

A Dissertation on

**STUDY ON SERUM MAGNESIUM LEVELS IN DIABETIC
PATIENTS WITH MICROVASCULAR COMPLICATIONS.**

Submitted to

**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032**

In partial fulfilment of the Regulations
for the Award of the Degree of

M.D. BRANCH - I

GENERAL MEDICINE



**DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
CHENNAI – 600 001
APRIL 2017**

CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr.ARUNKUMAR.P.P**, Post - Graduate Student (May 2014 TO April 2017) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on “**STUDY ON SERUM MAGNESIUM LEVELS IN DIABETIC PATIENTS WITH MICROVASCULAR COMPLICATIONS**” under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2017.

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DECLARATION

I, **Dr.ARUNKUMAR.P.P**, declare that I carried out this work on “**STUDY ON SERUM MAGNESIUM LEVELS IN DIABETIC PATIENTS WITH MICROVASCULAR COMPLICATIONS**” at the out patient department and Medical wards of Government Stanley Hospital . I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

Dr.ARUNKUMAR.P.P

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Principal Investigator : Dr. Arun Kumar P.P

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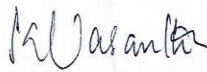
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INTRODUCTION

Type 2 Diabetes mellitus is a metabolic and endocrine disease characterized by hyperglycemia associated with both insulin resistance and defective insulin secretion. It accounts for approximately 90 to 95% of all diagnosed cases of diabetes mellitus. Type 2 DM may be associated with cardiovascular disease, nephropathy, retinopathy and polyneuropathy and complications like hypervolar coma and ketoacidosis (DKA).

Hypomagnesemia has been reported to occur at an increased frequency among patients with type 2 DM compared with their counterparts without diabetes. Excessive urinary magnesium loss associated with glycosuria is probably the most important factor in the genesis of hypomagnesemia in diabetic patients. Initially the cause of hypomagnesemia 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. Recent studies showed a specific tubular defect in diabetes which lead to hypomagnesemia causing defective tubular absorption of magnesium.

Although diabetes can induce hypomagnesemia, deficiency of magnesium has also been proposed as a risk factor for Type 2 DM. Magnesium is a necessary cofactor for several enzymes that play an important role in glucose metabolism. It is also essential for neuromuscular excitability and cell permeability, mitochondrial function regulation of ion channels and is important in both cellular and humoral immune reactions.

Magnesium is involved at multiple levels of insulin secretion, binding and activity.

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	• MASTER CHART	

INTRODUCTION

Type 2 Diabetes mellitus is a metabolic and endocrine disease characterized by hyperglycemia associated with both insulin resistance and defective insulin secretion. It accounts for approximately 90 to 95% of all diagnosed cases of diabetes mellitus¹. Type 2 DM may be associated with cardiovascular disease, nephropathy, retinopathy and polyneuropathy and complications like hyperosmolar coma and ketoacidosis (DKA).

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Although diabetes can induce hypomagnesemia, deficiency of magnesium has also been proposed as a risk factor for Type 2 DM. Magnesium is a necessary cofactor for several enzymes that play an important role in glucose metabolism. It is also essential for neuromuscular excitability and cell permeability, mitochondrial function regulation of ion channels and is important in both cellular and humoral immune reactions.

Magnesium is involved at multiple levels of insulin secretion, binding and activity. Deficiency at cellular level can alter the membrane bound sodium-potassium-adenosine triphosphate which is involved in the maintenance of gradients of sodium and potassium and in glucose transport. 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 tissues to insulin in the presence of adequate magnesium levels⁶.

Deficiency of Magnesium was found to be associated with micro vascular disease. Hypomagnesemia has been demonstrated in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severity of diabetic retinopathy⁵. Magnesium depletion was associated with multiple cardiovascular implications, arrhythmogenesis, hypertension, vasospasm and impaired platelet activity⁴. The clinical complications of magnesium deficiency include impairment of insulin secretion, insulin resistance and increased vascular complications.

The treatment of patients with diabetes mellitus requires a multidisciplinary approach where by every potential complicating factor must be monitored closely and treated. In particular, although hypomagnesemia has been reported to occur with increased frequency among patients with type 2 DM, it is frequently overlooked and undertreated.

Animal studies have shown that Mg deficiency has a negative effect on the post-receptor signaling of insulin. Short term studies prove oral magnesium supplementation has beneficial effect on Insulin action and glucose metabolism³. Paolisso et al⁷ demonstrated that oral magnesium supplements given for 4 weeks to elderly patients with Type 2 diabetes resulted in lower fasting plasma glucose levels, increased plasma and erythrocyte magnesium levels and a slight but statistically significant increase in β -cell response to glucose and arginine.

The present study is to evaluate serum magnesium levels in Type 2 diabetes mellitus.

AIMS & OBJECTIVES

- **TO FIND OUT THE RELATION BETWEEN SERUM MAGNESIUM AND DIABETES.**
- **TO FIND OUT THE RELATION BETWEEN SERUM MAGNESIUM AND DIABETIC MICROVASCULAR COMPLICATIONS.**

REVIEW OF LITERATURE

Type 2 diabetes is emerging as one of the major global health challenges of the 21st century. Hypomagnesemia has long been 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 type 1 and type 2 DM and is not affected by the type of therapy⁸. A change in glucose disposal at cellular level has been shown to be related to increased sensitivity of the tissues to insulin in the presence of adequate magnesium levels.

DIABETES MELLITUS

Definition: Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronicity of the disease is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels²⁴.

It is emerging as the chronic non –communicable disease of concern in developing countries with changing life styles, environment and urbanization. It is major cause of morbidity and mortality. The study by Mohan et al showed that Indians have high ethnic susceptibility for developing diabetes at a younger age group and develop vascular complications earlier and more frequently during the natural progression of the disease.¹⁰¹

Pathogenic processes involved in the development of diabetes range from auto-immune destruction of the beta cells of the pancreas with consequent insulin deficiency to abnormalities in carbohydrate, fat and protein metabolism. Deficient insulin action results from inadequate insulin secretion and diminished tissue responses to insulin at one or more points in the complex pathways of hormone action.

Diabetes is worldwide in distribution and the incidence of both types of primary diabetes, i.e. Type 1 and 2 is rising. However the prevalence of both varies considerably in

different parts of the world and this is probably due to differences in genetic and environmental factors.

Etiologic Classification of Diabetes mellitus¹

- I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)
Immune mediated
Idiopathic
- II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)

III. Other specific types:

- Genetic defects of beta cell function
- Genetic defects in insulin action
- Disease of the exocrine pancreas
- Infection
- Drug or chemical related Uncommon factors of immune mediated diabetes
- Endocrinopathies
- Other genetic syndromes associated with diabetes

IV. Gestational Diabetes Mellitus (GDM).

Though patient may present with ketoacidosis, they can shortly return to normoglycemia without requiring continuous therapy (Honeymoon remission)

In rare incidences, patients in these categories (e.g.: Type 1 Diabetes, vacor toxicity presenting in pregnancy) may require insulin for survival.

Symptoms of Diabetes Mellitus

Symptoms of marked hyperglycaemia include increased thirst, increased urination, intense hunger, weight loss, blurred vision, fatigue, slow-healing sores or frequent infections

Type 2 diabetes frequently goes undiagnosed for many years because the hyperglycaemia develops gradually.

TYPE 2 DIABETES²⁴

Type 2 DM is characterized by insulin resistance and usually relative (rather than absolute) insulin deficiency due to predominantly an insulin secretory defect. Mostly patients with this form of diabetes are obese. Ketoacidosis may seldom occur spontaneously. These patients are at increased risk of developing macrovascular complications. Insulin secretion is defective in these patients and insufficient to compensate for the insulin resistance.

Genetics: Genetic factors are more important in the etiology of type 2 than type 1 diabetes.

The majority of the cases of type 2 diabetes are multifactorial in nature, with interaction of environmental and genetic factors.

Environmental factors:

Age: Type 2 diabetes is principally a disease of the middle aged and elderly affecting 10% of the population over the age of 65.

Life Style: A number of lifestyle factors are known to be important for the development of Type 2 diabetes mellitus including obesity, physical activity, diet, stress and urbanization. Chronic obesity probably acts as a diabetogenic factor by increasing resistance to the action of insulin.

Malnutrition in Utero: Studies have shown that intrauterine as well as infancy under nutrition can damage beta cell development at a crucial period leading to type 2 diabetes later in life.

PATHOGENESIS OF TYPE 2 DIABETES²⁴

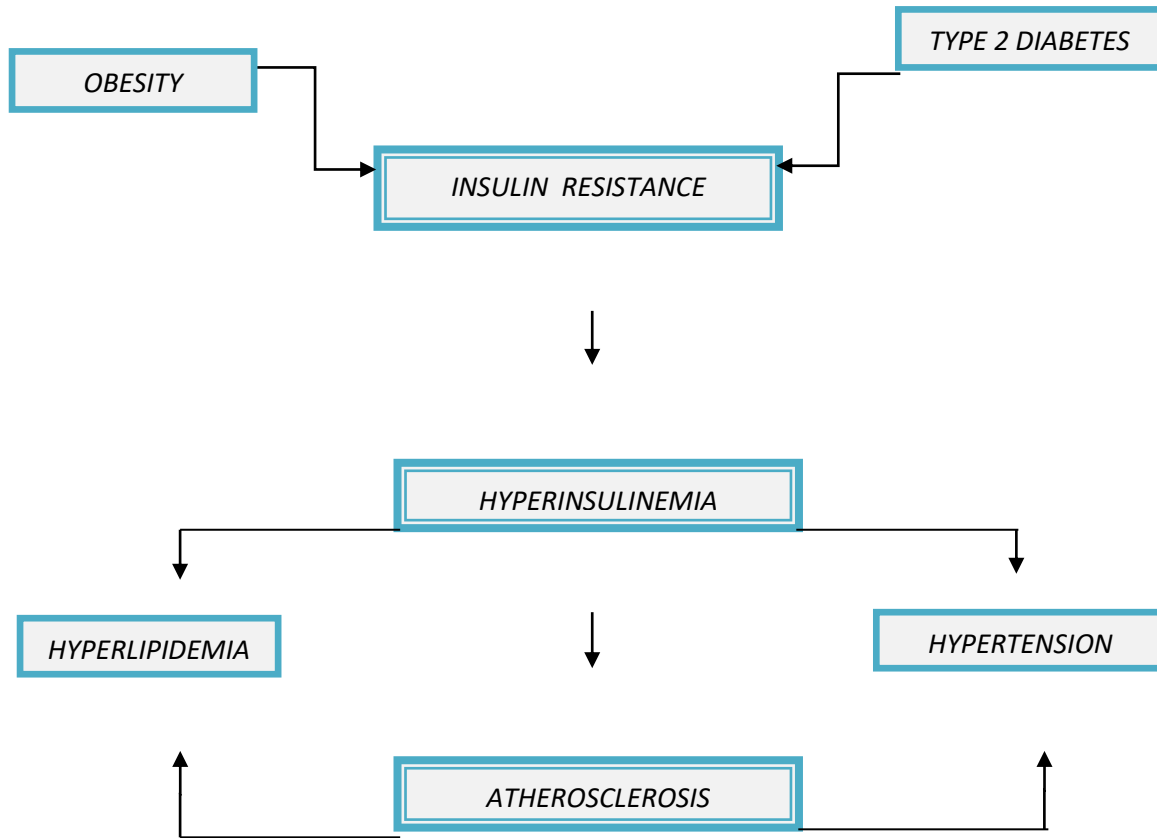


Figure 1

Insulin Resistance:

Insulin resistance may be due to any one of the three causes:

- An abnormal insulin molecule
- Excessive amount of circulating antagonists
- Target tissue defects.

In obese and non-obese individuals, increased hepatic production of glucose and resistance to the action of insulin in muscle are invariable

The characteristic feature of type 2 diabetes is that it is often associated with obesity, hypertension and hyperlipidemia. It has been suggested that this cluster of conditions, all of which predispose to cardiovascular disease, is specific entity (the metabolic syndrome or syndrome X) with insulin resistance being the primary defect.

