A Dissertation on

A STUDY OF FASTING SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS AND ITS CORRELATION WITH ITS COMPLICATIONS

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CERTIFICATE

This is to certify that this dissertation entitled **" A STUDY OF FASTING SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS AND CORRELATION WITH ITS COMPLICATIONS "** submitted by **DR.R.PANDICHELVAN** to the Tamil Nadu Dr.MGR Medical University is in partial fulfillment of the requirement of the award of **M.D. DEGREE (BRANCH -1)** and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation entitle **"A STUDY OF FASTING SERUM MAGNESIUM LEVEL IN TYPE 2 DIABETES MELLITUS AND CORRELATION WITH ITS COMPLICATIONS "** was done by me at the Government Stanley Medical College and Hospital during 2009-2011 under the guidance and supervision of **PROF. Dr. K.H.NOORUL AMEEN M.D.** The dissertation is submitted to the Tamilnadu Dr. MGR Medical University towards the partial fulfillment of requirements for the award of **M.D.DEGREE (BRANCH – I)** in **GENERAL MEDICINE.**

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CONTENTS

LIST OF ABBREVIATIONS

DM	-	Diabetes Mellitus
FBS	-	Fasting Blood Sugar
GDM	-	Gestational Diabetes Mellitus
HbAIc	-	Glycosylated Haemoglobin
HTN	-	Hypertension
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
NIDDM	-	Insulin Dependent Diabetes Mellitus
OGTT	-	Oral Glucose Tolerance Test
UKPDS	-	United Kingdom Prospective Diabetes Study
IHD	-	Ischemic Heart Disease
NPDR	-	Nonproliferative Diabetic Retinopathy
PDR	-	Proliferative Diabetic Retinopathy
AOD	-	Age of onset of diabetes
LDL	-	Low Density Lipoprotein
HDL	-	High Density Lipoprotein
TGL	-	Triglyceride
Mg	-	Magnesium
CPG	-	Capillary Blood Glucose
CHD	-	Coronary Heart Disease
ADA	-	American Diabeties Association
MI	-	Myocardial infarction

INTRODUCTION

Diabetes mellitus, the metabolic disease characterized by hyperglycemia results from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs like eyes, kidneys, nerves, heart and blood vessels.

Majority of cases of diabetes fall into two broad categories, Type 1 and Type 2 Diabetes mellitus[1,2]. Type 2 Diabetes accounts for approximately 90 to 95 percentage of all diagnosed cases of diabetes. Long term complications of diabetes are include retinopathy, nephropathy and peripheral neuropathy and foot ulcers. Patients with diabetes have an increased risk of atherosclerotic, cardiovascular diseases. Hypertension and abnormalities of lipid metabolism are often found in diabetes.

There are several pathogenic processes involved in the development of either form of diabetes and long term complications .The basis of the abnormalities in carbohydrate, fat, protein metabolism in diabetes is deficient action of insulin on target tissues. Defective insulin action results from inadequate insulin secretion and or reduced tissue response to insulin action. Defect in insulin secretion or action on

target organ frequently coexist in the same patient. Several vitamins and minerals act as cofactors in the enzyme reaction regulated by insulin. Deficiency of several vitamins and minerals such as vitamin E, potassium, magnesium, zinc and chromium may worse the carbohydrate intolerance. Of these the need for potassium or magnesium replacement is relatively easy to detect based on low serum levels[57].

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation[32]. Magnesium plays an essential role in carbohydrate metabolism and in the insulin action[41]. Magnesium acts as a cofactor in glucose transport mechanism of the cell membranes and various intra cellular enzymes involved in carbohydrate metabolism[41,42].The concentrations of serum magnesium in healthy people are remarkably constant where as30 to 35% of diabetes have low serum magnesium concentration[43-45].Magnesium deficiency has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes[46,47] as well as the evaluation of the complications like retinopathy[11] cardiovascular diseases[49] ,nephropathy[50] and neuropathy. Moreover, low serum magnesium is a strong, independent predictor of development of type 2 diabetes[51] The present study was undertaken with an aim to estimate prevalence of

hypomagnesemia in patients with type 2 diabetes and correlate serum magnesium concentrations with micro and macro vascular complications of diabetes

AIMS AND OBJECTIVES

1. Estimating fasting serum magnesium concentration in patients with type 2 diabetes mellitus

2. Correlating serum magnesium concentrations with micro and macro vascular complications of type 2 diabetes mellitus-retinopathy, nephropathy, neuropathy, hypertension and ischemic heart diseases

DIABETES MELLITUS

Diabetes mellitus (DM) is a common disease of the general population worldwide which has as the basic abnormality hyperglycemia. Few of the mechanisms behind the production of hyperglycemia include decreased level of insulin secretion, reduced level of glucose utilization, and increased endogenous production of glucose[2].Diabetes mellitus causes various microscopic and macroscopic changes in virtually all organs of the body . It is the major cause of cardiovascular morbidity and mortality ,renal disease often progressing to end stage renal disease ,peripheral vascular disease of extremities causing non traumatic amputation of digits and toes and blindness. With an increasing incidence worldwide, diabetes mellitus is expected to be the scourge of mankind in the near future.

CLASSIFICATION

Depending upon the causes that lead to hyperglycemia, diabetes mellitus can be classified[2] as shown on the table :

Classification:

I. Type 1 diabetes

In type 1 there is beta cell destruction due to autoimmune factors; this can be sub classified into a). Idiopathic b). Immune mediated

II. Type 2 diabetes :

Here the basic pathology is not mainly in the production of insulin but rather more of a resistance to insulin at the receptor level occurs due to factors like obesity etc,

III. Other types of diabetes:

a. Genetic defects of beta cell function characterized by mutations in :

i. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
ii. Glucokinase (MODY 2)
iii. HNF – 1a (MODY 3)
iv. Insulin promoter factor -1 (IPF-1; MODY 4)
v. HNF-1 B (MODY 5)
vi. NeuroD1 (MODY 6)
vii. Mitochondrial DNA
viii. Subunits of ATP-sensitive potassium channel

ix. Proinsulin or insulin

b. Genetic defects in insulin action:

i. Type A insulin resistance

ii. Leprechaunism

iii. Rabson – Mendenhall syndrome

iv. Lipodystrophy Syndromes

c. Diseases of the exocrine pancreas – Pancreatitis, Pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis

d. Endocrinopathies – Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism

e. Drug-or chemical – induced – Glucocorticoids, Vacor (a rodenticide), Pentamidine, Nicotinic acid,

f. Infections – Congenital rubella, Cytomegalovirus, Coxsackievirus.

g. Uncommon forms of immune – mediated diabetes – "Stiff-person" syndrome, Anti-insulin receptor antibodies.

h. Other genetic syndromes sometimes associated with diabetes – Wolfram's syndrome, Down's syndrome,

IV. Gestational diabetes mellitus (GDM)

Currently the terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) are obsolete[2].

TYPE 1 DIABETES MELLITUS

Type 1 DM is due to destruction of majority of the pancreatic beta cells which leads to insulin deficiency. It is not due to a single etiology but a complex interplay of genetic autoimmune and environmental factors. The trigger for destruction of beta cells may be an infectious process like coxsackie , rubella, and entero viruses or environmental factors like bovine milk proteins, and chemicals like nitrosourea[1]

The concordance of type 1 DM in identical twins ranges from 40 to 60%[2]. The major susceptibility gene for type 1 DM is located in the HLA region on chromosome 6. Polymorphisms in the HLA complex carries 40-50% of the genetic risk to develop type 1 DM. Most individuals with type 1 DM have the HLA DR 3 and / or DR4 haplotype. With type 1 DM. most strongly associated haplotypes are

DQA 1*0301, DQB1 *0302, and DQB1 *0201. Insulin, glutamic acid decarboxylase, ICA-512/IA-2 and a beta cell-specific zinc transporter (Zn T-8).are major target for autoimmune destruction[2]

As the basis of diabetes is believed to be autoimmune there is an association with other auto immune disorders like Graves disease, Hashimoto thyroiditis, Addison's disease, Vitiligo, Celiac sprue and Pernicious anemia[2]

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus is not associated with predominant destruction of beta cells as in type 1 diabetes; here the onus is more on relative or absolute resistance to the action of insulin at the receptor level; there is abnormal release of insulin in response to a glucose load and symptoms do not develop till the insulin secretion is grossly inadequate.

Type 2 DM is polygenic. If both parents of an individual have type 2 DM, the risk of that individual acquiring diabetes approaches 40%. The concordance of type 2 DM in identical twins is between 70 and 90 %[2]. Many first-degree relatives of individuals with type 2 DM; though they don't manifest overt diabetes have insulin resistance. In addition to genetic susceptibility, factors like obesity, physical inactivity and lack of exercise, improper diet modulate the clinical expression of diabetes mellitus.

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production; even fat metabolism is abnormal. More than 80 % of diabetic patients are obese with a predilection for central or visceral obesity which can be gauged by waist hip ratio[2]

RISK FACTORS FOR TYPE 2 DIABETES MELLITUS[2]

Family history of diabetes (i.e. parent or sibling with type 2 diabetes)

Obesity (BMI≥25kg/m^2) and Physical Inactivity

Race/Ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander)

Previously identified with IFG, IGT, or an A1C of 5.7-6.4%

History of GDM or delivery of baby > 4kg (9lb)

Hypertension (blood pressure >140/90 mmHg)

HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/ or a triglyceride level > 250 mg/dL (2.82 mmol/L)

Polycystic ovary syndrome or acanthosis nigricans

GESTATIONAL DIABETES MELLITUS (GDM)

In females sometimes a relative insulin deficiency develops for the first time during pregnancy. This has been termed gestational diabetes mellitus. In pregnancy there is an increase in insulin requirement and also the metabolic milieu of the body is altered by

pregnancy hormones leading to impaired glucose tolerance or frank diabetes.GDM occurs in 7% (range 2-10%) of pregnant females. Usually they revert to normal glucose tolerance in the postpartum state but some have a substantial risk (35-60%) of developing DM in the next 10-20 years[1].

EPIDEMIOLOGY

The disease burden of type 2 DM is increasing at an alarming rate when compared to type 1 DM .This can be ascribed to the changing lifestyle of modern man with altered diet and a sedentary lifestyle.

In 2010 around 1.6 million individuals were diagnosed to have newly detected diabetes mellitus[1]. In 2010, the prevalence of DM is 0.2% in individuals aged <20 years and 11.3% in individuals aged >20 years. In individuals aged >65 years, the prevalence of DM is 26.9%. In both the sex the prevalence is similar in throughout the age ranges (11.8% and 10.8% respectively, in individuals aged >20 years). In 2030 the greatest number of individuals with diabetes will be in the age group of 45-64 years[2]

DIAGNOSIS

A person's handling of his glucose load may place him into any of the following three categories 1. Frank diabetes mellitus 2. Impaired glucose tolerance 3. Normal glucose homeostasis

Normal glucose tolerance is defined as when an FPG 100 mg/dL, plasma glucose <140 mg/dL 1 following an oral glucose challenge, and an A1C <5.6% [2]

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS[1]

- Symptoms of diabetes plus random blood glucose concentration $\geq$ 11.1 mmol/L (200 mg/dL) or
- Fasting plasma glucose $\geq$ 7.0 mmol/L (126 mg/dL) or
- A1C> 6.5% or
- Two – hour plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test

An FPG $\geq$ 7.0 mmol/L (126 mg/dL), a glucose > 11.1 mmol/L (200 mg/dL) 2 hrs after an oral glucose challenge, or an A1C >6.5% warrant the diagnosis of DM[1]. A random plasma glucose concentration >11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM

(polyuria, polydipsia, weight loss) also is sufficient for the diagnosis of DM

In asymptomatic individuals Fasting plasma glucose and HbA1c are the most reliable and convenient tests for diagnosing DM[2].

Nowadays FPG or the A1c may be used as a screening test ,because most of the individuals who meet the current criteria for DM are asymptomatic and unaware of their predicament; persons of diabetes mellitus when first diagnosed itself may have complications ; early treatment may alter the disease course so that a better screening procedure is always needed[2].

ADA recommends screening of all individuals >45 yrs every 3 years and at an earlier age if BMI >25kg/m^2.

COMPLICATIONS OF DIABETES MELLITUS

Acute complications may be one of excess or deficiency as in diabetic ketoacidosis ,hyperglycemic non ketotic coma and hypoglycemic illness respectively.

Chronic complications of diabetes mellitus may be micro vascular affecting the eye, nervous system and kidneys or macro

vascular affecting the heart , peripheral arteries and arteries of the central nervous system ; other than this broad classification of vascular complications diabetes is a universal pathogen of all organs in the human body affecting gastrointestinal (gastro paresis, diarrhea), genitourinary (uropathy/sexual dysfunction),systems, skin, lens of the eyes, and hearing apparatus

TREATMENT GOALS FOR DIABETES IN ADULTS[2]

HbA1c	< 7 %
Preprandial CPG	3.9-7.2 mmol/l (70-130 mg/dl)
Peak postprandial CPG	<10.0 <1.7 mmol/l (<180 mg/dl)
Blood pressure	< 130 / 80 mmhg
LDL	< 100mg/dl
HDL	> 40 mg /dl-males ; > 50 mg/dl females
TGL	< 150 mg/dl

NUTRITIONAL RECOMMENDATIONS FOR ADULTS WITH DIABETES[2]

Fat in diet :-Minimal Trans fat consumption

Carbohydrate in diet:

- Monitor carbohydrate intake in regards to calories ;Sucrose-containing foods are better to be restricted
- Glycemic index reflects how consumption of a particular food affects the blood glucose

Protein in diet: as part of an optimal diet

Other components:

- Routine supplements of vitamins, antioxidants, or trace elements not advised.

