolic blood pressure and diastolic blood pressure, which reduced by 18.7 mmHg and 10.9mmHg respectively.[45]

Study done by Dowson et al, between the drinking water Mg^{2+} & blood pressure in hypertensions showed an inverse relation & also association with mortality which was more in patients with low magnesium.[46] In a similar study, there was no association between Mg^{2+} excreted in urine and blood pressure. In a meta analysis by Jee SH, Miller ER, Guallar E, et al, there was no association seen between dietary supplementation of magnesium and reduction in blood pressure.[47] Observational studies done to find association between serum Mg^{2+} level with hypertension showed conflicting results.[48,49]A study done in Sweden showed an association between serum Mg levels^{2+} & blood pressure recordings.

Magnesium, Cardiovascular system and Left Ventricular Hypertrophy

Magnesium metabolism in myocardial cells is still not completely understood but it is evident that action of magnesium on cardiac cells involves change in the calcium concentration, tone of the vessels, peripheral resistance and cardiac output. Magnesium is thought to affect the electrical property of cardiac cells by acting on the ion channels which will change the concentration gradient of ions. Magnesium also controls the movement of calcium across the cells controlling the cardiac contraction property. Even though magnesium increases the contractility of the cells in cardiac tissue it causes vasodilatation on giving intravenously which sometime can cause hypotension and opposite action is seen in its deficiency i.e. vasoconstriction, increased tone in vessels.[50,51] It is also known that magnesium has anti-inflammatory property and ability to control vascular tone, very less is known about the complete magnesium homeostasis . Extensive research have lead to the discovery of few of the receptors involved in the regulation of magnesium balance, but still the mechanisms are not extensively studied.

"Study of health in Pomerania (SHIP)", which is a population study was used to obtain data for analysis of correlation between the magnesium levels & left ventricular mass. The total no of subjects in this study was 4310. Study showed lower magnesium levels were associated with increase in mass of left ventricle and emphasized the need for strict blood pressure control and intensified treatment along with magnesium supplementation.[52]

In 1964 experimental studies in animals named "Magnesium deficiency cardiomyopathy" showed large number of cardiac cells with fibrogenesis after increased levels of oxidative stress in animals with magnesium deficiency .[53]'SHIP' study notes that serum magnesium was inversely related to the increase in mass of the left ventricles over 5 years period. Early evaluation , identification of magnesium deficiency & supplementation of magnesium can help in preventing the gain in mass of left ventricle.[52]

Magnesium has an important role in myocardial cell metabolism, calcium regulation, cardiac output & tone of coronaries. Magnesium has action on the ionic channels in myocytes which alters the electrical properties of cardiac cells, magnesium has anti-inflammatory action, magnesium also regulates the calcium influx affecting the contractility as shown in figure 1.Action potential in cardiac cells, divided into five phases where: phase0 -Influx of Na^+ causing rapid depolarization, phase1- efflux of k^+ causing rapid re-polarization, phase-2-plateau phase where calcium enters cells, phase 3 where membrane potential is restored & finally phase 4 – resting potential is attained. Magnesium plays an important role in phase 2 and phase 3 by controlling the movement of K^+ & $Ca^{2+,}$ which is done by regulating the ionic channels like inhabitation of L-type calcium channels.[54,55] Delayed rectifier k^+

currents effect the phase-3. Recent studies have implicated role of magnesium in contraction-excitation coupling mechanism.[56] Magnesium directly acts as calcium channel blocker & binds with troponin-c & calmodulin. It also acts on sodium – calcium exchanger (NCX), sarcoplasmic reticulum calcium-ATPase (SERCA) and the ryanodine receptors, all of which alter the availability of calcium inside myocytes as as shown in figure 1.

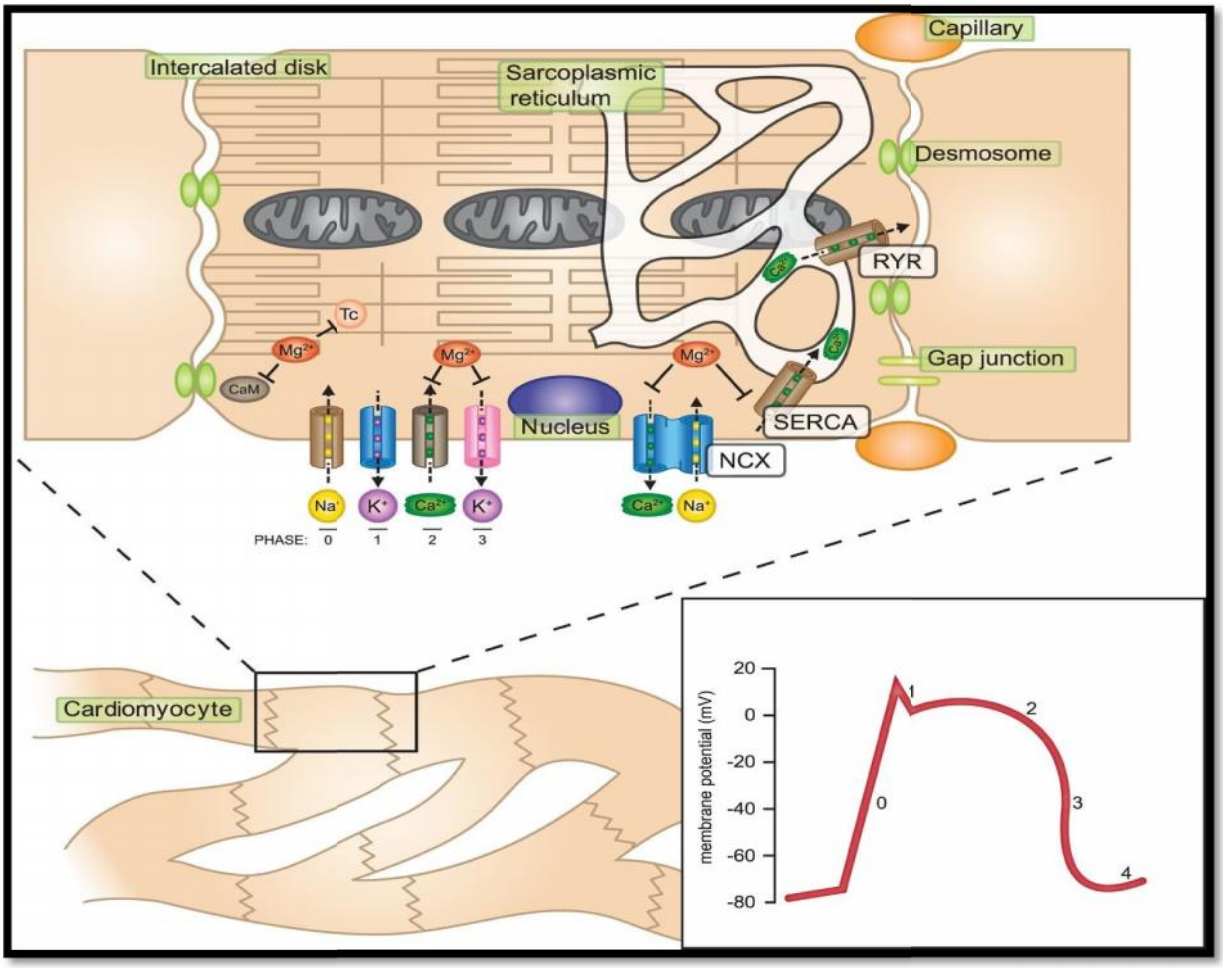


Figure1: figure depicts the action of magnesium on cardiac muscles and magnesium transporters in cardiac cell. Magnesium prevents the attachment of troponin and calmodulin by affecting calcium through NCX (Na-Ca-exchanger)and SERCA (sarcoplasmatic-endoplasmic reticulum Ca-ATPase).Numbers on the action potential graph represent the phases.

*Tc -troponin C *RYR-ryanodine receptor *CaM –calmodulin.

Magnesium Transport in Hypertension

The transport of magnesium out of the cells happens in two different ways. Sodium –dependent magnesium transport and the other is sodium-independent transport system. Na^+ dependent transport is through Na^+/Mg^{2+} exchanger and Na^+ independent system includes Ca^{2+}/Mg^{2+} exchanger, Mn^{2+}/Mg^{2+} antiporter, Cl^-/Mg^{2+} co-transporter.[57] Na^{2+}/Mg^{2+} exchanger is present in cardiac cells & smooth muscle cells of vessels. These are controlled by various biochemical substances which determine the vascular dynamic & contribute to the pathogenesis of hypertension, they are angiotensin II, insulin, ET-1 , isoproteronol & vasopressin.[58]

Na^+-independent transport of magnesium is seen in RBCs and hepatocytes. All the transporters responsible for magnesium efflux are under study and are not cloned till date. Unlike the efflux transporter channels the influx transporter channels shown in figure 2 have been studied in great detail. The process is both active & passive. Magnesium utilizes the electrochemical gradient of sodium ion in counter transport pathway. Magnesium is also transported through Mg^{2+}-anion co-transport. Recently many of these magnesium transporters have been cloned ,which has lead to discovery of 7 transcellular channels of magnesium. These channels are transient receptor potential melastatin cation channels (TRPM6 and TRPM7), magnesium transporter 1(MagT1), mitochondrial RNA slicing 2 protein (Mrs2p), ancient conserved domain protein 2 (ACDP 2) and the human solute carrier family 41, member 1 and 2(SLC41 A1, SLC41 A2). Initially presence of TRPM7 was thought to be mandatory for cells viability, but later studies have revealed cells without these receptors had normal concentration of magnesium inside them.[59] TRPM7 has 6 transmembrane subunits

with a kinase domain attached on inner surface, both of which function independent of each other. Kinase is responsible for phosphorylation of these ion channels.[60,61]

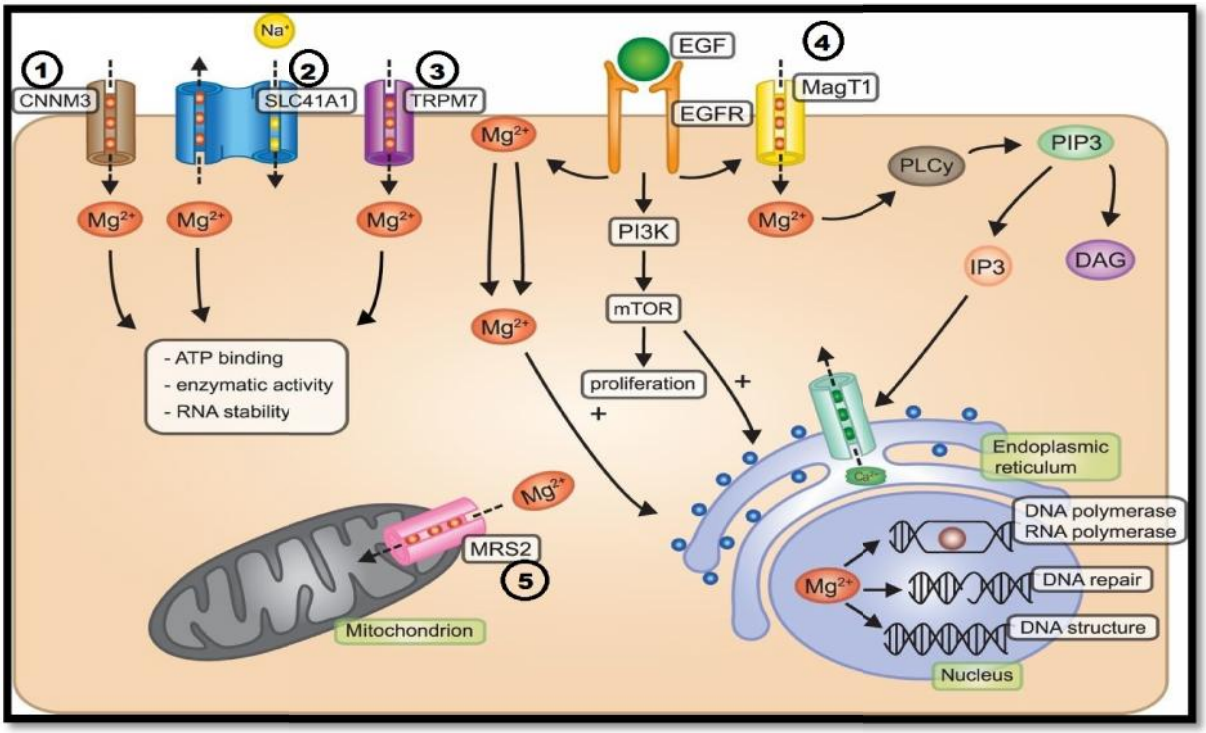


Figure 2: Regulation of magnesium homeostasis and magnesium transporters which are as follows

