“SERUM MAGNESIUM AND END ORGAN DAMAGE IN TYPE 2 DIABETES MELLITUS”

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CERTIFICATE

This is to certify that the dissertation entitled **"SERUM MAGNESIUM AND END ORGAN DAMAGE IN TYPE 2 DIABETES MELLITUS"** is a bonafide work of **Dr.K.KARTHIKEYAN,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2012.

Dr. MOSES.K.DANIEL M.D.,
Professor and HOD,
Department of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

Dr.J.SANGUMANI M.D.,
Professor,
Department of General Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr.K.KARTHIKEYAN,** solemnly declare that, this dissertation **"SERUM MAGNESIUM AND END ORGAN DAMAGE IN TYPE 2 DIABETES MELLITUS"** is a bonafide record of work done by me at the Department of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.J.SANGUMANI.M.D.,** Professor, Department of General Medicine, Madurai Medical college, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch-I, examination to be held in April 2012.

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Date:

Dr.K.KARTHIKEYAN.

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CONTENTS

INTRODUCTION

Diabetes mellitus (DM), characterized by metabolic disorders related to high levels of serum glucose, is probably the most associated disease to Mg depletion in intra and extra cellular compartments[5]. Hypomagnesemia has been related as a cause of insulin resistance, also being a consequence of hyperglycemia, and when it is chronic leads to the installation of macro and microvascular complications of diabetes, worsening the deficiency of Mg. The mechanism involving the DM and hypomagnesemia was still unclear, although some metabolic studies demonstrate that Mg supplementation has a beneficial effect in the action of insulin and in the glucose metabolism.

Hypomagnesemia has long been known to be associated with diabetes mellitus. Low serum magnesium level has been reported in children with insulin dependent diabetes mellitus and through the entire spectrum of adult type1 and type 2 diabetes mellitus regardless of the type of therapy.

Initially the cause of hypomagnesaemia was attributed to osmotic renal losses from glycosuria decreased intestinal magnesium absorption and redistribution of magnesium from plasma into red blood cells caused by insulin effect. Recently a specific tubular magnesium defect in diabetes has been postulated. Hypermagnesuria results specifically from a reduction in tubular absorption of magnesium.

Magnesium is involved on multiple levels in insulin secretion, binding and activity. Cellular magnesium deficiency can alter of the membrane bound sodium-potassium-adenosine triphospatase which is involved in the maintenance of gradients of sodium and potassium and in glucose transport.

The concentrations of magnesium in serum of healthy people are remarkably constant, whereas 25-39% of diabetics have low concentrations of serum magnesium[6,7]. Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes[8,9], as well as on the evolution of complications such as retinopathy[10], arterial atherosclerosis and nephropathy. Moreover, low serum magnesium is a strong, independent predictor of development of type 2 diabetes.

The present study was undertaken with an aim to estimate prevalence of hypomagnesaemia in patients with type 2 DM and to correlate the serum magnesium concentrations with micro and macrovascular complications of diabetes – retinopathy, nephropathy, neuropathy and ischemic heart disease.

AIM OF THE STUDY

This study is aimed at,

1. Estimating fasting serum magnesium concentrations in patients with type 2 diabetes mellitus.
2. Correlating serum magnesium concentrations with micro and macrovascular complications of type 2 diabetes mellitus - retinopathy, nephropathy, neuropathy and ischemic heart disease.

DIABETES MELLITUS

Diabetes is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed.[1] A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

Major advances in the understanding of diabetes and metabolism have included:

A. The sequencing of insulin in 1955 by Frederick Sanger and elucidation of its three dimensional structure in 1969 by Dorothy Hodgkin.

B. The measurement of insulin concentration using the first radio immunoassay, by Solomon Berson and Rosalyn Yalow in 1959.

C. The isolation of proinsulin in 1967 by Donald Steiner's group.

D. Identification of specific insulin receptors by Pierre Freychet and colleagues in 1971, and

E. The sequencing of the insulin receptor in 1985.

Mile stones in the management of diabetes have included,

A. The development of long acting insulin preparations in 1936,

B. The testing of sulfonylureas by Auguste Loubatieres in 1944.

C. First therapeutic use of a biguanide (phenformin) by G. Ungar in 1957.

D. Introduction in the late 1970's of dry reagent test strips suitable for self monitoring of blood glucose, and

E. Definitive proof from the diabetes control and complications trial (DCCT) published in 1993, that strict glycemic control could slow or prevent the development of diabetic microvascular complications.

F. Emergence of Metformin in 1995.

The classification of diabetes includes four clinical classes:

- Type 1 diabetes (results from cell destruction,usually leading to absolute insulin deficiency)
- Type 2 diabetes (results from a progressive insulin secretory defect on the Background of insulin resistance)
- Other specific types of diabetes due to other causes,

e.g., genetic defects in cell function,

- Genetic defects in insulin action,

- Diseases of the exocrine pancreas (such as cystic fibrosis), drugs or chemical-induced diabetes (in the treatment of AIDS or after organ transplantation)
- gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy)

Diagnosis of diabetes

Criteria for the diagnosis of diabetes

1. HbA1C -6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

2. FPG -126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

OR

3. Two-hour plasma glucose -200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose -200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Categories of increased risk for diabetes*

FPG 100–125 mg/dl (5.6–6.9 mmol/l)[IFG]
2-h PG on the 75-g OGTT 140–199 mg/dl(7.8–11.0 mmol/l) [IGT]
HbA1C 5.7–6.4%

***** Adopted from ADA 2010 guidelines.

Criteria for testing for diabetes in asymptomatic adult individuals

1. Testing should be considered in all adults who are overweight (BMI 25 kg/m^2) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- Members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing 9 lb or were diagnosed with GDM
- Hypertension (140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level 35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250mg/dl (2.82 mmol/l)
- Women with polycystic ovary syndrome
- HbA1C 5.7%, IGT, or IFG on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity,acanthosis nigricans)
- History of CVD

2. In the absence of the above criteria, testing diabetes should begin at age 45 years

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results.

DIABETIC CARE

Initial Evaluation

A complete medical evaluation should be performed to classify the diabetes, detect the presence of diabetes complications, review previous treatment and glycemic control in patients with established diabetes, assist in formulating a management plan, and provide a basis for continuing care.

Components of the comprehensive diabetes evaluation

Medical history

- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history

- Review of previous treatment regimens and response to therapy (HbA1C records) Current treatment of diabetes, including medications, meal plan, physical activity patterns,and results of glucose monitoring
- DKA frequency, severity, and cause
- Hypoglycemic episodes
- Hypoglycemia awareness
- Any severe hypoglycemia: frequency and cause
- History of diabetes-related complications
    - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
    - Macrovascular: CHD, cerebrovascular disease, Pheripheral arterial disease.
    - Other: psychosocial problems, dental disease

Physical examination

- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination
- Thyroid palpation

- Skin examination (for acanthosis nigricans and insulin injection sites)
- **Comprehensive foot examination:**
    - Inspection
    - Palpation of dorsalis pedis and posterior tibial pulses
    - Presence/absence of patellar and Achilles reflexes
    - Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation

- HbA1C, if results not available within past 2–3 months
- If not performed/available within past year:
- Fasting lipid profile, including total, LDL- and HDL cholesterol and triglycerides
- Liver function tests
- Test for urine albumin excretion with spot urine albumin/creatinine ratio
- Serum creatinine and calculated GFR
- TSH in type 1 diabetes, dyslipidemia, or women over age 50 years

Referrals

- Annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietician for MNT

- Dental examination

Complications of Diabetes

DIABETIC RETINOPATHY

Diabetic retinopathy is the most frequent cause of blindness among adults aged 20-74 years. During the first two decades of disease, nearly all patients with type 1 diabetes mellitus and > 60% with type 2 diabetes mellitus have retinopathy. In type 2 diabetes mellitus, 21% of patients have retinopathy at first diagnosis.

CLASSIFICATION (MODIFIED FROM AMERICAN ACADEMY OF OPTHALMOLOGY)

Non Proliferative Diabetic Retinopathy (NPDR)

1. Mild NPDR

At least one retinal microaneurysm and one or more of the following : retinal hemorrhage, hard exudate, soft exudate.

2. Moderate NPDR

Hemorrhages or microaneurysms or both in atleast on quadrant and one or more of the following: soft exudates, venous beading and IRMA.

3. Severe NPDR

Hemorrhages or microaneurysms or both in all quadrants, venous beading in two or more quadrants , IRMA in at least one quadrant.

PDR

1. Early PDR

One or more of the following:

- NVE
- NVD
- Vitreous or preretinal hemorrhage
- NVE< ½ disc area.

2. High risk PDR

One or more of the following.

- NVD > ¼- $^{1}/_{3}$ disc area
- NVD with vitreous or preretinal hemorrhage
- NVE > ½ disc area. Preretinal or vitreous hemorrhage.

3. ***Advanced PDR***

High risk PDR, traction retinal detachment involving macula or vitreous hemorrhage obscuring ability to grade NVD or NVE.

- IRMA – Intraretinal microvascular abnormalities.
- NVE – Neovascularisation elsewhere.
- NVD – Neovascularisation disc.

Screening of Retinopathy[1]

- Adults and children aged 10 years or older with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes.
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes.
- Subsequent examinations for type 1 and type 2 diabetic patients should be repeated annually by an ophthalmologist or optometrist.
- Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counselled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum.

Diabetic Nephropathy

- Diabetes has become the most common single cause of end stage renal disease (ESRD) world wide[1]. About 20-30% of patients with type 1 or type 2 diabetes mellitus develop evidence of nephropathy, but in type 2 diabetes a considerably smaller fraction of these progress to ESRD.

Category	Spot collection (g/mg.creatinine)
Normal	<30
Microalbuminuria	30–299
Macroalbuminuria(clinical)	>300

Diabetic Neuropathy

Classification

SYMMETRIC	ASYMMETRIC
Distal sensorimotor Polyneuropathy	Cranial Neuropathies
Chronic Proximal motor neuropathy	Limb Mononeuropathy
Autonomic Neuropathy	Radiculopathy & Plexopathies.

FDA approved Drugs for Diabetic Neuropathy are Pregabalin & Duloxetine

Other Drugs-Amitryptylin,Gabapentin,Imipramine.

CARDIOVASCULAR DISEASE IN DIABETES[1]

Cardiovascular disease incidence is increased in individuals with type 1 or type 2 diabetes mellitus. The American Heart Association recently designated type 2 diabetes mellitus as a coronary risk equivalent i.e. they have a similar 10 year risk of MI, as those who have had a prior MI. In addition to coronary artery disease, cerebrovascular disease is increased in individuals with diabetes

mellitus (three fold increase in stroke). Proof that improved glycemic control reduces cardiovascular complications in diabetes mellitus is lacking.

Summary of recommendations for adults with diabetes	
Glycemic control	
HbA1C	< 7.0%
Preprandial plasma glucose	90 – 130 mg/dl (5.0 – 7.2 mmol/l)
Postprandial plasma glucose	< 180 mg/dl (< 10.0 mmol/l)
Blood Pressure	< 130/80 mmHg
Lipids	
LDL	< 100 mg/dl (<2.6 mmol/l)
Triglycerides	< 150 mg/dl (<1.7 mmol/l)
HDL	> 40 mg/dl (> 1.1 mol/l)

Key concepts in setting glycemic goals :

• Goals should be individualized

• Certain populations (children, pregnant women, and elderly) require special considerations

• Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia

• More stringent glycemic goals (i.e. a normal HbA1C < 6%) may further reduce complications at the cost of increased risk of hypoglycemia

• Postprandial glucose may be targeted if HbA1C goals are not met despite reaching preprandial glucose goals.

MAGNESIUM

MAGNESIUM is the fourth most common cation in the body and the second most common intracellular cation after potassium. The central role of magnesium within the chlorophyll molecule and as a cofactor for the enzymes in the 12- transphosphorylation reactions in photosynthesis makes it probably the most important inorganic element in the production of food and fossil fuel.[11] In addition, it has a fundamental role as a cofactor in more than 320 enzymatic reactions involving energy metabolism and nucleic acid synthesis.[12]

Until recently, the function of magnesium in biological processes was largely ignored to the point where it was described as the ‘forgotten’ ion. In recent years, there has been an explosion of interest in the physiological and therapeutic properties of this essential element. It is involved in several processes, including hormone receptor binding and gating of calcium channels, transmembrane ion flux, regulation of adenylate cyclase, muscle contraction and neuronal activity, control of vascular tone, cardiac excitability and neurotransmitter release.[13,14] Magnesium increases the body’s ability to utilize calcium, phosphorus, sodium, potassium, vitamins C, E and B complex.[15]

From a physiological perspective, magnesium is primarily regarded as a calcium antagonist, as most of its actions are linked to calcium. Calcium is an ideal agent for fast signal transduction and cell activation as cytosolic free calcium is only 1/10,000 of the corresponding extracellular species, traditionally called ionized calcium.

Magnesium, on the other hand, having a slight gradient over the plasma, plays the complementary role of a more long-term regulatory element. Alterations of intracellular or extracellular magnesium concentration may affect cell function through its effect on calcium handling. Most of the intracellular magnesium is located within the mitochondria apparently because magnesium binds strongly with ATP. In general, the more metabolically active the cell is, the higher is its magnesium content. Levels of magnesium in the plasma of healthy people are remarkably constant, being on an average of 1.3–2.4 mg/dl (0.7–1.0 mmol/l).

It has been estimated that refining and processing of food causes a substantial loss of magnesium. For example, the refining and processing of wheat to flour, rice to polished rice and corn to starch depletes magnesium by 82, 83 and 97% respectively.[16]

Normal Mg Metabolism

Gastrointestinal Metabolism

On an average diet, 250 to 350 mg of Mg is consumed daily. Twenty-five to 60% of dietary Mg is absorbed in the gastrointestinal tract. Gastrointestinal absorption occurs predominantly in the small intestines *via* paracellular simple diffusion at high intraluminal concentrations and active transcellular uptake *via* Mg-specific transporters at low concentrations.[21] Active intestinal Mg absorption is presumed to involve transient receptor potential channel melastatin 6 (TRPM6), which is expressed along the brush border membrane of the small intestine.[18] Mutations of TRPM6 have been reported to be associated with hypomagnesemia with secondary hypocalcemia.[19,20]

Renal Metabolism

Glomerular Filtration.