DIABETES MELLITUS AND CARDIOVASCULAR MORBIDITY

An increase in the incidence of sudden death, congestive heart failure and coronary atherosclerosis in diabetics has been conclusively proven by the landmark Framingham study. The American Heart Association has classified Diabetes mellitus as a CHD risk equivalent[1].The risk for MI in Type 2 diabetes patients without a prior

MI is equivalent to that of risk of MI in nondiabetic individuals who have had a prior MI. Diabetic patients are prone to have myocardial infarction without any pain as aptly described by the acronym silent killer; atherosclerosis affects multiple coronary vessels at the same time in diabetics when compared to non diabetics; As the prevalence of vascular morbidity due to atherosclerosis is more in diabetics it is better to screen for underlying ischemic heart disease and peripheral arterial disease. Dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking increase the occurrence of macro vascular complications in diabetics; Most of the diabetics have hypertriglyceridemia and reduced HDL cholesterol levels. The disease state itself has no role in increasing LDL levels per se but the type of LDL so called small dense type of LDL is more atherogenic because it is liable to oxidation more easily.

Albuminuria, an elevation of serum creatinine, and abnormal platelet function are other abnormalities found in increased incidence in diabetic patients .Even if there is no frank diabetes insulin resistance per se carries an increased risk of damage to the heart. Such individuals have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which aids and

accelerates the coagulation process and deters fibrinolysis, thus providing a thrombogenic milieu. Diabetics tend to have more frequent and more severe episodes of congestive heart failure. There is increased myocardial cell dysfunction due to chronic hyperglycemia which predisposes to frequent failure of a weak heart. Smoking and hypertension when associated with diabetes mellitus become a formidable risk association causing more morbidity.

DIABETIC NEUROPATHY

Among the causes of peripheral neuropathy diabetes mellitus is one of the foremost ; longer duration of diabetes , poorer control of diabetes , development of retinal disease and renal disease are indicators of increased risk for neuropathy.

CLASSIFICATION OF DIABETIC NEUROPATHY

Somatic:

- Polyneuropathy

  Symmetrical, mainly sensory and distal

  Asymmetrical, mainly motor and proximal (including amyotrophy)

- Mononeuropathy (including mononeuritis multiplex)

Visceral (autonomic):

Cardiovascular	Sudomotor
Gastrointestinal	Vasomotor
Genitourinary	Pupillary

Diabetic neuropathy presents usually as a distal symmetrical polyneuropathy. The patient will have progressive sensory loss affecting all modalities starting in legs and moving up; usually as the duration of diabetes increases there is development of associated autonomic neuropathy; patients afflicted with autonomic neuropathy have abnormal sweating, abnormal temperature regulation, dry eyes and mouth, pupillary abnormalities, cardiac arrhythmias, postural hypotension, gastro paresis, postprandial bloating, chronic diarrhea or constipation, impotence, retrograde ejaculation, incontinence.

One-third of patients have radicular involvement; they have severe pain in the low back, hip, and thigh in one leg. Rarely, the symptoms begin in both legs simultaneously. Within a few days or weeks, atrophy of muscles becomes apparent.

Peripheral mononeuropathy and cranial mononeuropathy are also common; of these median neuropathy at the wrist ,ulnar neuropathy at the elbow, peroneal neuropathy at the fibular head, and sciatic neuropathy occur commonly and among the cranial nerves seventh nerve palsy is most common, followed by third nerve, sixth nerve, and less frequently, fourth nerve palsies. Diabetic third nerve palsies are characteristically pupil sparing.

DIABETIC NEPHROPATHY

Of all the causes of renal disease in the present world diabetes is the most commonly implicated. Hyperglycemia, hypertension, dyslipidemia, smoking a family history of diabetic nephropathy, and gene polymorphisms of the renin-angiotensin – aldosterone axis are associated with increased risk of renal disease.

The basic anomaly is the presence of glomerular hyperfiltration. Albuminuria is the indicator of renal damage, seen in around 40% of diabetic nephropathy patients. Microalbuminuria is excretion of albumin in the range of 30 – 300 mg/ 24 hrs; latent period for development of microalbuminuria is usually 5 – 10 years in type 2 diabetic patients. Screening for proteinuria is advised at the time of diagnosis and every 5 years in type 1 diabetes whereas in type 2

diabetes, screening is advised at the time of diagnosis and every year thereafter[2].

Diabetic retinopathy seen in more than 90% of patients with type 1 diabetes and nephropathy; whereas only 60% of patients with type 2 diabetes with nephropathy have diabetic retinopathy. The presence of Kimmelstiel-Wilson nodules correlates well with the onset of retinopathy[2].

DIABETIC RETINOPATHY

Diabetes mellitus is the major cause of blindness between 20 to 74 years of age group. Diabetic patients are 25 times greater risk to become blind than persons without DM. Individuals with >20yrs of duration diabetes are more prone to develop retinopathy .In type 2 DM around 21% of patients have retinopathy at the time of diagnosis

UKPDS study revealed that 35% reduction in the risk of development of retinopathy for every percentage reduction of HbA1c[48] and tight BP control results in 34% reduction in progression of retinopathy[54].More than 90% type1 DM nephropathy patients have diabetic retinopathy, where as only 60% of diabetic nephropathy have retinopathy.

MAGNESIUM HOMEOSTASIS

Introduction :

Magnesium (Mg) is the fourth most abundant cation and second most abundant intracellular cation[55]. Magnesium plays an essential role in a wide range of fundamental biological reactions[32]. Kruse and associates made the first systemic observations of magnesium deficiency in rats and dogs[22].Early description of clinical depletion of magnesium in man published in 1934[23]

Distribution :

Bone has the maximum content of magnesium in the body with more than 50 % segmented in it[32]. Rest is in the soft tissues; the total intracellular content of mg is 8 to 10 mmol/l[33]. Approximate daily intake averages between 250 – 300 mg/day; fecal excretion is 2.5 mg / kg / day; urinary excretion is 1.5 mg/ kg/day[55].

Total body content	24 g in adult man
Bone	> 50 %
Extracellular fluid	1 %
Serum	1.7 – 2.4 mg /dl
Ultrafiltrable Mg	75 %
Ionized	60 %
Complexed	15 %
Protein bound	25 %

Role of intestine:

About 30-40% of ingested magnesium is absorbed, in the small intestine mainly in jejunum and ileum. This absorption is enhanced by 1, 25 $(OH)_2$ Vitamin D[45,55]. Growth hormone slightly increases Mg absorption. Aldosterone and Calcitonin appear to reduce it. Vitamin B6 has been reported to enhance the absorption.

Role of kidney:

Kidneys regulate the excretion of magnesium and thus form the main control of plasma levels[4]. Around 25% of filtered Mg is reabsorbed in the proximal tubule and 65% is reabsorbed in thick

ascending loop of Henle and 5% in distal convoluted tubule[33]. Para thyroid hormone, Vasopressin, calcitonin, glucagon increase tubular magnesium reabsorption, whereas acetyl choline, bradykinin, and atrial natriuretic peptide stimulate urinary magnesium excretion[55]

DAILY RECOMMENDED INTAKE[2] (mg/day)

Age group	Male needs	Female needs
9 – 13 yrs	240	240
14 – 18yrs	410	360
19 – 30 yrs	400	310
31 – 50 yrs	420	320
51 – 70 yrs	420	320

Biological role of magnesium:

Enzymes of the intermediary metabolism and nucleic acid metabolism depend on magnesium for their effective action. Almost five enzymes of the glycolytic pathway depend on magnesium ;This comes as no surprise since four of the five (hexokinase , phosphofructokinase, phosphoglycerate kinase , pyruvate kinase and enolase) ;three of the four key enzymes in the gluconeogenesis pathway require

magnesium[41]. Lipid metabolism and RNA, DNA polymerases also need magnesium; transketolase reaction in thiamine metabolism; transfer of CO2 to biotin in carboxylation reactions; glutathione has an Mg requirement for its synthesis[24]. The second messenger cyclic adenosine monophosphate formed by the action of the enzyme adenylate cyclase is activated by Mg.

HYPERMAGNESEMIA

Exclusive hypermagnesemia is very rare unless there is underlying renal failure. Kidneys excrete normally 250 mmol/d of magnesium daily[2].

Causes:

1. Impaired excretion

   Renal failure

   Familial hypocalciuric hypercalcemia

2. Rapid mobilization from soft tissues

   Trauma, Shock, Sepsis, Cardiac arrest

3. Excessive intake

   Cathartics, Parenteral nutrition, Urologic irrigants

4. Others

Adrenal insufficiency, Hypothyroidism, Hypothermia

Signs and symptoms:

Unless the level of magnesium raises above 4.8 mg / dl patients are asymptomatic ; when such a situation occurs three types of manifestations can occur namely neuromuscular, cardiovascular, hypocalcemic symptoms.

Neuromuscular effects:

These are the most commonly observed and most consistently observed effects of hypermagnesemia. Hypermagnesemia decreases the release of acetyl choline and suppresses the transmission across the neuromuscular junction producing curare like effects[25,26] .With a plasma magnesium level of 4.8-7.2 mg/dl patients develop lethargy, drowsiness, muscle weakness, decreased deep tendon reflexes leading to flaccid quadriplegia, and respiratory depression

Cardiovascular effects:

Bradycardia and hypotension occur at plasma concentration of 4.8-6mg/dl. At concentration of 6 to 12g/dl prolongation of PR interval, widening of QRS duration and increase in QT interval occur.

At plasma concentration of 18 mg/dl complete heart block and cardiac arrest can occur[27]

Hypocalcemic effects:

Moderate hypermagnesemia can inhibit the secretion of parathyroid hormone, causing reduction in plasma level of calcium causing hypocalcemic symptoms[28]

Other symptoms:

Nonspecific symptoms like nausea, vomiting and flushing can occur

Treatment:

Maintain hydration

Calcium 100-200mg over 1-2 hrs intravenously given, can improve symptoms temporarily

Treatment of the cause for Hypermagnesemia

Haemodialysis is effective and required in case of renal failure

HYPOMAGNESEMIA

Hypomagnesemia refers to low serum magnesium concentrations, clinically it is defined as serum concentration less than or equal to1.6 mg/dl or >2 SD below the mean general population[16,29]. In patients suspected with magnesium deficiency a low serum magnesium concentration is sufficient to confirm the diagnosis[57].

Causes of Hypomagnesemia[2]:

1. Drugs and toxins
    - Ethanol
    - Diuretics
    - Cisplatin
    - Aminoglycosides
2. Renal diseases
    - Tubulointersitial disease
    - ATN diuretic phase
    - Renal transplantation
    - Gitelman syndrome

Barters syndrome

3. Intestinal disorders

    Malabsorption syndromes

    Intestinal drainages, fistulas

    Protracted vomiting, diarrhea

4. Metabolic causes

    Hyperaldosteronisum

    SIADH

    Diabetes mellitus

    Hypercalcemia

    Metabolic acidosis

    Hyperthyroidism

5. Others

    Pancreatitis

    Burns

    Excessive sweating

    Pregnancy 3rd trimester

Incidence:

Hospitalized patients show an increased incidence of hypomagnesemia with studies showing incidence of 12 %[30]. This is more in intensive care settings due to the drugs being used there ; studies have shown incidence of around 60% [31,32].

Symptoms and signs:

Only when serum magnesium concentration falls below1.2mg/dl symptoms and signs occur, till then usually patients are asymptomatic[56]. The symptoms are muscle cramps, hyperactive deep tendon reflexes, and dysphagia, irritability, disorientation, trousseau and chvostek signs. Ataxia, nystagmus and seizures occurs at the serum level of <0.8mg/dl .Paroxysmal atrial and ventricular dsarrhythmias may also develop.

ECG:

ECG shows nonspecific findings. Modest depletion of Mg (1.2 to 1.7 mg/dl) leads to QRS complex widening with peak T waves, where as severe magnesium depletion (<1.2mg/dl) shows PR interval prolongation, progressive widening of QRS complex, flattening or inversion of T waves and U waves[58]

Lab studies:

Because of only small fraction of magnesium present in ECF the serum Mg is not a reliable indicator of total body magnesium depletion. Nevertheless a deficiency of magnesium is clearly present if serum magnesium is low[57] .Serum magnesium is measured by calmagite dye method, equilibrium dialysis, atomic absorption spectrometry, ion selective electrodes and neutron activation analysis

Treatment:

Asymptomatic mild hypomagnesemia can be treated with oral magnesium salts like magnesium chloride ($MgCl_2$),magnesium oxide (MgO), magnesium hydroxide ($Mg(OH_2)$) in dose of 40-60meq/day, whereas severe hypomagnesemia requires parenteral therapy with magnesium chloride($MgCl_2$) as a continuous infusion of 100 meq/day in case of normal renal function. During management serum magnesium should be monitored at intervals of 12-24hrs.

HYPOMAGNESEMIA AND DIABETES MELLITUS

Most common disorder associated with magnesium depletion is diabetes mellitus[32, 33]. Hypomagnesemia occurs in 13.5 to 47.7% of non hospitalized type 2 DM patients compared to 2.5% to 15% among their

counterparts without diabetes[16, 34-37].There is inverse relationship between serum Mg levels and glycemic control[16, 34, 38-40]. Hypomagnesemia alters the glucose transport, and decreases the insulin secretion, affects the post receptor insulin signaling and interactions[60]. Studies show correlation between serum Mg levels and glycemic control and also improvement of glycemic control with Mg supplementation[9,35,59,]

Causes of hypomagnesemia in Type 2 Diabetes Mellitus[3]:

1. Decreased intake

    Poor oral intake

    Esophageal dysfunction

    Diabetic gastro paresis

2. Increased GI loss

    Diarrhea due to autonomic dysfunction

3. Increased renal loss

    Glomerular hyper filtration, osmotic diuresis, volume expansion, metabolic acidosis, hypoalbuminemia, microalbuminuria, Overt proteinuria, Insulin deficiency or resistance status and diuretics.