1. Cyclin and CBS domain divalent metal cation transport mediator 3 (CNNM3)
2. The human solute carrier family 41(SLC41A1)
3. Transient receptor potential melastatin cation channels 7 (TRPM7)
4. Magnesium Transporter1 (MagT1)
5. Mitochondrial RNA slicing 2 protein (MRS2 or Mrs2p)

MagT1 i.e magnesium transporter1 is responsible for sudden influx of magnesium into cells on stimulation of these receptors. The complete mechanism is still under study but it is suggested that functions are similar when compared to TRPM7.[62,63] Mrs 2p (mitochondrial RNA slicing 2 protein) is seen on mitochondrial

membrane & is responsible for influx of magnesium into mitochondria, this plays important role in synthetic functions.[64] Damage to these receptors will cause mitochondrial lysis & cell death. These receptors are crucial for maintenance of msagnesium concentration inside the mitochondria.[65]

Magnesium and Diuretics

Patients on diuretics for control of blood pressure have shown low levels of serum magnesium, the mechanism of development of hypomagnesaemia here is due to loss of both magnesium & calcium due to the action of drugs like furosemide. Furosemids acts on TAL (thick ascending loop) & DCT (distal convoluted tubule) & inhibits NKCC2 (Na^+-K^+-Cl^- cotransporter) which decreases the transmembrane potential of magnesium, this decreases the re-absorption of magnesium in TAL.[66] A recent study showed that furosemide use did not cause low serum magnesium because of excessive expression of TRPM6 in DCT to compensate for the decreased magnesium absorption from TAL.[67] It is thought that the incidence of magnesium deficiency in patients on furosemide depends on ability of each patient to compensate for reduced absorption in TAL by increasing expression of TRPM6 at DCT level. Other diuretic in use which can cause hypomagnesaemia in patients is thiazides. The mechanism here is by 2 different ways. By inhibition of NCC(Na^+ -cl^- co transporter) in DCT there is loss of magnesium. other mechanism is by decreased expression of TRPM6 induced by thiazide use.[59]

Magnesium and Proton pump inhibitors

Use of PPIs is associated with low magnesium levels in patients. This has been proved in patient with history of chronic use of PPIs (for>1year duration). Studies have been done in patients with history of omeprazole use, the exact mechanism for

development of hypomagnesaemia is not known , but based on animal studies the hypothesis which better explains is due to the reduction of H^+-K^+ -ATPase activity by the action of omeprazole. As a result the H^+ concentration drops in the colon. This decreases the TRPM6 activity in colon. Some patient may show compensatory increase in expression of TRPM6 but this may not be sufficient enough to compensate for the magnesium lost in the colon.[68]

Antimicrobials & other Drugs

Antimicrobials like aminoglycosides are known to cause low serum magnesium levels with incidence ranging from 20% to 80%. The mechanism of magnesium loss is reduced magnesium transport in TAL due to activation of CaSR(calcium sensing receptors) & prevention of transport of magnesium in DCT. Amphotericin B is also associated with low magnesium levels. Mechanism is renal loss of magnesium, detailed receptor abnormalities are under research.[69,70]

Magnesium and Endothelial dysfunction

The regulation of vasomotor tone in endothelium is done by release of cyclo-oxygenase/proteinoid like prostacyclin (PGI2), Endothelin-1,nitric oxide and endothelial derived hyperpolarizing factor.[71]Sudden changes in intracellular magnesium causes vasodilatation for a brief duration with is followed by vasoconstriction for a longer duration. In patients with damaged endothelium the initial brief vasodilatation is lost, there will be only vasoconstriction. The intact endothelial layer is found to be protective against the harmful effects caused due to acute drop in magnesium concentration in extracellular fluid. The brief duration of vasodilatation is due to release of nitric oxide. The nitric oxide release is calcium dependent.[72] It is seen that magnesium levels are significantly lower in patients with

metabolic syndrome in middle aged population & there is correlation with systemic inflammation & low magnesium levels.[73]

"CARDIA Study showed – Magnesium rich diet may help reduce the risk of metabolic syndrome & Heart attack or Diabetes".[74] A defect in a mitochondrial transfer RNA has shown to present with high BP, dyslipidemia, low serum magnesium levels & metabolic defects.[75] Studies have shown that diet rich in magnesium (500-1000 mg/dl) lowers Blood pressure although the results of some study are inconsistent.[76-78]The variation seen may be due to inadequate information regarding the blood pressure and magnesium levels before treatment, varying duration of trials, use of drugs like diuretics & thiazides which may lead to hypomagnesaemia and unavailability of information regarding plasma renin activity & lipid profile. A study done on 60 patients with hypertension,who were supplemented with magnesium oxide (20mmol/day for 8 weeks) showed significant reduction in ambulatory BP, home BP & office BP.

Studies have shown that patient with low magnesium levels require higher dose of antihypertensive medications when compared to patients with normal magnesium levels.[79] Trials have shown decreased levels of magnesium in tissues erythrocytes and serum as well as reduced excretion in urine in patients with hypertension correlating blood pressure & low magnesium levels. In "ARIC" study involving a total of 15,248 participants aged 45-64 years. The total magnesium content of RBCs was estimated, this study concluded that there was an inverse correlation between primary hypertension & systolic blood pressure.[80]"The Honolulu heart study included 615 patients with 61 variables with no history of hypertension in

family members revealed the relation between dietary magnesium & blood pressure". Dietary Mg^{2+} consumption had inverse relation with blood pressure readings.[81]

In a clinical trial, magnesium supplementation (oral) was associated with significant decrease in BP, both systolic & diastolic in patients with mild hypertension. When the Mg^{2+}, K^{+}, Na^{+} & Ca^{2+} levels were assessed after supplementation, results showed increase in both intracellular & serum magnesium. K^{+} levels were increased within the cells, calcium & sodium were decreased intracellularly.[82]

A meta-analysis which included 1220 patients from 20 RCTs revealed that blood pressure recording showed significant decrease after giving magnesium supplements.[83] Similar studies also demonstrated effect of magnesium administration (oral/iv) on blood pressure.[84,85] Studies done on rats demonstrated magnesium induced smooth muscle relaxation indicating the potency of magnesium to cause vasodilatation in large arteries, resistance vessels, mesenteric vessels & cerebral vessels.[86-91]

"The trial of hypertension prevention study (TOHP)", which included 698 patients who were supplemented with magnesium and followed up for a duration of 6 months revealed no reduction in BP."The Cochrane collaboration review 2009 done with 545 patients from 12 RCTs showed no reduction in systolic BP but there was a statistically significant decrease in the diastolic BP".[92] A meta-analysis of 44 studies revealed that the effectiveness of antihypertensives could be enhanced by supplementing magnesium in patient with primary hypertension.[93]

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Study design

The study design was a one year cross sectional study.

Study period and duration

This study was conducted for the period of one year from January 2018 to December 2018.

Source of Data

Patients with Primary Hypertension attending OPD and/or admitted in the Department of Medicine , KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi during the study period were enrolled in the study.

Sample size

- Sample size: 100

Sampling procedure

As this is a cross- sectional study,

- Sample size is calculated by the following

formula:

- $N= 4PQ/D^2$

Where,

N=Sample size

P = Prevalence of the disease Q= 100- P

D = Absolute error taken as 10%

(P = 50; Q = 50; D=10)

Therefore,

$N=4x50x50/10^2$

N=100

Therefore,100 cases fulfilling selection criteria were enrolled in this study.

Selection criteria

Inclusion criteria:

Patients with Primary Hypertension.

Exclusion criteria:

- Known primary hypertensive patients on diuretics.
- Acute or chronic diarrheal / malabsorptive states. .
- Hypertensive with obvious cardiovascular (IHD, Cardiomyopathy), Neurological(Stroke), Renal complications (elevated sr creat >1.5)
- History of alcohol intake.
- Patients on vitamins / mineral supplementation.

- Recent metabolic acidosis, pregnancy, lactation.
- Known Thyroid /adrenal dysfunction.
- On any drugs known to affect magnesium levels. (aminoglycosides, cisplatin, cyclosporine etc)

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

The patients willing to participate in the study were enrolled after obtaining a written informed consent (Annexure I).

Method of collection of data

Demographic data such as age, sex were noted. Patients were interviewed and detailed history was obtained. Physical examination and blood pressure recording (2 recordings) was done followed by systemic examination. These findings were recorded on a predesigned and pretested proforma (Annexure II). Two groups were made based on blood pressure. Grade 1 and 2, where grade 1 patients had systolic BP from 140 to 159 or diastolic 90 to 99 & Grade 2 patients had systolic BP more than or equal to 160 or diastolic BP more than or equal to 100 mmHg. Serum magnesium was estimated by xylidyle ble technique. Range from 1.6 to 2.5mg/dl was taken as normal value. Skolow-Lyon criteria was used to determine left ventricular hypertrophy. Keith Wagener Barker grading was used to classify hypertensive retinopathy.

Investigations

The patients were evaluated for following laboratory markers.

- Fasting Blood Sugar
- HbA1c
- Serum Magnesium levels
- Serum Calcium level
- Serum Potassium levels
- Serum Sodium levels
- Serum Creatinine
- Electrocardiography
- Fundoscopy

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The data was analyzed using SPSS version 20.0 statistical software. The categorical data was expressed in terms of rates, ratios and proportions and the continuous data was expressed as mean±standard deviation (SD).The comparison of categorical data was done using Chi square and continuous data was compared using independent student 't' test. A'p' value (probability value)of less than or equal to 0.050 at 95% confidence interval was considered as statistically significant. Karl Pearson's correlation coefficient method and ANOVA test were also used to find association.

RESULTS

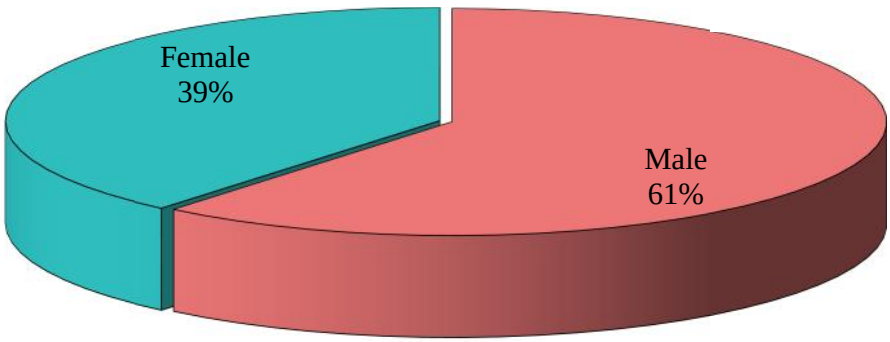
The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 100 patients with primary hypertension fulfilling the selection criteria attending OPD or admitted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi were studied.