Approximately 70 to 80% of plasma Mg is ultrafilterable in the ionic form (70 to 80%) and complexed with anions such as phosphate, citrate, and oxalate (20 to 30%).[21,22] The ultrafilterability of Mg depends on glomerular filtration, volume status, various metabolic states that would enhance the

selection for ionized Mg (*e.g.*, acidemia, reduced serum content of negatively charged species), and the integrity of the glomerular basement membrane.

Proximal Tubules.

Once Mg is filtered through the glomerulus, 15 to 25% is reabsorbed in the proximal tubules. Reabsorption at the proximal tubule is mainly passive and proportional to sodium and water reabsorption, although at a lower rate.[22]

Loop of Henle.

Approximately 65 to 75% of the Mg filtered load is reabsorbed *via* the paracellular pathway in the thick ascending limb of the loop of Henle (TAL). Paracellular Mg reabsorption at this nephron segment has been suggested to be facilitated by claudin 6, also known as paracellin 1. Paracellin 1 is a tight junction protein whose mutation is associated with severe hypomagnesemia with hypercalciuria and nephrolithiasis.[23,24] Parathyroid hormone, calcitonin, glucagon, and antidiuretic hormone have been suggested to enhance Mg transport in the TAL *via* the second messenger Cyclic AMP. Insulin also has been implicated to play a role at this nephron segment by increasing the favourable transepithelial potential difference for Mg reabsorption.

Distal Convoluted Tubules.

The distal convoluted tubule (DCT) reabsorbs approximately 5 to 10% of the filtered Mg *via* an active and regulated transcellular pathway. Although this

is a low percentage of the filtered Mg load, it represents 70 to 80% of Mg that is delivered from the TAL. In addition, because a negligible amount of Mg is reabsorbed distal to this segment, Mg reabsorption at the DCT is of great importance because it determines the final urinary Mg concentration.[21]

Recently, Mg reabsorption at the DCT was shown to occur *via* the transient receptor potential channel melastatin TRPM6. It has been postulated that upon entry into the cells, Mg binds to divalent-binding proteins such as parvalbumin or calbindin-D28K for transport across the cell to the basolateral membrane, where Mg is taken into the interstitium by a basolateral $Na^{2+/}Mg^{2+}$ exchanger and/or ATP dependent Mg pump.[22,]

It is interesting that the regulation of magnesium reabsorption at the DCT was studied extensively before the actual identification of TRPM6. Peptide hormones such as parathyroid hormone (PTH), calcitonin, glucagon, and vasopressin all have been implicated. The mediating mechanisms are unknown but seem to involve, in part, stimulation of cAMP release and activation of protein kinase A, phospholipase C, and protein kinase C. Insulin also has been suggested to enhance intracellular Mg uptake, presumably *via* tyrosine kinase. Moreover, insulin may stimulate the production of cAMP and potentiate Mg uptake *via* other cAMP-dependent hormones, including PTH. In addition, the

Ca/Mg sensing receptor on the basolateral side may modulate hormone-stimulated Mg transport through G-protein coupling. Finally, low dietary Mg intake and estrogens have been shown to upregulate renal TRPM6 expression and reduce urinary Mg excretion.[29]

Dietary Reference Intakes for Magnesium

Recommendations for magnesium are provided in the dietary reference intakes (DRI's) developed by the Food and Drug Administration (FDA).

Recommended Dietary Allowances (RDA) for magnesium are as per the table.

AGE IN YRS	**MALE**	**FEMALE**
1-3	80	80
4-8	130	130
9-13	240	240
14-18	410	360
19-30	400	310
31+	420	320

(Magnesium values in mg/day).

- During pregnancy 350mg/day
- During lactation 310mg/day

Hypermagnesemia

Hypermagnesemia is rarely seen in the absence of renal insufficiency, as kidneys can excrete large amounts of magnesium (up to 250 mmol/d).[30]

Causes of hypermagnesemia

- Impaired magnesium excretion

  Renal failure

  Familial hypocalciuric hypercalcemia

- Excessive magnesium intake

  Cathartics

  Antacid preparations

  Parenteral magnesium administration (eg.magnesium sulfate in PIH)

- Rapid magnesium mobilisation from soft tissues

  Trauma

  Extensive burns

  Shock, sepsis

- Other disorders

  Adrenal insufficiency

  Hypothyroidism

  Hypothermia

Clinical features

The most prominent clinical manifestation of hypermagnesemia are vasodilation and neuromuscular blockade, which appear at serum magnesium concentrations > 4.8 mg/dL (>2mmol/L). Hypotension, refractory to vasopressors and volume expansion, may be an early sign. Lethargy and weakness may progress to respiratory failure, paralysis and coma with hypoactive tendon reflexes (at serum magnesium levels > 4 mmol/L). Gastrointestinal hypomotility or ileus may occur. Prolongation of PR, QRS intervals, heart blocks and, at serum magnesium levels approaching 10 mmol/L, asystole.

Treatment

Generally involves identifying and avoiding the source of magnesium. Vigorous intravenous hydration and hemodialysis may be necessary. Calcium, given intravenously in doses of 100-200 mg over 1 to 2 hrs provides temporary improvement.

Hypomagnesemia

Hypomagnesemia signifies substantial depletion of body magnesium stores (0.5 to 1 mmol/Kg). Hypomagnesemia has varied etiology. Dietary magnesium deficiency is unlikely except in the setting of alcoholism.[30]

Causes of Hypomagensemia[30]

I. Impaired intestinal absorption

Primary infantile hypomagnesemia

Malabsorption syndromes

Vitamin D deficiency.

II. Increased intestinal losses

Protracted vomiting / diarrhea

Intestinal drainage, fistulae

III. Impaired renal tubular reabsorption

A. Genetic magnesium wasting syndromes.

Gitelman syndrome

Bartter syndrome

Na-K ATPase g-subunit mutations

B. Acquired renal disease

Tubulointerstitial disease

Post obstruction /ATN (diuretic phase)

Renal transplantation.

C. DRUGS

Ethanol

Diuretics (loop, thiazide and osmotic)

Cisplatin, cyclosporine

Aminoglycosides, Amphotericin B

IV. Metabolic causes

Hyperaldosteronism

SIADH

Diabetes mellitus

Metabolic acidosis

V. OTHERS

Pancreatitis

Excessive sweating

Osteoblastic metastases

Several genetic magnesium wasting syndromes are explained, but are extremely rare. Prolonged nasogastric suction, parenteral fluids, infectious diarrhea, steatorrhoea, inflammatory bowel disease may cause hypomagnesemia.[31] Magnesium deficiency is especially common in patients receiving furosemide diuretic.[32]

Frequency

Hypomagnesemia is a common entity occurring in up to 12% of hospitalized patients.[33] The incidence rises to as high as 60% in patients in intensive care settings in which nutrition, diuretics, hypoalbuminemia, and aminoglycosides may play important roles.[34]

Risk of incidence is as follows:[35]

2% in general population.

10 – 20% in hospitalized patients.

50 – 60% in ICU patients.

25% in diabetic outpatients.

Sex: Incidence is equal in males and females.

Clinical features.[2,36]

History

- Clues to the presence of hypomagnesemia can be found by obtaining history of potential causes.
- Historical complaints related to hypomagnesemia are nonspecific.
- Patients may report weakness, muscle cramping or rapid heartbeats.
- Altered mental status (irritability, apathy, psychosis, delirium) may be present in severe cases. Less severe cases may result in vertigo, ataxia, depression and seizure activity.

Physical signs

Symptoms and signs appear only when serum magnesium concentrations are <1.2 mg/dL (0.5 mmol/L). The primary clinical findings are neuromuscular irritability, CNS hyperexcitability, and cardiac arrhythmias.[37]

Signs

- Hyperactive deep tendon reflexes.
- Muscle cramps.
- Trousseau and Chvostek signs
- Dysphagia due to esophageal dysmotility
- Irritability/ disorientation
- Ataxia, nystagmus or seizures (at levels <0.8 mg/dl) Paroxysmal atrial and ventricular dysrhythmias.

ECG

Magnesium depletion can induce changes in the electrocardiogram. Findings in hypomagnesaemia are nonspecific. Modest magnesium depletion (1.2 to 1.7 mg/dl) leads to widening of QRS complex with peaking T-waves, while more severe magnesium depletion (<1.2 mg/dl) is associated with prolongation of PR interval, progressive widening of QRS complex, flattening / inversion of T-waves and U waves.[38]

Cardiac arrhythmias may occur including sinus tachycardia, other supraventricular tachycardia and ventricular arrhythmias.

Lab Studies

The serum magnesium level is not a reliable determinant of total body magnesium depletion, because only a small fraction of magnesium in the body is extracellular. Nevertheless, a deficiency of magnesium is clearly present if serum level is low.[39]

Serum magnesium levels may be estimated by several methods.

- Neutron activation analysis
- Atomic absorption spectrometry
- Ion selective electrodes (ISE)
- Equilibrium dialysis
- Calmagite dye method.

Calcium, potassium and phosphorous levels must be assessed.

BUN and creatinine levels.

Blood glucose level.

Treatment

The route of magnesium repletion varies with severity of the clinical manifestations. As an example, the hypocalemic-hypomagnesemic patient with tetany or the patient with hypomagnesemic ventricular arrhythmias should receive 50 mEq of IV magnesium given slowly over 8 to 24 hours. This dose

can be repeated as necessary to maintain plasma magnesium concentration above 1.0 mg/dl.[40]

Oral replacement should be given in less critical patients, preferably with a sustained release preparation. There are several such preparations available – Slow Mag (magnesium chloride) and MagTab-SR (Magensium lactate). These preparations provide 60-84mg (2.5 to 3.5 mmol) per tablet. Six to eight tablets should be taken daily in divided doses for severe magnesium depletion (<1.2mg/dL). Two to four tablets are sufficient for milder disease. The underlying disease should be corrected, if possible. It includes discontinuation of diuretic therapy, addition of potassium sparing diuretic in those who cannot discontinue diuretic therapy, treatment of chronic diarrhea etc.

MAGNESIUM AND DIABETES

Magnesium deficiency in diabetes

Magnesium ion has a fundamental role in carbohydrate metabolism in general, and in the action of insulin in particular.Magnesium is a cofactor in the glucose transporting mechanism of the cell membrane and various enzymes in carbohydrate oxidation. Cellular magnesium seems to play an important role in glucose metabolism as it is a critical cofactor for the activities of various enzymes involved in glucose oxidation and may play a role in the release of insulin. Magnesium is involved at multiple levels in insulin secretion, binding and activity.[41] It is also involved in many phosphorylation reactions and is a cofactor for ATPase and adenylate cyclase enzymes. Magnesium deficiency has recently been proposed as a novel factor implicated in the pathogenesis of diabetic complications.

Recognizing the signs of diabetes associated magnesium deficiency is important because the deficiency can occur long before it is reflected by serum values.

Diabetes mellitus has been suggested to be the most common metabolic disorder associated with magnesium deficiency, having 25 to 39% prevalence.[42] Recent evidences suggest that insulin can increase free magnesium entry into the cell. Glycemic control in patients with type-2 diabetes, however, may not correct

low magnesium concentration, suggesting that other factors may regulate magnesium levels in diabetic patients.[43]

HypoMagnesemia in Type 2 Diabetes

Causes of hypomagnesemia in diabetes mellitus

Hypomagnesemia in the patient with diabetes may result from poor oral intake, poor gastrointestinal absorption, and enhanced renal Mg excretion .

Gastrointestinal Causes

Diabetic autonomic neuropathies that may reduce oral intake and gastrointestinal absorption include esophageal dysfunction, gastroparesis, and diarrhea.[44] Whether gastrointestinal Mg absorption via TRPM6 is reduced in the patient with diabetes is not known.

Renal Causes

Enhanced Filtered Load.

In the patient with diabetes, the ultrafilterable Mg load may be enhanced by glomerular hyperfiltration, recurrent excessive volume repletion after hyperglycemia-induced osmotic diuresis, recurrent metabolic acidosis associated with diabetic ketoacidosis, and hypoalbuminemia.[45] The last two conditions may increase the serum ionized Mg fraction and, hence, ultra filterable Mg load and subsequent urinary loss. In addition, it is conceivable that significant microalbuminuria and overt proteinuria among patients with diabetic

nephropathy may contribute to renal Mg wasting as a result of protein-bound magnesium loss.

Enhanced Tubular Flow. Overly aggressive volume reexpansion and glomerular hyperfiltration also may induce renal Mg wasting at the proximal tubule and TAL, independent of the filtered load. Because Mg reabsorption parallels sodium reabsorption in the proximal tubules, volume expansion can decrease both sodium and Mg reabsorption at this level. Similarly, a high tubular flow through the TAL may reduce Mg reabsorption at this segment.[45]

Reduced Tubular Reabsorption. Because insulin has been implicated in enhancing Mg reabsorption at the TAL, insulin deficiency or resistance in the diabetic state can promote Mg wasting at this nephron segment.[46] The expression of paracellin 1 in TAL, however, has not been shown to be increased in diabetic rats.[47]

In the same diabetic rat model, Lee et al.[47] revealed that TRPM6 expression in the DCT is not reduced but rather enhanced.This is thought to be a compensatory mechanism for the increased Mg load that is delivered to the DCT or blunted activity of the TRPM6 channel in the diabetic state. Accordingly, despite the increase in TRPM6 expression, overall renal Mg wasting is observed.

Metabolic Disturbances:

Various metabolic disturbances that are associated with diabetes also have been suggested to promote urinary Mg excretion.

- **Hypokalemia**: At the TAL segment, hypokalemia may reduce Na-K-2Cl co-transport activity, the associated potassium extrusion through the potassium channel ROMK, and resultant diminution of the favorable transmembrane voltage that is required for paracellular Mg reabsorption. In addition, there is evidence to suggest that cellular potassium depletion may diminish Mg reabsorption at the DCT by yet unclear mechanisms.[48]
- **Hypophosphatemia**: Both micropuncture studies in phosphate-depleted dogs and in vitro studies involving phosphate depleted mouse DCT cells have demonstrated reduced Mg uptake.[49,50] Phosphate-induced reduction in cellular uptake of Mg is believed to be a posttranslational effect because the alteration in Mg uptake could be observed within 30 min of phosphate depletion.
- **Metabolic Acidosis:** In addition to its role in increasing serum ionized Mg concentration and, hence, ultrafilterable Mg load for renal excretion, metabolic acidosis has been suggested to enhance protonation of the Mg channel in the DCT and subsequent inhibition of cellular Mg uptake.[51]

More recently, Nijenhuis et al.[52] showed reduced expression of TRPM6 with induced chronic metabolic acidosis in mice.