METABOLIC DISTURBANCE IN DIABETES

Insulins actions are impaired by insensitivity of target tissues in Type 1 and Type 2 diabetes. The hyperglycemia of diabetes develops because of an absolute (type 1 diabetes) or a relative (type 2 diabetes) deficiency insulin .Hyperglycemia can also induce insulin resistance through glucose toxicity.

It is when the plasma glucose concentration exceeds the renal threshold (the capacity of renal tubules to reabsorb glucose from the glomerular filtrate) at approximately 10 mmol/L, glycosuria occurs which depends on the severity of the classical osmotic symptoms of polyuria and polydypsia . The renal threshold for glucose rises, and the symptoms of diabetes are mild if hyperglycemia develops slowly over months or years, as in type 2 diabetes²⁴.

Long term complications of diabetes include retinopathy with potential loss of vision; nephropathy resulting in increased morbidity and premature death, peripheral neuropathy with risk of foot ulcers, amputation and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary and cardiovascular symptoms and sexual dysfunction. Diabetic

patients have an increased incidence of atherosclerotic cardiovascular peripheral vascular and cerebrovascular disease. Hypertension, abnormalities of lipoprotein metabolism and periodontal disease are found in people with diabetes.

Acute complications include

- 1) **Nonketotic Hyperosmolar Syndrome:** It is characterized by severe hyperglycemia without significant hyperketonaemia or acidosis.
- 2) **Diabetic Ketoacidosis:** characterized by hyperglycemia, hyperketonemia and metabolic acidosis.
- 3) **Hypoglycemia:** The risk of hypoglycemia is the most important single factor limiting the attainment of the therapeutic goal, namely near normal glycemia. It occurs often in diabetic patients being treated with insulin.

Criteria for the diagnosis of Diabetes¹

A diagnosis of diabetes is made usually by the following criteria

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis a random Plasma glucose > 200 mg / dl (11.1 mmol/L)

OR

HBA1C $> 6.6\%$. The test should be performed in a laboratory using a method that is NGSP Certified and standardized to the DCCT assay.

OR

Fasting Plasma Glucose >126 mg/dl (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hrs.

OR

2-Hr 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.

MICROVASCULAR COMPLICATIONS OF DIABETES

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 thereafter².

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 retinopathy².

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 HbA1c⁴⁸ and tight BP control results in 34% reduction in progression of retinopathy⁵⁴.More than 90% type1 DM nephropathy patients have diabetic retinopathy, where as only 60% of diabetic nephropathy have retinopathy.

MAGNESIUM HOMEOSTASIS

MAGNESIUM

It is the fourth most abundant cation in the body and within the cell second only to potassium. The adult human body (70 kg) contains 21 to 28 gm of magnesium (approximately 1 mol). Of this, about 60% is in bone, 20% in skeletal muscle, 19% in other cells and 1 % in ECF.

BIOCHEMISTRY

Magnesium is an alkaline earth metal and has chemical properties distinctly different from those of the transition metals. Compared with transition metals, magnesium interacts with other chemical species with a stronger electrostatic bonding component and a relative preference for oxygen over nitrogen atoms¹¹. There are two major roles for magnesium in biological systems:

- It can form chelation with important intracellular anionic ligands, notably adenosine triphosphate (ATP).
- It can compete with calcium for binding sites on proteins and membranes.

Magnesium activates and catalyses more than 300 enzymes in the body. It acts as an essential cofactor for enzymes concerned with cell respiration, glycolysis and transmembrane transport of other cations such as calcium and sodium. Notably the activity of Na-K-ATPase depends on magnesium. It can affect enzyme activity by binding the active site of the enzyme (pyruvate kinase, enolase) by ligand binding (ATP-requiring enzymes), by causing conformational changes during the catalytic process (Na-K-ATPase) and by promoting aggregation of multienzyme complexes¹².

The permeability characteristics and electric properties of membranes are affected by magnesium. Decreased extracellular magnesium concentrations increase membrane excitability in tissues such as the heart. Magnesium acts to maintain a low resting

concentration of intracellular calcium ions .It competes with calcium for membrane binding sites and stimulates calcium sequestration by the sarcoplasmic reticulum a necessary prerequisite for triggering the function of calcium in several processes¹².

DISTRIBUTION

Magnesium is the fourth most abundant cation in the body and second most prevalent intracellular cation. The total body magnesium content is approximately 25 g (1.03 mol)of which about 60% resides in skeleton.One third of skeletal magnesium is exchangeable and serves as a reservoir for maintaining a normal extracellular magnesium concentration.40% of bodys magnesium is intracellular. The concentration of magnesium in the cells is approximately 1 to 3 mmol/L. In general, higher the metabolic activity of a cell, higher is its magnesium content ¹⁰.

Magnesium is compartmentalized within the cell and most of it is bound to proteins and negatively charged molecules.80% of cytosolic magnesium is bound to ATP. Significant amounts are found in the nucleus, the mitochondria and endoplasmic reticulum. Of the total cellular magnesium, free magnesium accounts for 0.5% to 5% of total cellular magnesium and it is this fraction that is probably important for enzyme activity. This free fraction is maintained at a constant concentration by a specific magnesium transport system that regulates the rate at which magnesium is taken up or extruded by the cell and because plasma membrane is quite impermeable to magnesium.

Extracellular magnesium constitutes about 1 % of total body magnesium content. The normal range is approximately 1.6 to 2.4 mg/dl about 55 % of magnesium is free, 30% associated with proteins (primarily albumin) and 15 % complexed with phosphates, citrates and other anions.

METABOLISM

Magnesium intakes vary appreciably, an approximate range for Indian population being 140 to 180 mg/dl. The recommended dietary allowance for magnesium is 20 -350 mg/dl for adults. The magnesium content of food varies widely. Drinking water especially hard water may be major source of magnesium¹⁰. Appreciable amounts are seen in vegetables containing chlorophyll, seafood, nuts and grains whereas oils, fats, sugars contain little amount.

GASTROINTESTINAL METABOLISM

Gastrointestinal absorption mainly occurs in the small intestines via paracellular simple diffusion at high intraluminal concentrations and active transcellular uptake via Mg-specific transporters at low concentrations. 25 to 60 % of dietary Mg is absorbed in the gastrointestinal tract. 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. Mutations of TRPM6 have been reported to be associated with hypomagnesemia with secondary hypocalcemia. Any process interfering with the above result in hypomagnesaemia. These include chronic alcoholism, childhood malnutrition, lactation, acute pancreatitis, prolonged intravenous feeding and various diseases causing malabsorption.

RENAL METABOLISM

The major excretory pathway for absorbed magnesium is through the kidney. The kidneys are the main organs of magnesium homeostasis in maintaining plasma homeostasis in maintaining plasma concentrations. During periods of magnesium depletion kidney magnesium excretion can be markedly reduced. Only 3 to 6 % of filtered load in the kidney is excreted¹³.

Approximately 25% of the filtered magnesium is reabsorbed in the proximal tubule and 50 to 60% in the ascending limb of loop of Henle. Reabsorption of magnesium in the distal tubule is load dependent. The renal clearance and plasma concentrations are often related to those of calcium, phosphate, sodium and potassium. There is evidence for hormonal regulation of renal clearance of magnesium similar to that of potassium. The major part of magnesium in plasma (about 60-70%) exists as free ions or in the form of various diffusible complexes, the remainder is bound to protein.

GLOMERULAR FILTRATION

Approximately 70 to 80 % of plasma Mg is unfilterable in the ionic form (70 to 80%) and complexed with anions such as phosphate, Citrate and oxalate (20 to 30 %). 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 glomerular basement membrane.

PROXIMAL TUBULES

About 15 to 25 % Mg is reabsorbed in the proximal tubules, once it is filtered through the glomerulus. Reabsorption takes place at the proximal tubule mainly by passive mechanism. It is proportional to sodium and water reabsorption, although at a lower rate

LOOP OF HENLE

In the thick ascending limb of loop of Henle (TAL) approximately 65 to 75 % of the magnesium filtered load is reabsorbed via the paracellular pathway. 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 and hypercalciuria and nephrolithiasis. Parathyroid hormone, calcitonin, glucagon, and antidiuretic hormone have been suggested to enhance Mg transport in the TAL via the second messenger cAMP. Insulin also has been implicated to play a role at

this nephron segment by increasing the favorable transepithelial potential difference for Mg reabsorption.

DISTAL CONVOLUTED TUBULE

Approximately 5 to 10% of the filtered Mg *via* an active and regulated transcellular pathway is reabsorbed in the distal convoluted tubule (DCT). However it represents 70 to 80% of Mg that is delivered from the TAL, though it is of a low percentage of filtered magnesium load. 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.

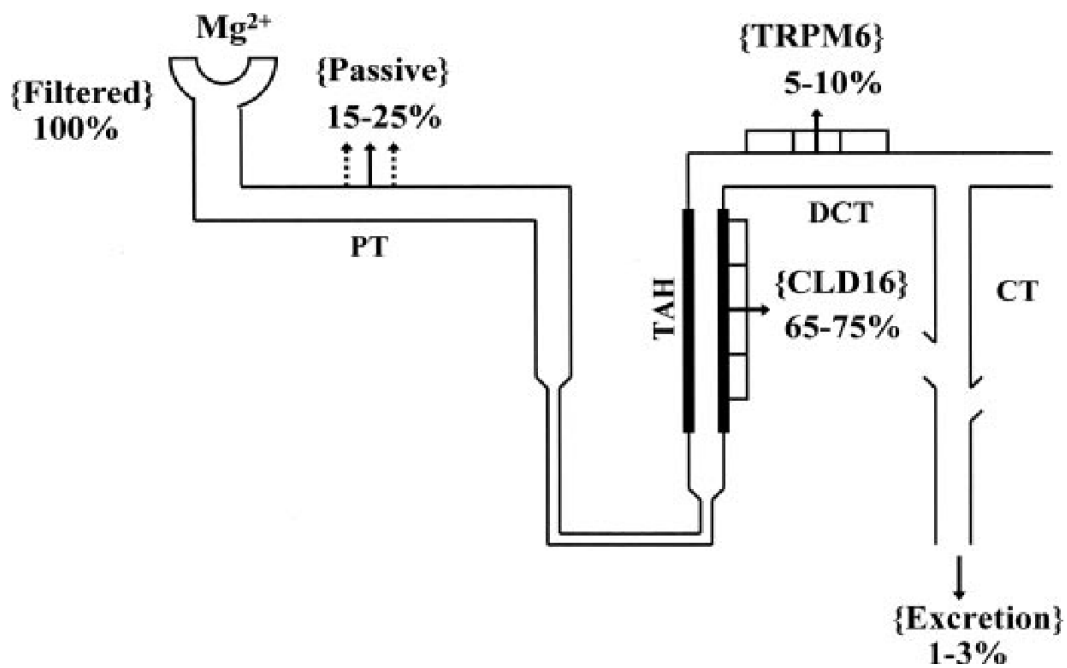


Figure 2

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 Na²⁺/Mg²⁺ exchanger and/or ATPdependent Mg pump. It is interesting that the

regulation of magnesium reabsorption at the DCT was studied extensively before the actual identification of TRPM6¹⁷.

Peptide hormones such as parathyroid hormone (PTH), calcitonin, glucagon, and vasopressin all had 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 $\text{Ca}^{2+}/\text{Mg}^{2+}$ 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 up regulate renal TRPM6 expression and reduce urinary Mg excretion¹⁸.