The data obtained was analysed and the final results were tabulated and interpreted as below.

Table 1. Distribution of study population according to the gender

Sex	No	%
Male	61	61.00
Female	39	39.00
Total	100	100.00

Graph1: Distribution of study population according to the gender

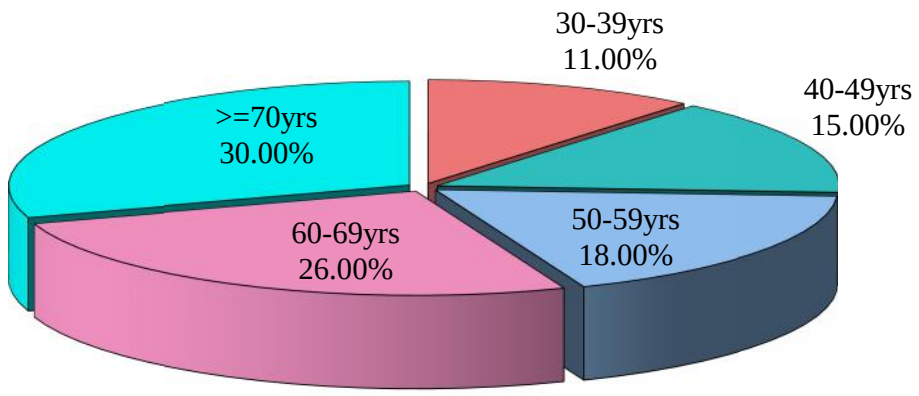


In the present study 61.00% of the patients were males while 39.00% of the patients were females. The male to female ratio was 1.6:1

Table 2: Distribution of study population according to age

Age groups	No	%
30-39yrs	11	11.00
40-49yrs	15	15.00
50-59yrs	18	18.00
60-69yrs	26	26.00
>=70yrs	30	30.00
Total	100	100.00
Mean age	**59.30**	
SD age	14.79	

Graph 2: Distribution of study population according to age

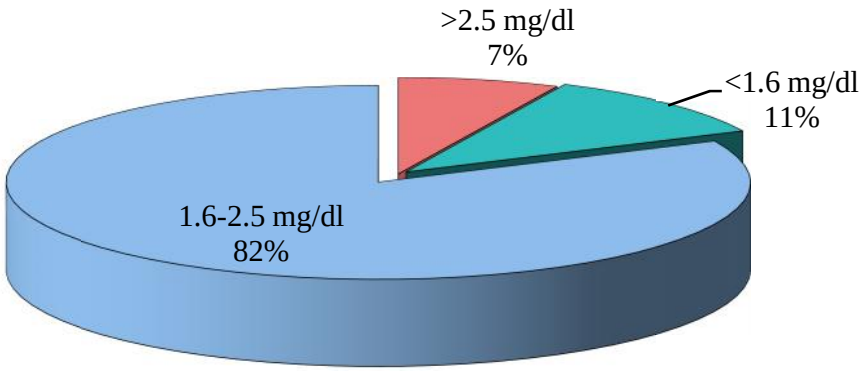


In this study, most number of patients were aged above 70 years which was about 30 % of the total study population. Youngest participant in the study was 30 years of age and oldest was 91years. The mean age was 59.30 years with SD $\pm$ 14.79.

Table 3: Distribution by levels of serum magnesium (mg/dl)

Serum Magnesium (mg/dl)	Number	%
<1.6	11	11.00
1.6-2.5	82	82.00
>2.5	7	7.00
Total	100	100.00

Graph 3:Distribution of patients by levels of serum magnesium(mg/dl)



In the study among 100 cases, 11% of patients had serum magnesium less than 1.6mg/dl , 82% of patients had serum magnesium between 1.6 mg/dl to 2.5mg/dl,7 % of patient had magnesium above 2.5 mg/dl. The mean serum magnesium levels of all the 100 patients in the study was 1.99 mg/dl.

Table 4 : Association between gender and serum magnesium

Serum Magnesium(mg/dl)	Male	Female	Total
<1.6	8	3	11
1.6-2.5	47	35	82
>2.5	6	1	7
Total	61	39	100
Chi-square= 2.901 p = 0.234			

In the present study, there was no statistically significant association between serum magnesium and gender.

Table 5: Association between Age groups and Levels of magnesium

Serum Magnesium(mg/dl)	30-39yrs	40-49yrs	50-59yrs	60-69yrs	>=70yrs	Total
<1.6	2	0	1	4	4	11
1.6-2.5	8	14	14	21	25	82
>2.5	1	1	3	1	1	7
Total	11	15	18	26	30	100
Chi-square= 2.123 p = 0.547						

Study did not show any statistically significant change in serum magnesium levels when compared with age group of the study population, All the Age groups were matched for serum magnesium levels.

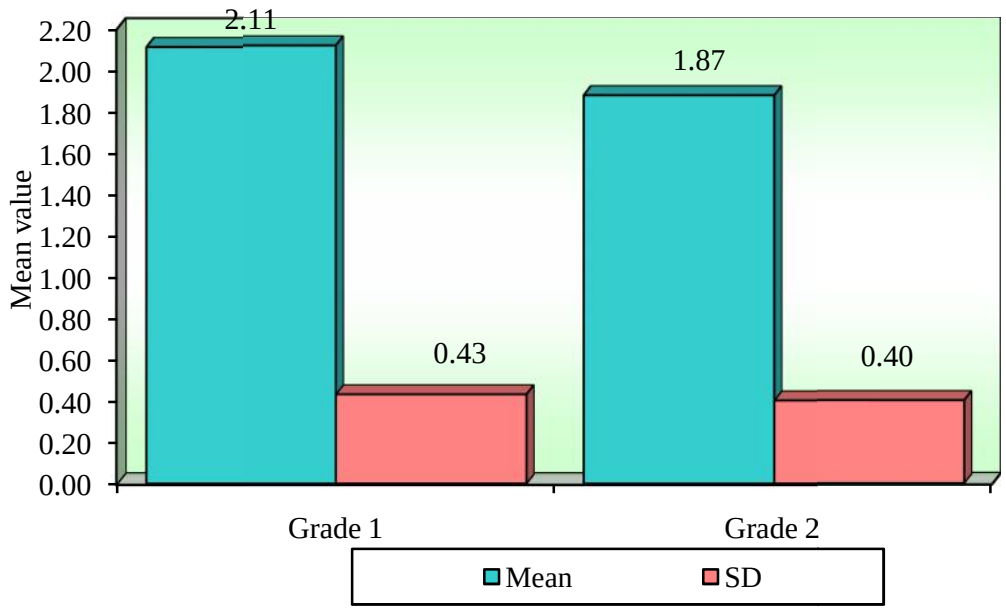
Table 6: Comparison of mean serum magnesium (mg/dl) levels with blood pressure (Grades) by independent t test.

(Where grade 1 patients had systolic BP from 140 to 159 or diastolic 90 to 99 and grade 2 patients had systolic BP more than or equal to 160 or diastolic BP more than or equal to 100 mmHg.)

Hypertension	n	Mean	SD	SE	t-value	P-value
Grade 1	62	2.11	0.43	0.05	2.7390	0.0073*
Grade 2	38	1.87	0.40	0.07		

*p<0.05

Graph 4: Comparison of mean serum magnesium level with blood pressure



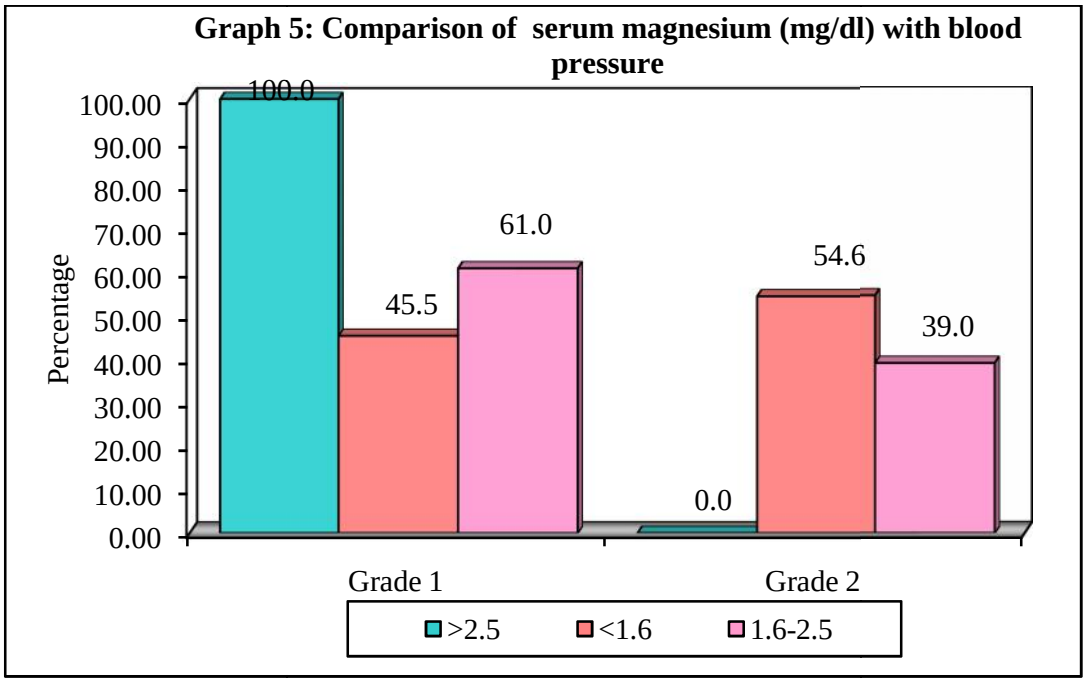
In the present study, the mean serum magnesium levels in subjects with grade 1 hypertension was of 2.1mg/dl compared to mean value of 1.87 mg/dl in grade 2 hypertension. Comparison between serum magnesium levels and blood pressure done using independent-t test revealed statistically significantassociation with a p-value of 0.0073.

Table 7: Association between levels of serum magnesium (mg/dl) and blood pressure.

(where grade 1 patients had systolic BP from 140 to 159 or diastolic 90 to 99 & Grade 2 patients had systolic BP more than or equal to 160 or diastolic BP more than or equal to 100 mmHg).