Insulin Deficiency and/or Resistance. As previously discussed, insulin deficiency or resistance may exacerbate renal Mg wasting because insulin has been shown to have antimagnesiuric effects in both the TAL and the DCT.[54]

Use of Diuretics

The common use of diuretics among patients with diabetes also may contribute to magnesiuria. The degree of magnesiuria is traditionally thought to be lower for thiazides compared with loop diuretics.[55,56] This difference has been explained by the site of action of the two types of diuretics because a smaller amount of intraluminal Mg is available for wasting at the DCT compared with that at the loop of Henle. In addition, inhibition of the Na_-Cl_ co-transporter by thiazides has been suggested to induce hyperpolarization of the DCT plasma membrane and, hence, a more favorable transmembrane electrical gradient for Mg reabsorption.[58] Recently, reduced TRPM 6 expression and enhanced magnesiuria were shown in mice given chronic thiazide therapy.[59] Given these observations and the lack of good direct comparative data between the two classes of diuretics, it must be assumed that significant magnesiuria may occur with either.

Others

Finally, the more common use of antibiotics and antifungals such as aminoglycosides and amphotericin in patients with diabetes may also contribute to renal Mg wasting.[60]

The role of magnesium in insulin action

Magnesium is involved in multiple levels in insulin secretion, binding and activity. Magnesium is a critical cofactor of many enzymes in carbohydrate metabolism. Cellular magnesium deficiency can alter the activity of the membrane bound Na- K- ATPase, which is involved in the maintenance of gradients of sodium and potassium and in glucose transport. Low levels of magnesium can reduce secretion of insulin by the pancreas.[61]

In addition to these effects of magnesium, magnesium deficiency has been shown to promote insulin resistance in multiple studies. In isolated soleus muscle, magnesium deficiency inhibits both basal and insulin-stimulated glucose uptake. This insulin resistance is a post receptor defect and may be linked to calcium mediation of insulin signal.[67] In diabetics, there is a direct relationship between serum magnesium level and cellular glucose disposal, that is independent of insulin secretion. This change in glucose disposal has been, shown to be related to increased sensitivity of the tissues to insulin in the presence of adequate magnesium levels.[62]

In a recent study, the cellular uptake of magnesium, which is normally stimulated by insulin, was shown to be attenuated in diabetics.[63] There is also evidence that magnesium deficiency itself produces insulin resistance. Nadler et al.[8] studied 16 non diabetic subjects and found that insulin sensitivity fell after induction of magnesium deficiency.

Likewise, elderly nondiabetic subjects were shown to have improved glucose handling, when they received magnesium supplements for 4 weeks.[64] There was a direct relationship between intracellular magnesium concentration and glucose metabolism, thus implicating magnesium deficiency in the insulin resistance of aging. In non diabetic obese subjects, insulin resistance was found along with low magnesium levels, when compared with non obese subjects, again highlighting the association between hypomagnesemia and insulin resistance.[65]

An intriguing theory, suggested by Tonyai, et al.[66] is that a low erythrocyte magnesium content can alter membrane viscosity, and this may impair the interaction of insulin with its receptor on the membrane.

Paolisso, et al.[64] were able to correct the increase in erythrocyte microviscosity with long-term magnesium administration.

Role of magnesium deficiency in diabetic end organ damage

Magnesium deficiency has been found to be associated with diabetic microvascular disease. Hypomagnesemia has been demonstrated in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe diabetic retinopathy.[10] Magnesium depletion is also found to play a role in the pathogenesis of diabetic polyneuropathy. Corsonello, et al have reported an association between diabetic nephropathy and magnesium depletion.

Microalbuminuria and clinical proteinuria, as well as poor glycometabolic control and hypertriglyceridemia, are associated to relevant alterations in serum ionized magnesium. Magnesium depletion has been associated with multiple cardiovascular implications: arrhythmias, vasospasm, hypertension and platelet activity.[69,70]

Three exciting theories link diabetes and its vascular complications to hypomagnesemia: the inositol transport theory, the ionic hypothesis of metabolic disease and oxidative stress theory.

Grafton, et al[4] have focussed on the inositol transport theory. It has been one of the favored explanations for the origin of diabetic complications. The theory suggests that hyperglycemia induces increased activity of the enzyme aldose reductase, which leads to the intracellular accumulation of sorbitol. The accumulated sorbitol inhibits transport of inositol, leading to a decrease in

intracellular inositol and inhibition of the Na –K- ATPase activity. The data of Grafton, et al show that hypomagnesaemia causes a decrease in the affinity of the inositol transport protein for inositol, leading to a two fold reduction in rate of inositol transport and accelerated development of diabetic complications.

The association between magnesium deficiency, essential hypertension, insulin resistance, hyperinsulinemia, and ischemic heart disease (Reaven-Modan Syndrome) may be explained by the ionic hypothesis of cardiovascular and metabolic disease, proposed by Resnick.[68] Suppression of intracellular free magnesium and an increase of intracellular free calcium are linked in these varied biologic processes: hypertension, decreased insulin secretion, and insulin resistance. Therefore, Resnick proposed that the 'primary' defect present in all organ systems is an abnormality of cellular ion handling. Magnesium deficiency would be the link, since its role in maintaining cellular pumps necessary for peripheral vascular tone (Na-K-ATPase and calcium activated K+ channels) would be diminished. Indeed, magnesium deficiency may lead to a reduction in insulin action by increasing free intracellular calcium levels.

Diabetes is a state of increased free radical activity. Lipid peroxidation of cellular structures, a consequence of free radical activity, is thought to play an important role in aging, atherosclerosis and late diabetic complications. In recent years, there has been a growing interest in magnesium and its correlation with

oxidative states. Weglicki, et al have proposed that during magnesium deficiency, natural antioxidant defences present in mammalian tissues against oxidative stress may be compromised. Magnesium deficiency has been shown to impair functions of natural antioxidants such as glutathione, ascorbic acid and Vit.E.

Management of Hypomagnesemia in Type 2 Diabetes

Because the literature suggests adverse outcomes in association with hypomagnesemia in patients with type 2 diabetes, measures to minimize this abnormality are warranted

Suggested management of hypomagnesemia in patients with type 2 diabetes

Increase Mg intake

Dietary consult

High Mg-containing food types

soya products, legumes, and seeds such as almonds and cashews, whole grains and fruits and vegetables such as spinach, okra, Swiss chard, dried apricots, and avocados

Control of diabetic gastroparesis

Eat multiple small meals instead of two to three large meals per day

Tight glucose control

Use of prokinetic medications to enhance gastric motility

Others: pyloric botulinum toxin injection, enteric feeding, gastric pacing[71,73]

Decrease gastrointestinal loss (diarrhea)

Trial of soluble fiber

Regular effort to move bowels

Trials of gluten-free diet, lactose restriction

Others: cholestyramine, clonidine, somatostatin analog, supplemental

Pancreatic enzyme, and antibiotics such as metronidazole[44]

Decrease renal Mg loss

Decrease filtered load

Use angiotensin-converting enzyme and/or angiotensin receptor blockers

Tight glycemic control[44]

Avoid excessive volume replacement during periods of hyperglycemia

Increase renal reabsorption

Tight glycemic control; measures to decrease insulin resistance (exercise)

Replacement of phosphate and potassium as needed

Replacement of diuretic-induced magnesiuria (based on 24-h urine output).

MATERIALS AND METHODS

This study was undertaken with the aim to determine serum magnesium level in patients with Type 2 Diabetes Mellitus without it's associated complications and Type 2 Diabetes mellitus patients with its various macro and microvascular complications namely Coronary atherosclerosis, Hypertension, retinopathy, neuropathy and nephropathy respectively.

STUDY POPULATION:

The study was conducted at Government Rajaji Hospital, Madurai on total of 120 subjects of age group 40 - 70 years; of whom 20 were apparently healthy and served as control.

Inclusion criteria

- ✓ All cases of type 2 diabetes mellitus coming to Dept of Diabetology, GRH, Madurai. During the period of April 2011 to October 2011

Exclusion criteria

1. Patients with chronic renal failure.
2. Acute myocardial infarction in last 6 months.
3. Patients on diuretics.
4. Patients with history of alcohol abuse.
5. Patients receiving magnesium supplements or magnesium containing antacids.

6. Malabsorption or chronic diarrhea.

Data collection

The 100 type 2 diabetics (with median diabetic history of 6.25 years) were included in the study. Detailed history – including duration of diabetes, treatment mode, symptoms suggestive of diabetic neuropathy, associated diseases such as hypertension and ischemic heart disease was obtained, as per the proforma. Followed by physical and neurological examination, and ECG. Retinopathy was assessed by direct opthalmoscopy. Blood samples were collected for measurement of fasting blood glucose and serum magnesium. Blood urea, serum creatinine and 24 hour urinary albumin were estimated. Serum magnesium was estimated by Calmagite dye method. HbA1C estimation was carried out by a modified calorimetric method.

Calmagite dye method for quantitative estimation of serum magnesium *Test principle:*

Under alkaline conditions, magnesium ions react with calmagite dye to produce a red complex which is measured spectrophotometrically at 530 nm. Intensity of the colour produced is directly proportional to magnesium concentration in the serum. To eliminate the interference of calcium during estimation, EDTA is included in the reagent. Heavy metal interference is

prevented by the presence of cyanide and a surfactant system is included to prevent protein interference.

Magnesium + Calmagite ⟶ Red coloured complex

Test procedure:

Three test tubes labeled Blank, Standard and Test are prepared as in table.

In test tubes	**Blank**	**Standard**	**Test**
Calmagite reagent	1.0ml	1.0ml	1.0ml
Standard sample	-	10ml	-
Patient's sample	-	-	10ml
Distilled water	10ml	-	-

Three test tubes are incubated at room temperature (22-28ºC). The absorbance of Test (A_T), Standard (A_S) and Blank (A_B) are read at 530nm in spectrophotometer. Magnesium concentration is calculated by the following formula.

Magnesium concentration (mEq/L) = $(A_T - A_B / A_S - A_B) \times 2$

Serum magnesium concentration is expressed in mg/dl by linearity of 1 mEq/L = 1.2 mg/dl.

Subsequently patients were divided into three groups based on their serum magnesium concentrations defined as follows: Normal, 1.3 to 2.5 mg/dl, low

<1.3mg/dl. Patients were also categorized on the basis of duration of diabetes, presence of ischemic heart disease or hypertension, mode of treatment, presence/absence of retinopathy, neuropathy and nephropathy, and glycemic control (FBS and HbA1C). Patients with diabetic retinopathy were further classified as those with nonproliferative diabetic retinopathy (NDPR) and those with proliferative diabetic retinopathy (PDR). Diabetic nephropathy was graded depending on 24 hour urinary excretion of albumin as follows: No nephropathy, < 30mg/24hour, microalbuminuria 30 – 299mg/24hour and macroalbuminuria (clinical proteinuria) > 300 mg/24hour.

Statistical Tools (To be included at the end of Materials and Methods)

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated using this software. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's chi square test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Fig – 1: AGE DISTRIBUTION

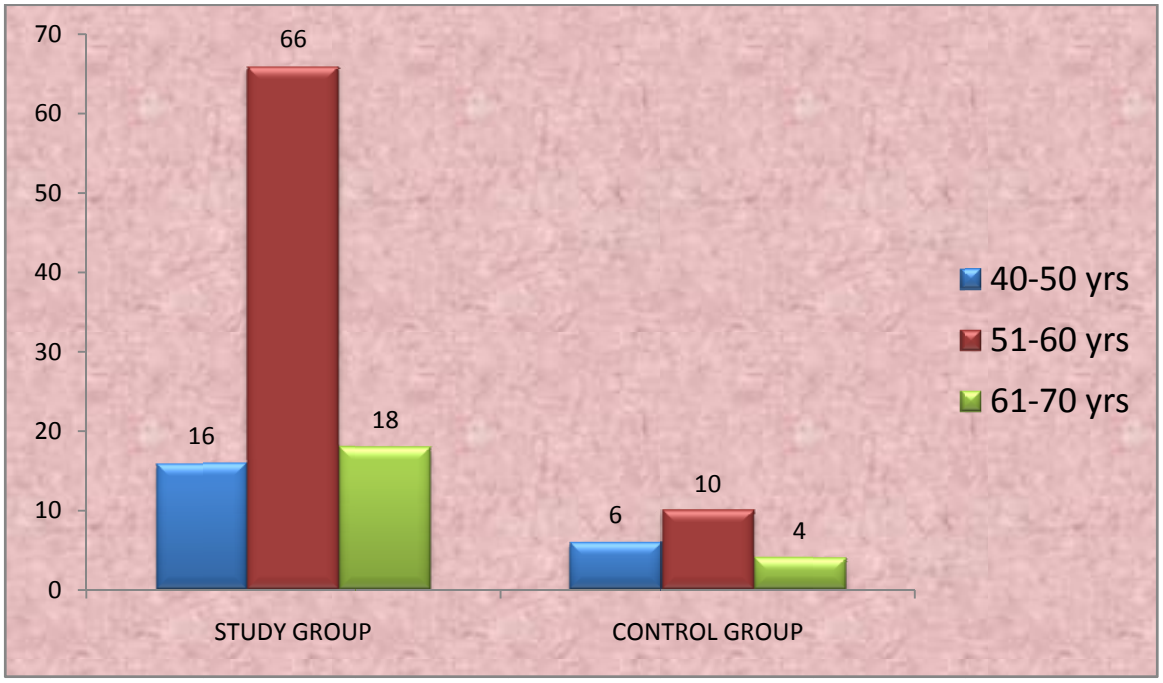
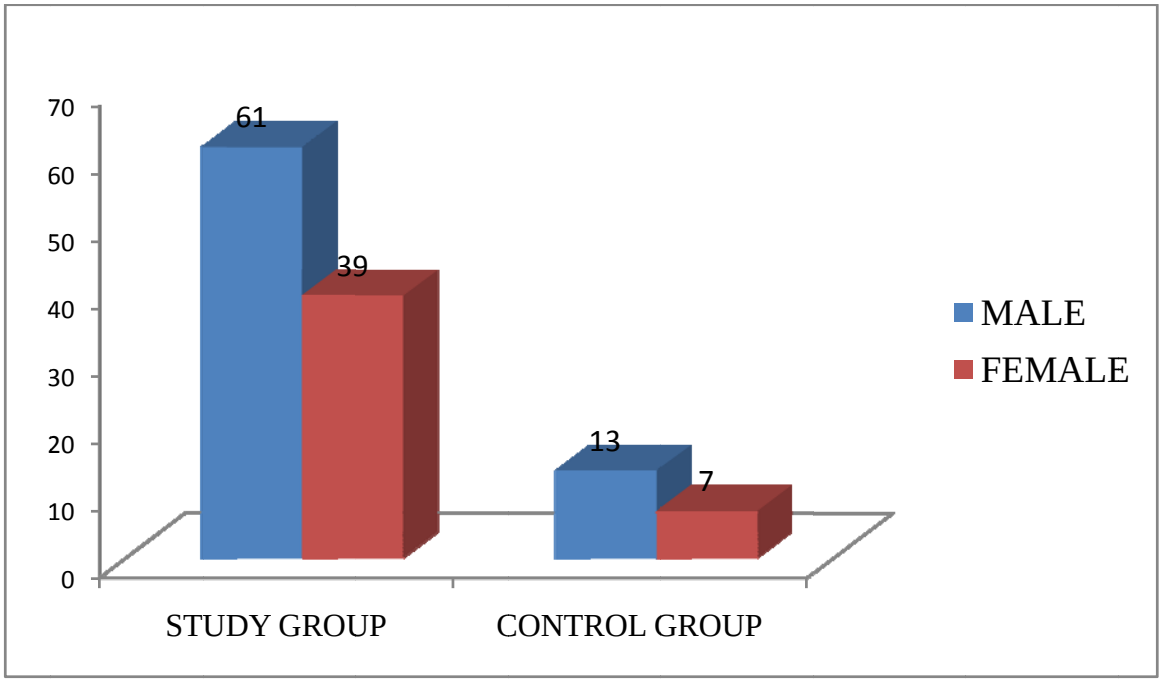