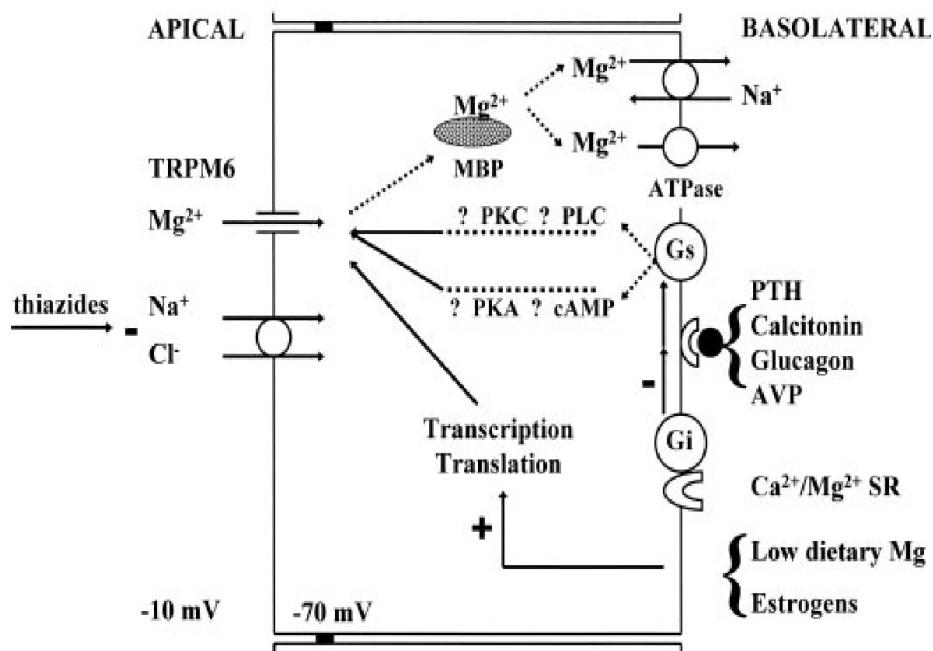


Figure 3

CLINICAL SIGNIFICANCE

The best defined manifestation of magnesium deficiency is impairment of neuromuscular junction; examples are hyperirritability, tetany, convulsions and electrocardiographic changes. Magnesium deprivation has been associated with cardiovascular disease through epidemiological evidence that relates low magnesium intake to a high incidence of cardiac deaths, particularly in soft water areas where waterborne magnesium is low and a low incidence of cardiac deaths in hard water areas where magnesium intakes are higher¹⁹. Hypertension, myocardial infarction, cardiac dysrhythmias, coronary vasospasm and premature atherosclerosis also have been linked to magnesium depletion^{20, 21}.

Human magnesium deficiency as indicated by reduced serum magnesium amounts (hypomagnesemia) occurs with either normal or reduced serum calcium concentrations²². Hypomagnesemia may be secondary affect in hypocalcemia or calcium deficient tetany. Yet a hypomagnesemic-normocalcemic tetany has been described that can be effectively treated with magnesium supplementation alone. During tetany serum magnesium concentrations of 0.15 to 0.5 mmol/lit accompanied by normal serum calcium and pH have been reported. There is evidence that tetany accompanied by hypocalcemia and hypomagnesemia may not be optimally treated with calcium administration alone. Decreased serum potassium concentrations (hypokalemia) have also been found to accompany magnesium depletion. The occurrence of otherwise unexplained hypokalemia or hypocalcemia should suggest magnesium deficiency^{10, 15}.

Magnesium depletion occurs in conditions that disrupt the normal renal conservation of magnesium, for example in patients with renal tubular reabsorption defects and those taking chlorothiazides, ammonium chloride or mercurial diuretics for congestive heart failure²³. Its also seen in chronic glomerulonephritis, aldosteronism, and digitalis intoxication.

Increased serum magnesium concentrations have been observed in dehydration, severe diabetic acidosis and Addison's disease. Conditions like uremia which interfere with glomerular filtration results in retention of magnesium and hence elevation of serum concentrations of the same. Hypomagnesaemia leads to an increase in atrioventricular conduction time on the electrocardiogram³.

DIAGNOSIS OF HYPOMAGNESEMIA

Clinically, hypomagnesaemia may be defined as a serum Mg concentration ≤ 1.6 mg/dl or ± 2 SD below the mean of the general population. However, because Mg is mostly an intracellular cation, it has been questioned whether one can use measurements of serum Mg concentrations to study the impact of Mg on various physiologic conditions. Some investigators, instead, have used measurements of intracellular Mg concentrations. Clinically, it has been suggested that in a patient with suspected Mg deficiency, a low serum Mg concentration is sufficient to confirm the diagnosis. If the serum Mg level is normal in the same patient, then other more sensitive tests should be performed. Although controversies still exist as to how hypomagnesaemia is best gauged, the current understanding on the clinical impact of hypomagnesaemia in human is influenced by studies that have relied predominantly on the measurements of serum Mg concentrations³.

INCIDENCE OF HYPOMAGNESEMIA AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

Hypomagnesaemia, defined by low serum Mg concentrations, has been reported to occur in 13.5 to 47.7% of nonhospitalized patients with type 2 diabetes compared with 2.5 to 15% among their counterparts without diabetes²⁵⁻²⁷. The wide range in the reported incidence of hypomagnesaemia most likely reflects the difference in the definition of hypomagnesaemia, techniques in Mg measurements, and the heterogeneity of the selected patient cohort. In terms of gender difference, it is interesting to note that independent studies

have reported a higher incidence of hypomagnesaemia in women compared with men, at a 2:1 ratio²⁸⁻³⁰. In addition, men with diabetes may have higher ionized levels of Mg³¹.

Hypomagnesaemia and Diabetes: Cause and Effect

Not only has hypomagnesaemia been associated with type 2 diabetes, but also numerous studies have reported an inverse relationship between glycemic control and serum Mg levels³²⁻³⁴. Although many authors have suggested that diabetes *per se* may induce hypomagnesaemia, others have reported that higher Mg intake may confer a lower risk for diabetes³⁵⁻³⁷. It is interesting that the induction of Mg deficiency has been shown to reduce insulin sensitivity in individuals without diabetes, whereas Mg supplementation during a 4-wk period has been shown to improve glucose handling in elderly individuals without diabetes^{38, 39}. In patients with type 2 diabetes, oral Mg supplementation during a 16-wk period was suggested to improve insulin sensitivity and metabolic control⁹. The mechanisms whereby hypomagnesaemia may induce or worsen existing diabetes are not well understood. Nonetheless, it has been suggested that hypomagnesaemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post receptor insulin signaling, and/or altered insulin–insulin receptor interactions^{40, 41}. Not all studies, however, observed a correlation between glycemic control and serum Mg levels or improvement of diabetic control with Mg replacement⁴²⁻⁴⁴. The conflicting data may reflect different study designs and populations studied.

Hypomagnesaemia and Adverse Clinical Associations in Type 2 Diabetes

Hypomagnesaemia at the Cellular Level

There is considerable evidence to suggest that hypomagnesaemia may adversely affect various aspects of cellular physiology. Available data suggest that low Mg levels may promote endothelial cell dysfunction and thrombogenesis *via* increased platelet aggregation

and vascular calcifications⁴⁵. Low Mg levels also may lead to the induction of proinflammatory and profibrogenic response²⁰, reduction of protective enzymes against oxidative stress, induction or augmentation of vasoconstriction and hypertension⁴⁶⁻⁴⁸, and stimulation of aldosterone⁴⁹, among others. Moreover, because Mg is crucial in DNA synthesis and repair⁵⁰, it is possible that Mg deficiency may interfere with normal cell growth and regulation of apoptosis.

Hypomagnesemia in the Clinical Setting

Clinically, there are significant data linking hypomagnesaemia to various diabetic micro- and macro vascular complications.

Cardiovascular: In a study that involved 19 normotensive individuals without diabetes, 17 hypertensive individuals without diabetes, and 6 hypertensive individuals with diabetes, Resnick et al⁵¹ documented the lowest mean intracellular Mg concentration among the last group. Similarly, based on data from the Atherosclerosis Risk in Communities (ARIC) Study, a multicenter, prospective cohort study that lasted 4 to 7 yr and involved 13,922 middle-aged adults who were free of coronary heart disease at baseline, an inverse association between serum Mg and the risk for coronary heart disease was observed among men with diabetes⁵².

Diabetic Retinopathy. The link between hypomagnesaemia and diabetic retinopathy was reported in two cross-sectional studies that involved both insulin-dependent patients and patients with type 2 diabetes. Not only did patients with diabetes have lower serum Mg levels compared with their counterparts without diabetes, but also the serum Mg levels among the cohort with diabetes had an inverse correlation with the degree of retinopathy^{53, 54}. A similar link, however, was not observed when Mg was measured within mononuclear cells. In a study that involved 128 patients with type 2 diabetes and poor glycemic control (glycosylated hemoglobin $\geq 8.0\%$), intramononuclear Mg concentrations were not observed to be lower

among those with diabetic retinopathy but rather among those with neuropathy and coronary disease.

Foot Ulcerations: Given the link between hypomagnesaemia and risk factors for the development of diabetic foot ulcers (*e.g.*, polyneuropathy, platelet dysfunction), Rodriguez-Moran and Guerrero-Romero⁵⁵ suggested that hypomagnesaemia may be associated with an increased risk of diabetic foot ulcers. Indeed, they observed a higher incidence of hypomagnesemia among their patients with diabetic foot ulcers compared with those without the condition (93.9% of the 33 patients with diabetic foot ulcers compared with 73.1% of the 66 patients without diabetic foot ulcers; $P = 0.02$).

Diabetic Nephropathy: In a comparative study that involved 30 patients who had type 2 diabetes without microalbuminuria, 30 with microalbuminuria, and 30 with overt proteinuria, Corsonello et al⁵⁶ (49) observed a significant decrease in serum ionized Mg in both the microalbuminuria and overt proteinuria groups compared with the nonmicroalbuminuric group. Accordingly, in a recent retrospective study, an association between low serum Mg levels and a significantly faster rate of renal function deterioration in patients with type 2 diabetes was reported.

Others: Finally, there also are data to suggest the association between hypomagnesaemia and other diabetic complications, including dyslipidemia⁵⁷⁻⁵⁹ and neurologic abnormalities⁶⁰. Because hypomagnesaemia has been linked to various micro and macrovascular complications, a better understanding of Mg metabolism and efforts to minimize hypomagnesaemia in the routine management of diabetes are warranted.

Possible Causes of Hypomagnesaemia in Type 2 Diabetes

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 diarrhea⁶⁰. 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 ultra filterable 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 hypoalbuminemia¹³. The last two conditions may increase the serum ionized Mg fraction and, hence, ultrafilterable 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 thick ascending Loop of Henle [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 segment¹³.
- **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. The expression of paracellin 1 in TAL, however, has not been shown to be increased in diabetic rats⁶².

In the same diabetic rat model, Lee *et al*⁶² 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 $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ 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 mechanisms⁶³.

Hypophosphatemia: Both micropuncture studies in phosphate-depleted dogs and *in vitro* studies involving phosphate depleted mouse DCT cells have demonstrated reduced Mg uptake^{64, 65}. 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 uptake⁶⁶. More recently, Nijenhuis *et al*⁶⁷ 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 DCT⁶⁸.

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^{69, 70}. 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 reabsorption⁷¹.

Despite these theoretical advantages of thiazides over loop diuretics, severe hypomagnesemia is observed more frequently with Gitelmans compared with Bartters syndrome, two syndromes that have traditionally been equated to the administration of thiazides and furosemide, respectively. Recently, in support of this observation, reduced TRPM6 expression and enhanced magnesiuria were shown in mice given chronic thiazide therapy⁷². 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: More common use of antibiotics and antifungals such as aminoglycosides and amphotericin in patients with diabetes may also contribute to renal Mg wasting⁷³.

MANAGEMENT OF HYPOMAGNESEMIA IN TYPE 2 DIABETES

Because the literature suggests adverse outcomes in association with hypomagnesaemia in patients with type 2 diabetes, measures to minimize this abnormality are warranted. Among apparently healthy subjects, the beneficial effects of magnesium supplements are scarce but show a consistent significant increase in insulin sensitivity among non-diabetic subjects who received magnesium supplements. The use of magnesium supplements could be an alternative for the prevention of type 2 diabetes mellitus considering that low serum magnesium is a risk factor strongly associated with development of Type 2 diabetes mellitus. It remains as a hypothesis which still needs a confirmation.

Optimization of Gastrointestinal Absorption

Dietary Mg intake may be optimized with the help of a nutritionist. Poor dietary intake as a result of gastrointestinal autonomic dysfunction must be controlled. Lifestyle modification such as eating multiple small meals at a time instead of two or three large meals a day; tight glucose control; and the use of prokinetic medications such as metoclopramide, domperidone, or erythromycin to improve gastric motility are indicated in patients with diabetic gastroparesis associated with erratic blood sugar control⁶⁰. In intractable cases, pyloric botulinum toxin injection, enteric feeding, and gastric pacing may be explored⁷⁴⁻⁷⁶. For those with severe and intermittent diarrhea alternating with constipation, a trial of soluble fiber, gluten and lactose restriction, and regular efforts to move the bowels are recommended. Other measures including cholestyramine, clonidine, somatostatin analog, supplemental pancreatic enzyme, and antibiotics such as metronidazole have been suggested⁶⁰.