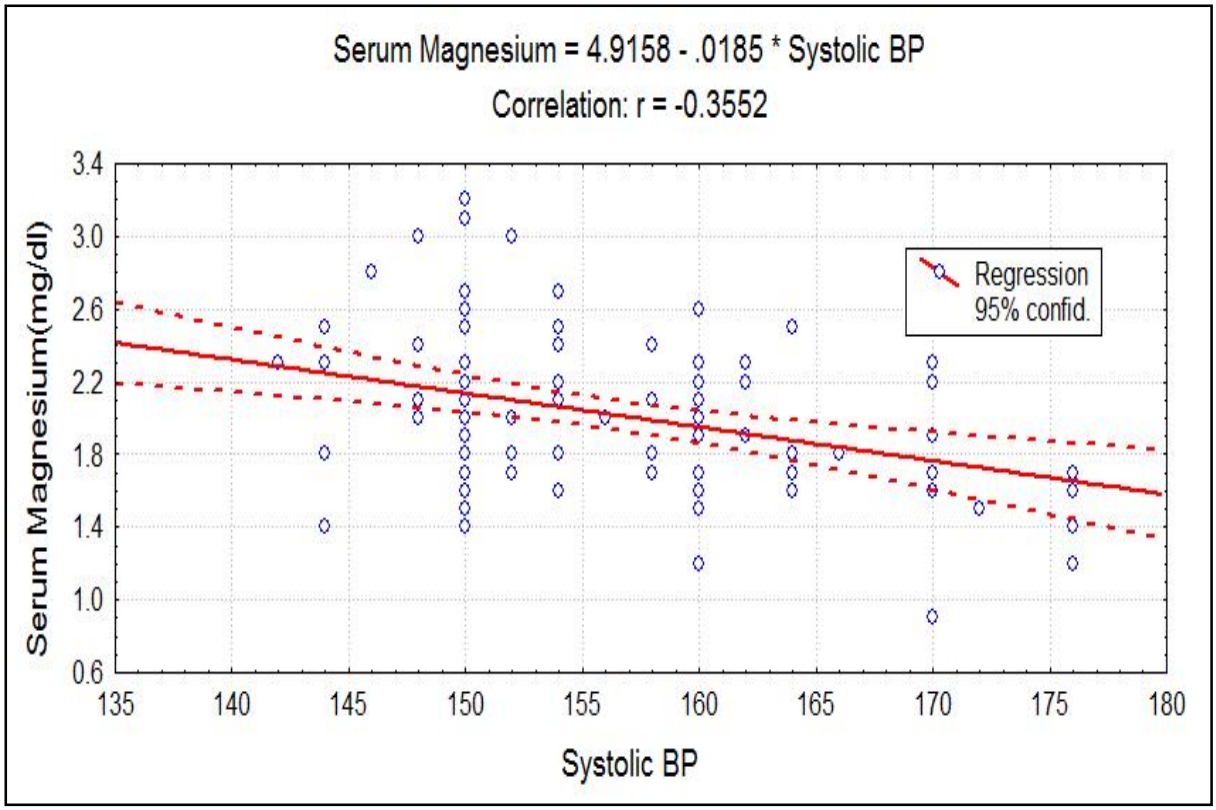
Serum Magnesium(mg/dl)	Grade 1	%	Grade 2	%	Total
>2.5	7	100.00	0	0.00	7
<1.6	5	45.45	6	54.55	11
1.6-2.5	50	60.98	32	39.02	82
Total	62	62.00	38	38.00	100
Chi-square= 5.7361 P = 0.0500*					

*p<0.05



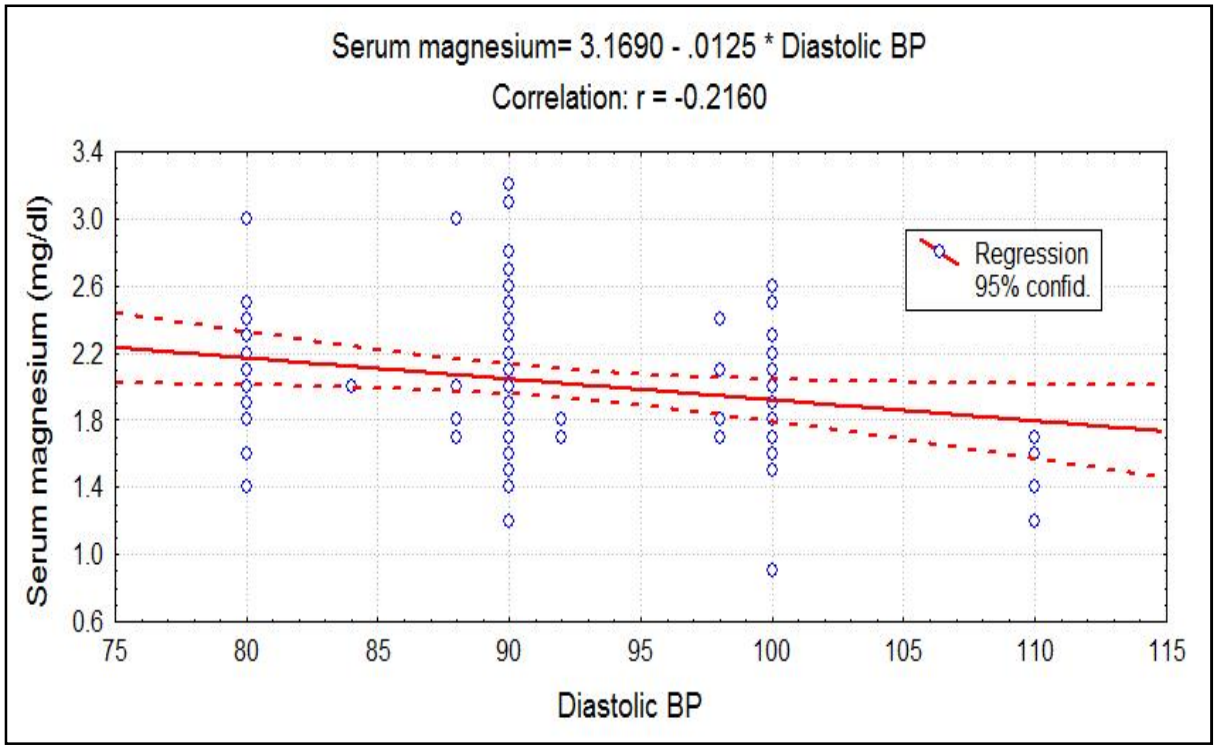
In the study, comparison between serum magnesium levels and blood pressure done using chi-square test showed statistically significant association with p-value 0.050. Indicating inverse association between serum magnesium levels and blood pressure levels.

Figure 3: Scatter diagram of correlation between systolic blood pressure and serum magnesium (mg/dl)



The present study showed inverse association of serum magnesium levels with systolic blood pressure recordings.

Figure 4: Scatter diagram of correlation between diastolic blood pressure and serum magnesium (mg/dl)



The present study showed inverse association of serum magnesium levels with diastolic blood pressure recordings.

Table 8: Association between serum magnesium and fasting blood sugars

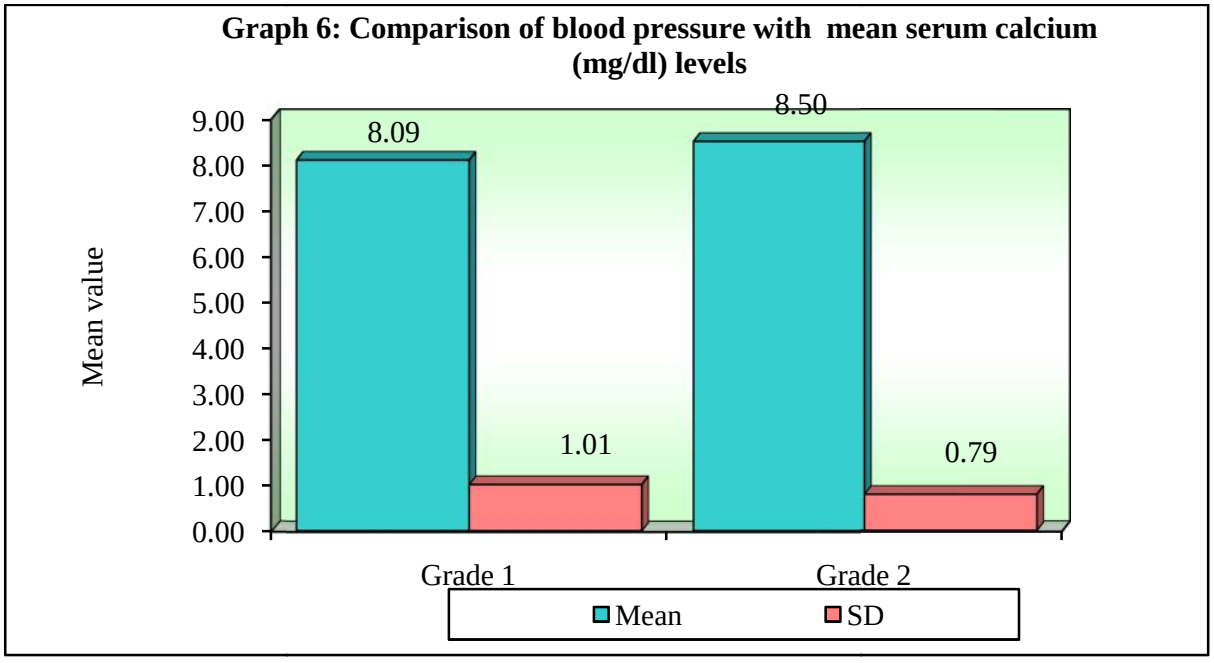
Levels of magnesium	FBS		
	Normal	Pre-diabetics	Grand Total
<1.6	2	9	11
1.6-2.5	30	52	82
>2.5	1	6	7
Total	33	67	100
Chi-square= 2.678 p = 0.262			

Majority of the subjects i.e 67% were in prediabetic (100-125mg/dl) range and the number of patients with abnormal serum mg levels was higher in prediabetic group. Fasting blood sugars when compared with the serum magnesium levels in Chi square test showed no significant association between the two with p value of 0.262.

Table 9: Comparison of blood pressure with mean serum calcium (mg/dl) levels by independent t test.

Grades	n	Mean	SD	SE	t-value	P-value
Grade 1	62	8.09	1.01	0.13	-2.1053	0.0378*
Grade 2	38	8.50	0.79	0.13		

*p<0.05

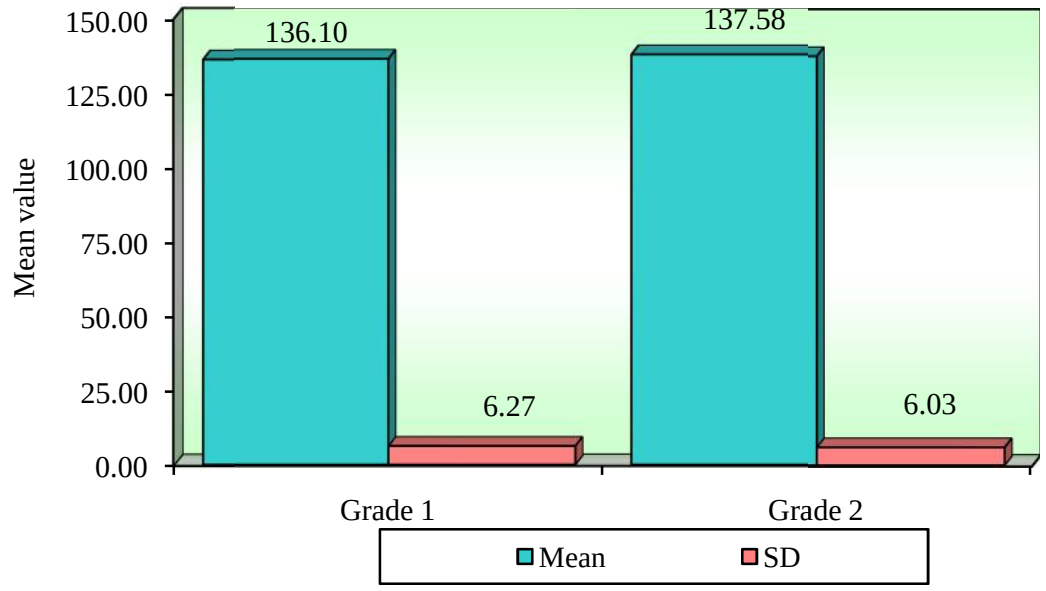


In the present study ,the mean serum calcium levels in subjects with grade 1 hypertension was of 8.09 mg/dl compared to mean value of 8.50 mg/dl in grade 2 hypertension. Comparison between serum calcium levels and blood pressure done using independent-t test revealed statistically significant association with a p-value of 0.0378*.