Fig – 2: SEX DISTRIBUTION



RESULTS

AGE DISTRIBUTION (Table 1):

Age group	Cases in			
	Study group		Control group	
	No.	%	No.	%
40 – 50 years	16	16	6	30
51- 60 years	66	66	10	50
61-70 years	18	18	4	20
Total	100	100	20	100
Range	40-70 years		43-67 years	
Mean	57.1		54.9 years	
SD	5.8 years		6.7 years	
'p'	0.2392 Not significant			

The 100 cases included in the study had an age of 57.1 $\pm$5.8 years. The 20 control cases had an age of 54.96 $\pm$6.7 years. There was no significant difference in the age composition of the two groups compared. ($p > 0.05$).

Table 2 : Sex distribution

Sex	Study group		Control group	
	No.	%	No.	%
Male	61	61	13	65
Female	39	39	7	35
Total	100	100	20	100
'p'	0.7893 Not significant			

61% of the study group and 65% of the control group were males. The sex composition of the two groups was not significantly different ($p = 0.7893$).

Fig – 3: MEAN FASTING BLOOD SUGAR IN CONTROL AND STUDY GROUP

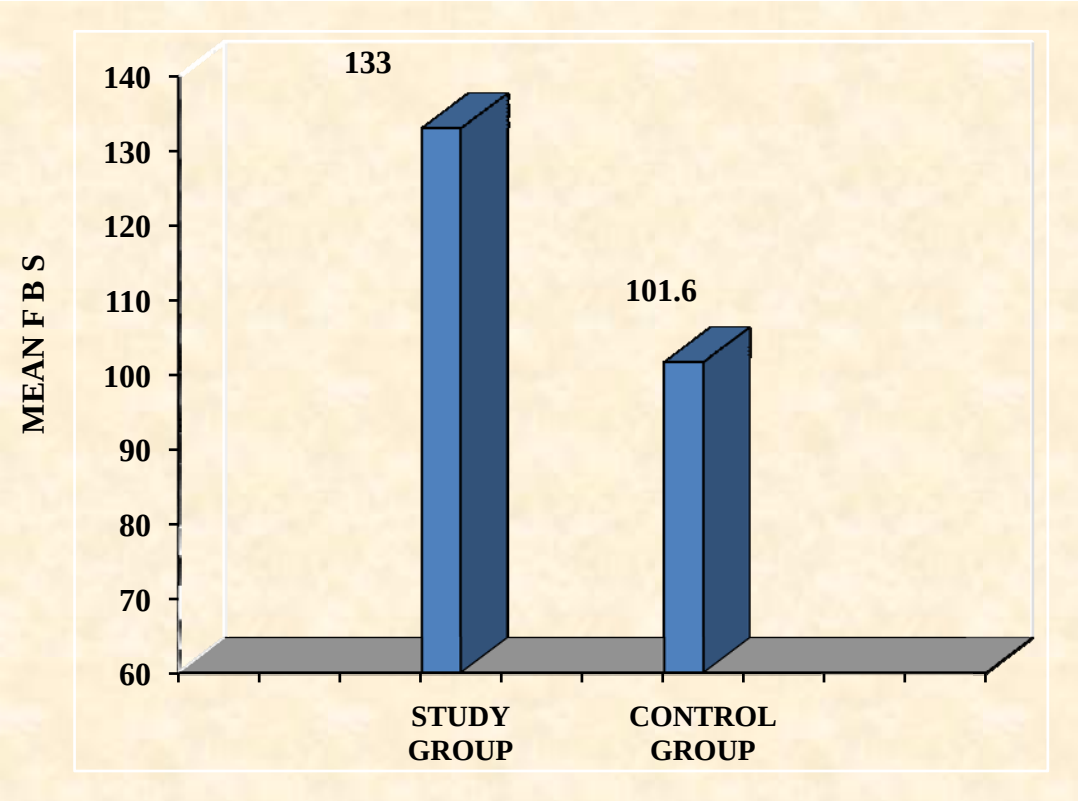


Table 3 : Fasting blood sugar in diabetics & control group

Fasting blood sugar	Cases in			
	Study group		Control group	
	No.	%	No.	%
Controlled	41	41	20	100
Uncontrolled	59	59	-	-
Total	100	100	20	100
Range	100-155 mg/dl		96-110 mg/dl	
Mean	133.0 mg/dl		101.6 mg/dl	
SD	13.6 mg/dl		3.9 mg/dl	
'p'	**0.0001 Significant**			

In the study group, the fasting blood sugar values were 133 $\pm$13.6 mg/dl. These values were significantly higher than the values of the control group (101.6$\pm$3.9).

Fig – 4: PREVALENCE OF HYPOMAGNESEMIA IN TYPE 2 DIABETES

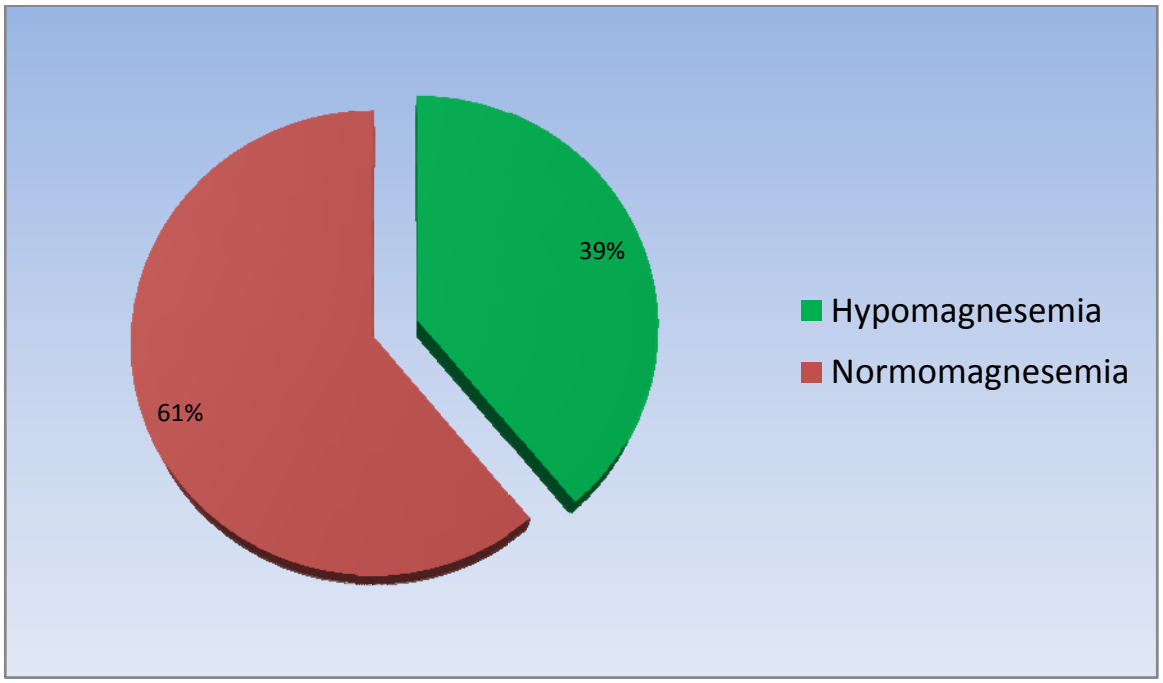


Table 4 : Magnesium levels in diabetic and control group

Magnesium	Cases in			
	Study group		Control group	
	No.	%	No.	%
Hypo magnesemia (< 1.3)	39	39	-	-
Normal (≥ 1.3)	61	61	20	100
Range	0.6-2.2		1.3 – 2.4	
Mean	1.42		1.94	
SD	0.37		0.27	
'p'	**0.0001** **Significant**			

The magnesium values of the diabetic group (1.42 ±0.37) and the control group (1.94 ±0.27) were statistically significant (p = 0.0001). In control group no hypomagnesemia was noticed .

Fig 5. CHARACTERISTICS OF STUDY GROUP

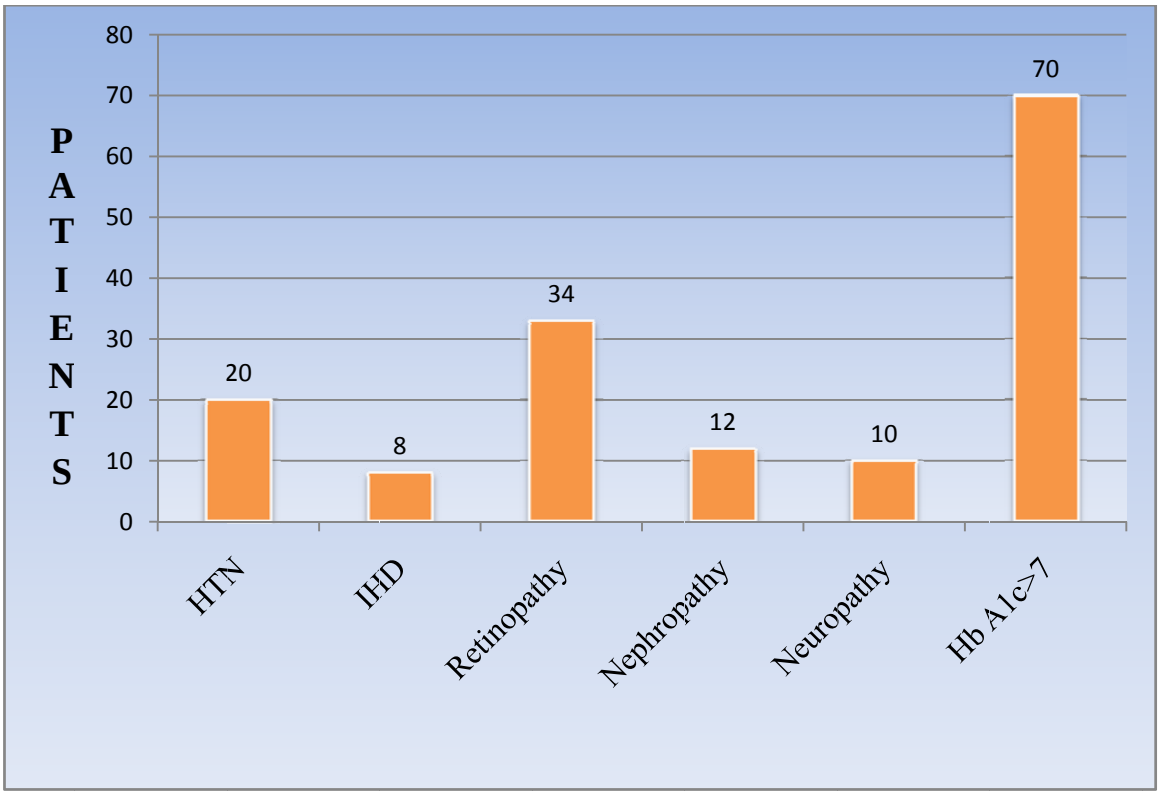
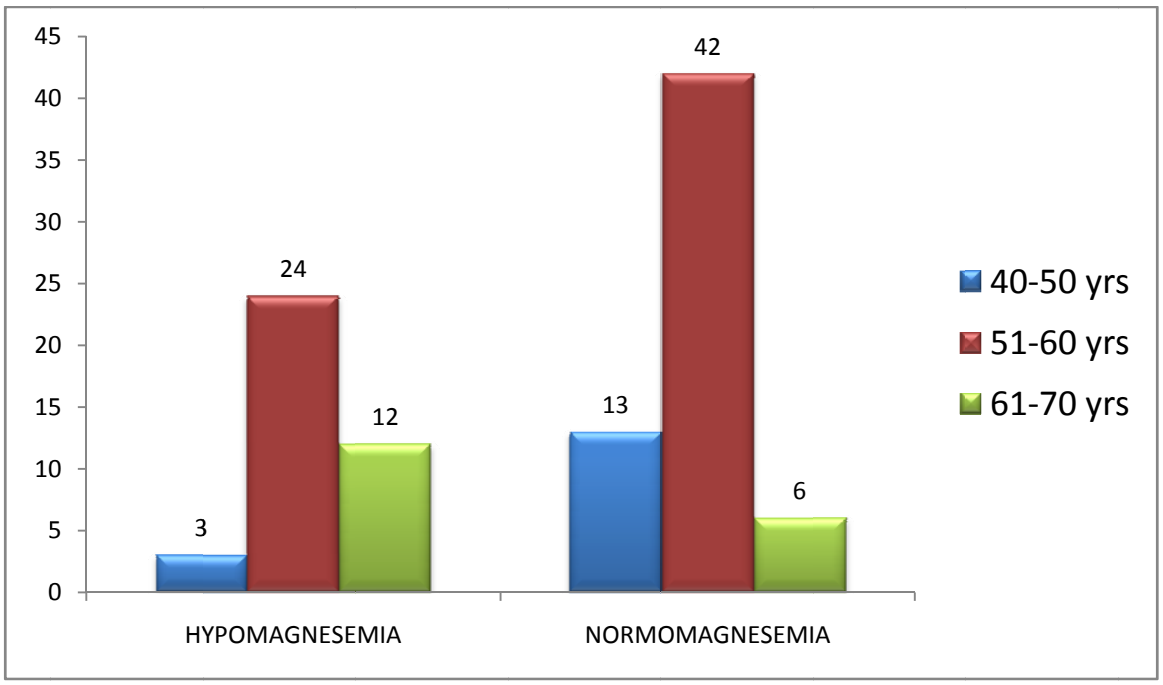