Minimization of Renal Mg Wasting

Tight glycemic control is recommended to minimize recurring renal Mg wasting in association with osmotic diuresis and metabolic acidosis. Excessive volume replacement after hyperglycemia-induced osmotic diuresis should be avoided. Associated hypophosphatemia

and hypokalemia must be corrected. When indicated, a 24-h urinary Mg measurement may be considered to assess diuretic-induced renal Mg wasting and replacement. Finally, control of glomerular hyperfiltration with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or both may offer additional benefits in reducing renal Mg wasting. When hypomagnesemia persists despite all measures, oral Mg supplementation is indicated.

Target Serum Mg Levels

Although no study has ever documented an optimal serum Mg concentration in patients with diabetes, we speculate that a level between 2.0 and 2.5 mg/dl may be favorable. Although the correction of low serum Mg levels has never been proved to be protective against chronic diabetic complications, intervention is justified because hypomagnesemia has been linked to many adverse clinical outcomes but, to our knowledge, never physiologic benefits. In addition, Mg supplementation is inexpensive and, with the exception of diarrhea, a relatively benign medication. Nonetheless, close observation must be given to those with renal insufficiency.

Relation between magnesium and diabetes

Husmann MJW, Fuchs P, Truttman AC, et al (1997) confirmed findings of reduced circulating ionized magnesium but normal circulating total magnesium in adults with Type 2 Diabetes Mellitus. In India, B.K.Ghoshal and P.K.Banerjee (1975) studied 100 patients of whom 50 served as control and 30 were established diabetics and showed elevation of serum magnesium in juvenile and elderly diabetics⁷⁷. Riduara RL, Stamfer MJ, Willet WC, et al. followed 85,060 women and 48,872 men who had no history of diabetes, cardiovascular diseases or cancer at base line for 18 yrs and significant inverse relationship between magnesium intake and diabetes risk was found. This study recommends the increased consumption of foods rich in magnesium⁹⁴. Isbir T, TamerL, Taylor A, Isbir M.(1994) stated

that the concentrations of copper were higher and the magnesium levels were lower in Type 1 DM patients than in control subjects which may be associated with the development of insulin resistance and it was proposed that patients will improve if trace elements are given as a part of the therapy⁸. Betrelloni S (1992) also suggested that hypomagnesaemia is involved in the genesis of the altered mineral metabolism in children with type 1 diabetes⁹⁵.

Yajnik CS (1984) studied 30 non diabetics and 87 diabetics and interpreted that plasma concentrations of magnesium were lowest in the insulin treated group, intermediate in the non diabetics and highest in the non-insulin treated diabetics. They also concluded that magnesium may be an important determinant of insulin sensitivity in maturity onset diabetes⁷⁹.

Tosiello L (1996) stated that low serum magnesium levels has been reported in children with IDDM and through the entire spectrum of adult type I and type II diabetics regardless of the type therapy. Hypomagnesaemia has been correlated with both poor diabetic control and insulin resistance in non diabetic elderly patients²⁶. De Leeuw I, Engelen W, Vertommen J, Nonneman L. (1997) studied the effect of a 10 week intensive oral +IV supplementation of Mg in 11 depleted IDDM patients with stable metabolic control. Ionized Mg decreased and erythrocyte Mg increased significantly together with an increased storage of Mg in the body demonstrated with a classical retention test⁸⁷.

Jacomella V, Sauser A, Truttman AC, Kuhlmann-Siegenthaler BV, Branchetti MG. (1997) concluded that in healthy humans the circadian pattern of extracellular magnesium is not modulated by the metabolic and hormonal mechanisms that adjust the concentration of glucose⁸⁸.

Kao WH, Aaron R, Folsom H, et al (1999) concluded that low serum Mg level is a strong, independent predictor of incident type 2 diabetes. That low dietary magnesium intake does not confer risk for type 2 diabetes implies that compartmentalization and renal handling

of magnesium may be important in the relationship between low serum magnesium levels and the risk for type 2 diabetics⁹³

Effects of magnesium supplementation

De Valk HW, Verkaaik R, Van Rijn HJM, et al (1998) stated that three months oral Mg supplementation of insulin-requiring patients with type 2 DM increased plasma Mg concentration and urinary Mg excretion but had no effect on glycemic control or plasma lipid concentration⁸⁹. Martha Rodríguez-Morán, and Fernando Guerrero-Romero conducted a clinical randomized double-blind placebo-controlled trial. A total of 63 subjects with type 2 diabetes and decreased serum magnesium (serum magnesium levels mmol/l) treated by glibenclamide received either 50 ml MgCl₂ solution (containing 50 g MgCl₂ per 1,000 ml solution) diarrhea, alcoholism, use of diuretic and/or calcium antagonist drugs, and reduced renal function were exclusion criteria. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the parameter of insulin sensitivity and glucose and HbA1c as parameters of metabolic control. Oral supplementation with MgCl₂ solution restores serum magnesium levels, improving insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum magnesium levels⁹. Alzaid AA, Dinnean SF, Moyer TP, Rizza RA. (1995) sought to determine whether insulin-induced stimulation of magnesium uptake is impaired in Type 2 DM and enhanced by acute hyperglycemia and concluded that insulin resistance in subjects with Type 2 DM impairs the ability of insulin to stimulate magnesium as well as glucose uptake⁸³..

Magnesium and diabetic complications

White JR Jr, Campbell – RK (1993) in their conclusion suggested a link between hypomagnesemia and hyperglycemia, as well as an association between hypomagnesaemia and the complications of DM². Gillian Grafton, Bunce M, Sheppard MC, Brown G, Baxter MA (1992) suggested that hypomagnesaemia may be linked to the development of diabetic

complications via reduction in the rate of inositol transport and subsequent intracellular inositol depletion⁴¹.

Renal complications

Mc Nair P et al (1982) indicated that the net tubular reabsorption of magnesium is decreased in diabetic patients in presence of hyperglycaemia, leading to hypermagnesuria and hypomagnesemia²⁵. Srivastava VK, Chauhan AK, Lahiri VL. (1993) studied the significance of serum magnesium in diabetes mellitus and concluded that all diabetic patients, having normal renal function exhibited hypomagnesemia. They also observed a positive correlation between blood urea level and serum magnesium and it was significant. The magnesium correlated with major diabetic complications too. Thus serum magnesium can be used for prognostic assessment in diabetic individuals⁸²

Cardiovascular complications

Rude RK (1992) suggested that it would be prudent for physicians who treat patients to consider magnesium deficiency as a contributing factor in many diabetic complications and in exacerbation of disease itself. Repletion of the deficiency or prophylactic supplementation with oral magnesium may help avoid or ameliorate such complications as arrhythmias, hypertension, and sudden cardiac death and may even improve the course of the diabetic condition⁸¹. Resnick LM, Altura BT, Gupta RK, Laragh JH, Alderman MH and Altura BM (1993) suggested that magnesium deficiency, both extracellular and intracellular, is a characteristic of chronic stable mild type 2 diabetes, and as such, may predispose to the excess cardiovascular morbidity of the diabetic state³⁴. Ma J, Folsom AK, Melnick SL, et al.(1995) studied the relationships of serum and dietary magnesium(Mg) with prevalent cardiovascular disease (CVD), hypertension, diabetes mellitus, fasting insulin, and average carotid intimal medial wall thickness measured by B-mode ultrasound. They concluded that low serum and dietary magnesium may be related to the etiologies of CVD, hypertension,

diabetes and atherosclerosis¹⁹. Nadler JL et al (1992) suggested that type 2 diabetic patients have intra cellular Mg²⁺ deficiency and that Mg deficiency may be a key factor in leading enhanced platelet reactivity in type 2 diabetes. Therefore, Mg supplementation may provide a new therapeutic approach to reducing vascular disease in patients with diabetes³⁹. Corica F, Allegra A, Di Benedetto A, Giacobbe MS, Romano G, Cucinotta D (1994) evaluated the effects of oral magnesium supplementation on plasma lipid concentrations in patients with Type 2 DM. They suggested that oral supplementation of magnesium may be useful in the treatment of hyperlipidemia in patients with Type 2 DM⁵⁷. Lima M, Cruz T, Posuda JC, Rodrigues LE, Barbosa K, Cangacu V.(1998) concluded Mg depletion is common in poorly controlled patients with type 2 diabetes, especially in those with neuropathy or coronary disease. More prolonged use of Mg in doses that are higher than usual is needed to establish its routine or selective administration in patients with type 2 diabetes to improve control chronic complications⁹⁰.

Corica F Allegra A, Buemi MJ, et al (1996) showed both normotensive and hypertensive diabetics showed a reduction in plasma, erythrocyte and platelet concentration of magnesium compared to controls. No significant difference was found between hypertensive and normotensive diabetics with regard to plasma and erythrocyte magnesium⁸⁵. Paolisso G, Barbagallo M (1997) concluded that intracellular magnesium may play a key role on modulating insulin-mediated glucose uptake and vascular tone. They also suggested that a reduced intracellular magnesium concentration might be the missing link helping to explain the epidemiological association between NIDDM and hypertension⁸⁶. A.P.Jain, N.N.Gupta and Abhay Kumar (1976) studied clinical, electrocardiographic and magnesium in the serum, erythrocytes and urine in diabetics and controls. The severe, poorly controlled and those diabetics with hypomagnesemic symptoms showed low serum, normal erythrocytic and high urinary magnesium levels⁷⁸.

Diabetic retinopathy

HatwalA,Gujral AS, Bhatia RP, Agarwal JK, Bajpai HS. (1989) provided data which seem to point towards as association between hypomagnesemia and diabetic retinopathy⁵⁴. Garland HO (1992) stated that studies have speculated on a potential link between the magnesium deficit of diabetes and several diabetic complication including cardiovascular problems and retinopathy⁸⁰. De Valk HW (1999) stated that the plasma magnesium level has been shown to be inversely related to insulin sensitivity. Mg supplementation improves insulin sensitivity as well as insulin secretion in type 2 diabetes. Patients with severe retinopathy have a lower plasma magnesium level compared to patients without retinopathy and a prospective study has shown the plasma magnesium level to be inversely related to occurrence or progression of retinopathy⁹².

MATERIALS AND METHOD

PLACE OF STUDY

Study conducted among patients with Diabetes Mellitus with and without microvascular complications attending the out-patient and in-patient facility of Government Stanley Medical College between March 2016 and August 2016.

SAMPLE SIZE

Fifty Diabetes Mellitus patients with micro vascular complications satisfying our inclusion criteria are included in the study.

Fifty Diabetic individuals without microvascular complications are also included in the study.

STUDY SUBJECT

Inclusion criteria for Case selection:

Diabetic patients who are obeying the operational definition

OPERATIONAL DEFINITION; Diabetes was defined by; History of diabetes mellitus, or the presence of any one of the followings

1.symptoms of diabetes plus casual plasma concentration $\geq 200\text{mg/dl}$

2.FPG $\geq 126\text{mg/dl}$

3.HbA1C $\geq 6.5\%$

Diabetic Neuropathy

United Kingdom screening test — In the United Kingdom, investigators have developed a two-part diagnostic test, consisting of a simple symptom score and physical examination :

- What is the sensation felt? Burning, numbness, or tingling in the feet (2 points); fatigue, cramping, or aching (1 point). Maximum is 2 points.
- What is the location of symptoms? Feet (2 points); calves (1 point); elsewhere (0 points). Maximum is 2 points.
- Have the symptoms ever awakened you at night? Yes (1 point).
- What is the timing of symptoms? Worse at night (2 points); present day and night (1 point); present only during the day (0 points). Maximum is 2 points.
- How are symptoms relieved? Walking around (2 points); standing (1 point); sitting or lying or no relief (0 points). Maximum is 2 points.

The total symptom score can then be determined:

- 0 to 2 points: Normal
- 3 to 4 points: Mild neuropathy
- 5 to 6 points: Moderate neuropathy
- 7 to 9 points: Severe neuropathy

A similar quantitative score can be made for the physical findings

- What is the Achilles tendon reflex? Absent (2 points for each foot); present with reinforcement (1 point for each foot).
- What is vibration sense? Absent or reduced (1 point for each foot).