Table 10: Comparison of blood pressure with mean serum sodium levels by independent t test

Grades	n	Mean	SD	SE	t-value	P-value
Grade 1	62	136.10	6.27	0.80	-1.1645	0.2471
Grade 2	38	137.58	6.03	0.98		

Graph 7: Comparison of blood pressure with mean serum sodium levels

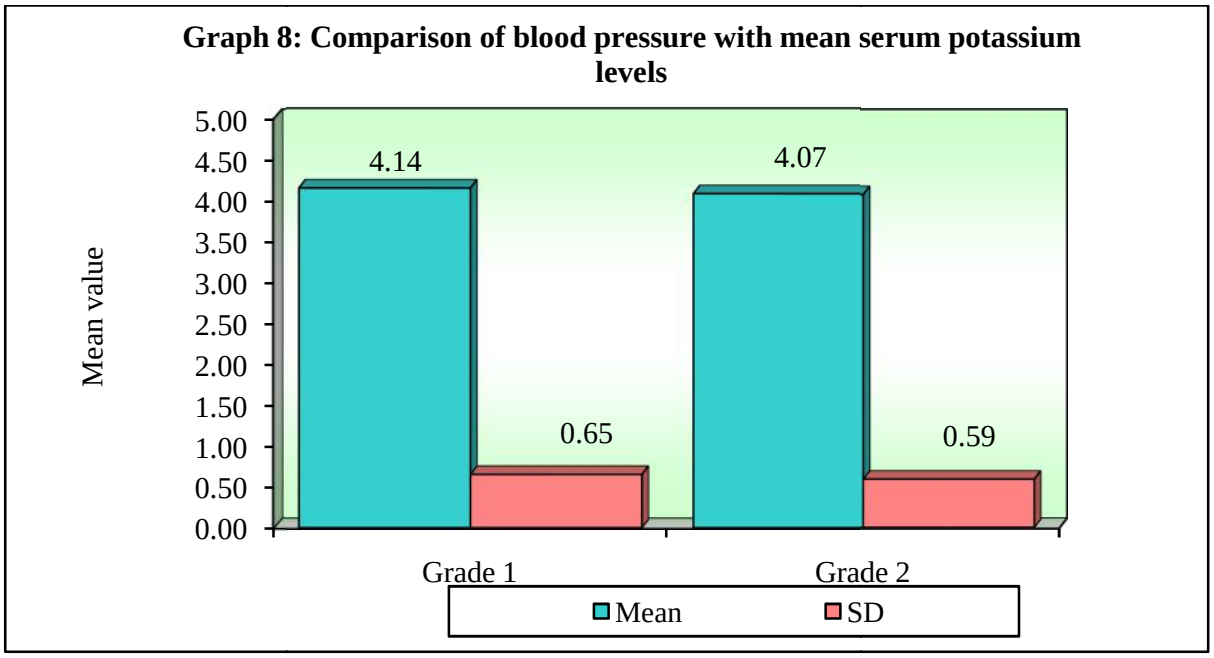


In the present study, the mean serum sodium level was 136.10mg/dl in grade1 and 137.58mg/dl in grade 2 hypertension. Comparison between serum sodium levels and blood pressure did not show statistically significant association.

Table 11: Comparison of blood pressure with mean serum potassium levels by independent t test

Grades	n	Mean	SD	SE	t-value	P-value
Grade 1	62	4.14	0.65	0.08	0.5069	0.6134
Grade 2	38	4.07	0.59	0.10		

Graph 8: Comparison of blood pressure with mean serum potassium levels



In the present study, the mean serum potassium level was 4.14 mg/dl in grade1 and 4.07 mg/dl in grade 2 hypertension. Comparison between serum potassium levels and blood pressure did not have statistically significant association.

Table 12: Correlation between investigations and blood pressure by Karl Pearson's correlation coefficient method.

	Summery	Systolic BP	Diastolic BP
Serum Magnesium	**r-value**	**-0.3552**	**-0.2160**
	P-value	**0.0001***	**0.0310***
Serum Calcium	r-value	0.1885	0.1145
	P-value	0.0600	0.2560
Serum Sodium	r-value	0.1750	0.2064
	P-value	0.0820	0.0390*
Serum Potassium	r-value	-0.1693	-0.2202
	P-value	0.0920	0.0280*

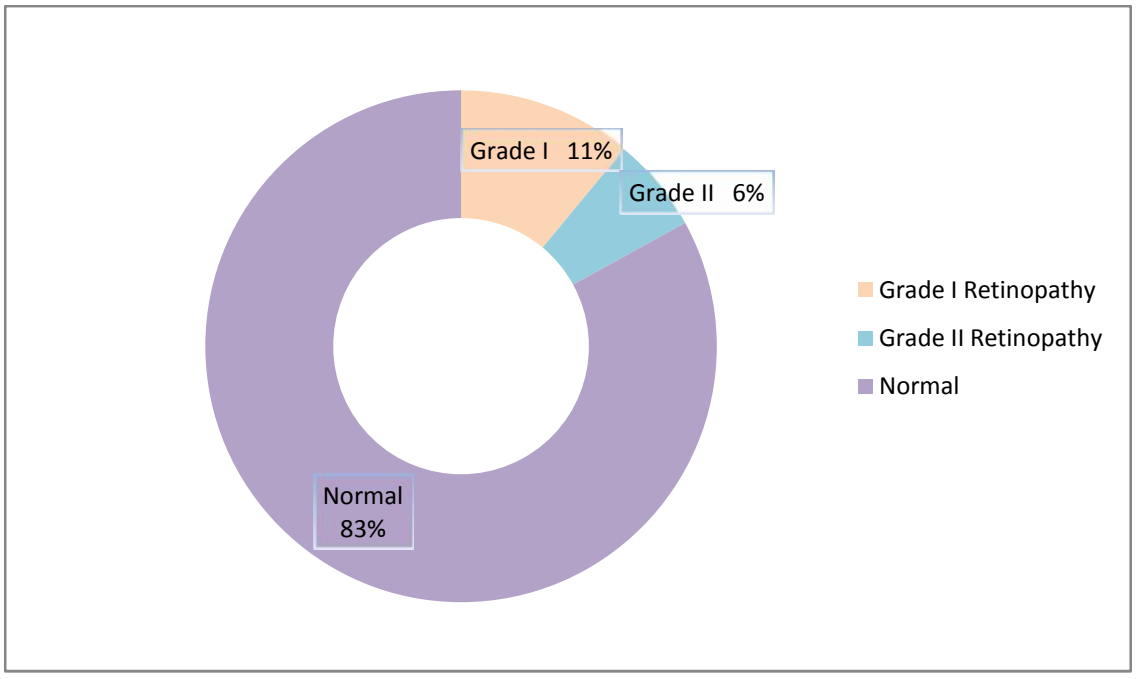
*$p<0.05$

In the present study, comparison done by Karl Pearson's correlation coefficient, the serum magnesium levels in patients showed inverse correlation with both systolic blood pressure and diastolic blood pressure, both of which were statistically significant with p-values 0.0001 and 0.031 respectively. Similarly serum calcium level also showed correlation with both systolic blood pressure and diastolic blood pressure, but the association is not statistically significant. Serum sodium, potassium level had association with diastolic blood pressure which were statistically significant.

Table 13: Distribution of study population according to the Fundoscopy changes

Fundoscopy	Number	Percentage
Grade I Retinopathy	11	11.00
Grade II Retinopathy	6	6.00
Normal	83	83.00

Graph 9: Distribution of study population according to the Fundoscopy changes



In the present study, 11% patients had Grade 1 hypertensive retinopathy, 6% patients had Grade 2 hypertensive retinopathy and 83% patients had normal fundus.

Table14: Correlation between Creatinine and Fundoscopy with investigative parameters.

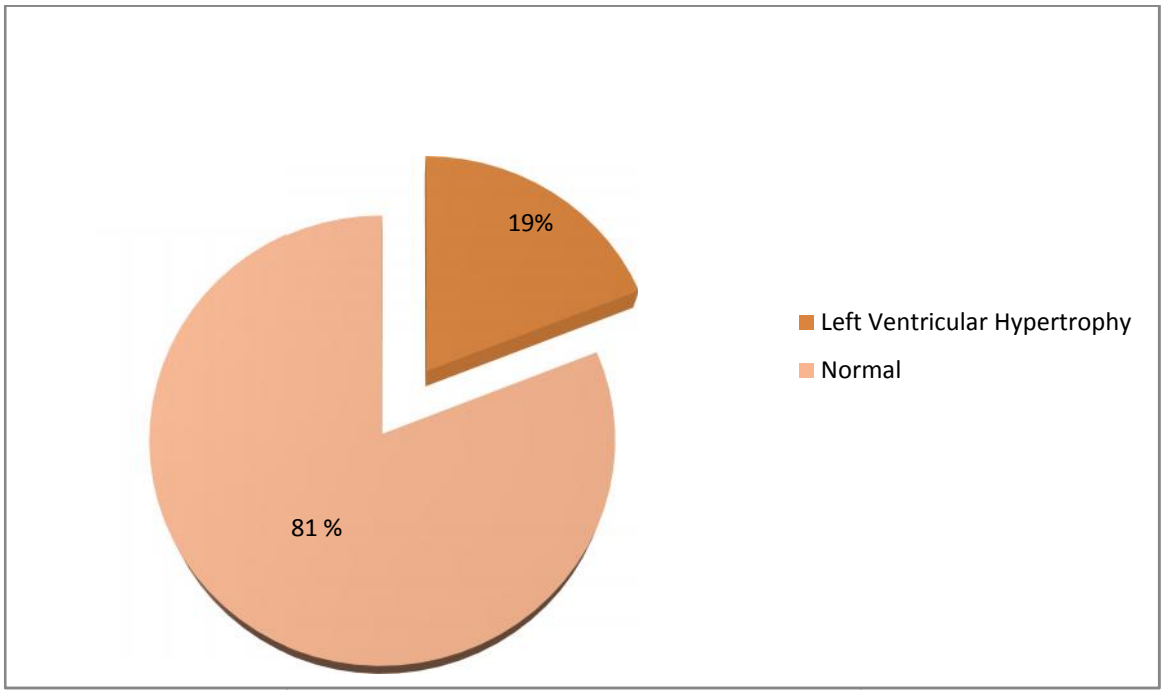
Variables	Sr Creatinine		Fundoscopy	
	Correlation (r)	p-value	Correlation (R)	p-value
Fasting Blood sugar	-0.1251	0.2150	0.1332	0.1866
Serum Magnesium(mg/dl)	0.0667	0.5100	0.1799	0.0732
Serum Calcium(mg/dl)	0.0014	0.9890	0.1029	0.3085
Serum Sodium	-0.0098	0.9230	-0.0856	0.3971
Serum Potassium	0.0811	0.4230	-0.1489	0.1392

The comparison done between markers of end organ damage assessment like serum creatinine and fundoscopy with the investigative parameters serum magnesium, calcium, sodium, potassium and FBS did not show any significant association.

Table 15: Distribution of study population according to the ECG changes

ECG	Number	Percentage
Left Ventricular Hypertrophy	19	19.00
Normal	81	81.00
	100	100.00

Graph 10: Distribution of study population according to the ECG change



The electrocardiography findings revealed that 19% of the patient had ECG changes which fulfilled the criteria for Left ventricular hypotrophy, 81% had normal ECG .