Table 5. Characteristics of study population

Characteristics	Numbers
No. Of subjects	100
Mean Age in years (range)	57.1 (40-70 years)
Males	61
Females	39
Mean Duration of diabetes in years(range)	6.25(3-15 years)
Medications	
OHA	90
OHA+Insulin	10
Comorbidity	
Hypertension	20
IHD	8
Diabetic complications	
NPDR	31
PDR	3
Diabetic nephropathy	
Micro albuminuria	10
Macro albuminuria	2
Diabetic neuropathy	10
Poor glycemic control (HbA1c > 7)	70

Fig –6 : AGE & SERUM MAGNESIUM IN DIABETES MELLITUS



B : RELATIONSHIP BETWEEN SERUM MAGNESIUM AND OTHER VARIABLE IN

DIABETIC (STUDY) CASES

Table 6 : Age and hypomagnesemia in DM cases

Age group	Magnesium				Mean ±SD
	Hypo		Normal		
	No.	%	No.	%	
40 – 50 years (16)	3	18.8	13	81.3	1.61 ±0.38
51-60 years (66)	24	36.4	42	63.6	1.43 ±0.37
61-70 years (18)	12	66.7	6	33.3	1.24 ±0.27
'p'	**0.177** **Not Significant**				

The relationship between age and incidence of hypomagnesemia in diabetic cases was statistically not significant ($p > 0.05$).

Fig -7 : SEX & SERUM MAGNESIUM IN DIABETES MELLITUS

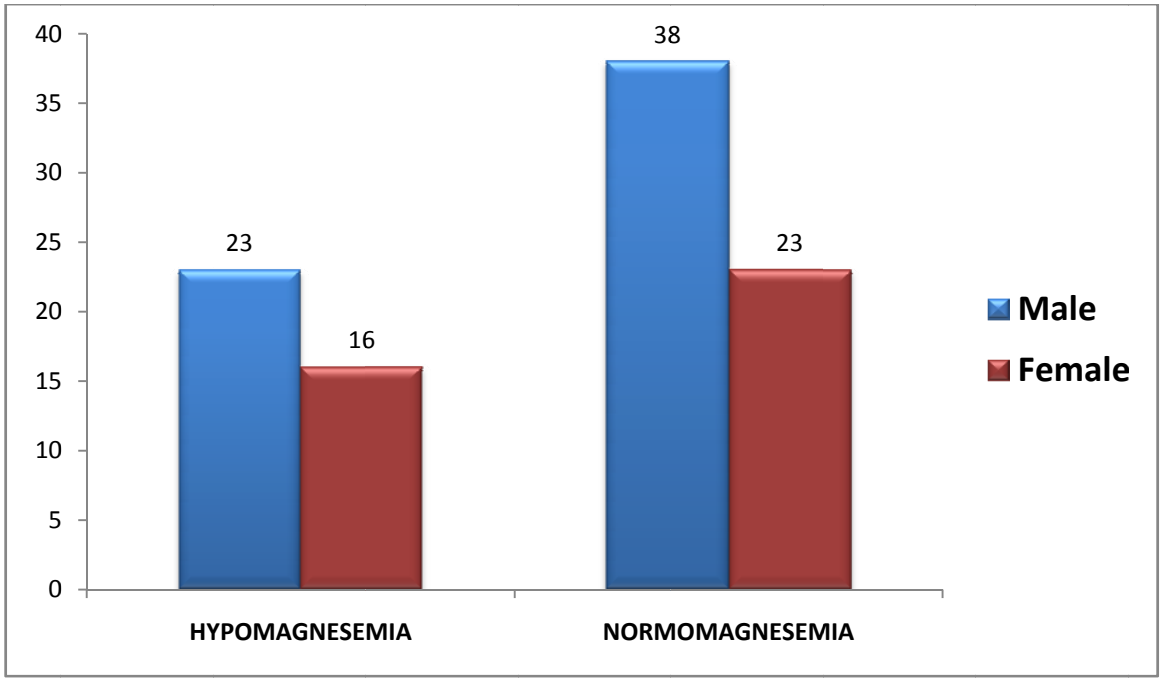


Table 7 : Sex and hypomagnesemia in diabetic cases

Sex	No. of cases	Magnesium				
		Hypo		Normal		Mean ±SD
		No.	%	No.	%	
Male	61	23	37.7	38	53.5	1.39 ±0.35
Female	39	16	41	23	79.3	1.47 ±0.35
'p'	**0.268** **Not Significant**					

Prevalence of hypomagnesemia in diabetic males and females were 23%&16% respectively.there is no statistical significance between sex of the patient and hypomagnesemia.

Fig -8: DURATION OF DIABETES AND MAGNESIUM

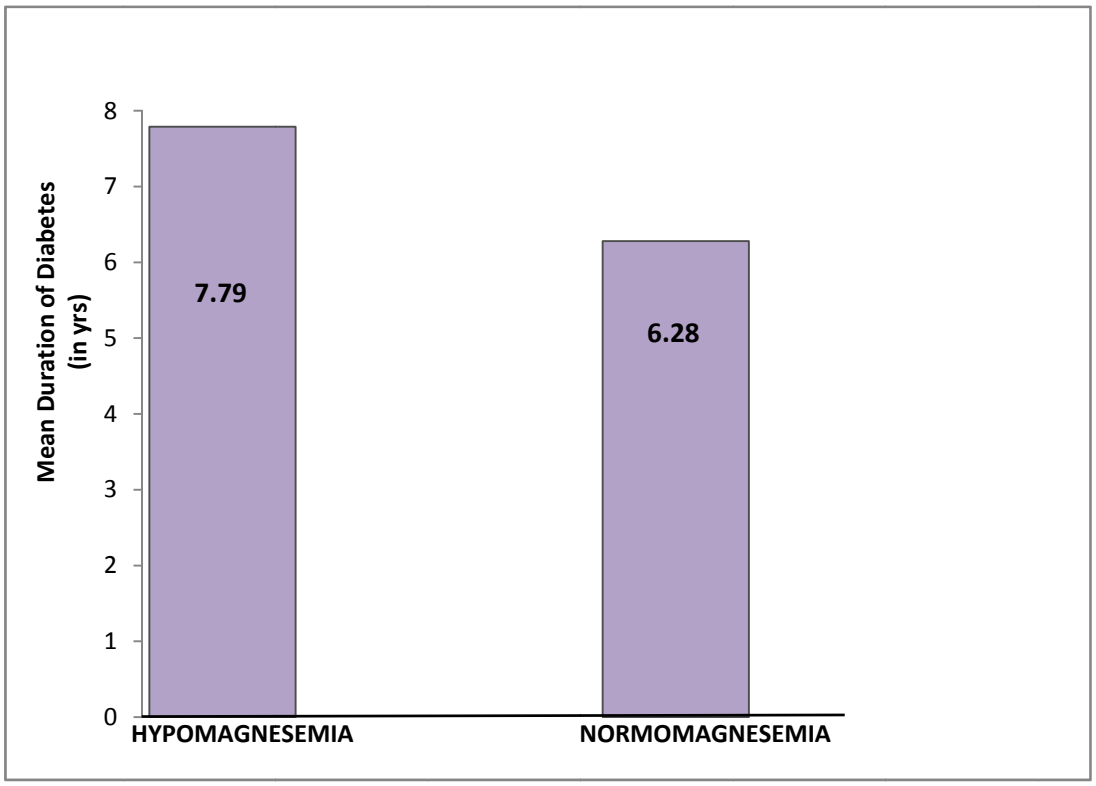


Fig – 9 : Mode Of Treatment And Hypomagnesemia

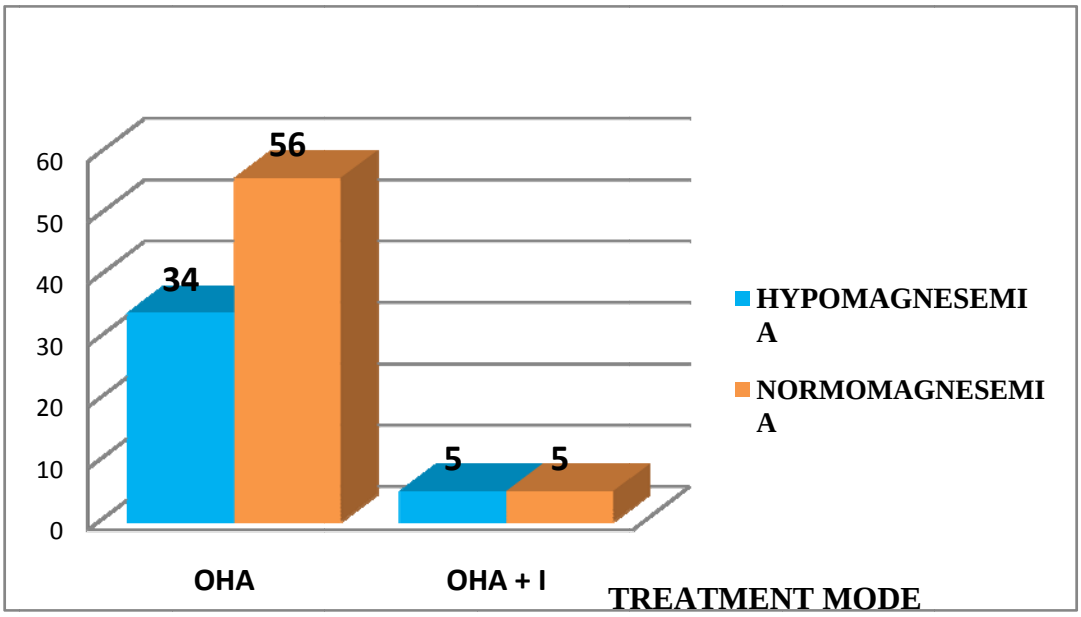


Table 8 : Duration of diabetes and magnesium

Magnesium levels	Duration of diabetes (years)	
	Mean	**SD**
Hypo magnesia	7.79	2.13
Normal cases	6.28	1.66
'p'	**0.0006** **Significant**	

Duration of diabetes was 7.79. ±2.13 years in hypomagnesemia cases and 6.25 ±1.66 years in cases with normal magnesium values. This difference was statistically significant (p = 0.0006).

Table 9 : Treatment and magnesium levels in diabetic cases

Treatment	No. of cases	Magnesium				
		Hypo <1.3mg		Normal		Mean ±SD
		No.	%	No.	%	
OHA	90	34	37.8	56	62.2	1.42 ±0.37
OHA + I	10	5	50	5	50	1.42 ±0.4
'p'	0.9028 Not significant					

There was no significant relationship between type of treatment given and prevalence of hypomagnesemia in diabetic cases. (p > 0.05).