- What is pin prick sensation? Absent or reduced (1 point for each foot).
- What is temperature sensation? Reduced (1 point for each foot).

The neurologic signs score can then be determined:

- 0 to 2 points: Normal
- 3 to 5 points: Mild neuropathy
- 6 to 8 points: Moderate neuropathy
- 9 to 10 points: Severe neuropathy

Peripheral neuropathy is considered to be present if there are moderate or severe signs (≥ 6 points), even in the absence of symptoms, or if there are at least mild signs (≥ 3 points) in the presence of moderate symptoms (≥ 5 points). A neurologic sign score of 8 or more indicates that the patients feet are at high risk for ulceration.

Diabetic nephropathy:

Screening should include:

- Measurements of urinary PCR in a spot urine sample.
- 2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification.

In most patients with diabetes, CKD should be attributable to diabetes if:

Macroalbuminuria is present or

Microalbuminuria is present

- in the presence of diabetic retinopathy.
- in type 1 diabetes of at least 10 years duration.

Diabetic retinopathy:

Diabetic retinopathy is classified according to the presence or absence of abnormal new vessels as:

- Non-proliferative (background/preproliferative) retinopathy
- Proliferative retinopathy

DIABETIC RETINOPATHY DISEASE SEVERITY SCALE AND INTERNATIONAL CLINICAL DIABETIC RETINOPATHY DISEASE SEVERITY SCALE

Disease Severity Level Findings Observable upon Dilated Ophthalmoscopy

No apparent retinopathy No abnormalities

Mild NPDR - Microaneurysms only

Moderate NPDR - More than just microaneurysms but less than severe NPDR

Severe NPDR U.S. Definition Any of the following (4-2-1 rule) and no signs of proliferative retinopathy:

- Severe intraretinal hemorrhages and microaneurysms in each of four quadrants
- Definite venous beading in two or more quadrants

- Moderate IRMA in one or more quadrants

International Definition Any of the following and no signs of proliferative retinopathy

More than 20 intraretinal hemorrhages in each of four quadrants

- Definite venous beading in two or more quadrants
- Prominent IRMA in one or more quadrants

PDR One or both of the following:

- Neovascularization
- Vitreous/preretinal hemorrhage

Exclusion criteria for Case selection:

1. Hypertensives
2. Known case of CAD/ CVA
3. Chronic Alcoholics
4. Patients on diuretics
5. Patients on long term PPIS
6. Patients with acute or chronic diarrhoeal disease

Inclusion criteria for Controls:

Age and sex matched Diabetic individuals without microvascular complications attending out-patient and in-patient facilities of the hospital were taken as controls after applying the same exclusion criteria for cases.

TYPE OF STUDY

Hospital based Case Control Study.

STUDY DESIGN

Data will be collected from patients attending the in-patient and out-patient facility of the hospital. Detailed history and clinical examination findings were recorded using a pre-tested structured questionnaire.

STATISTICAL ANALYSIS

Data were entered in Microsoft Excel spread sheet and analyzed statistically using SPSS (Statistical Programme for Social Science, version 13) software for windows.

OBSERVATION & RESULTS

Study Design: A comparative study consisting of 50 Diabetic Mellitus patients with microvascular complications were taken as cases and 50 Diabetic patients without microvascular complications were taken as controls to investigate the change pattern of serum magnesium in Type 2 Diabetes Mellitus.

I. Results of comparison between serum magnesium levels in patients with Type 2 Diabetes Mellitus with microvascular complications and in patients with diabetes mellitus without microvascular complications

Table 1: Age distribution Table-1

Age group (years)	Group					
	Case		Control		Total	
	N	%	N	%	N	%
40 – 49	11	22.0	15	30.0	26	26.0
50 -59	10	20.0	30	60.0	40	40.0
60 – 69	14	28.0	5	10.0	19	19.0
70 – 79	11	22.0	0	.0	11	11.0
≥ 80	4	8.0	0	.0	4	4.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square test to compare proportions between groups

Table 2: Sex distribution

Gender	Group					
	Case		Control		Total	
	N	%	N	%	N	%
Male	29	58.0	36	72.0	65	65.0
Female	21	42.0	14	28.0	35	35.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square Test	Value	P-Value
Pearson Chi-Square	2.154	0.142

The mean age of diabetics with microvascular complications was 61.52±11.96 years whereas it was 52.84±4.63 years for controls. Among cases sex distribution was 58 & 42% males and females respectively and among controls the sex distribution was 72% and 28% males and females respectively. The maximum number of patients was in the age group of 60-69 i.e. 28% in cases and 50-59 i.e. 40% in controls.

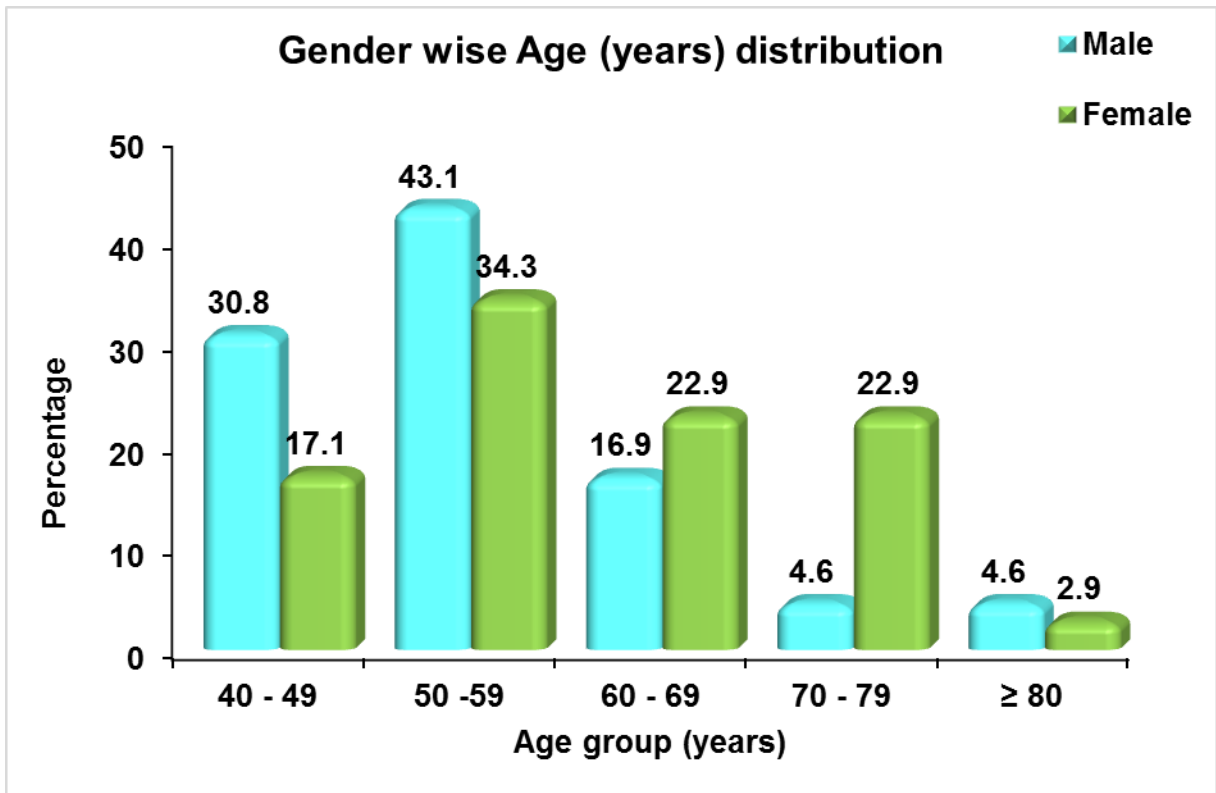
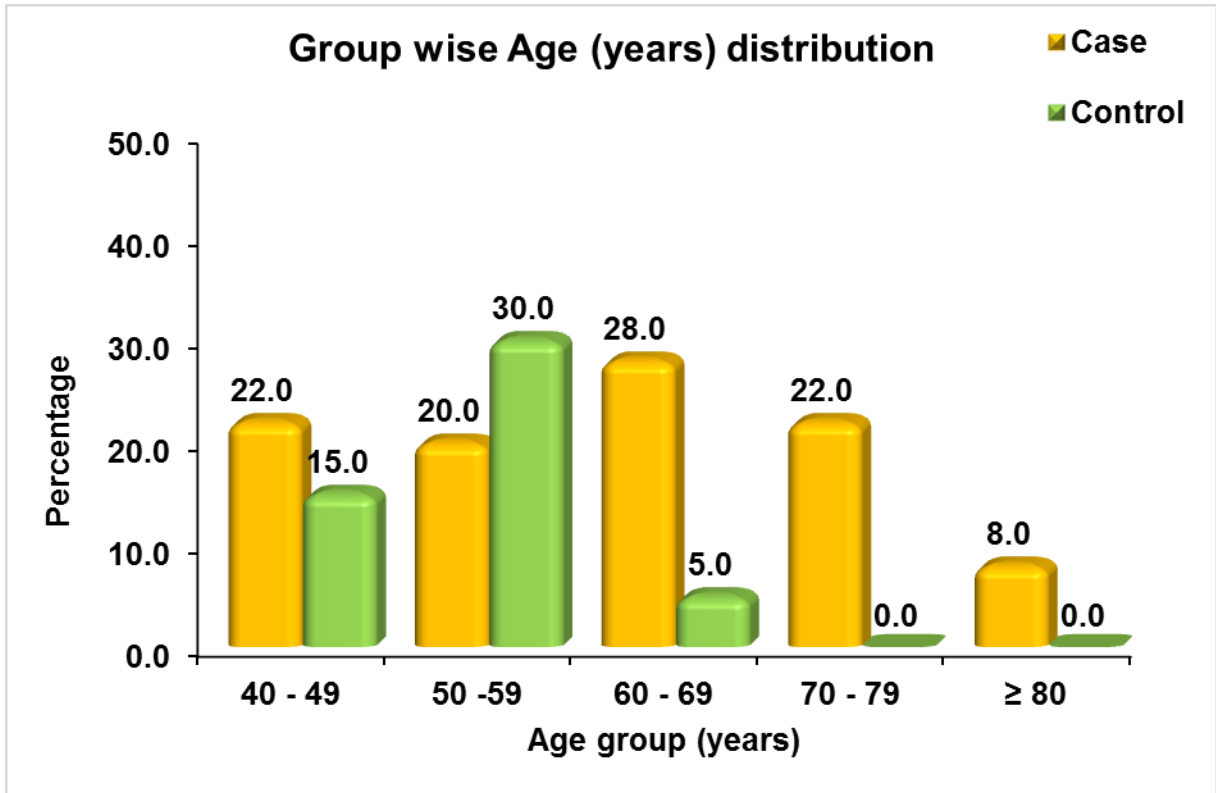
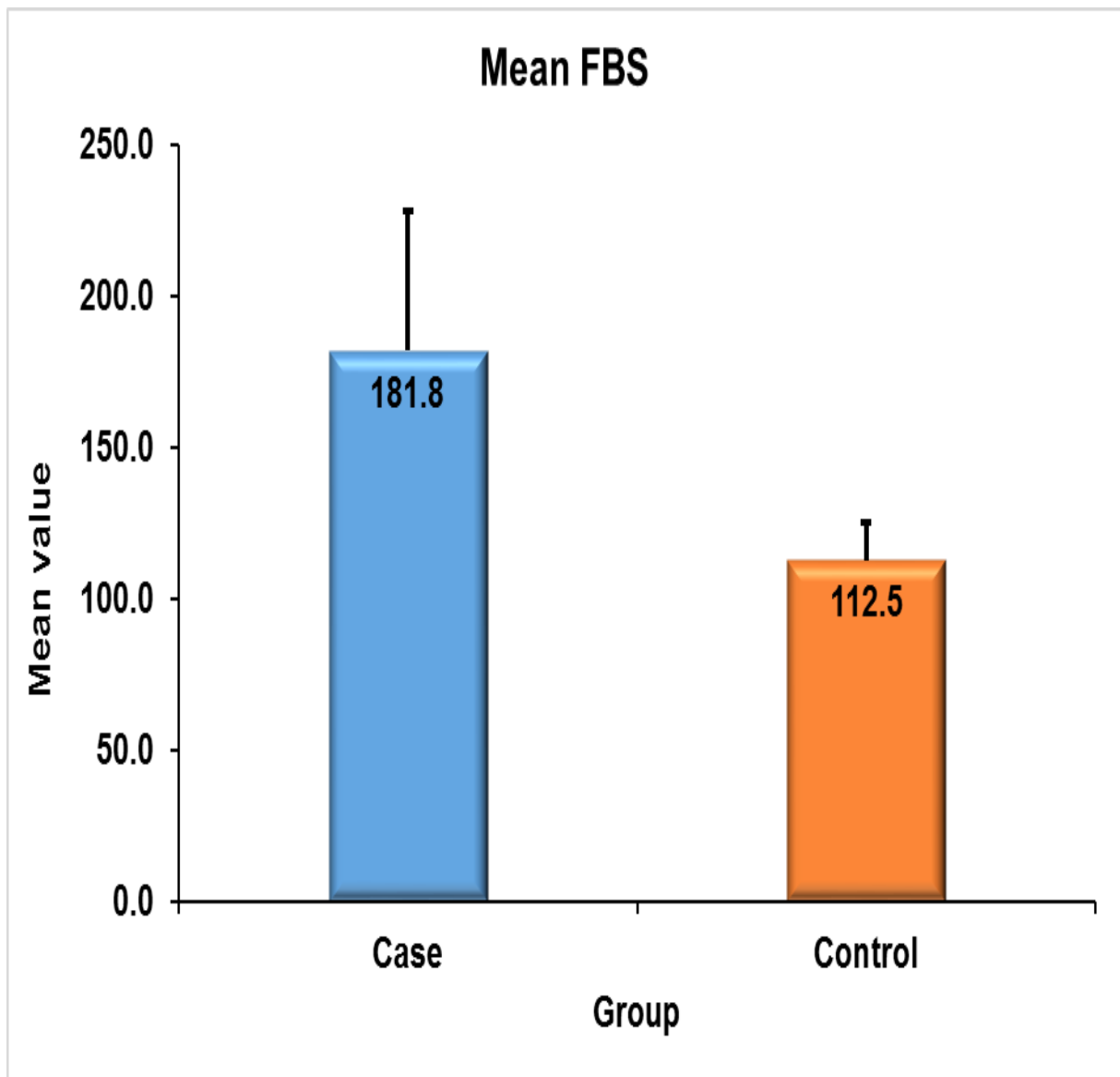