Table 16: Comparison of ECG finding with investigative parameters by one way ANOVA

		Normal	LVH	Total	F-value	p-value
Fasting Blood sugar	Mean	104.59	108.43	105.21	0.7949	0.4545
	SD	10.98	7.81	10.85		
Serum Magnesium(mg/dl)	Mean	2.00	2.17	2.02	0.7453	0.4773
	SD	0.42	0.51	0.43		
Serum Calcium(mg/dl)	Mean	8.24	8.40	8.25	0.0965	0.9081
	SD	0.98	1.14	0.95		
Serum Sodium	Mean	136.72	137.29	136.66	0.1576	0.8544
	SD	6.60	2.06	6.19		
Serum Potassium	Mean	4.17	4.08	4.12	3.2276	0.0439*
	SD	0.62	0.52	0.63		

*$p<0.05$

The analysis done between the creatinine & fundoscopy findings with investigative parameter like $Mg^{2+,}$ K^{+}, Na^{+}, Ca^{2+} & FBS did not reveal any statistically significant association.

Table 17: Comparison of serum magnesium (mg/dl) levels with ECG changes.

Serum Magnesium (mg/dl)	Normal ECG	Left ventricular hypertrophy	Total
<1.6	5	6	11
≥1.6	76	13	89
	81	19	100
chi-square=10.14 p=0.00144*			

*p<0.05

In the present study, out of 100 patients, 19 patients had left ventricular hypertrophy in ECG, among these 6 patients had serum magnesium level less than 1.6 mg/dl and 13 patient had magnesium level more than or equal to 1.6 mg/dl. 81 patients had normal ECG, out of this 81 patients 5 patients had serum magnesium level less than 1.6 mg/dl and 76 patient had magnesium level more than or equal to 1.6 mg/dl. This association between serum magnesium and left ventricular hypertrophy in ECG was statistically significant with p value 0.00144*.

DISCUSSION

Primary hypertension is a major health challenge, prevalence of which is increasing with every passing year. The etiology of primary hypertension is multi-factorial & every possible effort is being made to identify the risk factors which go unnoticed during routine work up in patients with hypertension.

Magnesium is one of the important ions responsible for maintenance of vascular tone and cardiac output which determine the blood pressure of an individual. Serum magnesium level assessment gives information about the Mg^{2+} status in human body. The manifestations of reduced Mg^{2+} are seen only in patient with severe depletion of Mg^{2+} stores (0.5 to 1 ml/kg), hence the routine analysis of Mg levels can be justified. Although the prevalence of hypomagnesaemia in hypertension varied from different ranges in different studies, the actual prevalence is thought to be dependent on many factors like the dietary intake, genetics & age of a person. Our study, "Serum magnesium level and its correlation with primary hypertension - one year cross sectional study" had the following observations.

Gender and Age

The present study had 100 subjects out of which 61% were males & 39% were females. The male to female ratio was 1.6:1. The study population when classified accordingly to age. Out of 100 patients, 11% patients were with age between 30-49 years, 15% patients were between 40-49 years,18% patients were between 50-59 years,26% patients were between 60-69 years and 30 patients were above or equal to 70 years. The mean age was 59.30 years with SD± 14.79. The youngest person in our study was 30 years of age & oldest was 91 years. The gender and age groups were

matched across all ranges of serum magnesium levels. No association of age and gender was noticed in our study with serum magnesium levels.

Serum Magnesium Levels:

The present study the analysis of serum magnesium levels revealed that 11% of patient had serum magnesium level less than 1.6 mg/dl (hypomagnesaemia), 82% of patient had magnesium level between 1.6 to 2.5 mg/dl and 7% of patient had magnesium >2.5 mg/dl . The low levels of serum magnesium was responsible and is implicated in the pathophysiology of development of primary hypertension as discussed previously in the review of literature. The conditions which could lead to low Mg^{2+} levels like reduced absorption of Mg^{2+} in intestines, increased loss from intestines, reduced absorption from kidneys & drugs causing Mg^{2+} deficiency were excluded based on history before enrolling the patient into the study. It is noticed that the prevalence of hypomagnesaemia is general population ranges from 10% and 65% in patient requiring Intensive care for any critical illness as mentioned in the study by Ryzen E et al.[94]

Magnesium levels & Blood pressure

The magnesium levels were compared with the two groups divided into grade 1 & grade 2, where grade 1 patients had systolic blood pressure from 140 to 159 or diastolic 90 to 99 and grade 2 patients had systolic blood pressure more than or equal to 160 or diastolic blood pressure more than or equal to 100 mmHg. The mean magnesium level in grade 1 was 2.11 mg/dl with standard deviation 0.43 which had a total number of 62 patients. The mean serum Mg^{2+} levels in 38 patient belonging to grade 2 was 1.87 mg/dl with standard deviation of 0.40. This data when analyzed

using independent-t test showed a statistical significance with p-value 0.0073 indicating a inverse correlation between the serum magnesium levels & the blood pressure.

The data from the study, revealed an inverse correlation between the blood pressure & serum magnesium levels, when analyzed using chi-square test with p value of 0.050 the study was statistically significant. When compared using Karl Pearson's correlation coefficient, the serum magnesium levels in patients showed inverse correlation with both systolic blood pressure and diastolic blood pressure, both of which were statistically significant with p-values 0.0001 and 0.031 respectively.

The above results were found to be consistent with "The Cochrane collaboration review 2009",where there was a statistically significant decrease in the diastolic blood pressure.[92] But, the systolic blood pressure although showed reduced values did not show statistical significance unlike our study results. Studies have shown that patient with low Mg^{2+} levels require higher dose of antihypertensive medications when compared to patients with normal Mg^{2+} levels.[95] Trials have shown decreased levels of Mg^{2+} in tissues erythrocytes and serum as well as reduced excretion in urine in patients with hypertension correlating blood pressure & low Mg^{2+} levels. The "ARIC" study concluded that there was an inverse correlation between primary hypertension & systolic blood pressure.[96]"TheHonolulu heart study" revealed the relation between dietary Mg^{2+} & blood pressure. Dietary Mg^{2+} consumption had inverse relation with blood pressure readings.[97]

In a clinical trial, mg supplementation (oral) was associated with significant decrease in blood pressure, both systolic & diastolic in patients with mild

hypertension. A meta-analysis revealed that blood pressure recording showed significant decrease after giving Mg^{2+} supplements.[76] Similar studies also demonstrated effect of Mg^{2+} oral/iv administration on blood pressure.[77,78] Studies done on rats demonstrated Mg^{2+} induced smooth muscle relaxation indicating the potency of Mg^{2+} to cause vasodilatation in large arteries, resistance vessels, mesenteric vessels & cerebral vessels.[86-91]A meta-analysis of 44 studies revealed that the effectiveness of antihypertensives could be enhanced by supplementing Mg^{2+} in patient with primary hypertension.[93]

A number of studies done could not find a significant association between magnesium and blood pressure in hypertensive."The trial of hypertension prevention study (TOHP)", patients who were supplemented with Mg and followed up for a duration of 6 months revealed no reduction in BP. Studies have shown that Diet Rich in magnesium (500-1000 mg/dl) lowers Blood pressure although the results of some study are inconsistent .[76-78] The variation seen may be due to inadequate information regarding the blood pressure and magnesium levels before treatment. Varying duration of trials, use of drugs like diuretics & thiazides which may lead to hypomagnesaemia and unavailability of information regarding plasma renin activity.

Fasting blood sugar & serum Magnesium

The serum Mg were compared with FBS in two subgroups i.e Normal & pre diabetic which showed 33% patient had a normal value of FBS & 67% were in prediabetic range. The chi-square test did not show any statistically significant co-relation between the groups with p value 0.262. This result was similar to the previous results obtained in some studies, where low magnesium was associated with T_2DM but not prediabetes.[78,96]

Co-relation with serum calcium, sodium & potassium

The Ca^{2+} levels when compared with the grades showed that the mean calcium levels in grade 1 was 8.09mg/dl with a standard deviation of 1.01 & the mean Ca^{2+} levels is grade 2 was 8.50mg/dl with a standard deviation of 0.79. The means when compared using independent-t test revealed a statistically significant p value of 0.0378. Indicating direct association between the serum calcium levels & blood pressures, i.e Higher the blood pressure values, higher was the serum calcium level.

This significant association was consistent with study done by Resnik on 102 hypertensive patient who were either untreated or stopped treatment for atlest 2 weeks. Showed an inverse co-relation with magnesium and positive co-relation with the serum calcium and blood pressure (Both with SBP & DBP). The proposed mechanism was due to high levels of angiotension II causing release of calcium from its stores leading to increase in serum calcium concentration and secondary hyperaldosteronism decreasing the serum Mg^{2+} levels .In contrary to the results obtained in our study , studies done by McCarrin DA, Morris CD , showed inverse relation of calcium with blood pressure.[99] This was due to increased intercellular calcium causing reduction in extracellular calcium or serum calcium & increased vasoconstriction & higher blood pressure.[99] When comparison was done by Karl Pearson's correlation coefficient serum calcium level also showed correlation with both systolic blood pressure and diastolic blood pressure, but the association was not statistically significant.

The comparison of serum sodium with hypertension showed mean sodium of 136.10 mg/dl in grade 1 with a standard deviation of 6.27 & in grade 2 mean sodium was 137. 58 mg/dl with a standard deviation of 6.03. The lack of association between

blood pressure was consistent with previous studies. The comparison of serum potassium with blood pressure revealed grade 1 had mean of 4.14 mg/dl with standard deviation of 0.65 & grade 2 had mean of 4.07mg/dl with standard deviation of 0.59 & p value 0.6134 showing no statistical significance in independent t test which is comparable to the studies done previously by Albert DG, Morita Y, Iseri LI. In studies, when the Mg^{2+}, K^{+}, Na^{+} & Ca^{2+} levels were assessed after supplementation, results showed increase in both intracellular & serum Mg. K^{+} levels were increased within the cells, calcium & sodium were decreased intracellularly.[98]

Assessment of complications

The complications of hypertension were accessed by markers of end organ damage like serum creatinine for kidneys, retinopathy for changes in eyes & left ventricular hypertrophy is the electrocardiography for cardiovascular system. In the present study out of 100, 11 patients had grade 1 hypertensive retinopathy, 6 patients had grade 2 hypertensive retinopathy and 83 patients had normal fundoscopy. The analysis done between the creatinine & fundoscopy findings with investigative parameter like $Mg^{2+,}$ K^{+}, Na^{+}, Ca^{2+} & FBS did not reveal any statistically significant association.

The electrocardiography findings revealed that out of 100 patients, 19 patients had left ventricular hypertrophy in ECG, among these 6 patients had serum magnesium level less than 1.6 mg/dl and 13 patient had magnesium level more than or equal to 1.6 mg/dl. 81 patients had normal ECG, out of this 81 patients 5 patients had serum magnesium level less than 1.6 mg/dl and 76 patient had magnesium level more than or equal to 1.6 mg/dl. This association was statistically significant with p value 0.00144.This result was comparable to the result obtained from “Study of health

in Pomerania (SHIP)", which is a population study was used to obtain data for analysis of correlation between the magnesium levels & left ventricular mass. The "SHIP" study showed lower magnesium levels were associated with increase in mass of left ventricle and emphasized the need for strict blood pressure control and intensified treatment along with Magnesium supplementation.[52] In our study although it was statistically significant we cannot conclude that the gain in left ventricular mass was associated with low serum magnesium, as it was a cross sectional study, the initial magnesium levels before the gain in mass of left ventricle is not known and left ventricular hypertrophy can be a complication of hypertension alone.