HYPOMAGNESEMIA AND ADVERSE CLINICAL EVENTS IN TYPE 2 DM

Non enzymatic glycosylation is the basic process underlying many of the long term complications of diabetes mellitus ; low magnesium levels also play a role in this regard[5]. Abou seif et al found that low serum magnesium is associated with defective anti oxidative processes in type 2 DM .Paolisso and Barbagallo et al[61] found that low serum magnesium diminishes the tyrosine kinase activity and increases the vascular resistance by calcium. This mechanism may account for hypertension and peripheral insulin resistance. The etiological role of magnesium in diseases like cerebrovascular disease, peripheral vascular disease and cardiac disease may be due to its role in inducing atherosclerosis ; It is observed that the serum Mg has inverse association with fasting serum glucose, insulin and systolic arterial blood pressure[4,6]. Hypomagnesemia has been seen in patients with diabetic retinopathy; with lower levels carrying an increased risk of severe diabetic retinopathy. Corsonello et al reported that low serum Mg is associated with diabetic nephropathy. Recent retrospective studies show an association between low serum Mg and renal function deterioration in type 2 DM[16]. Dee leewu et al[62] observed

that polyneuropathy was related to the duration of disease and low serum Mg concentration and with supplementation of magnesium decreasing the incidence of neuropathy .In type 2 DM development of feet ulcers are associated with low serum Mg levels[21]

MAGNESIUM SUPPLEMENTATION IN TYPE 2 DM

Various studies have proved that magnesium replacement can lessen the pathogenic factors and morbidities associated with type 2 diabetes mellitus like platelet reactivity, cardiovascular morbidity and insulin resistance[19]. In a case control study done by Paolisso et al[61], oral supplementation of 250 mg twice daily decreased the insulin requirements especially in elderly patients. They demonstrated an increase in beta cell response in response to glucose and arginine. Magnesium supplementation has been shown to decrease systolic blood pressure by > 5 mm hg in diabetic patients[14] . It also has a beneficial effect on lipid profile;

The response to insulin is increased thereby decreasing the insulin requirement in patients who are supplemented with magnesium. This has been also proved conclusively by Poonam Agrawala et al[63] .

METHODOLOGY

Study Population:

Patients with type 2 diabetes mellitus admitted in general medical ward in Government Stanley medical college hospital.

Methods:

100 patients with type 2 DM who were admitted in general medical ward in Stanley Medical College Hospital were randomly selected for this study . From all patients detailed history, thorough clinical examination and relevant biochemical investigations were obtained.

Inclusion criteria:

All case of type 2 DM admitted in Stanley medical hospital in general medical wards.

Exclusion criteria:

- Chronic Diarrhea
- Malabsorption
- Patients with Renal Failure
- Patients on Diuretics

- Acute Myocardial Infarction in Last 6 Months
- Patient Having Alcohol Abuse
- Patients Receiving Mg Supplements or Mg containing Antacid

Investigation:

Fasting blood glucose

Post prandial blood sugar was measured 2 hrs after a standard meal.

24 hr urine albumins were estimated.

Serum magnesium - Calmagite dye with spectrophotometric testing at 530 nm

Blood urea, serum creatinine.

Chest X ray ECG, Echocardiogram

Direct opthalmoscopy

Nerve conduction studies

Normal serum magnesium was defined as 1.7 – 2.4 mg / dl.

Patients were divided into three groups as follows normal 1.7-2.4mg/dl, low <1.7mg/dl, high>2.4mg/dl .Patients were categorized on the basis of diabetic duration, presence of IHD, HTN, mode of treatment, presence/absence of retinopathy, neuropathy, nephropathy

and glycemic control. Diabetic retinopathy were classified as nonproliferative diabetic retinopathy and proliferative retinopathy .Diabetic nephropathy was graded by using 24 hr urine albumin as follows no nephropathy if <30mg/24hr, microalbuminuria 30-299mg/24hr and macroalbuminuria >=300mg/24hr;

Statistical method:

Statistical method analysis was done using chi square test and sample variable t test to compare proportions. Results were considered significant at p value <0.05

RESULTS

This study was composed of 100 patients of type 2 DM of which 54 were men and 46 were women. These patients were further grouped according to their age, duration of diabetes, mode of treatment, glycemic control, presence or absence of co morbidities (ischemic heart disease and hypertension) and presence /absence of diabetic complications(retinopathy, neuropathy and nephropathy).

TABLE 1: AGE DISTRIBUTION & MAGNESIUM LEVELS

Age Group	No of Patients	%
41 - 50	22	22.00
51 - 60	47	47.00
61 - 70	26	26.00
>70	5	5.00
Total	**100**	**100**
Mean	57.73	
Sd	7.90	

Age Group (Yrs)	Hypomagnesemia		Normomagnesemia		Total	
	N	%	N	%	N	%
41 – 50	2	4.76	20	34.48	22	22
51 – 60	16	38.10	31	53.45	47	47
61- 70	19	45.24	7	12.07	26	26
≥ 71	5	11.90	0	0	5	5
Total	42	100	58	100	100	100

In our study maximum number of diabetics occurred in the age group 51 – 70 years .Youngest patient in our study was of the age 45 years . The mean age of diabetic patient in our study was 57.73 years.

In our study maximum number of hypomagnesemia patients occurred in the age group 61 – 70 years (45.24 %). All patients who were more than 70 years old had hypomagnesemia (100 %) .

Chart 1

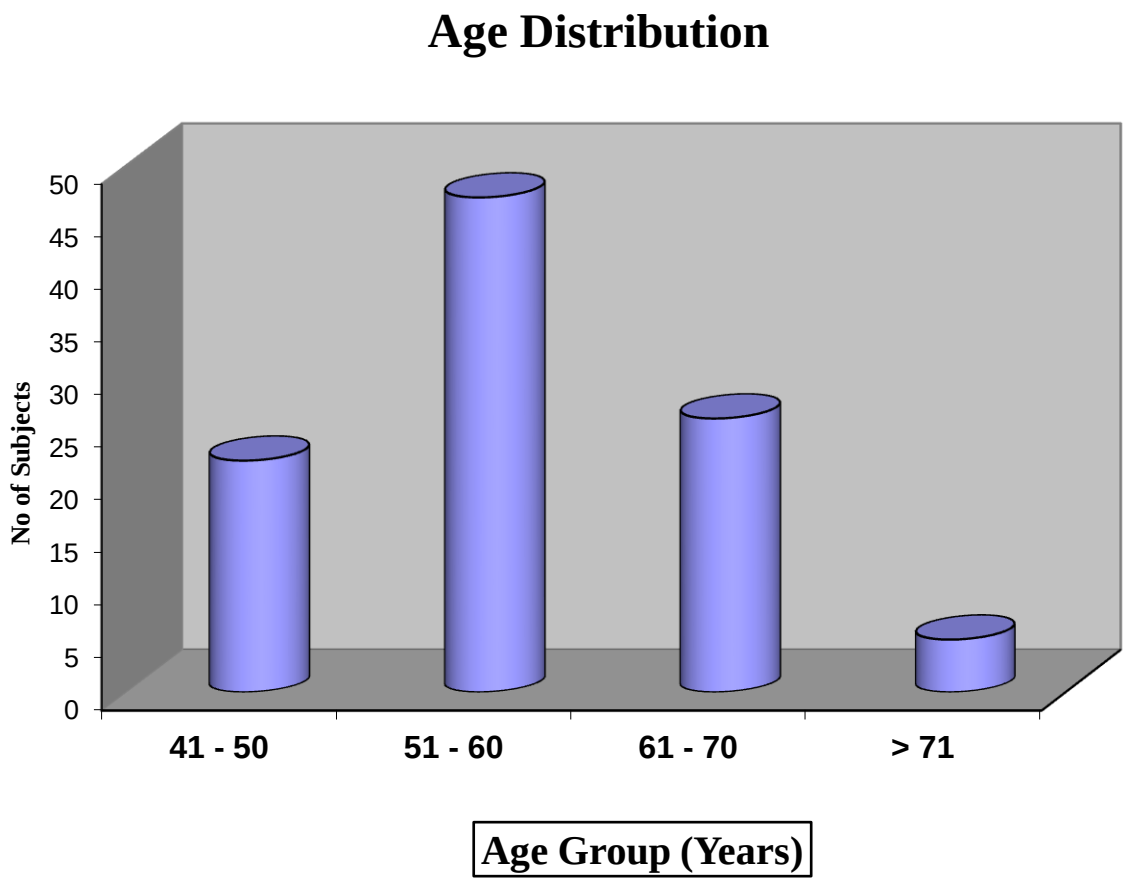


Chart 2

Age Distribution with Hypomagnesemia & Normomagnesemia

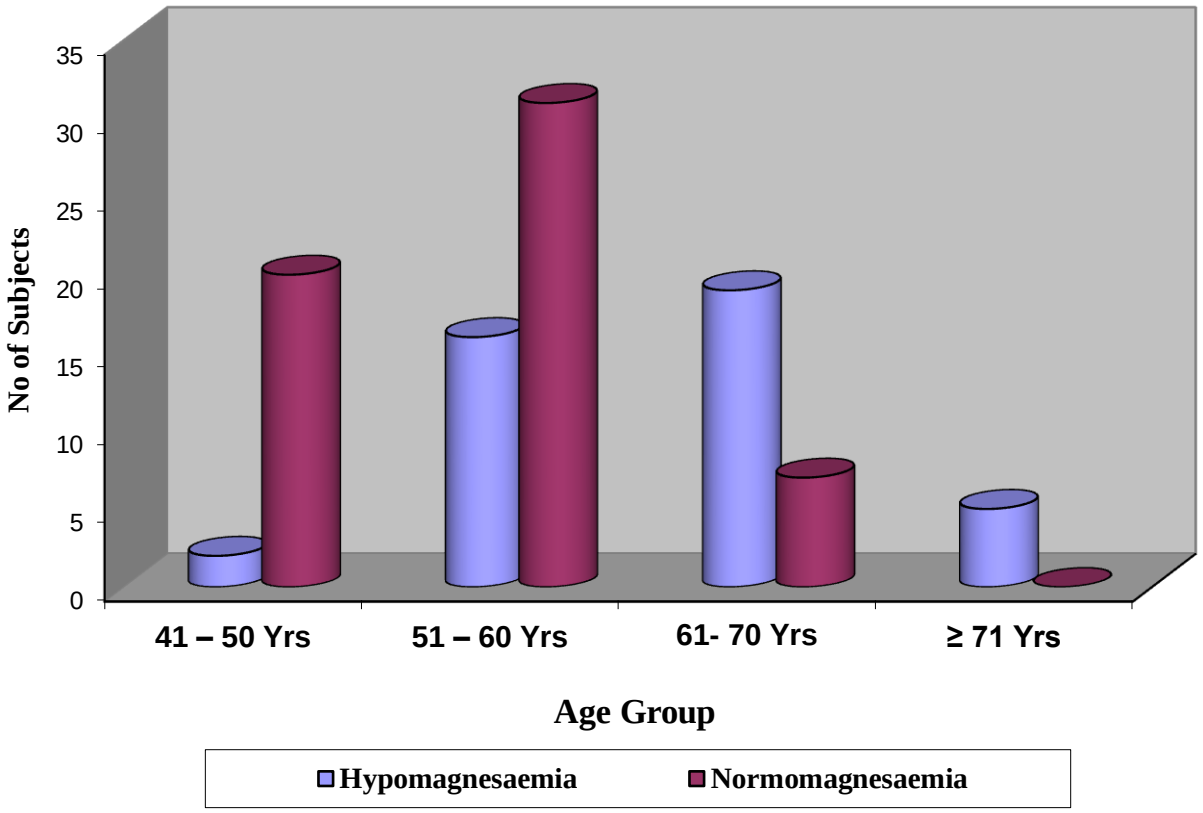


Chart 3

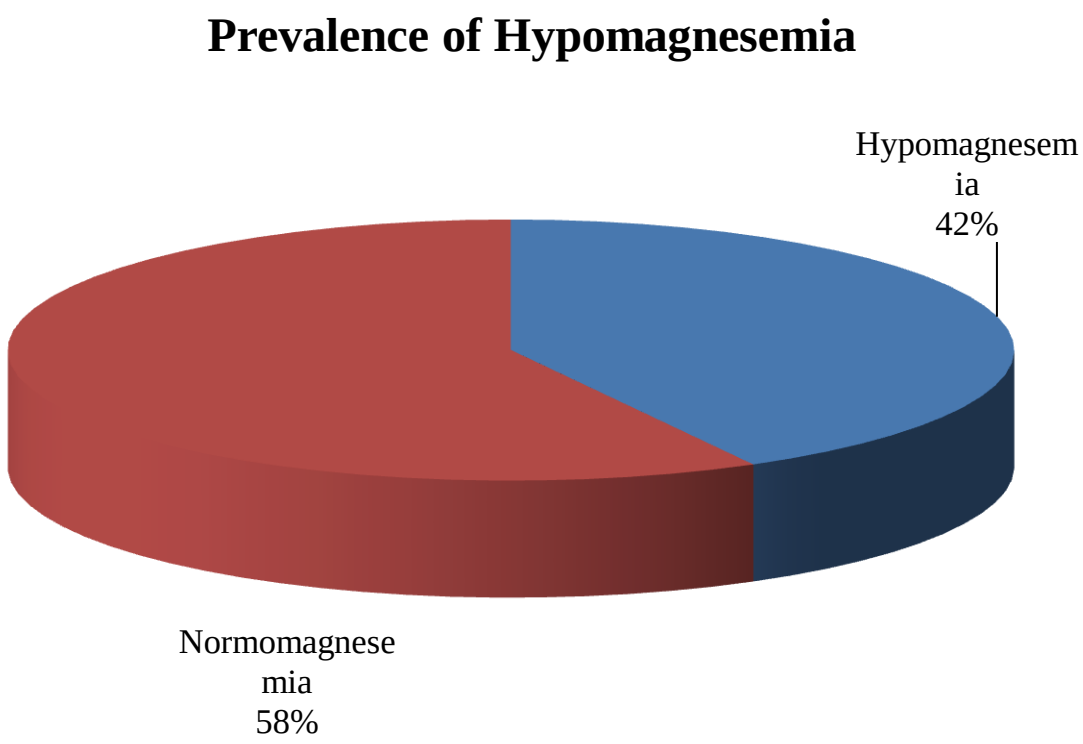

Prevalence of Hypomagnesemia
Hypomagnesemia
42%
Normomagnesemia
58%

TABLE 2: AGE DISTRIBUTION

	Hypomagnesemia	Normomagnesemia	Total
Mean	63.14	53.81	57.73
Sd	7.46	5.58	7.90
t-value	7.16		
Df	98		
Significant	0.0001 Significant		

The mean age group of the patients having hypomagnesemia in our study was 63.14. As the age increased the prevalence of hypomagnesemia increased and this association was statistically significant as shown by the p value 0.0001 ;

CHARACTERISTICS OF STUDY POPULATION

Sl. No.	Characteristics	Value
1	**No of Subject**	100
	Men	54
	Women	46
2	**Age in Years**	57.73 ± 7.90 (45 – 82)
	Men	55.69 ± 6.82
	Women	60.13 ± 8.46
3	**Medication**	
	Insulin	44
	OHA	56
4	**Co morbidities**	
	Hypertension	10
	Ischemic Heart Disease	34
5	**Diabetic Retinopathy**	
	NPDR	28
	PDR	6
6	**Diabetic Neuropathy**	4
7	**Diabetic Nephropathy**	14
	Microalbuminuria	5
	Macroalbuminuria	9

The average duration of diabetes in our study population was 9.39 years and range from 2 yrs to 25 yrs ; among the 100 patients 44 persons were receiving insulin and 56 persons were receiving OHAs; Among these individuals 10 patients had hypertension (10%) and 34 patients had ischemic heart diseases (34%) total 28 patients had retinopathy (28%) and out of them 22 had nonproliferative retinopathy and 6 had proliferative retinopathy. Total 14 patients had diabetic nephropathy (14%) among them 5 patients were microalbuminuria and 9 patients were macroalbuminuria and 4 persons had neuropathy (4%).