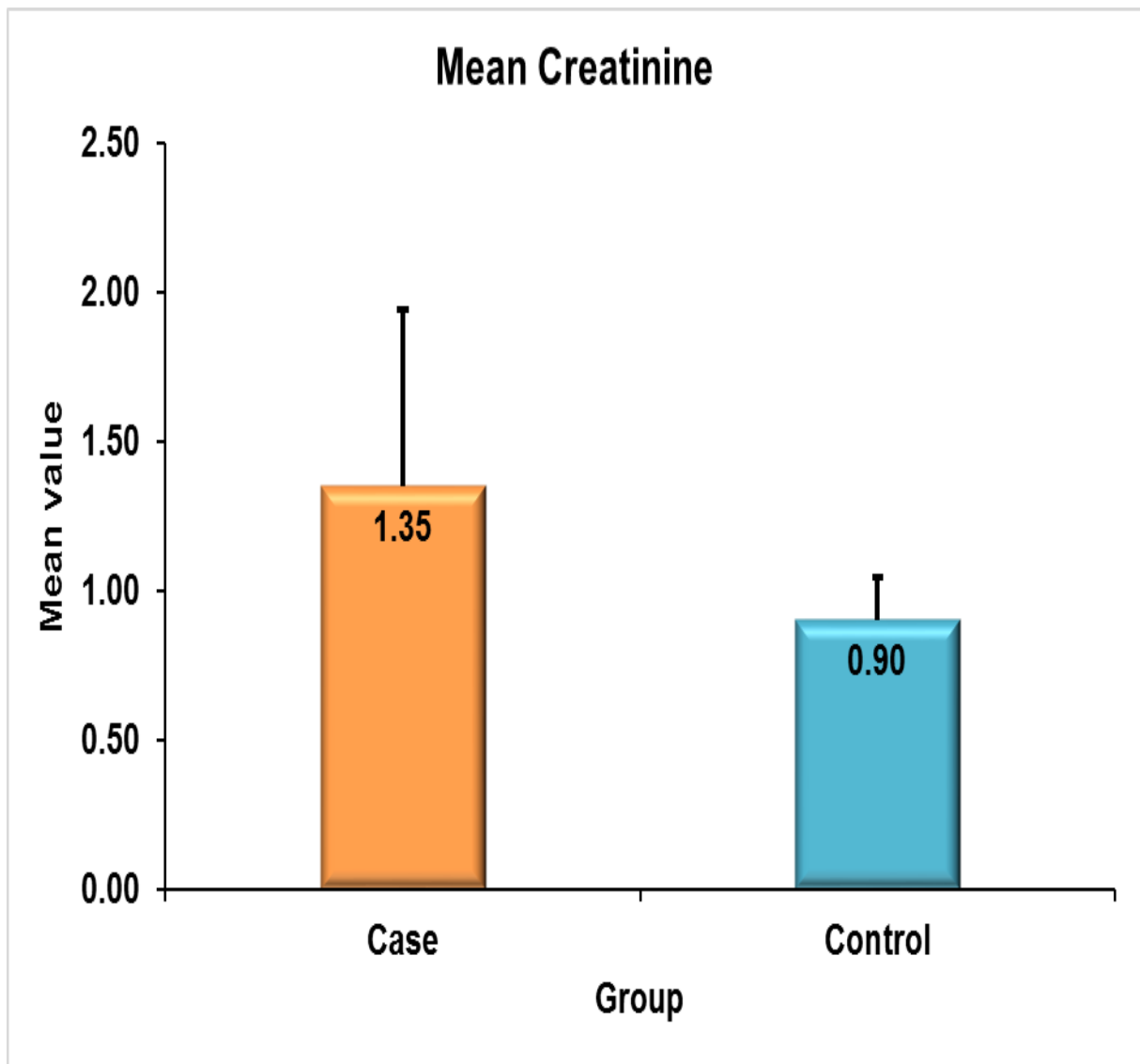
Table 3: Mean pattern of FBS, Serum creatinine and HbA1c

Variable	Group	N	Mean	Std. Dev	t-Value	P-Value
FBS	Case	50	181.84	45.993	10.278	<0.001
	Control	50	112.54	12.564		
HbA1c	Case	50	9.616	1.6866	14.125	<0.001
	Control	50	6.050	.5849		
Creatinine	Case	50	1.352	.5867	5.271	<0.001
	Control	50	.902	.1421		

There was significant difference between cases and controls with respect to Fasting Blood Sugar, HbA1c and serum creatinine levels. The mean Fasting Blood Sugar levels among cases and controls were 181.8 mg/dL and 112.5mg/dL respectively. The mean HbA1c levels among cases and controls were 9.62 and 6.05 respectively. The mean serum creatinine levels between cases and controls were 1.35mg/dl and 0.90mg/dl respectively.