This study reveals a strong association between serum magnesium level and blood pressure in patients with primary hypertension.

Limitations

The study had certain limitations like confounding variables such as demographic characteristics, lack of information regarding dietary magnesium content and limited sample size and study design which was cross sectional. Further studies considering the confounding factors and a larger sample size will focus on higher accuracy of association between serum magnesium level and blood pressure.

CONCLUSION

In the study,11% of patients had serum magnesium less than 1.6mg/dl (hypomagnesaemia) , 82% of patients had serum magnesium between 1.6 mg/dl to 2.5mg/dl, 7 % of patient had magnesium above 2.5 mg/dl (hypermagnesaemia).

The study revealed a significant inverse association between serum magnesium level and blood pressure in patients with primary hypertension.

SUMMARY

The etiology of primary hypertension are multifactorial, magnesium status in human body is thought to be a crucial factor in pathogenesis of primary hypertension. Importance of magnesium is being increasingly recognized and constantly rediscovered and correlated with many medical conditions but still remains overlooked and undertreated in clinical practice. This study was aimed at finding the association between the serum magnesium level and blood pressure in primary hypertension.

The present one year hospital based cross-sectional study was done on 100 patients with primary hypertension from January 2018 to December 2018 in Department of Medicine, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

In the present study, 61.00% of the patients were males while 39.00% of the patients were females. The male to female ratio was 1.6:1. Youngest participant in the study was 30 years of age and oldest was 91years. The mean age was 59.30 years with SD $\pm$ 14.79. out of100 cases ,11% of patients had serum magnesium less than 1.6mg/dl , 82% of patients had serum magnesium between 1.6 mg/dl to 2.5mg/dl, 7 % of patient had magnesium above 2.5 mg/dl. The patients were divided into grade 1 and grade 2,where grade 1 patients had systolic BP from 140 to 159 or diastolic 90 to 99 & grade 2 patients had systolic BP more than or equal to 160 or diastolic BP more than or equal to 100 mmHg. The mean serum magnesium level in the study population was 1.99 mg/dl. The mean serum magnesium levels in subjects with grade 1 hypertension was 2.1mg/dl compared to mean value of 1.87 mg/dl in grade 2 hypertension. Comparison between serum magnesium levels and blood pressure revealed statistically significant association with a p-value of 0.0073. Study showed

inverse association of serum magnesium levels with both systolic and diastolic blood pressure recordings. The mean serum calcium levels in subjects with grade 1 hypertension was of 8.09 mg/dl compared to mean value of 8.50 mg/dl in grade 2 hypertension. The association between serum calcium levels and blood pressure was statistically significant with a p-value of 0.0378. Out of 100 patients, 19 patients had left ventricular hypertrophy in ECG, among these 6 patients had serum magnesium level less than 1.6 mg/dl and 13 patient had magnesium level more than or equal to 1.6 mg/dl. 81 patients had normal ECG, out of this 81 patients 5 patients had serum magnesium level less than 1.6 mg/dl and 76 patient had magnesium level more than or equal to 1.6 mg/dl. This association between LVH in ecg and serum magnesium was statistically significant with p value 0.00144.

The present study showed a significant inverse association between serum magnesium level and blood pressure in patients with primary hypertension. Hence routine assessment of serum magnesium levels in patients with primary hypertension has to be done and magnesium supplements should be given for strict control of blood pressure.

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ANNEXURE I – CONSENT FORM

"SERUM MAGNESIUM LEVEL AND ITS CORRELATION WITH PRIMARY HYPERTENSION - ONE YEAR CROSS SECTIONAL STUDY"

Principal Investigator:-

Dr ***

Post Graduate Student,

Department Of General Medicine,

JNMC, Belagavi.

Guide:-

Dr.********

Department of General Medicine,

JNMC, Belagavi.

Introduction and Purpose:-

Magnesium is second most abundant intracellular ion, most of which is concentrated in bone. Magnesium plays important role in maintaining normal cell membrane function ,energy transfer, metabolism, regulating vascular tone, heart rhythm, prevention of thrombosis, atherosclerosis, arrhythmias, osteoporosis & suppression of inflammation.

The role of magnesium in hypertensive disease has been suggested since 19th century when it was introduced in the therapy of preeclampsia & eclampsia.There is a significant inverse correlation between serum magnesium and incidence of cardiovascular diseases. Many cardiovascular disorders are associated with changes in

magnesium levels; in particular, those affecting the myocardium and involving blood pressure control .

Hence this study is being considered to fill the gaps in knowledge about the Serum Magnesium level and its effect on Blood Pressure control in Patients with Primary Hypertension.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness (rarely happens) at the site from where the blood is drawn.

You may not be benefitted by these investigations but you will be part of this study which is going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study. If you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belagavi as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons,

Dr.Roopa.Bellad,
Chairman,
J.N.M.C Ethical
Committee for Human Research

Dr.Arathi Darshan,
Professor and Head
Dept of General Medicine,
JNMC, Belagavi.
Phone No:08312473788,
Extn:1371/1520

Dr *******
Post Graduate Student,
Department Of General Medicine,
JNMC, Belagavi.
Phone No:8722284835

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, and have had all the questions answered.

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's Name: ……...

Signature / Left thumb impression: ……..., of the participant

Investigator's Name and Signature: ……...

Date:

Place:

ANNEXURE II - ETHICAL CLEARENCE

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http//www.jnmc.edu
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Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 35 **Date: 22/11/2017**

To.

[redacted]
PG student in Medicine,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"SERUM MAGNESIUM LEVEL AND ITS CORRELATION WITH PRIMARY HYPERTENSION – ONE YEAR CROSS SECTIONAL STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE III – PROFORMA

"SERUM MAGNESIUM LEVEL AND ITS CORRELATION WITH PRIMARY HYPERTENSION - ONE YEAR CROSS SECTIONAL STUDY"

CASE NO:

NAME: **AGE/SEX:**

IP NO.:

ADDRESS: **OCCUPATION**

PHONE NO

History

1)Are you Hypertensive?When was the Diagnosis of Hypertension made?

2)Are you on any Anti hypertensive medication

Drug

Diuretics/Thiazides

Other antihypertensives

Duration:-……..

Dose:-……..

3)Do you have any of the following mentioned condition?

Acute or chronic diarrheal / malabsorptive states.

IHD, Cardiomyopathy,Ventricular hypertrophy (enlarged heart)

Diabetes mellitus

Neurological(Stroke/TIA)

Kidney Disease (Protienuria, elevated sr creat >1.5)

Known Thyroid /adrenal dysfunction.

History of alcohol intake.

Vitamins / mineral supplementation.

Recent metabolic acidosis,

Pregnancy / Lactation.

Chronic use of proton pump inhibitors

On any drugs known to affect magnesium levels.(aminoglycosides, cisplatin, cyclosporine etc)

Other Chronic /Major health problem. …….

PHYSICAL EXAMINATION:

PALLOR- YES/NO ICTERUS-YES/NO

LYMPHADENOPATHY-YES/NO CYANOSIS- YES/NO

CLUBBING-YES/NO EDEMA-YES/NO

HEIGHT - WEIGHT-

BMI -

WAIST CIRCUMFERENCE-

VITALS:

TEMPERATURE:

PULSE RATE:

RESPIRATORY RATE:

BLOOD PRESSURE

READING 1

READING 2

SYSTEMIC EXAMINATION:

CVS:

RS:

P.A.:

C.N.S.:

INVESTIGATIONS

- Fasting Blood Sugar
- Serum Magnesium levels
- Serum Calcium level,
- Serum Potassium levels
- Serum Sodium levels
- HbA1c
- Serum creatinine
- Electrocardiography
- Fundoscopy

ANNEXURE IV – KEY TO MASTER CHART

Grade 1	Grade 1 hypertensive retinopathy
Grade 2	Grade 2 hypertensive retinopathy
WNL	Within normal limits
LVH	Left ventricular hypertrophy
Pd	prediabetic
n	normal
mg/dl	milligrams per deciliter
mmhg	millimeters of mercury