TABLE 3: SEX DISTRIBUTION AND MAGNESIUM LEVELS

Sex	Hypomagnesemia		Normomagnesemia		Total	
	No of patient	Percentage %	No of Patient	Percentage %	No of Patients	Percentage %
Male	18	42.86	36	62.07	54	54.00
Female	24	57.14	22	37.93	46	46.00
Total	42	100	58	100	100	100
Chi-square	3.62					
Df	1					
Significant	0.057 Not Significant					

In our study among the 100 patients, hypomagnesemia (serum Mg <1.7 mg/dl**)** was found in 42 patients of type 2 diabetic patients.58

patients had normal serum magnesium level. No patient had hypermagnesemia. No significant difference was found in the rate of hypomagnesemia in men and women (42.86% and 57.14% respectively).There was no significant statistical difference found between men and women p value=0.057

Chart 4

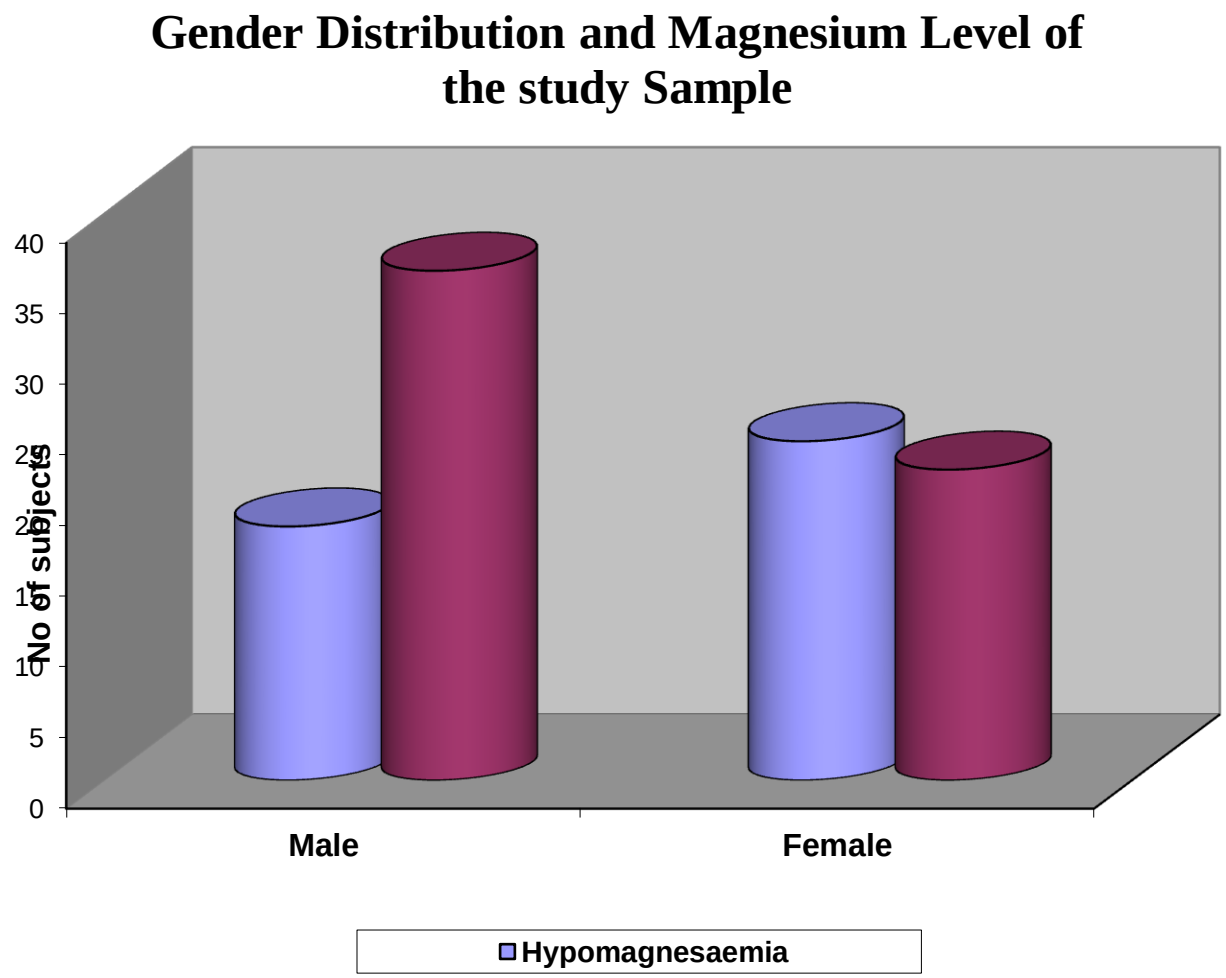

Gender Distribution and Magnesium Level of the study Sample
No of subjects
40
35
30
25
20
15
10
5
0
Male
Female
Hypomagnesaemia

Table 4: PREVALENCE OF HYPOMAGNESEMIA &

DURATION OF TYPE 2 DM

Duration of Diabetics (in Years)	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
00 –05	31	3	9.68
06 – 10	33	8	24.24
11 – 15	18	16	88.89
16 – 20	12	9	75.00
21 – 25	5	5	100.00
26 – 30	1	1	100.00

	Hypomagnesemia	Normomagnesemia	Total
Mean	13.76	6.34	9.46
Sd	6.20	3.78	6.14
t-value	7.42		
Df	98		
Significant	0.0001 Significant		

Based on duration of diabetes, we had 6 categories of patients; 1 patient had diabetes for > 25 years. 33 patients had diabetes for almost a decade. 35 patients had diabetic for > 1 decade. Applying the statistical analysis we found that as the duration of diabetes increases ,the prevalence of hypomagnesemia increases as shown by the p value=0.0001

Table 5: MODE OF TREATMENT & MAGNESIUM LEVELS

Treatment	Hypomagnesemia		Normomagnesemia		Total
	No of patients	Percentage %	No of Patients	Percentage %	No of Patients
OHA	7	16.67	49	84.48	56
Insulin	35	83.33	9	15.52	44
Total	42	100	58	100	100
Chi-square	45.47				
Df	1				
Significant	0.0001				

Chart 5a

Prevalence of Hypomagnesemia and Duration of Diabetes

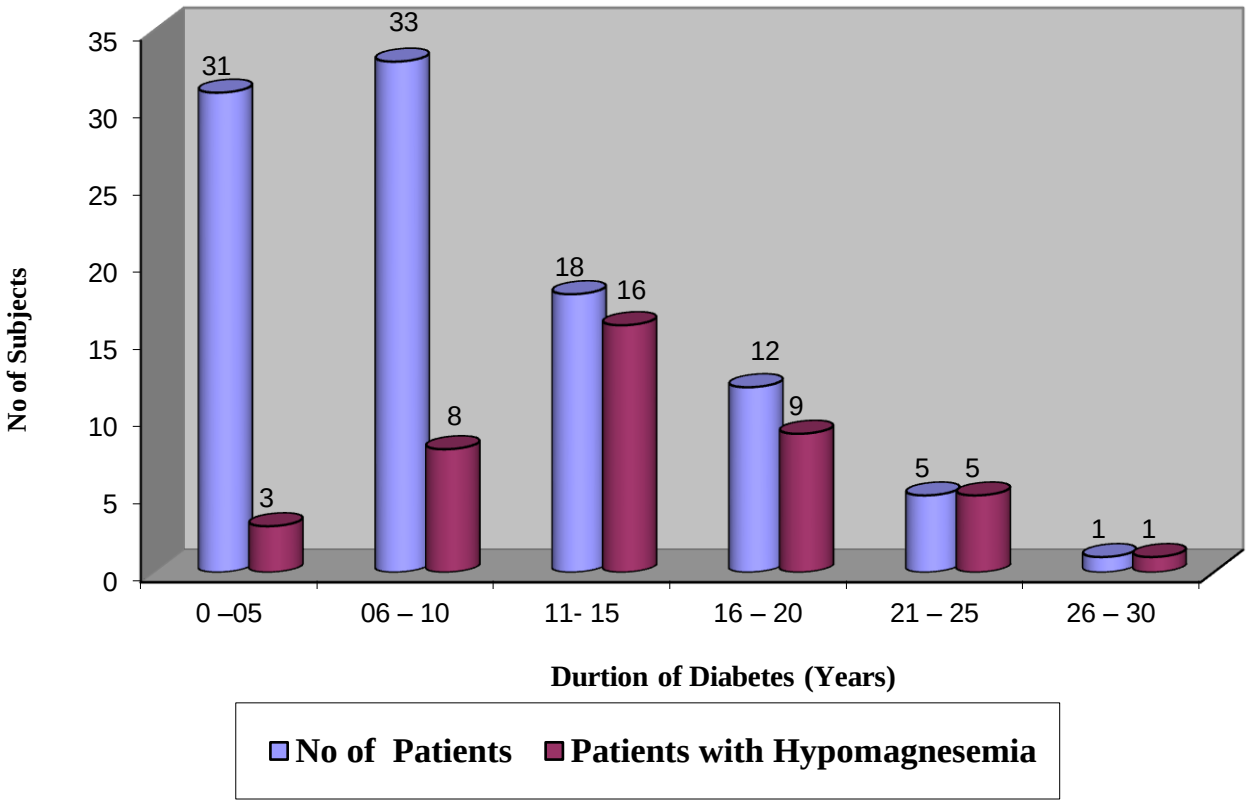
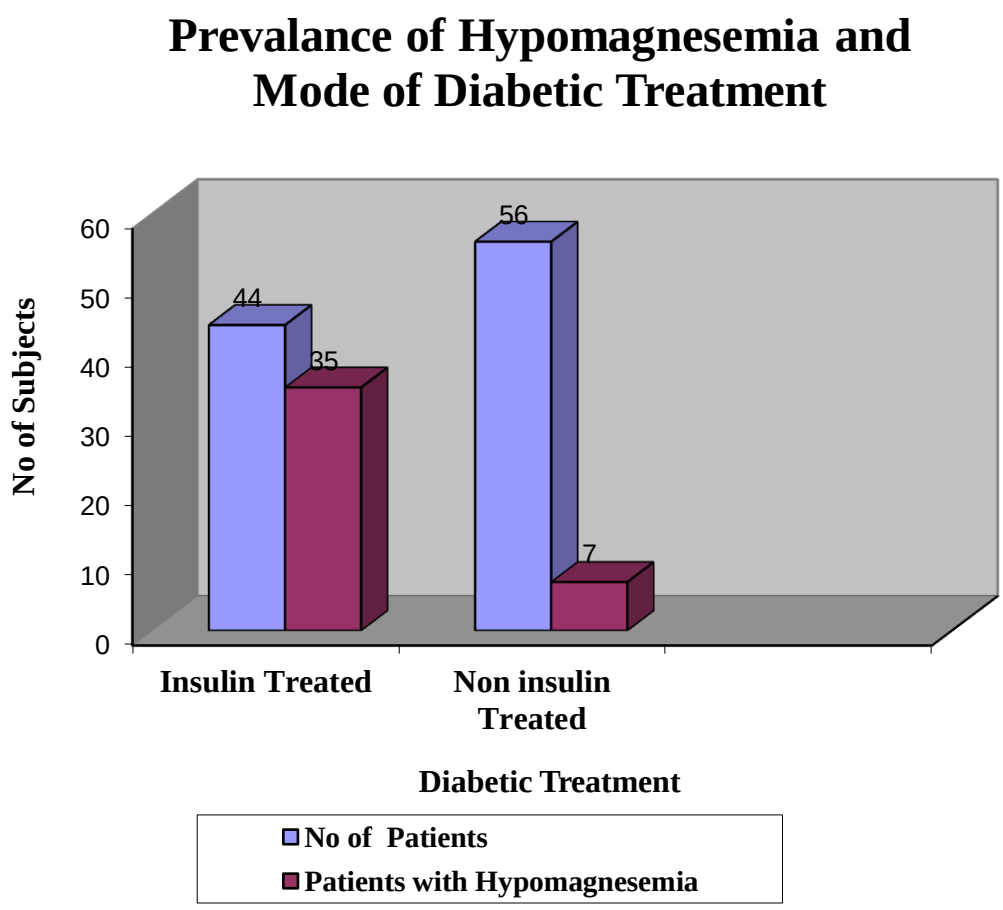


Chart 5b


Prevalance of Hypomagnesemia and Mode of Diabetic Treatment
No of Subjects
60
50
40
30
20
10
0
44
35
56
7
Insulin Treated
Non insulin Treated
Diabetic Treatment
No of Patients
Patients with Hypomagnesemia

In our study among the 100 diabetic patients 56 patients took OHA where as 44 patients took insulin therapy. Among the OHA receiving individuals 49 patients had normal magnesium level and only 7 patients had low serum magnesium level (84.48% versus 16.67%). Among the patients receiving insulin therapy 35 patients had low serum magnesium level; whereas 9 patients had normal serum magnesium level. This difference was statistically significant as shown by p value =0.0001.