Fig -10: SERUM MAGNESIUM & FASTING BLOOD SUGAR

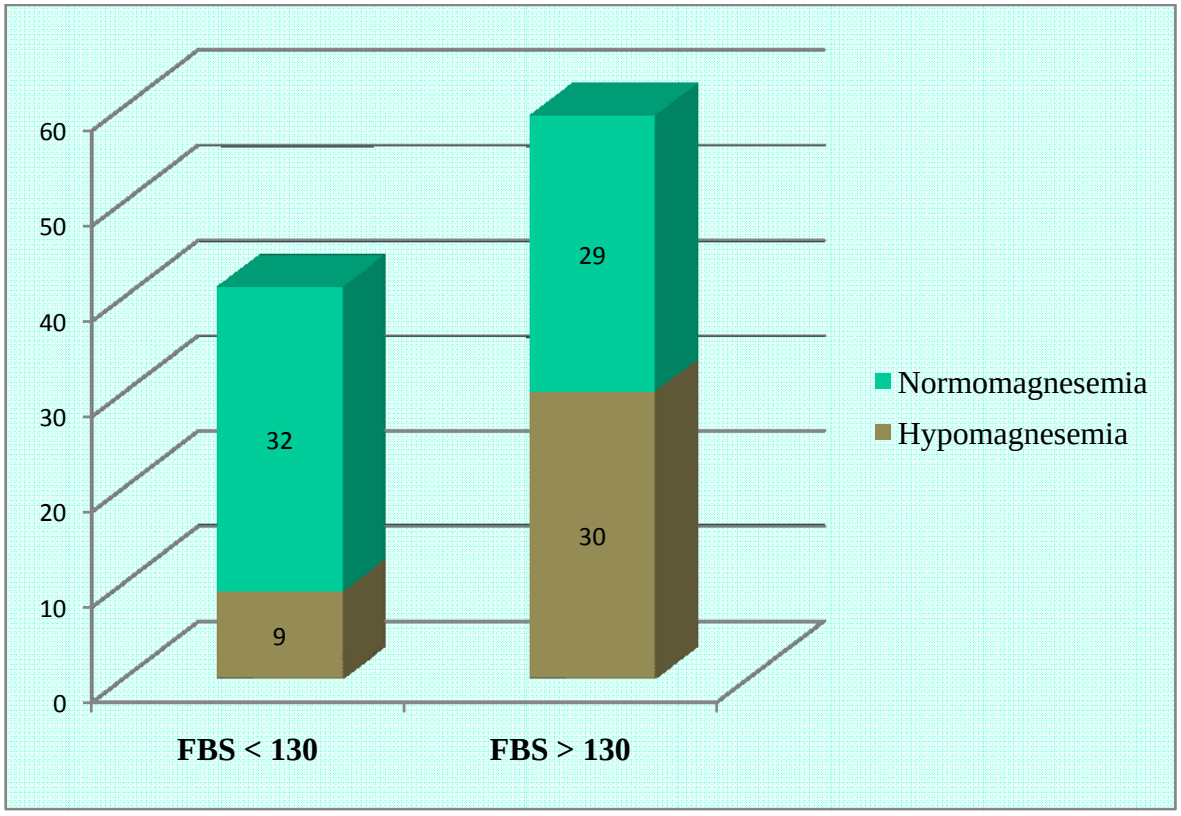


Fig – 11: Hb A1c & SERUM MAGNESIUM

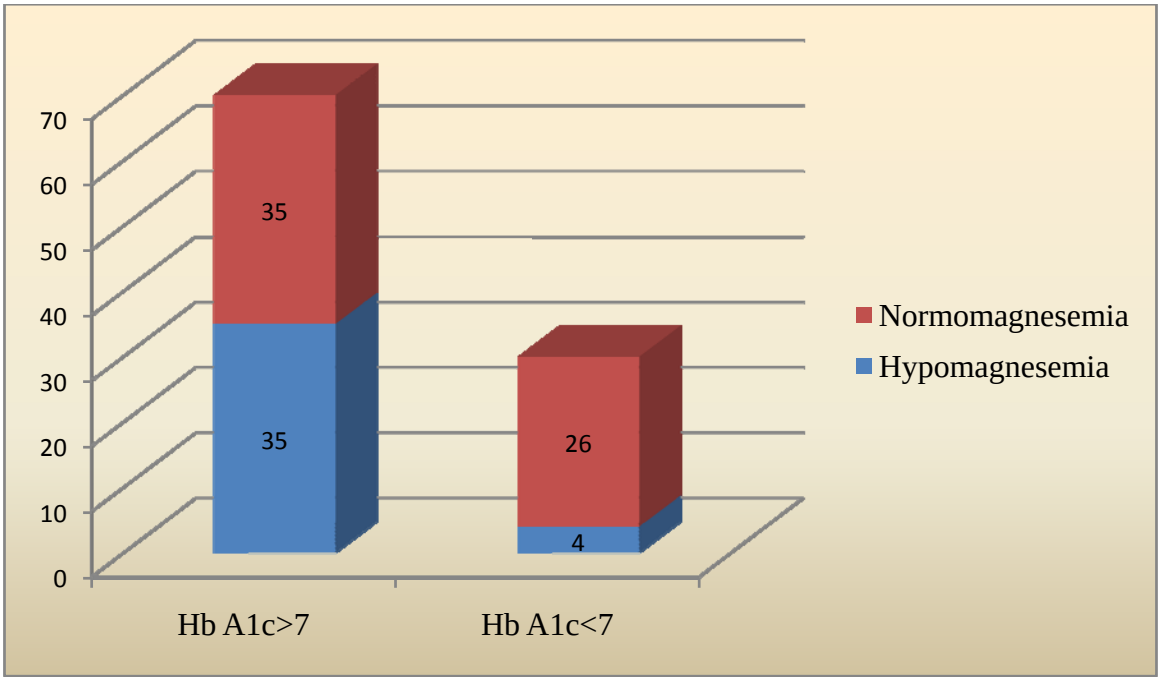


Table 10 : Relationship between fasting blood sugar and hypomagnesemia in diabetic cases

Fasting blood sugar	No.of cases	Magnesium			
		Hypomagnesmia <1.3mg /dl		Normal	
		No.	%	No.	%
Controlled(FBS<130)	41	9	22	32	78
Uncontrolled(FBS>130)	59	30	50.8	29	49.2
'p'		**0.0068 Significant**			

When fasting blood sugar was controlled, the incidence of hypomagnesemia was only 22% in diabetic cases. But when it was uncontrolled, this increased to 50.8%. This relationship was statistically significant ($p < 0.05$).

Table 11 : HbA1C values and hypomagnesemia in diabetic cases

HbA1C values	No.of cases	Magnesium			
		Hypo magnesemia <1.3mg / dl		Normal	
		No.	%	No.	%
Normal(HbA1c<7)	30	4	13.3	26	86.7
Abnormal(HbA1c>7)	70	35	50	35	50
'p'		**0.0013 Significant**			

Hypomagnesemia was present in 13.3% of cases with normal HbA1C values and in 50% of cases with abnormal HbA1C values. This was statistically significant ($p = 0.0013$).

Fig -12: ISCHEMIC HEART DISEASE AND HYPOMAGNESEMIA

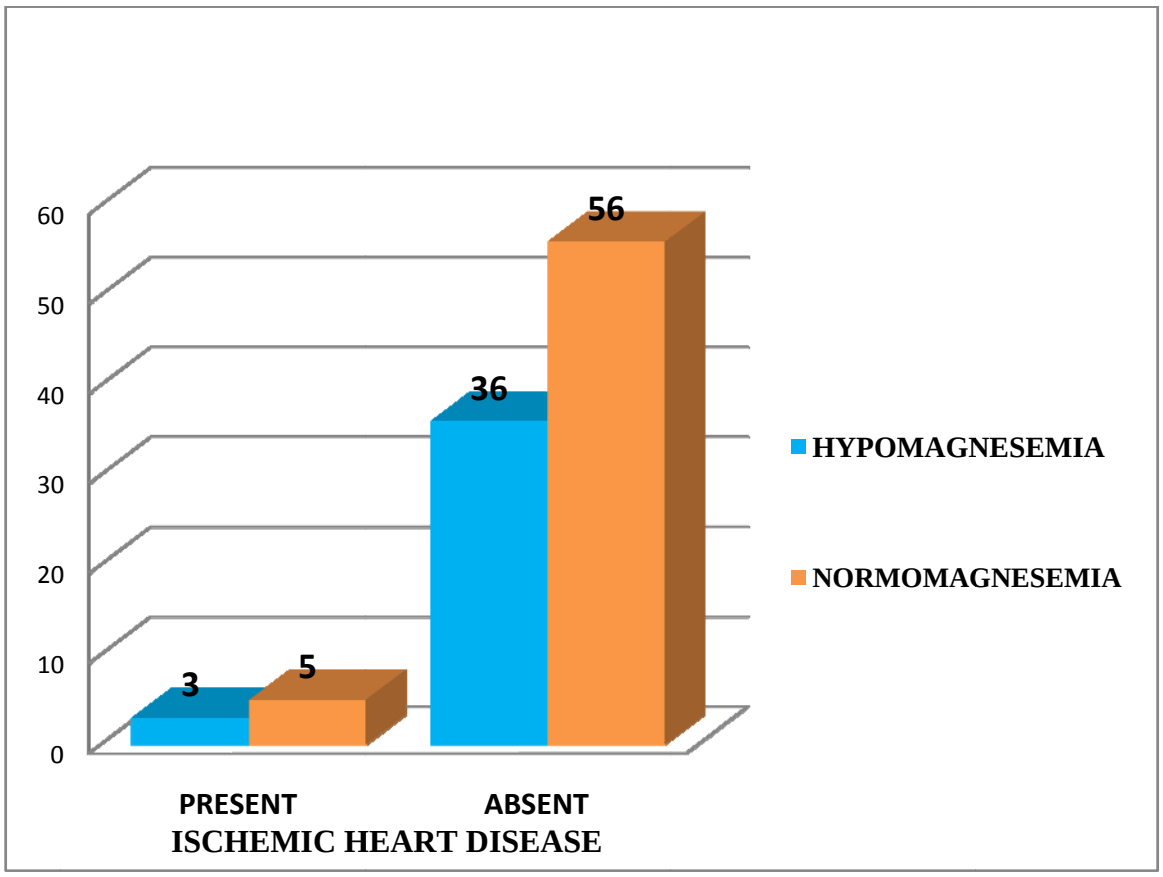


Table 12 : Ischemic Heart Disease and Magnesium in diabetic cases

IHD	No. of cases	Magnesium				
		Hypo		Normal		Mean ±SD
		No.	%	No.	%	
Present	8	3	37.5	5	62.5	1.4 ±0.33
Absent	92	36	39.1	56	60.9	1.43 ±0.37
'p'	0.9743 Not significant					

The association between incidence of IHD and hypomagnesemia was not statistically significant in diabetic cases (p = 0.9743).

Fig – 13: HYPERTENSION AND HYPOMAGNESEMIA

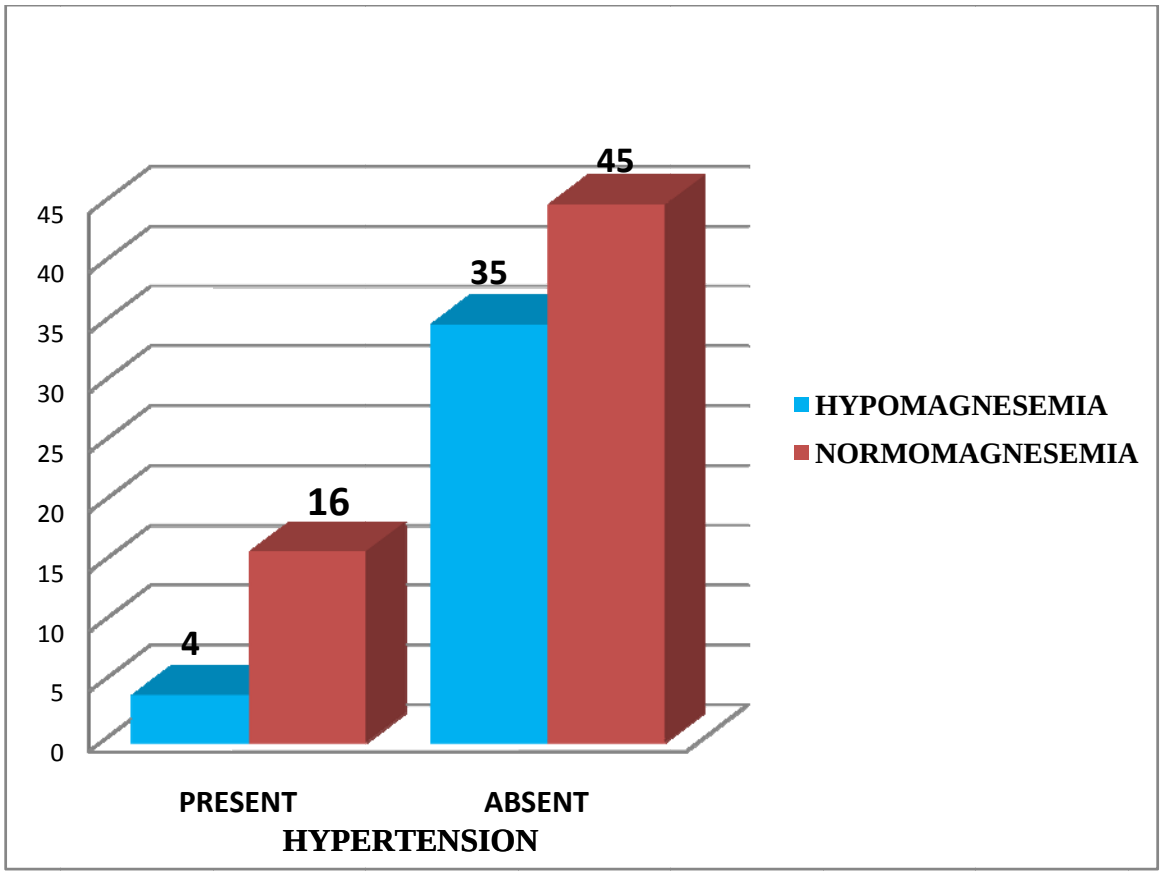


Table 13 : Hypertension and magnesium in diabetic cases

Hypertension	**No. of cases**	**Magnesium**				
		Hypo <1.3 mg /dl		**Normal**		**Mean ±SD**
		No.	**%**	**No.**	**%**	
Present	20	4	20	16	80	1.39 ±0.38
Absent	80	35	43.8	45	56.3	1.58 ±0.3
'p'	**0.22** **Not Significant**					

The relationship between hypertension and hypomagnesemia was statistically not significant (p = 0 .22)

Fig – 14: HYPOMAGNESEMIA AND DIABETIC RETINOPATHY

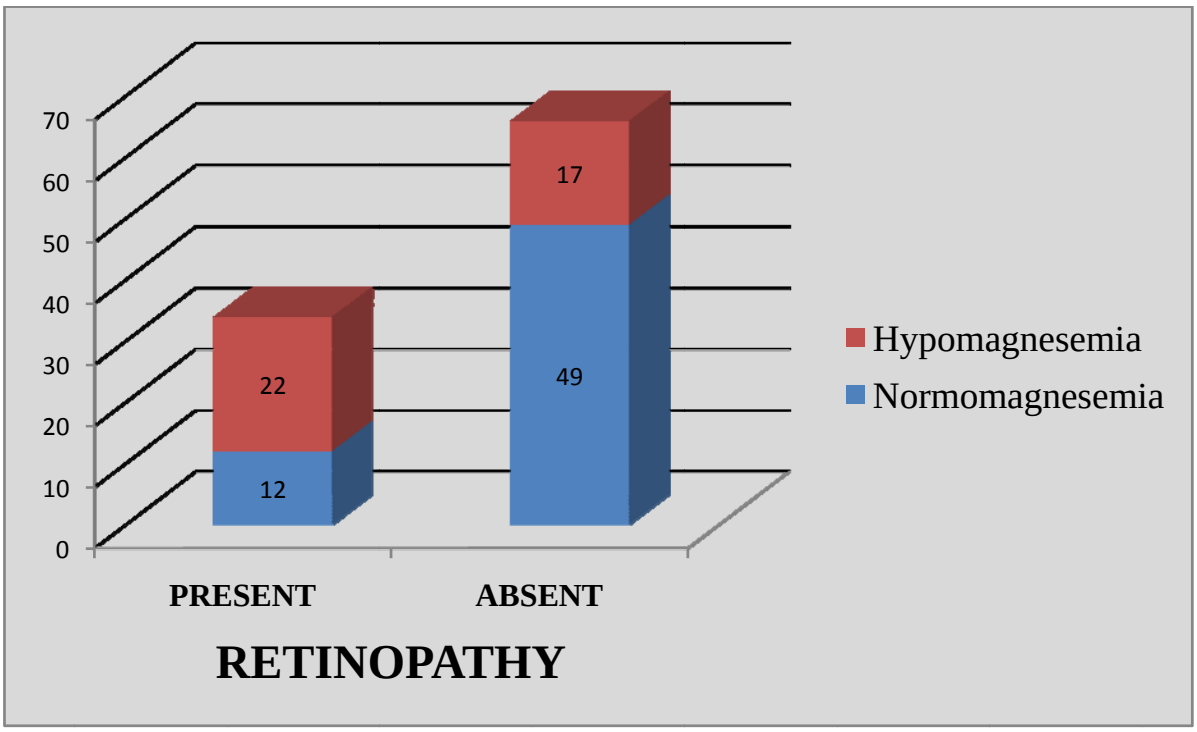


Table 14 : Retinopathy and magnesium in diabetic cases

Retinopathy	**No. of cases**	**Magnesium**				
		Hypo <1.3 mg /dl		**Normal**		**Mean ±SD**
		No.	**%**	**No.**	**%**	
Present (PDR -3 ; NPDR – 31)	34	22	64.7	12	35.3	1.22 ±0.31
Absent	66	17	25.8	49	74.2	1.53 ±0.36
'p'	**0.0001 Significant**					