ANNEXURE V- MASTER CHART

				Vitals						Investigations										
Serial number	Age in Years	Patient No	Sex	Temperature	Pulse Rate	Respiratory Rate	Mean Systolic BP	Mean Diastolic BP	Grades of HTN	Fasting Blood sugar		HbA1c	Serum Magnesium(mg/dl)	Serum Calcium(mg/dl)	Serum Sodium	Serum Potassium	creatinine	Fundus	ECG
1	69	940226	Female	96.8	86	19	160	80	2	108	pd	6.4	2	8.6	137	3.4	0.8	Grade 2	WNL
2	60	938742	Female	98	90	19	152	90	1	116	pd	6.2	1.8	8.1	136	3.53	1.1	WNL	WNL
3	45	938768	Female	98	86	18	150	90	1	110	pd	6.3	2.6	8.3	140	3.4	1	WNL	WNL
4	75	939838	Male	98	90	20	170	100	2	118	pd	6	1.9	8.7	139	4	0.7	WNL	LVH
5	65	936177	Male	96.8	82	16	150	90	1	112	pd	5.9	1.8	7.8	134	4.64	0.8	WNL	WNL
6	79	934727	Female	98	90	20	162	80	2	103	pd	6.1	1.9	6.8	125	3.9	0.9	WNL	WNL
7	50	939632	Male	98.2	90	20	160	100	2	110	pd	6	2.3	8.8	150	4	1	WNL	WNL
8	79	937091	Female	96.7	98	19	150	90	1	106	pd	5.8	1.5	8.2	128	3.04	1.1	Grade 1	LVH
9	65	857621	Female	97.8	86	17	162	80	2	100	pd	6.4	2.3	8.7	133	3.66	1.08	WNL	WNL
10	50	940143	Male	97.2	59	19	150	90	1	91	n	6.2	1.8	8.2	138	4.01	1	WNL	WNL
11	60	941359	Male	97.6	90	19	172	100	2	121	pd	6	1.5	8.1	134	3.51	0.99	WNL	WNL
12	45	941275	Male	96	82	18	162	80	2	101	pd	5.9	2.2	8.4	136	5.52	0.78	WNL	WNL
13	62	941287	Male	97.2	72	16	156	84	1	120	pd	5.8	2	6.8	144	5.09	0.89	WNL	WNL
14	55	941375	Male	98	78	17	166	92	2	96	n	6.2	1.8	7.3	147	4.25	1.09	WNL	WNL
15	55	941435	Female	98.4	72	19	170	100	2	98	n	6.3	1.6	7.9	139	4.32	1	WNL	WNL
16	61	941066	Male	97.8	78	16	142	90	1	94	n	6.2	2.3	8.3	137	4.63	8	WNL	WNL
17	63	940430	Female	97.8	88	17	150	90	1	86	n	6.3	2.1	8.2	135	3.6	0.86	Grade 1	WNL
18	65	941281	Male	98.2	86	16	160	100	2	100	pd	6.4	2.1	7.7	139	3.91	0.72	WNL	WNL
19	58	941512	Male	96.4	90	19	146	90	1	103	pd	5.4	2.8	8.5	135	5	0.68	WNL	WNL
20	69	941538	Male	97.3	86	16	164	92	2	114	pd	6.1	1.7	8.2	138	4.65	0.92	WNL	WNL
21	59	941393	Male	98.1	90	18	160	100	2	113	pd	6.2	2.6	7.6	129	4.3	0.63	WNL	WNL
22	30	938640	Male	98	94	19	150	90	1	99	n	5.5	1.4	8.6	139	5.2	0.88	WNL	LVH
23	62	936256	Male	97.8	84	17	160	100	2	86	n	6.3	2.6	7.1	136	4.6	1.1	WNL	WNL
24	69	938647	Male	98	92	16	154	90	1	108	pd	6.2	2.4	8.5	135	5.4	0.9	WNL	WNL
25	54	934411	Female	98.2	86	19	160	90	2	119	pd	6.4	1.6	7.8	135	4.85	0.59	WNL	LVH
26	59	930597	Male	98.4	78	16	150	90	1	115	pd	5.3	1.6	5.1	140	3.99	0.93	WNL	WNL
27	33	889816	Male	98	68	18	150	90	1	110	pd	5.5	2.1	7.5	137	5.28	0.85	Grade 1	WNL
28	80	932522	Female	98.1	94	18	164	100	2	111	pd	5.9	1.8	8.1	136	4.53	1.2	WNL	WNL
29	79	940957	Male	97.8	78	18	170	100	2	107	pd	6.1	1.6	8.3	134	3.91	1.09	WNL	WNL
30	51	931613	Female	96.8	90	18	154	80	1	119	pd	5.8	2.1	8.7	146	5.4	0.83	WNL	WNL
31	30	941599	Male	98	86	19	150	90	1	89	n	5	2.5	7	142	3.66	0.98	WNL	WNL
32	65	941097	Female	97.9	76	16	152	88	1	114	pd	5.5	1.8	7.9	132	3.91	1.06	WNL	WNL
33	59	917905	Male	98.2	78	18	148	80	1	113	pd	6.2	3	8.5	130	5.6	1.12	WNL	WNL
34	71	920594	Female	97.2	82	16	150	90	1	102	pd	6.1	2.1	7.8	130	4.85	1	WNL	WNL
35	59	924761	Female	97.8	80	17	144	80	1	122	pd	6.3	2.3	9.3	149	4.31	0.75	Grade 1	WNL
36	77	926280	Male	97.9	74	16	158	98	1	110	pd	5.7	1.7	8.3	138	3.28	0.86	WNL	WNL
37	79	927091	Female	98	87	18	150	90	1	99	n	6.2	2.5	8	114	4.22	0.98	WNL	WNL
38	43	935883	Female	97	76	16	150	90	1	110	pd	5.8	1.9	7.6	136	4.4	0.97	WNL	WNL
39	62	929328	Male	98	86	19	176	110	2	111	pd	6.4	1.2	8.5	138	2.11	0.77	WNL	LVH
40	58	928173	Male	97.8	78	18	150	90	1	108	pd	6.1	2.6	6.7	137	4.59	0.62	Grade 2	WNL
41	77	926280	Male	98.6	68	16	170	100	2	117	pd	5.6	1.7	8.2	140	3.28	1.2	WNL	WNL
42	59	930597	Male	98	90	19	160	100	2	115	pd	6.4	1.5	8.6	140	4.5	0.94	WNL	LVH
43	73	851226	Male	97.8	84	17	160	100	2	97	n	6.2	2.6	8.9	129	4.2	1.19	WNL	WNL
44	53	850646	Male	98	92	16	154	90	1	121	pd	5.7	2.7	7.6	127	3.44	0.93	Grade 2	LVH
45	36	847392	Female	98.2	86	19	160	90	2	110	pd	6.3	1.7	8.7	133	3.51	0.85	WNL	WNL
46	65	842917	Male	98.4	78	16	150	90	1	116	pd	6.3	3.1	7.4	135	4.47	0.72	WNL	WNL
47	63	888672	Male	98	68	18	150	90	1	111	pd	6.4	1.5	8.5	136	3.6	0.8	WNL	WNL
48	65	925712	Female	98.1	94	18	164	100	2	104	pd	5.9	2.5	8.8	128	3.9	1.05	Grade 1	WNL
49	70	845298	Female	97.8	78	18	170	100	2	106	pd	6.4	2.2	9.7	138	4.36	1.2	WNL	WNL
50	40	844717	Male	96.8	90	18	154	80	1	101	pd	6.2	1.8	8.6	134	4.43	1.16	WNL	WNL
51	46	843332	Male	98	86	19	150	90	1	96	n	5.4	1.8	8.4	136	3.28	0.7	WNL	WNL
52	35	740988	Male	97.9	76	16	152	88	1	103	pd	6	3	10.3	136	3.65	0.66	Grade 2	WNL
53	71	857728	Female	98.2	78	18	148	80	1	124	pd	6.4	2	8.5	137	4.05	0.82	WNL	WNL
54	40	858045	Male	97.2	82	16	150	90	1	86	n	6.3	2.6	7.1	140	4.6	1.08	WNL	WNL
55	78	857179	Male	97.8	80	17	144	80	1	96	n	5.6	2.5	8	114	4.22	0.72	WNL	WNL
56	52	857188	Male	97.9	74	16	158	98	1	124	pd	5.9	2.1	8.2	136	3.38	0.8	Grade 1	LVH
57	68	856245	Male	98	87	18	150	90	1	97	n	5.6	1.5	5.9	140	3.8	1	WNL	WNL
58	40	856257	Female	97	76	16	150	90	1	119	pd	5.3	2.7	7.9	139	5.6	0.88	WNL	WNL
59	40	856114	Male	98	86	19	176	110	2	114	pd	5.8	1.6	8.6	147	4.05	0.74	WNL	WNL
60	72	879772	Male	97.8	78	18	150	90	1	105	pd	6.4	1.8	8.1	133	4.35	0.66	Grade 1	WNL
61	71	849896	Female	98.6	68	16	170	100	2	117	pd	6.4	0.9	6.5	148	3.43	0.58	WNL	LVH
62	38	942031	Female	98	90	19	160	100	2	88	n	5.6	2	9.1	139	4.5	0.8	WNL	WNL
63	60	941664	Male	97.8	84	17	160	100	2	82	n	6.4	2	8.6	140	3.87	1.1	WNL	WNL
64	38	939661	Female	98	92	16	154	90	1	88	n	5.6	2.5	7	142	3.66	1.2	WNL	WNL

ANNEXURE V- MASTER CHART

				Vitals						Investigations									
Serial number	Age in Years	Patient No	Sex	Temperature	Pulse Rate	Respiratory Rate	Mean Systolic BP	Mean Diastolic BP	Grades of HTN	Fasting Blood sugar		HbA1c	Serum Magnesium(mg/dl)	Serum Calcium(mg/dl)	Serum Sodium	Serum Potassium	creatinine	Fundus	ECG
65	44	941326	Male	98.2	86	19	160	90	2	110	pd	5.8	1.9	9.4	134	4.4	0.79	WNL	WNL
66	40	941293	Female	98.4	78	16	150	90	1	101	pd	6.4	1.7	9.1	137	3.4	0.92	WNL	WNL
67	65	941281	Male	98	68	18	150	90	1	116	pd	6.1	2.1	7.7	140	3.8	0.85	WNL	LVH
68	56	940934	Male	98.1	94	18	164	100	2	119	pd	5.8	1.7	8.6	137	5.2	0.95	WNL	WNL
69	40	940876	Male	97.8	78	18	170	100	2	89	n	6.3	1.6	9.8	132	3.4	1.1	WNL	WNL
70	78	940145	Male	96.8	90	18	154	80	1	108	pd	5.7	1.6	9	135	4.38	1.06	Grade 1	LVH
71	70	940758	Male	98	86	19	150	90	1	92	n	6.3	2.3	8.7	138	4.2	0.82	WNL	WNL
72	41	940789	Female	97.9	76	16	152	88	1	86	n	5.2	2	9.1	137	4.09	0.68	WNL	WNL
73	71	940594	Female	98.2	78	18	148	80	1	98	n	6.1	2.1	8.6	132	4.3	0.91	WNL	WNL
74	40	939912	Female	97.2	82	16	150	90	1	102	pd	6.2	2.3	8.6	139	3.71	1.12	Grade 2	LVH
75	76	939688	Male	97.8	80	17	144	80	1	105	pd	5.4	1.4	9.3	141	5.2	0.86	WNL	WNL
76	60	939721	Female	97.9	74	16	158	98	1	87	n	6.3	1.8	8.4	134	4.35	0.9	WNL	WNL
77	59	939509	Male	98	87	18	150	90	1	96	n	6.3	1.9	8.9	138	4.08	0.66	Grade 1	LVH
78	70	939391	Male	97	76	16	150	90	1	94	n	5.6	2.2	8.1	156	3.86	0.72	WNL	WNL
79	30	938640	Male	98	86	19	176	110	2	111	pd	6.2	1.4	8.6	139	4.27	0.8	WNL	WNL
80	74	937663	Female	97.8	78	18	150	90	1	123	pd	6.2	2.3	8.6	137	4.14	1.16	WNL	WNL
81	80	937467	Female	98.6	68	16	170	100	2	88	n	5.5	2.2	9.7	151	4.3	0.94	WNL	LVH
82	71	937232	Male	98	90	19	160	100	2	118	pd	5.9	2	9.8	143	3.79	0.58	Grade 2	WNL
83	34	936723	Female	97.8	84	17	160	100	2	97	n	6.1	2.2	9.1	140	4.09	0.6	WNL	WNL
84	65	939844	Male	98	92	16	154	90	1	101	pd	5.8	2.2	8.9	136	4.11	0.84	WNL	LVH
85	73	939854	Female	98.2	86	19	160	90	2	104	pd	5.5	1.2	8.9	141	3.9	0.99	WNL	LVH
86	78	936265	Male	98.4	78	16	150	90	1	122	pd	6.3	2.1	3.51	132	4.2	0.86	WNL	WNL
87	80	939873	Female	98	68	18	150	90	1	94	n	5.7	1.9	7.8	141	4.01	0.72	WNL	WNL
88	37	939233	Male	98.1	94	18	164	100	2	113	pd	6	1.6	9.3	134	4.1	1.1	WNL	WNL
89	68	938780	Female	97.8	78	18	170	100	2	107	pd	6.3	2.3	8.1	128	4.72	0.66	Grade 1	WNL
90	68	939537	Male	96.8	90	18	154	80	1	114	pd	6.2	1.8	8.7	134	4	0.96	WNL	WNL
91	42	938366	Male	98	86	19	150	90	1	93	n	5.9	2	8	134	4.2	0.7	WNL	WNL
92	70	938265	Male	97.9	76	16	152	88	1	91	n	5.2	1.7	8.6	138	2.54	0.68	WNL	LVH
93	68	938221	Male	98.2	78	18	148	80	1	87	n	5.8	2.4	8.1	134	3.5	0.73	WNL	WNL
94	78	937951	Female	97.2	82	16	150	90	1	119	pd	6.2	2	8.7	140	3.5	0.86	Grade 1	LVH
95	60	938742	Female	97.8	80	17	144	80	1	109	pd	6.1	1.8	8.1	133	4.2	0.53	WNL	WNL
96	30	937911	Male	97.9	74	16	158	98	1	117	pd	5.8	2.4	9	136	3.94	0.71	WNL	WNL
97	70	937377	Male	98	87	18	150	90	1	97	n	5.4	3.2	7.5	139	3.6	1.03	WNL	LVH
98	50	936832	Female	97	76	16	150	90	1	99	n	5.5	1.7	9	134	4.3	1.09	WNL	WNL
99	44	938581	Male	98	86	19	176	110	2	99	n	6.2	1.7	9.3	142	3.63	0.82	WNL	WNL
100	91	936664	Female	97.8	78	18	150	90	1	106	pd	5.8	1.7	8.4	126	3.51	0.74	WNL	WNL