Table 6: PREVALENCE OF HYPOMAGNESEMIA & FBS

Fasting Blood Sugar (FBS) (mg/dl)	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
< 90	2	0	0
91 – 100	8	0	0
101-110	17	4	23.53
111-120	28	7	25.00
121-130	23	13	56.52
> 130	22	18	81.82

	Hypomagnesemia	Normomagnesemia	Total
Mean	128.83	112.40	119.30
Sd	11.26	12.16	14.29
t-value	6.88		
Df	98		
Significant	0.0001 Significant		

In our study, 22 patient had poor glycemic control as evidenced by FBS >130mg/dl (81.82%).While on treatment, the mean blood sugar level in patient with hypomagnesemia was 128.83 where as the mean blood sugar level in patients with normomagnesemia was 112.40.Thus the association between the poor glycemic control and hypomagnesemia was statistically significant as shown by the p value of 0.0001

Chart 6

Prevalance of Hypomagnesemia and Fasting Blood Sugar

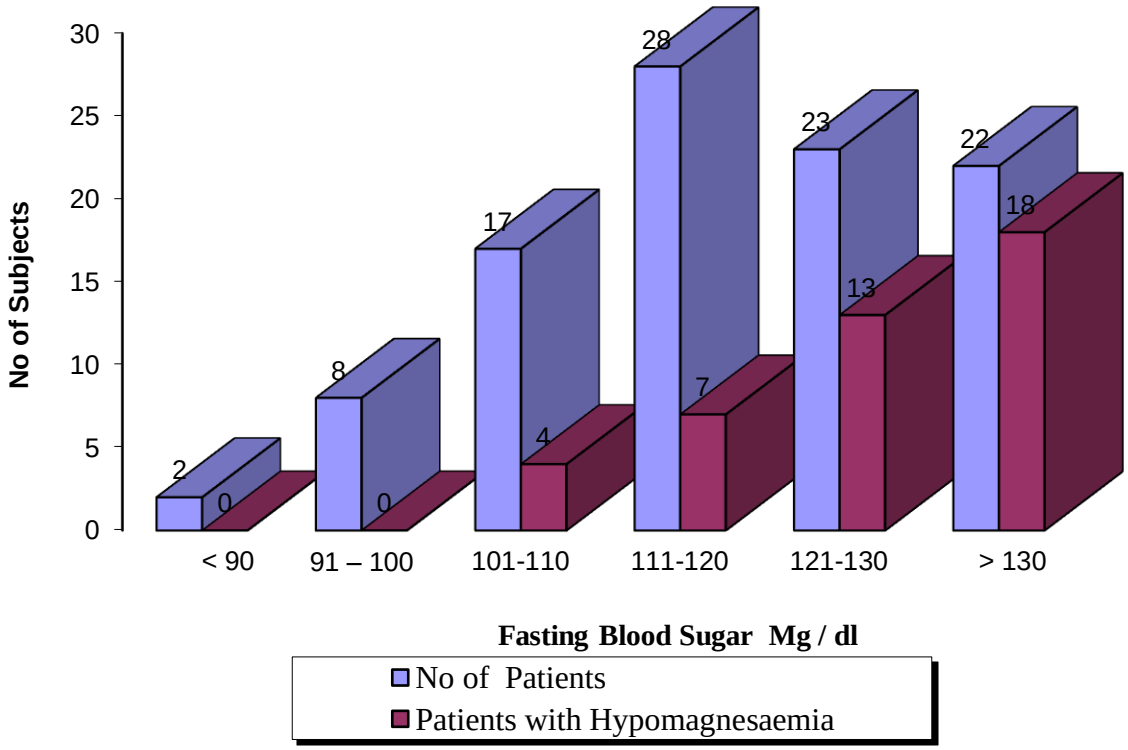


Table 7: PREVALENCE OF HYPOMAGNESEMIA & HbA1C %

HbA1c (%)	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
< 6	41	1	2.44
6 – 7	24	8	33.33
7 – 8	19	18	94.74
8 – 9	13	12	92.31
9 – 10	3	3	100

	Hypomagnesemia	Normomagnesemia	Total
Mean	7.77	5.91	6.69
Sd	0.84	0.49	1.13

t-value	13.93	
Df	98	
Significant	0.0001 Significant	

In our study, around 35 patient had poor glycemic control as evidenced by HbA1c>7% (95.68%). While on treatment the mean HbA1c level in patient with hypomagnesemia was 7.77 where as the mean HbA1c level in patients with normomagnesemia was 5.91.Thus the association between the poor glycemic control as evidenced by higher HbA1c and hypomagnesemia was statistically significant as shown by the p value of 0.0001

Chart 7

Prevalence of Hypomagnesemia and HbA1c %

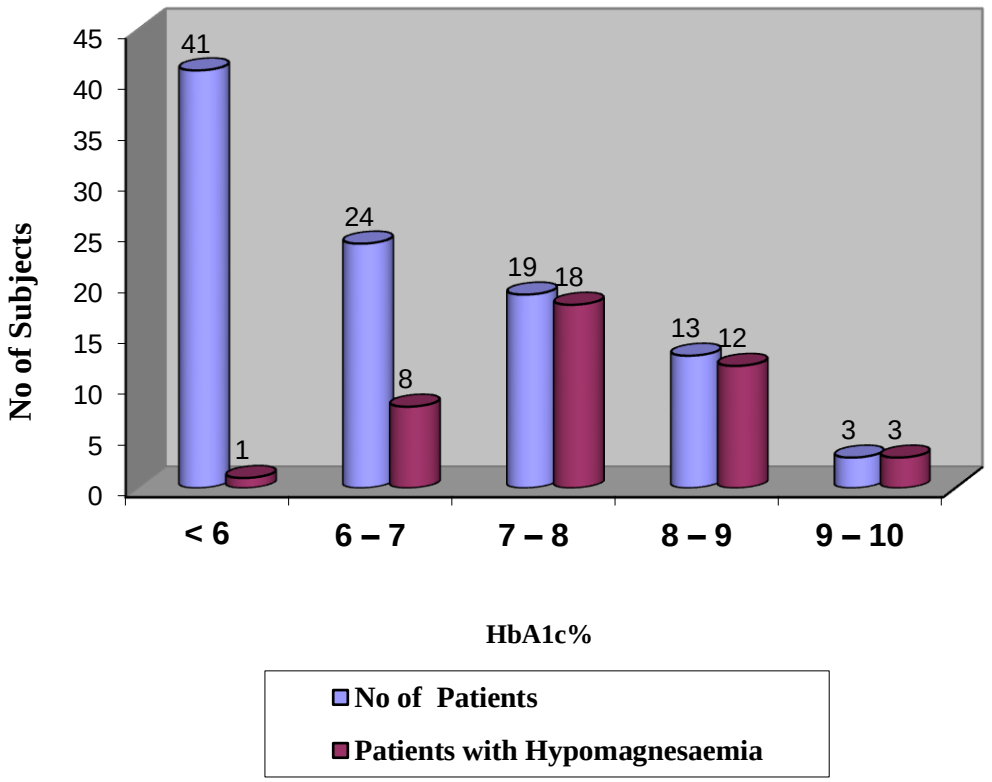


Table 8: HYPOMAGNESEMIA & DIABETIC RETINOPATHY

Retinopathy	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
NDPR	28	22	78.57
PDR	6	5	83.33
No Retinopathy	66	15	22.73

	Hypomagnesemia		Normomagnesemia		Total
	No of patient	Percentage %	No of Patient	Percentage %	No of Patients
No	15	35.71	51	91.07	66
Yes	27	64.29	7	12.50	34
Total	42	100	56	100	100
Chi-square	29.65				
Df	1				
Significant	0.0001				

Observations revealed that out of 100 diabetic patients 34 patients had retinopathy. Among these individuals 27 persons had low serum magnesium levels(64.29%). Rest of the individuals with retinopathy had normal serum magnesium level(12.50%).Using the statistical analysis by chi-square test the association between the presence of hypomagnesemia with retinopathy in diabetic patients was found to be significant as shown by the p value of 0.0001

Chart 8

Prevalance of Hypomagnesemia and Retinopathy

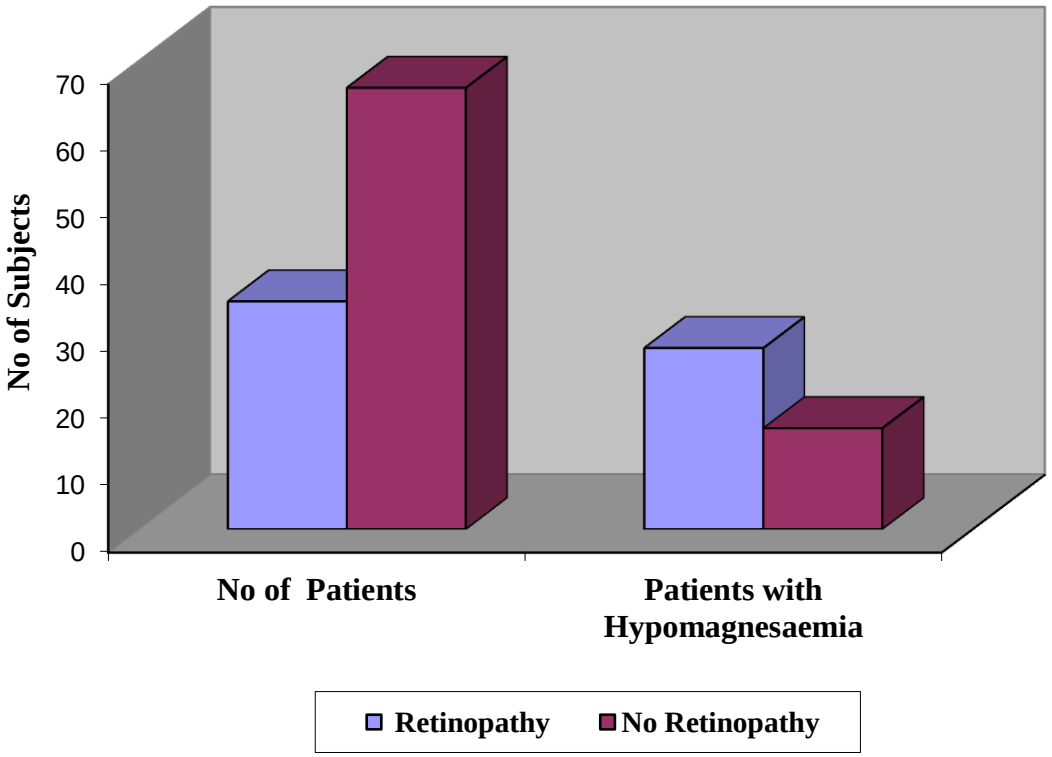


Table 9: HYPOMAGNESEMIA & DIABETIC NEUROPATHY

Neuropathy	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
Neuropathy	4	4	100
No Neuropathy	96	38	39.58

	Hypomagnesemia		Normomagnesemia		Total
	No of patient	Percentage %	No of Patient	Percentage %	No of Patients
No	38	90.48	58	100	96
Yes	4	9.52	0	0	4
Total	42	100	58	100	100
Chi-square	5.75				
Df	1				
Significant	0.016				

Observations revealed that out of 100 diabetic patients 4 patients had neuropathy. All of these individuals had low serum magnesium levels (100%).Using the statistical analysis by chi-square test the association between the presence of hypomagnesemia with neuropathy in diabetic patients was found to be significant as shown by the p value of 0.016

Table 10: HYPOMAGNESAEMIA & DIABETIC NEPHROPATHY

Diabetic nephropathy	**No of Patients %**	**Patients with Hypomagnesemia**	**Prevalence (%)**
Micro and macroalbuminuria	5 9	14	92.86
No Nephropathy	86	29	33.72

	Hypomagnesemia		Normomagnesemia		Total
	No of patient	**Percentage %**	**No of Patient**	**Percentage %**	**No of Patients**
No	29	69.05	57	98.28	86
Yes	13	30.95	1	1.72	14
Total	42	100	58	100	100
Chi-square	17.28				
Df	1				
Significant	0.0001				

In our study out of 100 diabetic patients 14 patients had the evidence of nephropathy (92.86%).Out of these diabetic nephropathy patients 13 patients were low serum magnesium level (30.95%).Presence of normal serum magnesium level in diabetic nephropathy in our study was low (1.72%).Thus the association between the hypomagnesemia and nephropathy in diabetic patient was found to be statistically significant with the p value of 0.0001

Chart 9

Prevalence of Hypomagnesemia and Diabetic Neuropathy

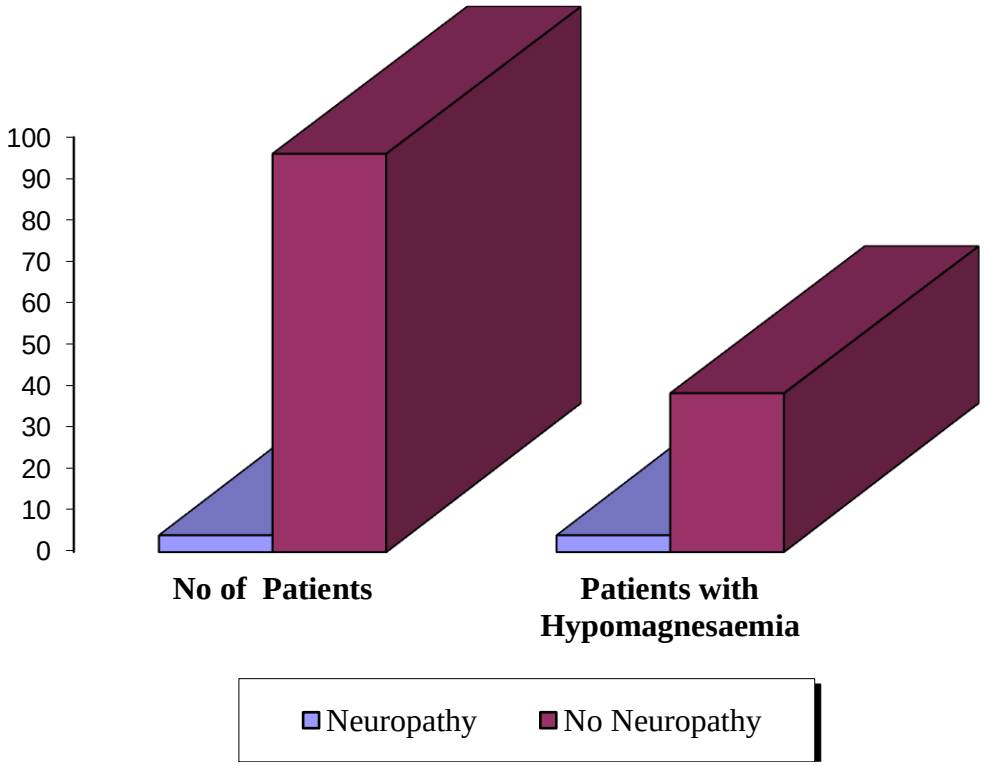


Table11. HYPOMAGNESAEMIA & IHD

Ischemic Heart Disease	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
Present	10	8	80.00
Not Present	90	34	37.78