Percentage of hypomagnesemia cases was 64.7% in diabetic cases with retinopathy and 25.8% in cases without retinopathy. This relationship was statistically significant.(p = 0.0001)

Fig -15: DIABETIC NEUROPATHY AND HYPOMAGNESEMIA

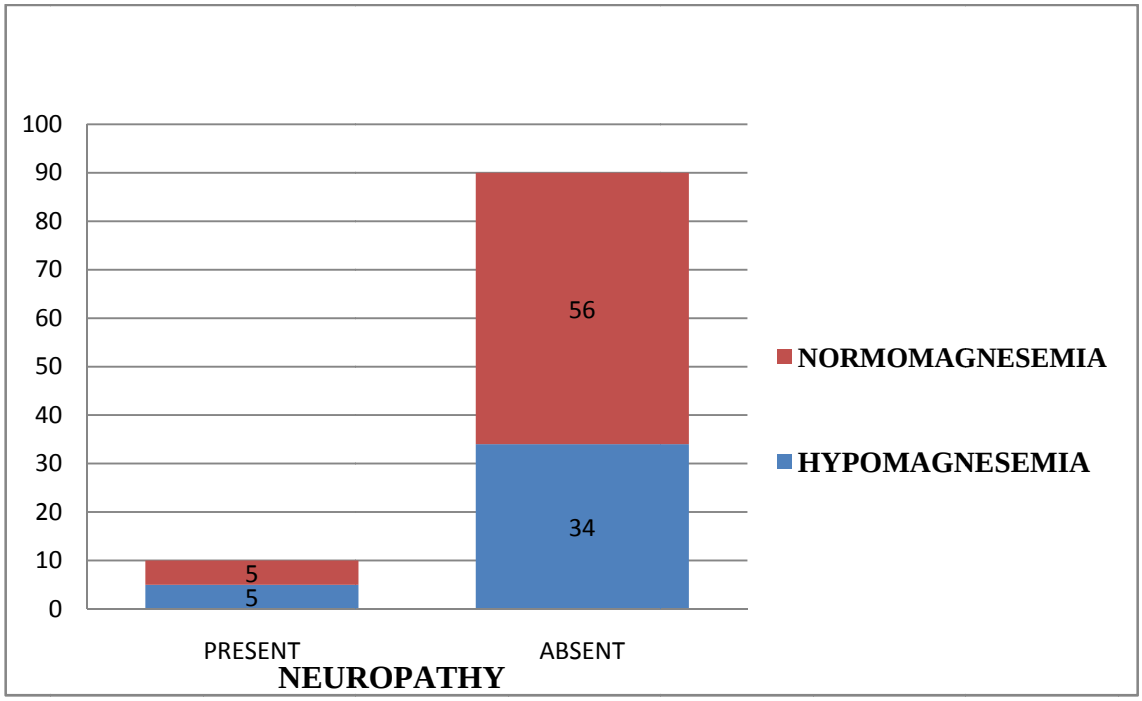


Fig – 16: DIABETIC NEPHROPATHY AND HYPOMAGNESEMIA

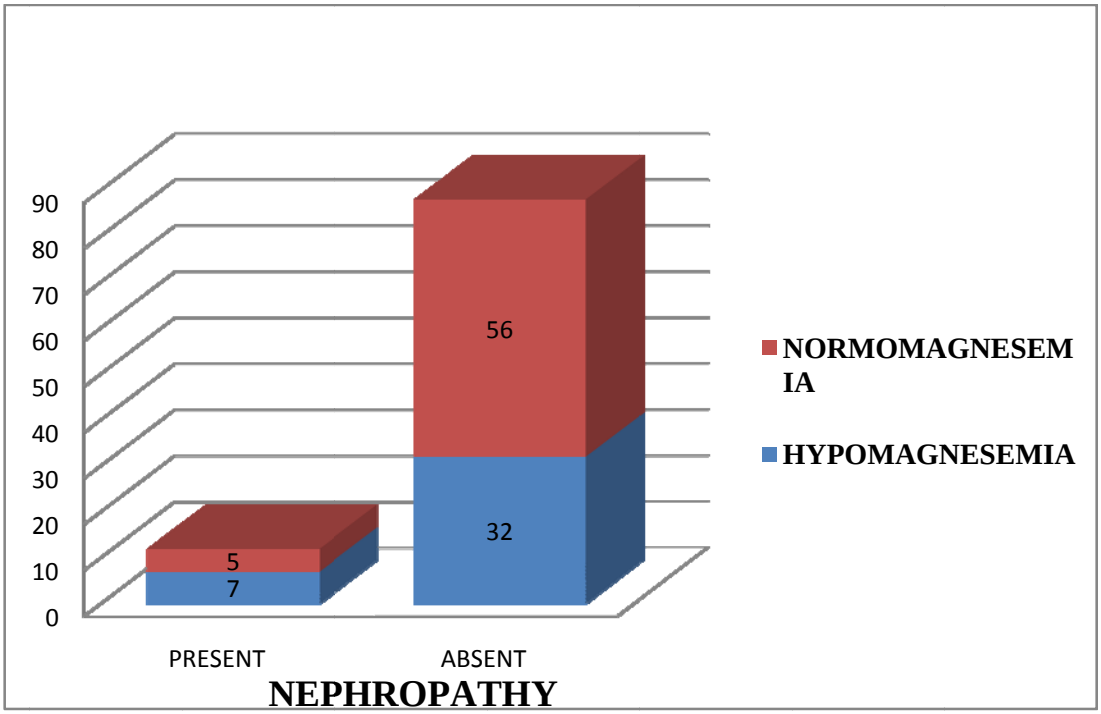


Table 15 : Neuropathy and magnesium in diabetic cases

Neuropathy	No. of cases	Magnesium				
		Hypo <1.3 mg /dl		Normal		Mean ±SD
		No.	%	No.	%	
Present	10	5	50	5	50	1.3 ±0.34
Absent	90	34	37.8	56	62.2	1.44 ± 0.37
'p'	0.2641 Not significant					

Relationship between incidence of neuropathy and hypomagnesemia was not statistically significant. (p = 0.2641).

Table 16 : Nephropathy and magnesium in diabetic cases

Nephropathy	No. of cases	Magnesium				
		Hypo <1.3 mg /dl		Normal		Mean ±SD
		No.	%	No.	%	
Present	12	7	58.3	5	41.7	1.29± 0.38
Absent	88	32	36.4	56	63.6	1.44 ±0.37
'p'	0.2129 Not significant					

Among 12 patients 10 patients had microalbuminuria 2 patients had macroalbuminuria There was no significant association between nephropathy and hypo magnesia in diabetic cases. (p = 0.2129).

DISCUSSION

Reported high prevalence of low plasma magnesium concentrations among diabetic subjects and possible association of hypomagnesemia with diabetic complications prompted this study.

Marked magnesium deficiency has been reported in the previous studies in patients with type-2 diabetes.[5,7] However, some workers have also reported normal and even high levels.[62] In the present study, prevalence of serum magnesium concentrations in type 2 diabetes patients was 39%. This confirms to the reported prevalence of low plasma magnesium status in type-2 diabetics in several studies, which ranged from 25 to 39%. Prevalence of hypomagnesemia in type – 2 diabetics in our study was similar to that reported by Nadler et al.[5] in type 2 diabetics attending outpatient clinics in the US. Walti MK et al.[64] also reported a prevalence of hypomagnesemia in type 2 diabetics at 37.6% versus 10.9% in nondiabetic controls in a study conducted in Zurich, Switzerland. The reasons for the high prevalence of magnesium deficiency in diabetes are not clear, but may include increased urinary loss, lower dietary intake, or impaired absorption of magnesium compared to healthy individuals. Several studies have reported increased urinary magnesium excretion in type 1

and type 2 diabetes.[7, 75] Recently a specific tubular defect in magnesium reabsorption in thick ascending loop of Henle is postulated.

This defect results in reduction in tubular reabsorption of magnesium and consequently hypomagnesemia. The reason for this tubular defect in diabetics in unclear. Insulin treatment has been shown to correct renal magnesium loss in diabetics. Low dietary intake is an unlikely cause of impaired magnesium status in diabetes. A dietary assessment conducted in Europe showed that only 5.4% of the diabetic group and 9.1% of the control group had intakes of magnesium below their individual requirements.[77] In addition, recently it has been shown that type 2 diabetics in reasonable metabolic control absorb dietary magnesium to a similar extent as healthy controls. Increased urinary magnesium excretion due to hyperglycemia and osmotic diuresis may contribute to hypomagnesemia in diabetes.

Serum levels of magnesium have been found by several investigators to correlate inversely with fasting blood glucose concentration[62,63] and the percentage of HbA1C.[62]

- Schlienger et al.[7] studied the influence of glycemic control (glycemic control evaluated by HbA1C) on various trace elements and reported significantly reduced plasma magnesium levels in patients with poor control of diabetes.

The study published in the Journal of Clinical Nutrition indicates that adequate levels of magnesium is closely related to normal level of blood sugar since the mineral has an important role in the good functioning of the insulin receptors found in the cells.[74] In this study, researchers from the University of Sao Paulo measured blood sugar and levels of magnesium of 51 patients who were being treated for type 2 diabetes. They found that 77 percent of the participants in the study had a deficiency of magnesium. They also found that there was a inverse relationship between the level of magnesium and the level of glucose.

The present study revealed statistically significant (‘P’=0.0068 &’P’=0.0013) correlation between serum magnesium levels and fasting blood sugar and HbA1C. Patients with poor glycemic parameters (FBS>130 mg/dl or HbA1c>7%) had a significantly higher prevalence of hypomagnesemia (50.8 & 50%) compared to overall prevalence in diabetics(39%).

Hypomagnesemia is reported to be both a cause and result of poor glycemic control. Magnesium is a cofactor in both glucose transporting mechanisms of cell membrane and various enzymes important in carbohydrate oxidation.[4] In addition, magnesium deficiency has been shown to promote insulin resistance in multiple studies. Nadler et al.[8] have reported that insulin sensitivity decreases even in nondiabetic individuals after induction of magnesium deficiency. Like wise, elderly subjects were shown to have improved glucose tolerance when they received magnesium supplements. Thus hypomagnesemia by itself results in poor glycemic control. Conversely, hyperglycemia and osmotic diuresis may lead to increased urinary magnesium excretion and hypomagnesemia in diabetics. However, high prevalence of hypomagnesemia have also been reported in type – 2 diabetics with good glycemic control.[5]

Sex, age and duration of diabetes were not the significant predictors of serum magnesium levels. Yajnick et al.[62] in 1984 reported that among diabetics plasma magnesium concentration was directly related to age and men had significantly higher concentrations than women. The increasing magnesium levels with age were probably due to impaired renal function and the sample size, (87 diabetics, 30 non diabetics) was relatively small to confirm male

preponderance. In our study, patients with impaired renal functions were excluded. Our results confirm to the recent reports that have not shown any significant associations between sex and age but duration of diabetes inversly correlates with serum magnesium levels. Duration of diabetic was 7.79±2.13meanyears in hypomagnesemia group where as 6.25±1.6 years in cases with normal magnesium.

Yajnik et al.[62] reported that insulin treated diabetics have significantly lower serum magnesium levels compared to non insulin treated ones. In that study prevalence of hypomagnesemia in insulin treated diabetics was higher than in noninsulin treated (32.2% v/s 30.4%). However, the difference was statistically not significant. Walti MK et al[77] have reported that diabetes treatment (insulin or OHA) did not significantly predict hypomagnesemia. Redistribution of magnesium from plasma in to red blood cells is caused by insulin. In a recent study Alzaida et al.[63] have found that cellular uptake of magnesium is normally stimulated by insulin. So insulin treatment may enhance cellular magnesium uptake and result in increased prevalence of hypomagnesemia.In present study there was no patient treated with Insulin alone and so the significance could not be determined.

In the present study, no correlation was found between incidence of ischemic heart disease and hypomagnesemia. However, several observational studies have associated lower serum levels of serum magnesium with higher risk of coronary artery disease. As part of Atherosclerosis risk in communities study, a cohort of 15,792 subjects were studied over 7 years and an increasing relative risk of coronary artery disease with decreasing serum magnesium was reported.[80] How a low serum magnesium predisposes to coronary artery diseases is not known. However, in the present study, no difference in prevalence of hypomagnesemia was found between those with ischemic heart disease and others. Similarly, no difference in prevalence of hypomagnesemia was found between the hypertensive and non hypertensive subjects.

Previously magnesium deficiency has been found to be associated with diabetic microvascular disease. In the present study too significantly higher prevalence of hypomagnesemia was observed in diabetics with microvascular complications and mean serum concentration of magnesium in diabetics with microvascular complications was comparatively lower than in diabetics with no microvascular complications.