Mean FBS between cases and controls

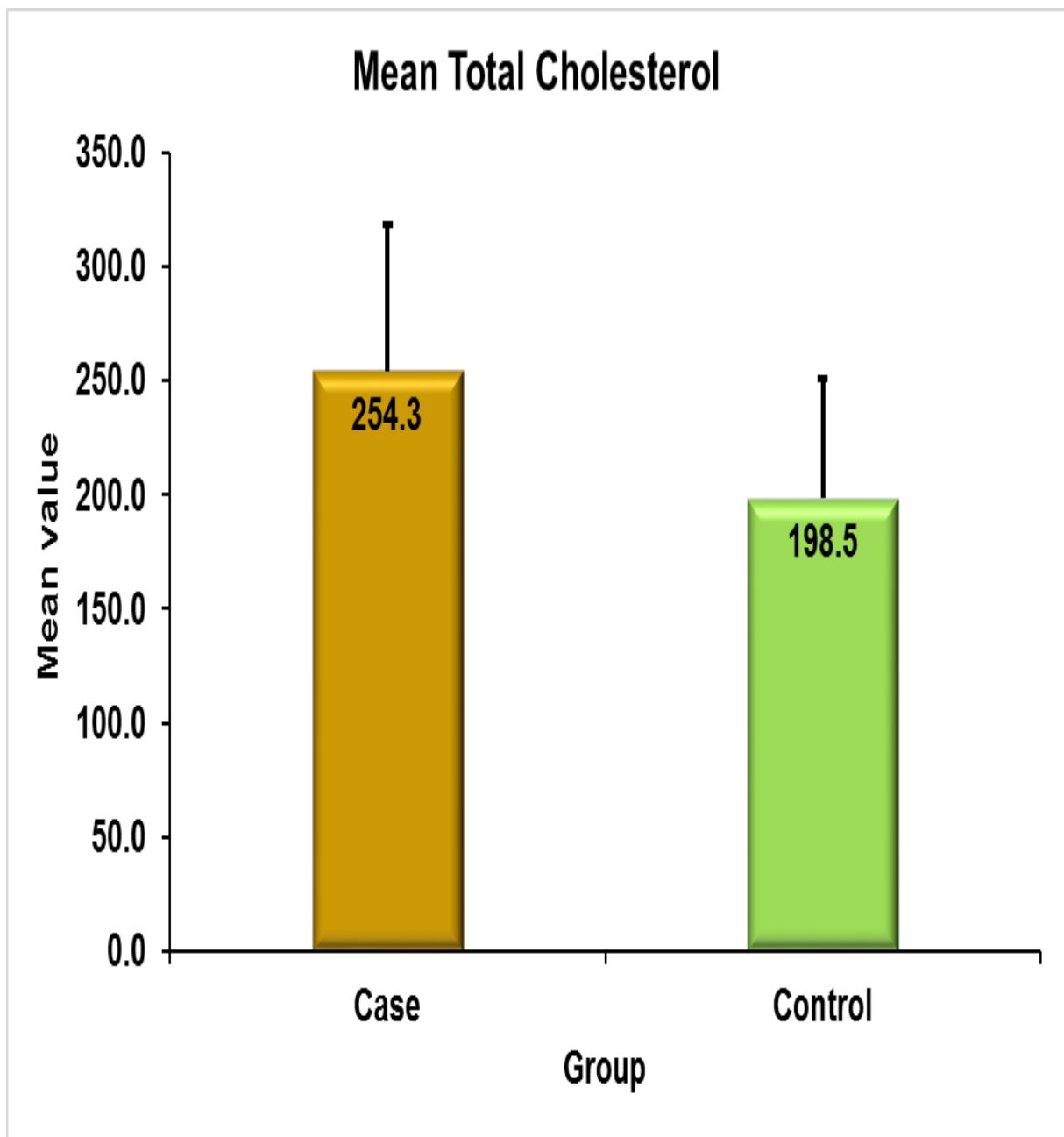


Mean serum creatinine between cases and controls

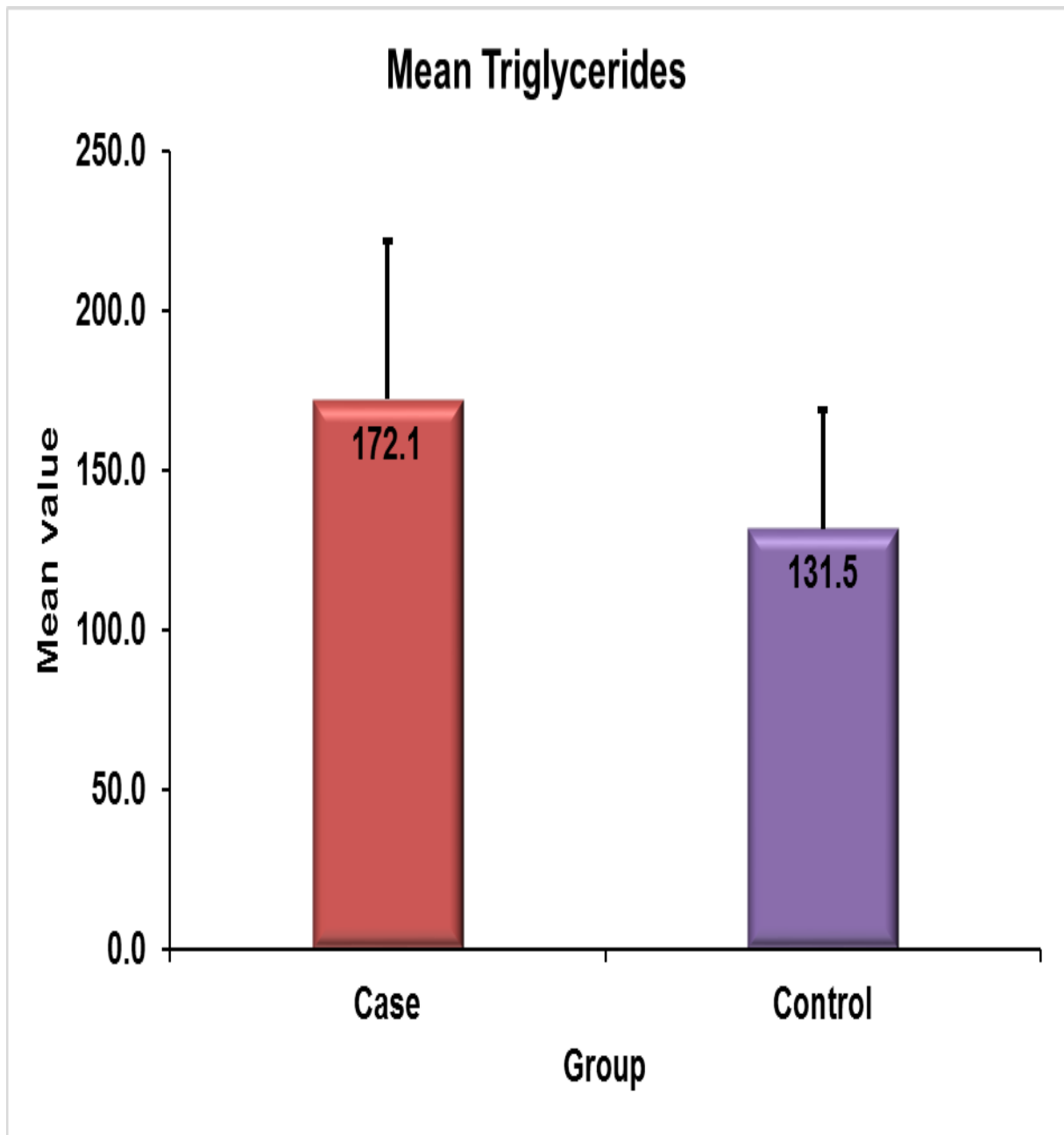
Table 4: Mean pattern of Total Cholesterol, Triglyceride & LDL

Variable	Group	N	Mean	Std. Dev	t-Value	P-Value
TC	Case	50	254.340	64.0604	4.771	<0.001
	Control	50	198.460	52.4923		
TGL	Case	50	172.100	49.7349	4.610	0.054
	Control	50	131.540	37.3654		
LDL	Case	50	136.740	32.8800	4.488	<0.001
	Control	50	109.320	28.0244		

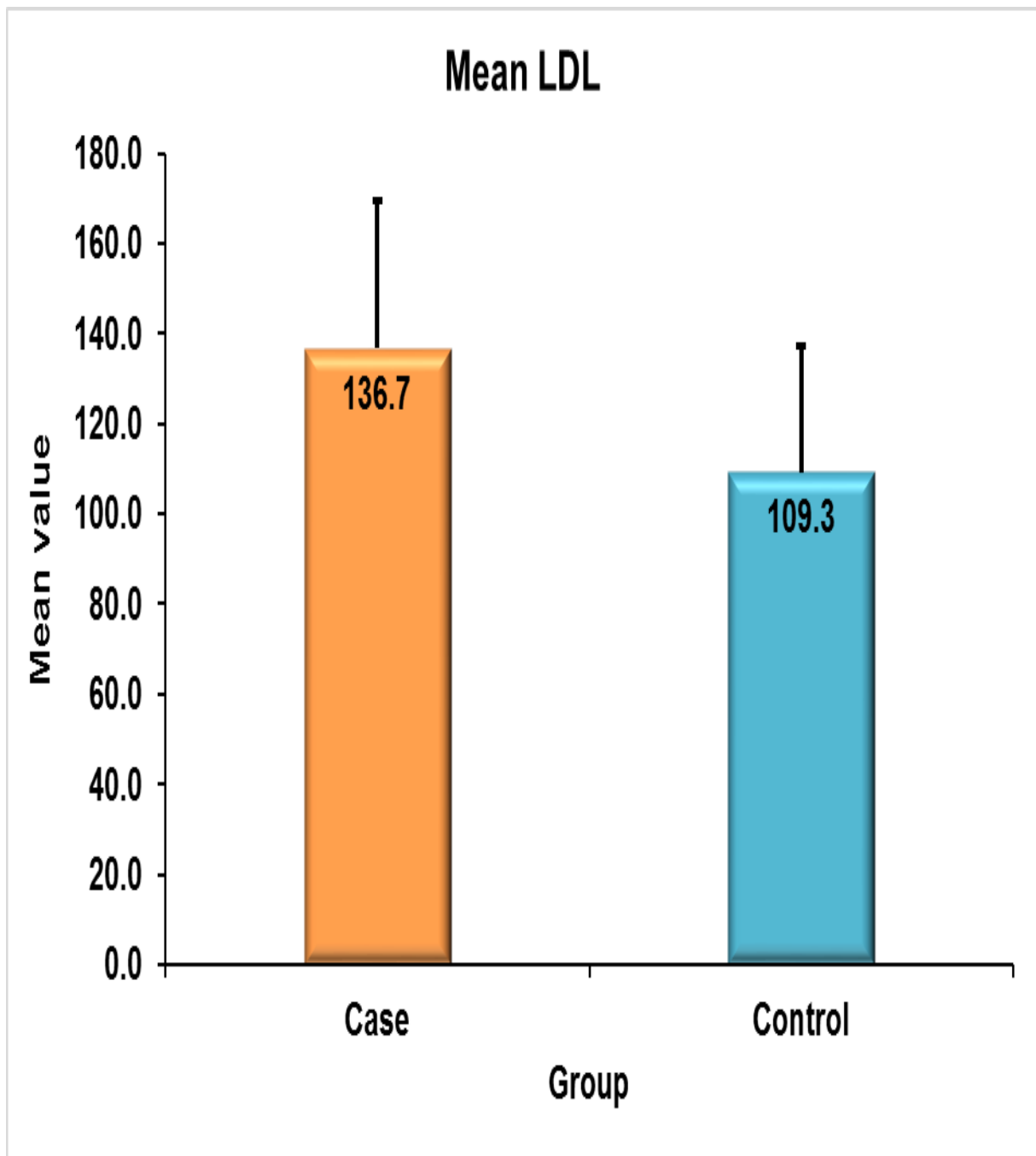
There was significant difference between cases and controls with respect to Serum cholesterol, triglycerides and LDL. The mean total cholesterol among cases and controls were 254.3mg/dl and 198.5mg/dl respectively. The mean triglyceride levels among cases and controls were 172.1mg/dl and 131.5mg/dl respectively. The mean LDL levels between cases and controls were 136.7mg/dl and 109.3mg/dl respectively.



Mean total Cholesterol between cases and controls



Mean Triglycerides between cases and controls



Mean LDL between cases and controls

Table 5: Effect of DM on Serum Magnesium Levels

Mg	Group					
	Case		Control		Total	
	N	%	N	%	N	%
< 1.6mg%	23	46.0	6	12.0	29	29.0
1.6-24mg%	24	48.0	44	88.0	68	68.0
>2.4mg%	3	6.0	0	.0	3	3.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square Test	Value	P-Value
Fishers Exact Test	18.733	<0.001

There is significant difference between levels of serum magnesium among diabetics with microvascular complications and controls. The mean serum magnesium among cases and controls were 1.67mg/dl and 1.93mg/dl respectively with a p value 0.002 statistically analyzed using student t test.

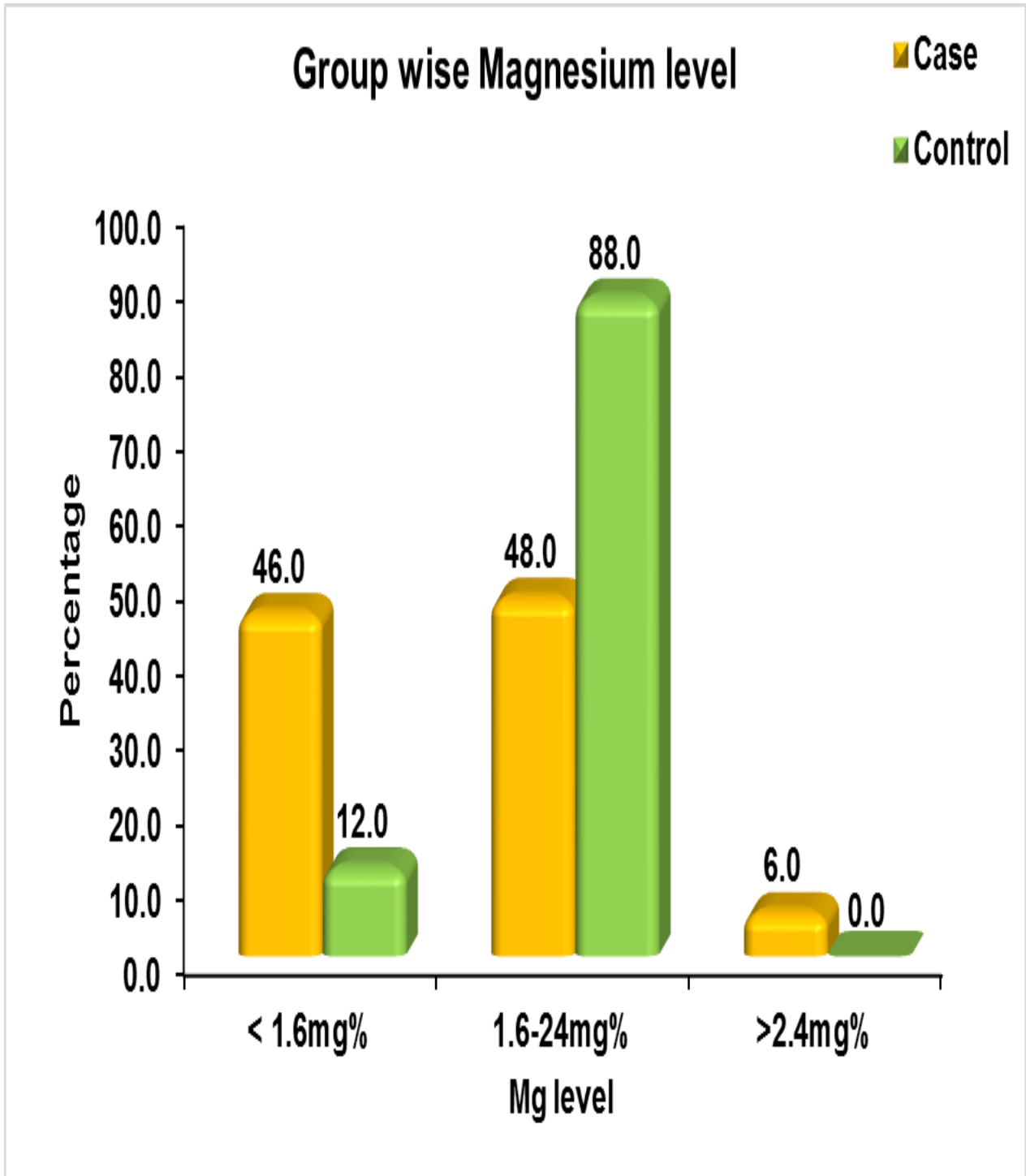
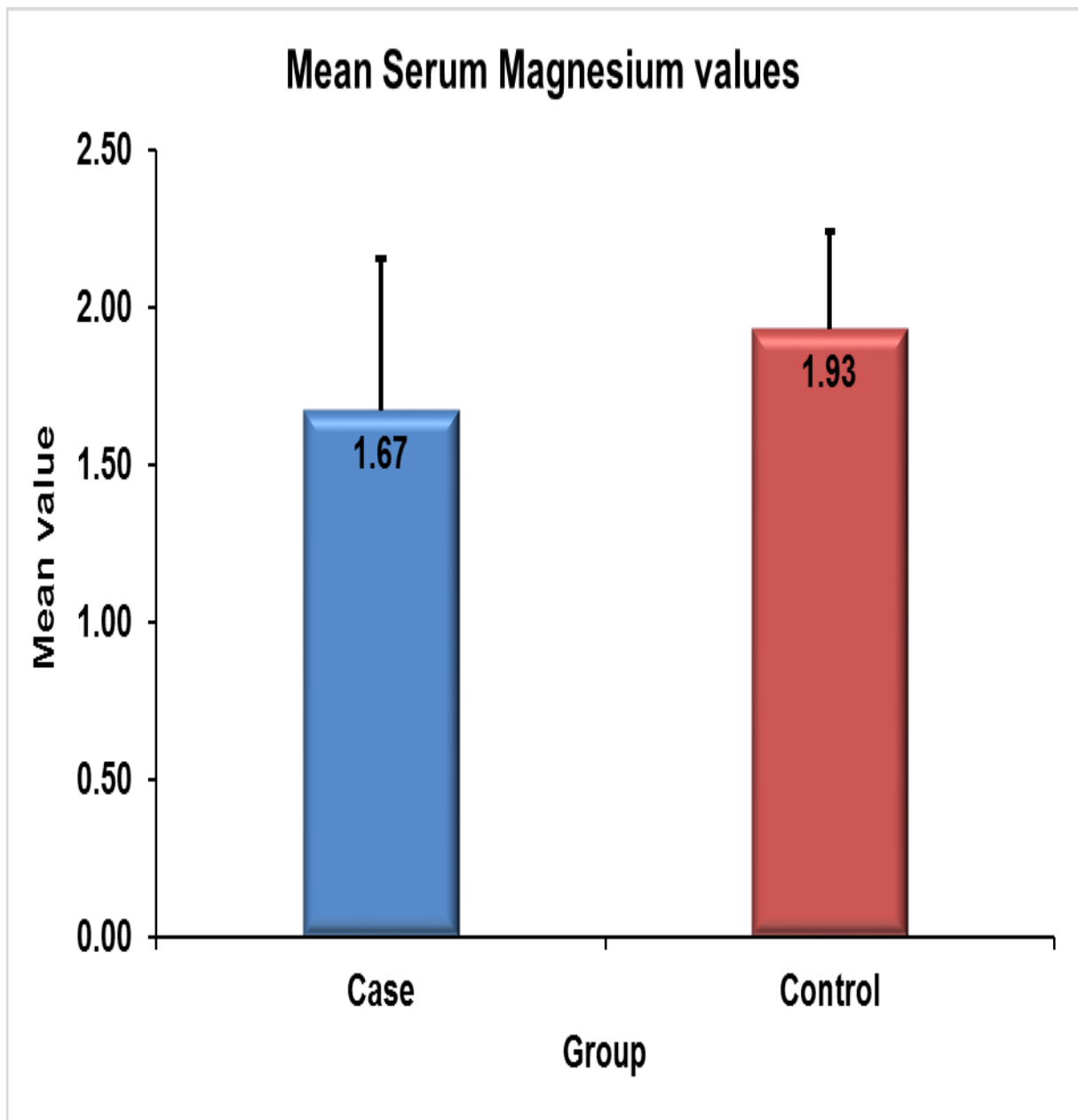