Treatment	Hypomagnesemia		Normomagnesemia		Total
	No of patient	Percentage %	No of Patient	Percentage %	No of Patients
No	34	80.95	56	96.55	90
Yes	8	19.05	2	3.55	10
Total	42	100	58	100	100
Chi-square	6.59				
Df	1				
Significant	0.010 Significant				

A total of 10 patients had IHD. Among them 8 had low serum magnesium level (80%). The prevalence of IHD was 19.05% in hypomagnesemia patients. The prevalence of IHD was 3.55% in normomagnesemia patients; thus the association between the hypomagnesemia and the IHD in diabetic patients was found to be statistically significant with p value of 0.010

Table 12: HYPOMAGNESEMIA & HYPERTENSION

Hypertension	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
Present	34	19	55.88
Not Present	66	23	34.85

Treatment	Hypomagnesemia		Normomagnesemia		Total
	No of Patients	Percentage %	No of Patients	Percentage %	No of Patients
No	23	54.76	43	74.14	66
Yes	19	45.24	15	25.86	34
Total	42	100	58	100	100
Chi-square	4.08				
Df	1				
Significant	0.044				

In our study there were 34 hypertensive patients .Among those 19 patients had low serum magnesium level (55.88%).The prevalence of HTN was more in patients with low serum magnesium level (45.24), when compare to patients with normal serum magnesium (25.86) .Thus the difference was found to be statistically significant as shown by p value 0.044

Chart 10

Prevalance of Hypomagnesemia and Diabetic Nephropathy

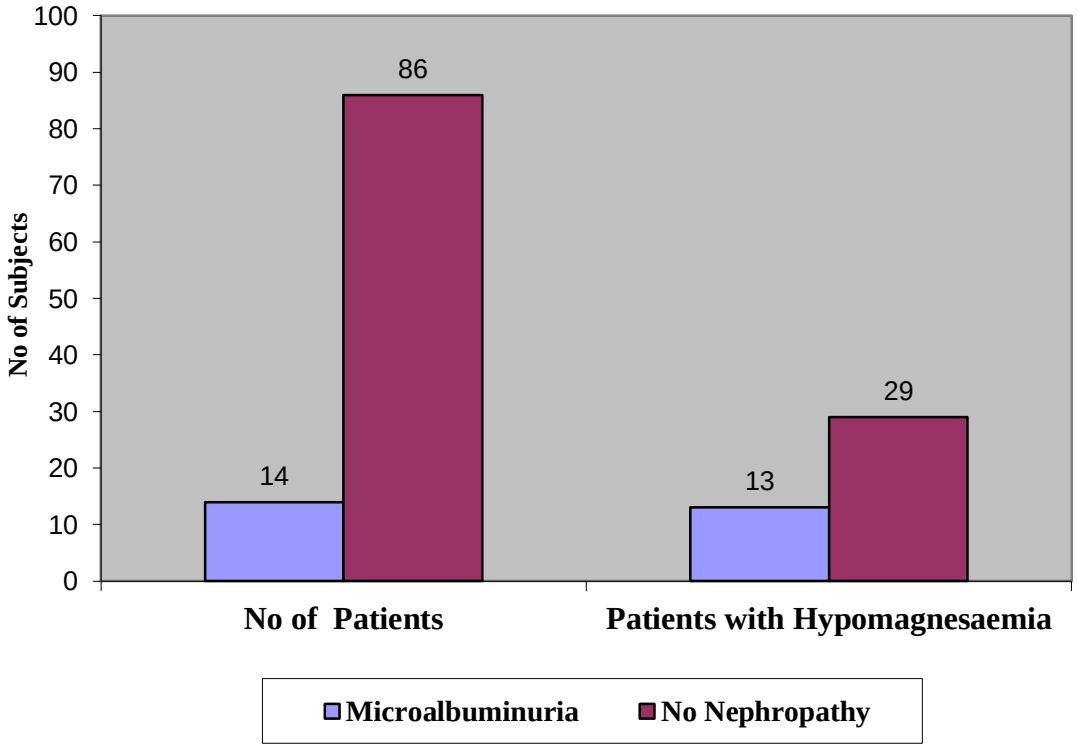


Chart 11

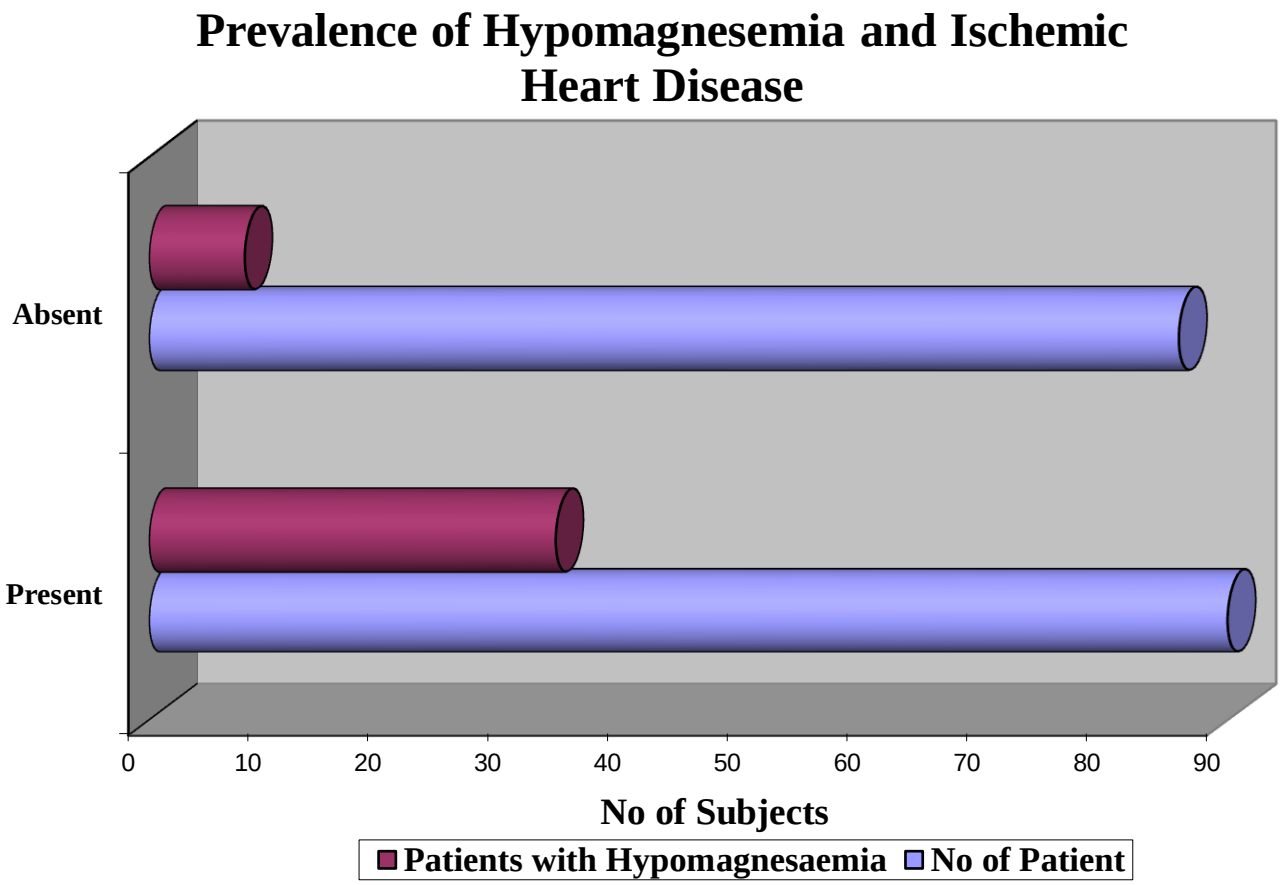

Prevalence of Hypomagnesemia and Ischemic Heart Disease
Absent
Present
0
10
20
30
40
50
60
70
80
90
No of Subjects
Patients with Hypomagnesaemia
No of Patient