Hypomagnesemia has been reported in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe

diabetic retinopathy.[10] Our observations revealed a definite association between diabetic retinopathy and lower serum magnesium levels. There was a significant difference in prevalence of hypomagnesemia in diabetics with retinopathy and without retinopathy (64.5% vs 25.8%; P< 0.0001). These observations are similar to other reports. The mechanism by which hypomagnesemia predisposes to diabetic retinopathy is not clear. Grafton et al.[4] have proposed the inositol transport theory to explain this association. But the exact reason remains obscure.

With reference to other diabetic microangiopathies, no significant association was found between prevalence of hypomagnesemia, diabetic neuropathy and diabetic nephropathy. . The patients with diabetic nephropathy(58.3%) had a slightly higher prevalence of hypomagnesemia compared to those with neuropathy(50%).But the difference was statistically insignificant. Even within the nephropathy group, no difference was found between patients with microalbuminuria and macroalbuminuria. These results are similar to those reported by Pickup et al.[77] who found no difference in serum magnesium concentrations between diabetics with microalbuminuria or clinical proteinuria compared to diabetics with normal albumin excretion.

In contrast, Corsonello, et al demonstrated significantly lower serum magnesium in type 2 diabetics with nephropathy compared to a normoalbuminemic group. They argued that in diabetics with nephropathy, serum magnesium might be reduced because of lower serum albumin concentration, as 30% of serum magnesium is bound to proteins, mainly albumin.

In summary, the present study has demonstrated that hypomagnesemia is common in type 2 diabetics and magnesium deficiency is conclusively associated with diabetic retinopathy. So it may be prudent to consider Magnesium Deficiency as a contributing factor in many Diabetic Complications and in the Exacerbation of the disease itself.

CONCLUSION

1. Prevalence of hypomagnesemia in type 2 diabetes is 39%.
2. Hypomagnesemia has significant association with glycemic control which was reflected in uncontrolled fasting blood sugar (FBS >130 mg%) and Hb A1C >7 (p value 0.0068) & (p value0.0013) respectively.
3. Hypomagnesemia have no significant relation with age, sex and treatment mode of the diabetic patients but it has significant association with duration of diabetes.
4. Hypomagnesemia is significantly associated with diabetic retinopathy (p value 0.0001).
5. No significant association between other diabetic microangiopathies (nephropathy and neuropathy) and diabetic comorbidities – ischemic heart disease and hypertension.

LIMITATION OF STUDY

- Study can be extended to large population.
- Study can be carried out in Type 1 diabetic patients .
- Correlation of Hypomagnesemia & dyslipedemia in diabetes can be studied because dyslipedemia is commonly associated diabetes.

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PROFORMA

Serial No. :

Patient Details

Name :

Hospital No. :

Age /Sex :

Occupation :

Diabetic History

Age of onset :

Total Duration :

Mode of Treatment : OHA/I/OHA+I

Symptoms Related to Complications

A) Symptoms of Neuropathy

- Postural dizziness
- Numbness/parasthesia /weakness/Pain/hyperaesthesia
- Bladder incontinence/Impotence

B) Symptoms of Nephropathy - Oliguria /Oedema

C) Symptoms of Retinopathy - Dimness of vision /Blindness

Past History : IHD/ HTN

Family History: DM / IHD/ HTN

Examination

Height : Weight :

General Examination:

Pulse Rate: Icterus : Cyanosis: Clubbing: Lymph Nodes: Edema:

BP: Supine: Standing:

A. Sensory motor Neuropathy

- Loss of pain and temperature/touch /position and vibration sense
- Rhomberg test

B. Proximal Muscle Neuropathy

- Wasting /Power/Tone
- Knee jerk /Ankle jerk

C. Eye Signs

- Diabetic retionopathy : Non Proliferative / Proliferative

D. Signs of nephropathy - Oedema / Facial puffiness

Investigations

1. FBS: HbA1C :
2. Serum Magnesium:
3. 24 hour albuminiuria:
4. Serum: Creatinine:
5. Routine Urine:Sugar:/Protein/Microscopy:
6. ECG/ Echocardiogram:
7. Direct opthalmoscopy :

LIST OF ABBREVIATIONS

DM	-	Diabetes Mellitus
FBS	-	Fasting Blood Sugar
GDM	-	Gestational Diabetes Mellitus
HbA1C	-	Glycosylated Haemoglobin
HTN	-	Hypertension
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
NIDDM	-	Non-Insulin Dependent Diabetes Mellitus
OGTT	-	Oral Glucose Tolerance Test
UKPDS	-	United Kingdom Prospective Diabetes Study
IHD	-	Ischemic Heart Disease
TRPM6	-	Transient Receptor Potential channel Melastatin 6
HTN	-	Hypertension
PDR	-	Proliferative diabetic retinopathy
NPDR	-	Non proliferative diabetic retinopathy
SrMg	-	Serum maganesium

MASTER CHART

No	AGE	sex	DURATION	TREATMENT	IHD	HTN	RETINOPATHY	NEUROPATHY	NEPHROPATHY	FBS in mg %	HbA1c	Sr.Mg. in mg
1	60	M	10	OHA + I	-	---	NPDR	-	-	140	8.5	1
2	55	F	7	OHA	-	-	-	-	-	135	7.2	1
3	59	M	8	OHA	-	-	NPDR	-	-	138	7.6	1.4
4	46	M	4	OHA	-	-	-	-	-	110	6.8	1.5
5	50	F	7	OHA	-	-	NPDR	-	-	150	8.6	0.9
6	66	F	8	OHA+ I	-	-	NPDR	+	MICROALBUM+	130	7	1.5
7	55	F	5	OHA	-	-	-	-	-	130	7	1.2
8	58	M	7	OHA	-	+	-	-	-	135	7.6	1.6
9	57	M	6	OHA	-	+	-	-	-	130	7.5	1.5
10	70	M	10	OHA	-	-	PDR	-	-	155	9	1.2
11	50	F	4	OHA	-	-	-	-	-	138	7.2	1.6
12	43	F	3	OHA	-	-	-	-	-	100	6.5	2
13	60	M	7	OHA + I	-	-	NPDR	-	-	135	7	1.5
14	54	M	6	OHA	-	-	-	-	-	145	8	0.9
15	58	F	7	OHA	-	+	-	-	-	110	6.5	1.5
16	48	F	4	OHA	-	-	-	-	-	128	7	2.2
17	65	M	10	OHA	-	-	NPDR	+	MICROALBUM+	145	8	1
18	66	M	10	OHA	+	-	-	-	-	117	6.8	1.5
19	55	F	7	OHA	-	-	-	-	-	148	8	1
20	59	M	8	OHA + I	-	-	NPDR	-	-	150	8	0.9
21	60	M	7	OHA	-	-	NPDR	-	-	143	7.5	1
22	48	F	4	OHA	-	-	-	-	-	142	7.8	1.7
23	52	M	6	OHA	-	-	-	-	-	146	8	1.2
24	54	F	6	OHA	-	-	-	-	-	150	8.5	1.6
25	57	F	7	OHA	-	-	NPDR	-	-	140	8	1
26	55	M	6	OHA	-	-	-	-	-	135	7.5	1.5

27	65	M	8	OHA	+	-	-	-	-	126	7	1.5
28	67	M	9	OHA	-	+	-	-	-	140	7.3	1.2
29	56	F	7	OHA + I	-	-	-	+	-	133	7	1.7
30	60	F	8	OHA	-	-	NPDR	+	-	138	7.4	1
31	66	F	12	OHA	-	-	NPDR	-	-	148	8.2	1
32	63	M	10	OHA	-	-	NPDR	-	-	145	8	1.5
33	58	M	8	OHA	-	+	-	-	-	124	7	2.2
34	55	M	7	OHA	-	+	-	-	MICROALBUM+	110	6.8	1.8
35	70	F	15	OHA	-	-	PDR	+	MICROALBUM+	150	8.6	0.9
36	53	F	5	OHA	-	-	-	-	-	110	7	1.7
37	60	M	7	OHA	-	+	-	+	-	140	7.8	1.5
38	54	M	5	OHA	-	+	-	-	-	136	7.2	2
39	60	M	6	OHA	+	+	-	-	-	128	7	0.6
40	58	M	7	OHA	+	+	-	-	-	124	7	1.2
41	50	F	4	OHA	-	-	-	-	-	100	7	2
42	56	F	5	OHA	-	-	-	-	-	105	7	1.9
43	60	M	10	OHA + I	-	-	NPDR	-	-	128	7.2	1.6
44	58	M	7	OHA	-	-	-	-	-	140	7.5	1.8
45	50	M	6	OHA	-	-	-	-	-	110	7	1.5
46	66	M	10	OHA	-	-	NPDR	-	-	138	7.4	1
47	55	M	5	OHA	-	-	NPDR	-	-	132	7	1.7
48	58	F	7	OHA	-	+	-	-	-	133	7	1.5
49	55	F	6	OHA	-	-	-	-	-	150	8.4	0.9
50	52	M	5	OHA	-	-	-	-	-	136	7.2	1.5
51	55	M	7	OHA + I	-	+	-	-	-	124	7	1.7
52	65	M	9	OHA + I	-	+	-	-	-	143	8	1
53	57	M	6	OHA	+	+	-	-	-	123	7	1.5
54	60	F	8	OHA	-	-	NPDR	-	-	130	7.2	1.6

55	54	F	5	OHA	-	-	-	-	-	136	7.5	1.4
56	58	M	7	OHA	-	+	-	-	-	145	8	1.5
57	48	F	4	OHA	-	-	-	-	-	130	7.2	1.6
58	62	M	7	OHA	-	-	NPDR	-	-	128	7.5	1.8
59	57	M	7	OHA + I	-	-	NPDR	-	-	140	7.5	1
60	55	F	7	OHA	-	+	-	-	-	113	6.8	1.2
61	50	F	4	OHA	-	-	-	-	-	155	8.3	1.7
62	43	F	3	OHA	-	-	-	-	-	145	8	1.5
63	58	F	7	OHA	+	+	-	-	-	118	7	1.5
64	60	M	8	OHA	-	-	NPDR	-	-	130	7.2	0.9
65	56	F	5	OHA	-	-	-	-	-	110	7.5	2.2
66	55	M	6	OHA	-	+	-	-	-	110	7.3	1
67	65	F	8	OHA	-	-	NPDR	-	-	128	7.5	1.2
68	70	M	10	OHA	-	-	PDR	-	-	135	7.8	1
69	58	M	7	OHA	-	-	-	-	-	140	8	1
70	56	M	7	OHA	-	-	-	-	-	136	7.2	1.2
71	50	M	5	OHA	-	-	-	-	-	110	6.8	1.5
72	56	F	6	OHA	-	-	NPDR	+	MICROALBUM+	135	7.2	1.9
73	45	F	5	OHA	-	-	-	-	-	100	7	1.7
74	54	M	6	OHA	-	-	-	-	-	100	6.5	2
75	65	F	8	OHA	-	-	NPDR	-	MACROALBUM+	130	7.2	1.1
76	48	F	4	OHA	-	-	-	-	-	128	6.8	2.2
77	55	M	10	OHA	+	-	NPDR	+	-	145	8	1
78	58	M	7	OHA	-	-	-	-	-	145	8	2
79	59	M	8	OHA	-	-	NPDR	-	MACROALBUM+	126	7	1.5
80	55	M	7	OHA	-	-	-	-	-	148	8	1.5
81	60	M	8	OHA	-	-	-	-	-	136	8.2	1.7
82	65	M	8	OHA	-	+	NPDR	-	MICROALBUM+	140	8.3	1

83	56	M	6	OHA	-	-	-	-	-	140	7.5	1.4
84	59	M	8	OHA	-	-	-	-	-	145	7.9	1.6
85	57	M	5	OHA	-	-	-	-	-	130	7.2	1.8
86	60	F	7	OHA	-	-	-	-	-	130	7.2	1.7
87	48	F	4	OHA	-	-	-	-	-	140	7.8	1.2
88	65	M	8	OHA	-	+	NPDR	-	MICROALBUM+	145	8	1.2
89	58	M	8	OHA	-	-	NPDR	+	-	130	7	1.5
90	55	F	6	OHA	-	-	-	-	-	145	7.9	1
91	60	M	7	OHA	-	-	-	-	-	145	8	1.5
92	60	M	7	OHA	-	-	-	-	-	150	8	1.5
93	65	M	8	OHA	-	-	-	-	-	135	7.5	1.7
94	55	M	5	OHA	-	-	-	-	-	110	7.5	2.2
95	60	M	10	OHA	+	-	NPDR	+	MICROALBUM+	145	8	1
96	48	F	4	OHA	-	-	-	-	-	155	8.3	1.7
97	54	M	8	OHA + I	-	-	NPDR	-	-	130	7.5	1
98	60	M	8	OHA	-	-	NPDR	-	MICROALBUM+	136	7.5	0.9
99	55	F	6	OHA	-	-	NPDR	-	MICROALBUM+	148	7.8	1.2
100	54	M	5	OHA	-	-	-	-	-	130	7.2	1.5

CONTROL GROUP

No	AGE	SEX	FBS	HbA1c	Sr.Mg.	HTN	IHD	RETINOPATHY	NEUROPATHY	NEPHROPATHY		
1	54	M	107	6.2	1.7	-	-	-	-	-		
2	45	M	96	6.5	2.2	-	-	-	-	-		
3	48	F	105	6.3	1.8	-	-	-	-	-		
4	60	M	98	6.9	2	-	-	-	-	-		
5	48	M	100	5.9	1.9	-	-	-	-	-		
6	46	F	100	6.7	1.5	-	-	-	-	-		
7	61	F	102	6.1	2.1	-	-	-	-	-		

8	55	M	102	5.5	2.4	-	-	-	-	-		
9	58	M	110	6	1.9	-	-	-	-	-		
10	49	M	98	5.8	1.7	-	-	-	-	-		
11	43	F	102	5.3	2.2	-	-	-	-	-		
12	59	M	101	6.2	2	-	-	-	-	-		
13	60	M	106	6.3	1.8	-	-	-	-	-		
14	67	F	100	7	1.3	-	-	-	-	-		
15	53	M	98	6.7	2.3	-	-	-	-	-		
16	64	M	97	6.6	2.1	-	-	-	-	-		
17	57	F	103	5.7	1.9	-	-	-	-	-		
18	56	M	108	6	1.8	-	-	-	-	-		
19	61	F	101	6.2	2.2	-	-	-	-	-		
20	53	M	98	6.3	2	-	-	-	-	-		