Chart 12

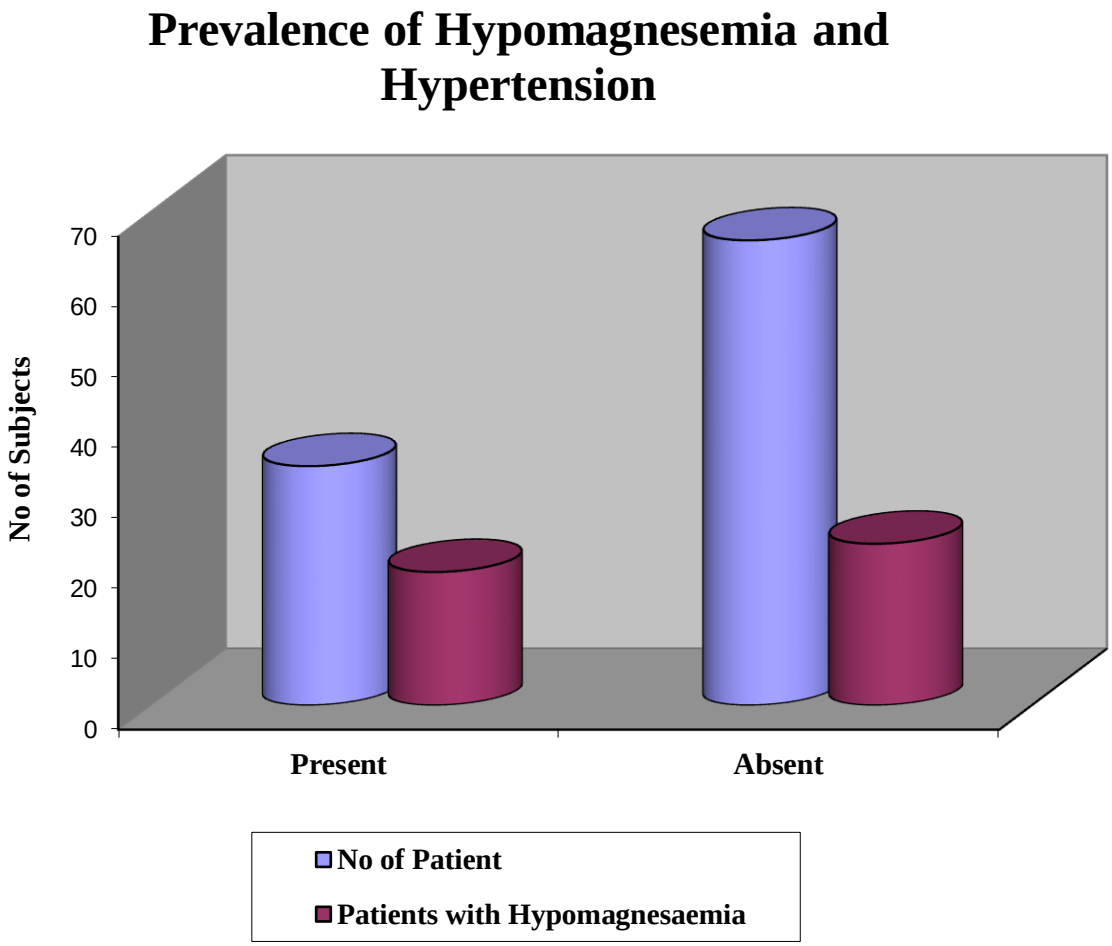


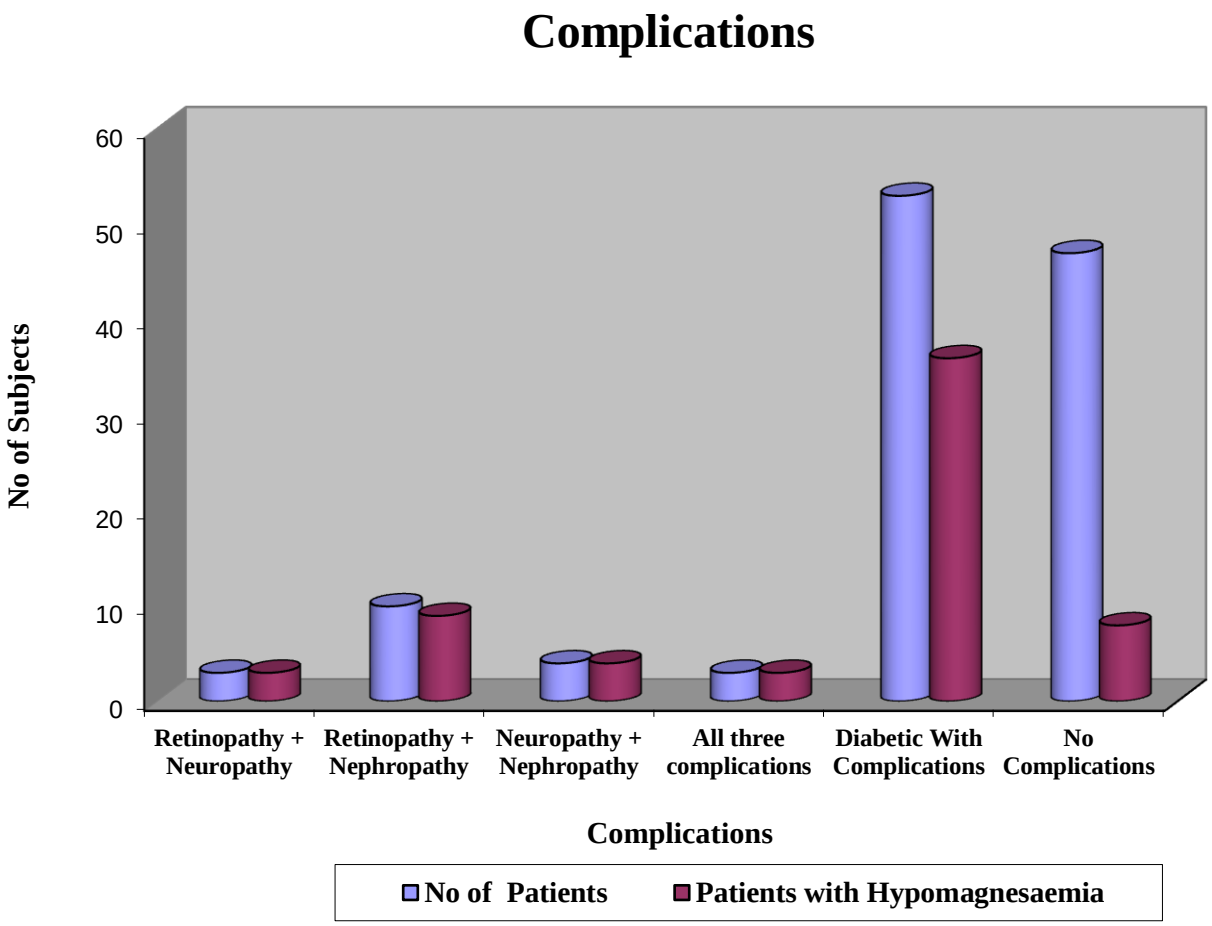
Chart 13

Table 13: DIABETIC COMPLICATIONS & HYPOMAGNESEMIA

Complications	No of Patients	Patients with Hypomagnesemia	Prevalence (%)
Retinopathy& Neuropathy	3	3	100
Retinopathy& Nephropathy	10	9	90
Neuropathy& Nephropathy	4	4	100
All three complications	3	3	100
Diabetic patients with Complications	53	36	67.92
Diabetic patient without Complications	47	8	17.02

Prevalence of hypomagnesemia in diabetic patients with complications was significantly higher when compared to diabetic patients with no complications (67.92% versus 17.02%).The difference was statistically significant with p value less than 0.05.

Chart 13


Complications
No of Subjects
60
50
40
30
20
10
0
Retinopathy + Neuropathy
Retinopathy + Nephropathy
Neuropathy + Nephropathy
All three complications
Diabetic With Complications
No Complications
Complications
No of Patients
Patients with Hypomagnesaemia

DISCUSSION

Many studies have proven beyond doubt the association between the presence of hypomagnesemia and diabetes mellitus ; it has also been proven that hypomagnesemia has been associated with increased incidence of complications in diabetics[7]; hence I found it worthy to take up this study in our settings.

DIABETES & HYPOMAGNESEMIA:

Previous studies by Nadler JC[43] and Rude RK[45] have reported low serum magnesium status in patients with type 2 DM. The reported prevalence of hypomagnesemia ranged from 13.5% to 47.7% in type 2 DM patients according to Pham PC , Pham PM ,Miller JM et al[3] .In our study there were a total of 100 diabetic patients ; among them 42 patients had serum Mg below the reference range;. Prevalence of hypomagnesemia in type 2 diabetes mellitus according to our study was similar to that reported by Nadler et al[43] .Walti mk et al[36] reported that prevalence of hypomagnesemia in type 2 diabetes at 37.6% versus 10.9% in non diabeteic controls in a study conducted in, Switzerland; this too is in concordance with our study results ;

The causes for the high prevalence of hypomagnesemia in diabetes may be due to increased urinary loss, low dietary intake or

impaired magnesium absorption compared to healthy individuals; Rude RK[45] , Mc Nair P, Christiansen MS et al [29] in their study found excessive urinary magnesium loss in diabetes. Recently defective tubular reabsorption in thick ascending loop of henle is postulated, that results in hypomagnesemia. The reason for the tubular defect is unclear. In diabetes low serum magnesium status due to low dietary intake is unlikely. Only 5.4% of the diabetic groups and 9.1% of the control group in European dietary assessment studies by Walti MK Zimmermann et al[36] had intake of magnesium below their individual requirements. In addition type 2diabetes patients with reasonable metabolic control absorb dietary magnesium to a similar extent as healthy controls. In diabetes hyperglycemia and osmotic diuresis may cause excessive urinary loss of magnesium and leads to low serum magnesium status.

AGE, SEX IN DIABETICS & HYPOMAGNESEMIA :

In our study maximum number of diabetics occurred in the age group 51 – 70 yrs(35 patients);youngest patient in our study was of the age 45 years ; mean age of diabetic patients in our study was 57.73 ; hypomagnesemia occurred maximally in the age group 61 – 70yrs (45 %) ; all patients who were > 70 years old were

hypomagnesemic (100 %) ; mean age of hypomagnesemia in our study was 63.14 years; As the age increased the prevalence of hypomagnesemia increased in diabetics ; p value was 0.0001 ; according to Yajinick et al[52] and Al Osali ME ,Al Qassabi SS et al[18] proved a significant correlation between age and magnesium levels ; the former also proved a correlation between the male sex and magnesium levels ; our study concurred with the above studies with regards to age but not with sex preponderance and magnesium levels ; In our study 54 patients were males and 46 were females ; 24 among the females had hypomagnesemia (52 . 17 %) ;18 of the males had hypomagnesemia (33 %) ;the association between gender and hypomagnesemia was not significant as seen by the p value 0.057 ;

DURATION, MODE OF TREATMENT OF DIABETES & HYPOMAGNESEMIA:

Among the 100 , 64 patients had diabetes for less than 10 years ; among them 11 had hypomagnesemia (17 %) ; 6 patients had diabetes mellitus for > 20 years ; all 6 had hypomagnesemia ; (100 %) ;30 patients had diabetes for 10 – 20 years and among them 83 % had hypomagnesemia ; the p value for the association between the

duration of diabetes and hypomagnesemia was significant namely 0.0001 ; thus longer the duration more the hypomagnesemia; this is in concurrence with the study of Sharma A , Dabla A et al[6] done in Bikaner.

Among the 100 patients ,44 had been treated with insulin and 56 had been on OHAs. The insulin treated group had higher prevalence of hypomagnesemia (83%) and the p value of 0.0001 proves its statistical significance ;Yajinik et al[52] also proved similarly ; the mechanism could be due to intracellular shifting of magnesium by insulin ; similar results were also obtained in Alzaida et al [53] . Though Walti MK[36] had differing results in his study ;

FASTING BLOOD SUGAR , HB A1C% & HYPOMAGNESEMIA:

Yajinick CS Smith RF et al[52] found that an inverse relationship exists between fasting blood glucose ,the percentage of HbA1c and serum magnesium. This was also corroborated by the study done by Alzaida A Dinneen SF[53] ; Schlienger et al[47] studied the relationship of glycemic control and various trace elements and reported low serum magnesium status in patients with uncontrolled diabetes.

In our study 22 patients had poor control of blood sugar as evidenced by FBS of > 130 mg /dl ;Among them 18 had hypomagnesemia (81.8 %) ;51 patients had FBS in the range 101 – 130 mg /dl ; among them 20 had hypomagnesemia (40 % . With statistical analysis it is seen that those with poor blood sugar control had higher prevalence of hypomagnesemia as evidenced by the p value of 0.0001 which is significant.

On analyzing the HbA1c% results , we found that 3 patients had values in the range of 9 – 10% all 3 of them had hypomagnesemia(100 %) 32 patients had a value in the range 7 – 9% among them 30 had hypomagnesemia (93.75 %). Only 2 % of the patients who had normal HbA1c values developed hypomagnesemia; the p value for this association is also 0.0001 making it statistically significant .This is similar to the study of Tosiello et al[4] . Normomagnesemic patients had better control of FBS & HbA1c than the hypomagnesemia groups; this is well supported by the study done by Prabodh ,Prakash et al[20].

DIABETIC RETINOPATHY & HYPOMAGNESEMIA:

In the 100 patients we had , 34 patients were found to have retinopathy , among whom 27 had hypomagnesemia (9 %) ; the

percentage of hypomagnesemic patients who had retinopathy was 64 % ; the normomagnesemic patients had only 12.5 % of retinopathy ; the p value indicating the association was 0.0001 which was statistically significant ; studies which show similar results as ours are Ceriello A et al[10,] , McNair et al[11], De walk HV et al[5],Hatwal A, Gujral AS et al[8] The exact pathogenesis of retinopathy is not yet proved although Grafton [42] et al hypothesed the inositol transport theory .

DIABETIC NEUROPATHY & HYPOMAGNESEMIA:

Only 4 patients had neuropathy but all 4 had hypomagnesemia in our study ; hypomagnesemia and presence of neuropathy were statistically correlating as shown by the p value 0.016 ; One study which correlates with our results by de Lordes Lima M , Cruz T et al [9]; but they measured intracellular magnesium ;Also Rodriguez morán M et al showed a correlation between hypomagnesemia and development of neuropathy & foot ulcer in diabetic patients[21] .

DIABETIC NEPHROPATHY & HYPOMAGNESEMIA:

Out of 100 , 14 patients had diabetic nephropathy;13 of the 42 in the hypomagnesemia group had nephropathy (30.95 %) and 1 out of the 58 in the normomagnesemia group had nephropathy (1.7 %). The p value too supported this association p = 0.0001. Studies done

by Pham PC et al[16] and Prakash DS Prabodh S et al[20] support this claim ; in a study by Corsanello , the explanation for this association was provided for this association ; i.e as there is albuminuria in diabetes mellitus , the 30 % of the serum Mg which is protein bound might be lost more in diabetic nephropathy.

CARDIOVASCULAR MORBIDITY & HYPOMAGNESEMIA:

Among the 42 hypomagnesemia patients, 8 had ischemic heart disease (19 %) ;and in the normomagnesemic group 2 had ischemic heart disease (3.5 %). The p value too is significant further reiterating the association ;(p = 0.01).

19 of the 42 hypomagnesemia were hypertensives (45 %) . whereas in the normomagnesemic patients 25 % were hypertensives [14,15] ; p value is significant for this association (p 0.04) ; Liao F ,Folsom AR et al [12] too did a similar study and confirmed this.

Reffelmann[13] T et al found that low magnesium levels increase left ventricular mass , which might prove detrimental in the long run ; Guerrero [17] et al found a significant association between metabolic syndrome , dyslipidemia and hypertension in patients with hypomagnesemia;In the Bikaner study Sharma[6] et al also proved the correlation between hypertension and hypomagnesemia in diabetics.

In the end after comparing all the variables and complications between the normomagnesemic and hypomagnesemic groups, it has been found that complication rate was more in the hypomagnesemia group(67 %) than the normomagnesemic group(40 %).

The three prominent complications analyzed in the study are retinopathy , nephropathy and neuropathy ; the p value that we got was < 0.005 emphasizing the significance of the association ; Sharma et al also found that hypomagnesemic diabetic patients had more complications than normomagnesemic diabetic patients.

SUMMARY AND CONCLUSIONS

In our study done in hundred patients admitted in general medical ward in Stanley Medical College Hospital following conclusions were obtained. Summarizing our study :

- 42 patients had hypomagnesemia (42 %)
- Youngest patient in our study was 45 years of age ; mean age of patients in our study was 57.73 years
- All patients who were > 70 years were hypomagnesemic
- As the age increased prevalence of hypomagnesemia increased ; this concurred with studies done before.
- As the duration of diabetes increased the prevalence of hypomagnesemia increased ; this was similar to the study result of Sharma et al ;
- Those who had a higher FBS and HbA1c% had higher prevalence of hypomagnesemia. This concurred with studies done before.
- Hypomagnesemic patients had a higher incidence of complications like neuropathy, retinopathy, and nephropathy.

- Hypomagnesemia correlated with higher incidence of ischemic heart disease and hypertensive heart disease.

CONCLUSION

- Low serum magnesium levels are commonly seen in diabetic patients.
- Hypomagnesemia is more common in diabetic patients with poor glycemic control.

Hypomagnesemia in diabetic patients correlates well with duration of illness, glycemic control and complications of diabetes mellitus - both macro vascular and micro vascular

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INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A study of fasting serum magnesium levels in type 2 diabetes mellitus and its correlation with complications

Principal Investigator : Dr.R.Pandichelvan PG in in MD(GM)

Designation : PG in MD(GM)

Department : Department of Medicine
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 18.04.2011 at the Modernized Seminar Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate form the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

PROFORMA

PATIENT DETAILS :

Name :

Inpatient No :

Age :

Sex :

Occupation :

DIABETIC HISTORY :

Age of onset :

Total duration :

Mode of treatment :

Oral hypoglycemic agents :

Insulin :

SYMPTOMS RELATED TO COMPLICATIONS :

a) Symptoms of neuropathy

Postural dizziness

Weakness

Numbness / Paraesthesia

Bladder incontinence

Impotence

b) Symptoms of nephropathy

Oliguria

Oedema

c) Symptoms of retinopathy

Dimness of vision

Blindness

PAST HISTORY :

Ischemic heart disease, Hypertension,
Chronic Kidney disease

PERSONAL HISTORY :

Smoking, Alcohol abuse

FAMILY HISTORY :

Diabetes mellitus

Ischemic heart disease

Hypertension

GENERAL EXAMINATION :

Pulse rate :

Blood pressure :

Consciousness :

Orientation :

Icteric/ Anemic :

Cyanosis / Clubbing

BPPE / Puffiness of face :

CARDIOVASCULAR SYSTEM EXAMINATION :

RESPIRATRORY SYSTEM EXAMINATION :

ABDOMINAL EXAMINATION :

CENTRAL NERVOUS SYSTEM EXAMINATION :

HIGHER MENTAL FUNCTION EXAMINATION :

CRANIAL NERVE EXAMINATION :

FUNDUS EXAMINATION :

MOTOR SYSTEM :

Wasting :

Power :

Tone :

Reflexes :

SENSORY SYSTEM EXAMINATION :

INVESTIGATIONS :

URINE :

Albumin :

Sugar :

Deposits :

24 HR URINE ALBUMINURIA :

RENAL FUNCTION TEST :

Urea :

Creatinine :

RANDOM BLOOD SUGAR :

FASTING BLOOD SUGAR :

POSTPRANDIAL BLOOD SUGAR :

ELECTROLYTES :

Sodium :

Potassium :

Chloride :

Bicarbonate :

Fasting Serum Magnesium :

ELECTRO CARDIOGRAM :

ECHO CARDIOGRAM :

NERVE CONDUCTION STUDY :

USG ABDOMEN :

FASTING LIPID PROFILE

MASTER CHART

Sl. No.	Name	Age	Sex	IP	AOD	DUR	TRT	FBS	PPBS	HBA1c	Mg	IHD	HT	RET.	NEU.	NEP.
1	vijaya	56yrs	female	11019	45yrs	11yrs	oha	145	222	8.07	1.5	-	-	npdr	-	-
2	mahesh	62yrs	male	12109	55yrs	7yrs	oha	132	210	7.5	2.2	-	+	npdr	-	-
3	jegan	49yrs	male	12211	45yrs	4yrs	oha	101	185	6.5	1.9	-	+	nil	-	-
4	sundar	58yrs	male	12218	51yra	6yrs	oha	118	167	6.9	1.2	-	+	npdr	-	-
5	meena	69yrs	female	13319	48yrs	21yrs	IN.	139	189	7.2	1.3	-	+	npdr	-	-
6	kumar	52yrs	male	13869	50yrs	2yrs	oha	127	192	6	1.8	+	+	nil	-	-
7	sundar	51yrs	male	13970	48yrs	3yrs	oha	101	169	6.2	2.1	-	-	nil	-	-
8	lalitha	72yrs	female	13982	52yrs	20yrs	IN.	120	180	7.6	1.1	-	+	npdr	-	-
9	muthu	51yrs	male	13990	44yrs	7yrs	oha	101	146	6.2	1.9	-	-	nil	-	-
10	bala	45yrs	male	13998	40yrs	4yrs	oha	98	139	5.9	2.1	-	-	nil	-	-
11	malar	48yrs	male	14011	41yrs	7yrs	oha	132	189	6.1	2	-	-	nil	-	-
12	anbumani	59yrs	male	14112	48yrs	11yrs	IN.	142	199	7.2	1.1	-	-	npdr	-	mac
13	velan	62yrs	male	14431	50yrs	12yrs	IN.	128	178	7.6	1.2	-	+	npdr	-	-
14	meenakshi	67yrs	female	14532	48yrs	19yrs	IN.	136	208	8	1.1	-	+	pdr	-	Mac
15	chandran	51yrs	male	14578	45yrs	6yrs	IN.	109	174	5.9	1.8	+	+	nil	-	-
16	elumalai	70yrs	male	15087	51yrs	19yrs	IN.	130	195	8.4	2.3	-	+	pdr	-	Mic
17	abdhulla	59yrs	male	15289	50yrs	9yrs	oha	120	178	6.2	2.2	-	+	nil	-	-
18	madavan	53yrs	male	15351	48yrs	5yrs	oha	115	178	5.9	2.1	-	+	nil	-	-
19	narayanan	48yrs	male	15467	41yrs	7yrs	oha	121	190	5.7	2.1	-	-	nil	-	-
20	karthikeyan	56yrs	male	15567	45yrs	11yrs	IN	126	191	7.2	1.1	-	-	nil	-	mac
21	pandiyan	62yrs	male	15860	50yrs	12yrs	IN.	120	188	8	1	+	-	nil	-	-
22	anthony	60yrs	male	15967	52yrs	8yrs	oha	112	178	5.9	2.3	-	+	nil	-	-

23	juli	48yrs	female	15991	45yrs	3yrs	oha	101	160	5.5	2	-	-	nil	-	-
24	padmavathy	75yrs	female	16011	5oyrs	25yrs	IN.	141	214	6.9	1	-	+	pdr	-	-
25	susila	65yrs	female	16098	52yrs	13yrs	IN.	98	145	6	1.7	-	-	npdr	-	-
26	jothi	60yrs	female	17031	53yrs	7yrs	oha	101	165	5.9	1.5	-	+	nil	-	-
27	karuppaye	68yrs	female	17132	45yrs	23yrs	IN.	139	222	9.1	1.2	-	+	nil	-	mac
28	zaheera bee	52yrs	female	17321	48yrs	4yrs	oha	99	155	5.8	1.9	-	-	nil	-	-
29	mohamed	47yrs	male	17451	45yrs	2yrs	oha	100	163	5.5	1.8	-	-	nil	-	-
30	muniammal	70yrs	female	17552	50yrs	20yrs	IN.	129	192	8.2	1.1	-	-	nil	neuropa	mic
31	raja	65yrs	male	17821	52yrs	7yrs	IN.	120	178	7.2	1.2	-	-	nil	-	-
32	angammal	70yrs	female	18011	55yrs	15yrs	IN.	113	189	8.4	1.1	-	+	npdr	-	mic
33	seetha	56yrs	female	18092	50yrs	6yrs	oha	125	209	5.8	2.2	-	-	nil	-	-
34	muthu	53yrs	male	18321	50yrs	3yrs	oha	101	189	6.2	2.1	-	-	nil	-	-
35	manivanan	48yrs	male	18534	40yrs	8yrs	oha	107	190	6.1	1.9	-	-	nil	-	-
36	murugan	62yrs	male	18689	51yrs	11yrs	IN.	126	185	6.4	1.1	-	+	npdr	-	-
37	pusbham	60yrs	female	18698	49yrs	11yrs	IN.	145	231	6.9	1.1	-	+	npdr	-	-
38	lakshmi	61yrs	female	18751	53yrs	7yrs	oha	134	189	5.8	2.3	-	-	nil	-	-
39	anandhan	56yrs	male	18761	48yrs	8yrs	oha	98	156	5.4	2.1	-	-	nil	-	-
40	ramesh	50yrs	male	18831	45yrs	5yrs	oha	116	189	6.1	2	niil	-	nil	-	-
41	alem bee	63yrs	female	19011	46yrs	17yrs	IN.	111	177	5.9	1.9	-	-	npdr	-	-
42	andalammal	70yrs	female	19023	53yrs	17yrs	IN.	109	167	8.9	1.2	-	+	npdr	-	-
43	dhanam	58yrs	female	19078	50yrs	8yrs	oha	120	180	5.7	1.8	-	-	nil	-	-
44	lakshmi	55yrs	female	19678	49yrs	6yrs	oha	103	156	5.5	2.1	-	-	nil	-	-
45	amaravathy	70yrs	female	19689	52yrs	18yrs	IN.	128	208	7.8	1.1	+	+	pdr	neuropa	mac
46	muthu	58yrs	male	19711	48yrs	10yrs	IN.	135	234	6.9	1	-	-	npdr	-	-
47	mani	55yrs	male	19845	51yrs	4yrs	oha	111	189	5.5	2.3	-	-	nil	-	-

48	kathiravan	50yrs	male	19878	47yrs	3yrs	oha	97	156	5.8	1.9	-	-	nil	-	
49	murugan	52yrs	male	19931	50yrs	2yrs	oha	103	170	6	1.8	-	-	nil	-	-
50	kristoper	49yrs	male	19967	41yrs	8yrs	IN.	108	190	6.5	1.1	-	-	nil	-	-
51	devi	48yrs	female	20012	45yrs	3yrs	oha	117	169	6.1	1.8	-	-	nil	-	-
52	uma	50yrs	female	20045	47yrs	3yrs	oha	89	152	5.7	1.9	-	-	nil	-	-
53	mangammal	75yrs	female	20089	50yrs	25yrs	IN.	129	189	8.4	1.2	-	+	npdr	-	mac
54	kuppu	68yrs	female	20131	52yrs	16yrs	IN.	140	190	7.4	1.1	-	-	npdr	-	-
55	malarkodi	54yrs	female	20341	45yrs	9yrs	oha	114	178	6.1	2.1	-	-	npdr	-	-
56	kamatchi	60yrs	female	20467	48yrs	12yrs	IN.	120	201	8.2	1.1	-	-	npdr	nbil	-
57	bala	48yrs	male	20489	45yrs	3yrs	oha	87	143	5.4	2.2	-	-	nil	-	-
58	jeyaraj	60yrs	male	20567	47yrs	13yrs	IN.	121	194	7.6	1	+	+	nil	-	-
59	raman	55yrs	male	20589	50yrs	5yrs	oha	111	158	5.5	2.4	-	-	nil	-	-
60	vadivelan	68yrs	male	20598	50yrs	18yrs	IN.	101	170	5.9	2.1	-	+	npdr	-	-
61	yesu	56yrs	male	20875	42yrs	14yrs	IN.	121	189	6.2	2.1	-	+	npdr	-	-
62	rajan	61yrs	male	20942	50yrs	11yrs	IN.	141	190	7.5	1.2	-	-	nil	-	-
63	banu	48yrs	male	20978	40yrs	8yrs	oha	101	167	5.9	2.3	-	+	nil	-	-
64	alagar	59yrs	male	21123	52yrsw	7yrs	oha	115	178	5.2	1.9	-	-	nil	-	-
65	ammu	60yrs	female	21341	45yrs	15yrs	IN.	129	189	7.9	1.3	-	-	npdr	l-	-
66	baskaran	49yrs	male	21451	40yrs	9yrs	IN.	115	156	5.8	1.8	-	-	nil	-	-
67	suresh	50yrs	male	21551	47yrs	3yrs	oha	98	146	5.4	2.1	-	-	nil	-	-
68	kumar	62yrs	male	21768	46yrs	16yrs	IN.	126	193	8.9	1.2	-	-	nil	-	mac
69	stalin	56yrts	male	21983	50yrs	6yrs	oha	117	182	5.7	2.1	-	+	nil	-	-
70	senthil	58yrs	male	22051	55yrs	3yrs	oha	101	168	5.5	2.3	-	-	nil	-	-
71	arokiyam	65yrs	male	22976	48yrs	17yrs	IN.	135	245	9.2	1.1	+	-	pdr	-	---
72	arul	63yrs	male	23674	51yrs	12yrs	IN.	132	223	8.7	1.1	-	-	pdr	-	-

73	prakasam	51yrs	male	25438	47yrs	4yrs	oha	95	178	5.5	2.4	-	-	nil	-	-
74	kala	56yrs	female	25798	46yrs	10yrs	IN.	121	189	6.1	2.4	-	-	nil	-	-
75	janaki	67yrs	female	25890	55yrs	12yrs	IN.	137	231	7.9	1.2	-	-	nil	-	-
76	pandiyammal	82yrs	female	26741	52yrs	30yrs	IN.	145	241	8.2	1	+	+	npdr	neurp	mic
77	perumal	78yrs	male	27061	57yrs	21yrs	IN.	139	221	8.8	1.1	+	+	npdr	-	mic
78	muthu	56yrs	male	27141	52yrs	4yrs	oha	120	199	5.6	2	-	-	nil	-	-
79	saravanan	49yrs	male	27431	42yrs	7yrs	oha	118	1899	5.9	1.8	-	-	nil	-	-
80	krishnan	51yrs	male	27561	47yrs	4yrs	oha	119	178	6.1	1.9	-	+	nil	-	-
81	vali	58yrs	female	28975	45yrs	13yrs	IN.	145	221	9.8	1.2	+	-	npdr	-	mac
82	annam	60yrs	female	29864	52yrs	8yrs	IN.	125	216	8.7	1.1	-	+	npdr	-	-
83	ponni	63yrs	female	29880	55yrs	8yrs	oha	118	187	5.9	2.4	-	-	nil	-	-
84	kaveri	65yrs	female	32171	45yrs	20yrs	IN.	136	243	7.9	1.3	+	-	npdr	-	-
85	sakthi	52yrs	female	33421	48yrs	4yrs	oha	129	212	7.2	1.1	-	-	npdr	-	-
86	palani	51yrs	male	33867	49yrs	2yrs	oha	120	178	6.8	1.1	-	-	nil	-	-
87	samy	49yrs	male	35678	44yrs	5yrs	oha	116	189	6.2	2.1	-	-	nil	-	-
88	thomas	58yrs	male	36789	50yrs	8yrs	oha	108	167	7.5	1.1	-	+	nil	-	-
89	bharathi	49yrs	female	37821	45yrs	4yrs	oha	124	179	5.5	1.9	-	+	nil	-	-
90	karpagam	59yrs	female	39801	52yrs	7yrs	oha	111	167	5.3	1.8	-	+	nil	-	-
91	selvi	48yrs	female	40124	45yrs	3yrs	oha	120	157	6.1	1.7	-	-	nil	-	-
92	surya	49yrs	female	41132	44yrs	5yrs	oha	121	197	6.9	1.2	-	-	nil	-	-
93	subha	47yrs	female	42361	43yrs	4yrs	oha	109	177	5.8	2.1	-	-	nil	-	-
94	padmini	55yrs	female	42382	50yrs	5yrs	oha	126	206	5.9	2.2	-	-	nil	-	-
95	thangam	60yrs	female	43351	51yrs	9yrs	IN.	145	225	6	2.1	-	-	nil	-	-
96	raman	65yrs	male	45367	50yrs	15yrs	IN.	135	256	8.4	1.1	-	-	npdr	neuropa	mac
97	punitha	54yrs	female	46731	48yrs	6yrs	oha	123	185	6.2	1.9	-	-	nil	-	-

98	shanthi	55yrs	female	47889	47yrs	8yrs	IN.	130	245	7.6	1.2	-	-	nil	-	-
99	sarasvathy	52yrs	female	48821	49yrs	3yrs	oha	120	186	5.9	1.8	-	-	nil	-	-
100	lakshmi	55yrs	female	49841	48yrs	7yrs	oha	124	187	5.4	2.2	-	-	nil	-	-