Table -6 Independent sample T-Test to compare mean Serum Magnesium values between Groups

Group	N	Mean	Std. Dev	95% CI for Mean		Min	Max	t-Value	P-Value
				LL	UL				
Case	50	1.672	.4832	1.535	1.809	1.0	2.6	3.174	0.002
Control	50	1.930	.3112	1.842	2.018	1.1	2.4		

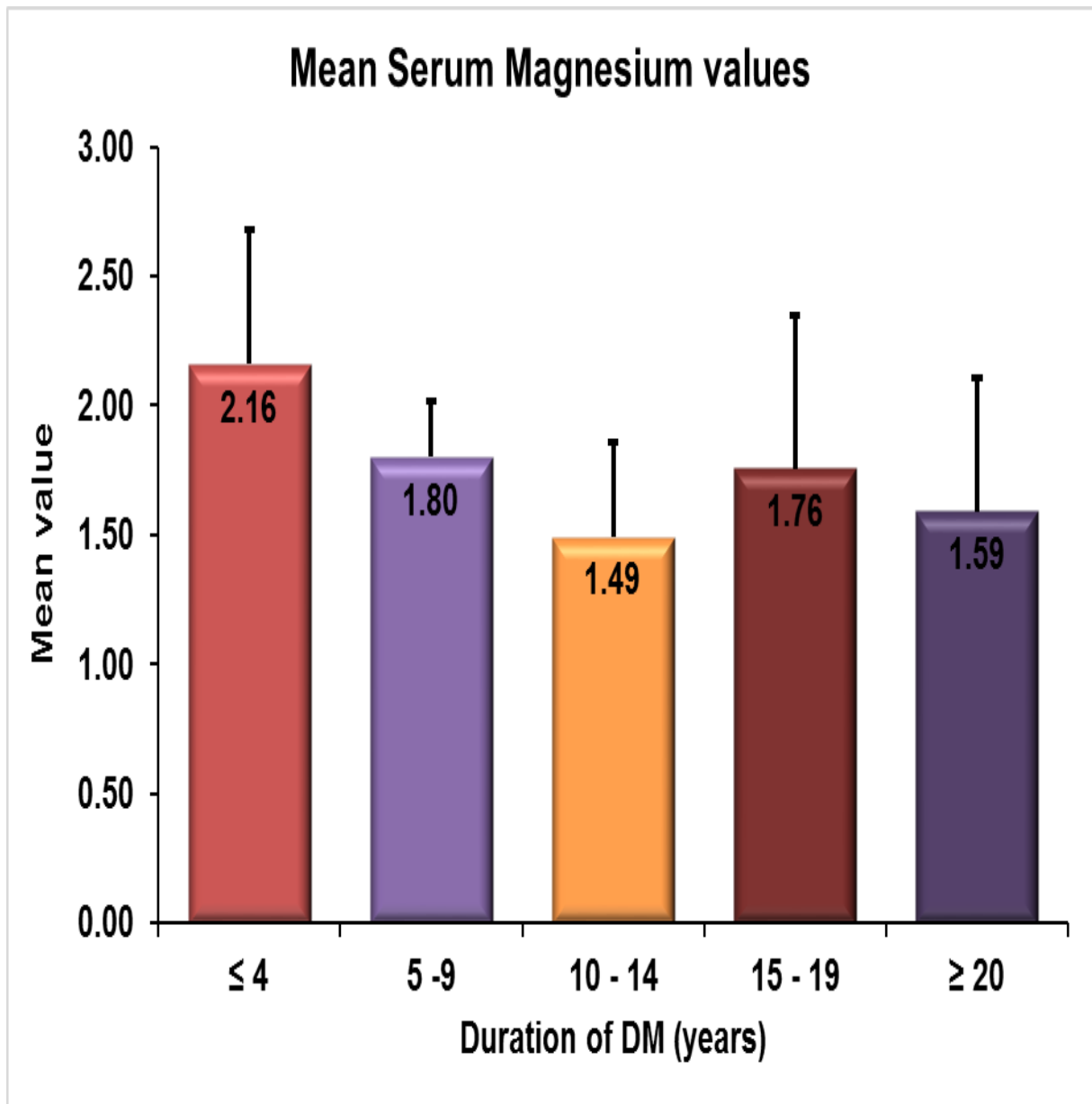


Mean Serum Magnesium between cases and controls

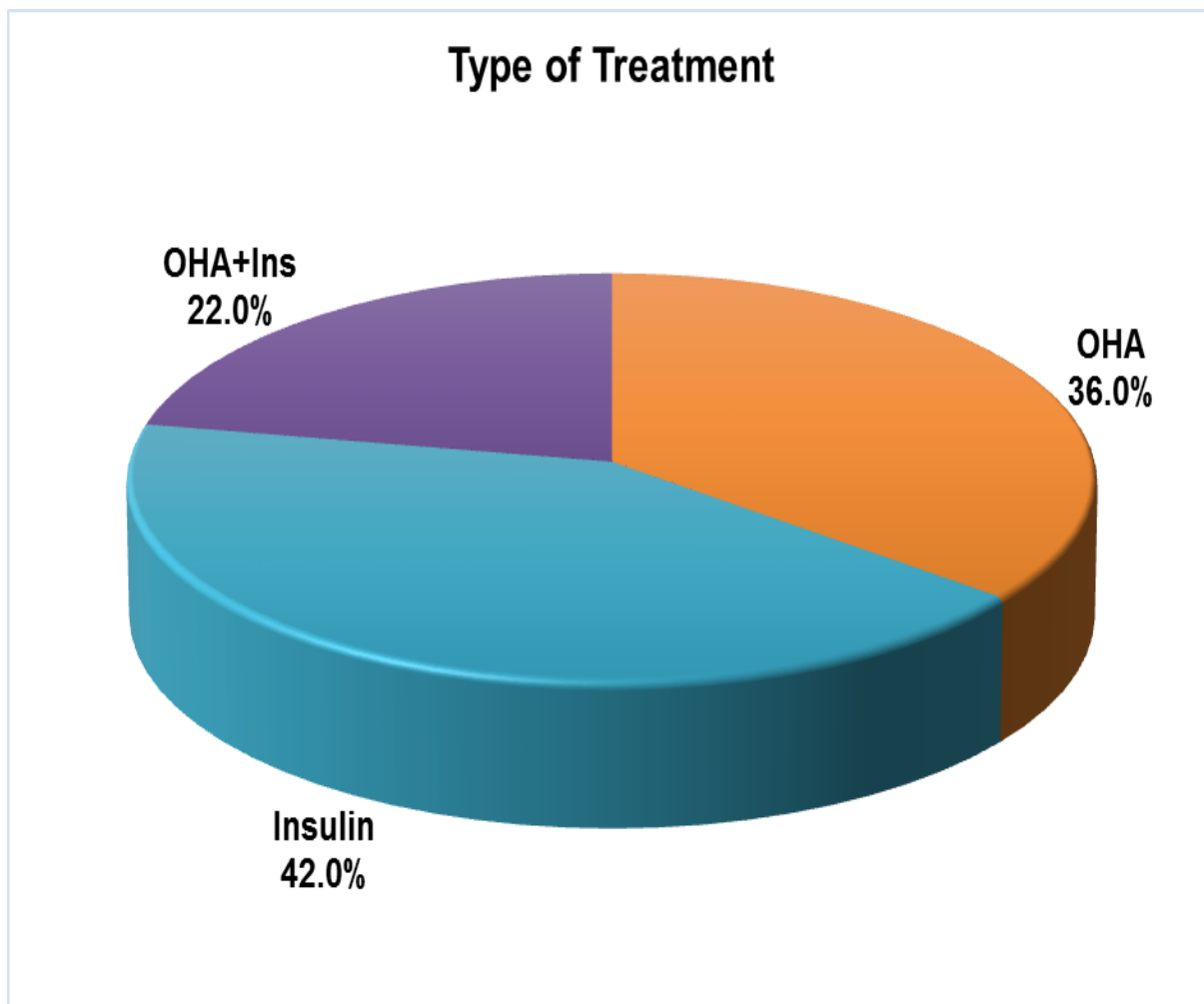
Table 7: Effect of duration of DM on Serum Magnesium levels

Duration of DM (yrs)	N	Mean Mg	Std. Dev	F-Value	P-Value
≤ 4	5	2.160	.5177	2.117	0.096
5 – 9	7	1.800	.2160		
10 – 14	13	1.492	.3639		
15 – 19	11	1.755	.5956		
≥ 20	11	1.591	.5186		
Total	47	1.694	.4896		

The mean serum magnesium levels and duration of diabetes was statistically analyzed using ANOVA and was found to be significant at the 0.05 level between the various groups of duration of diabetes. It was noticed that as the duration of diabetes increases the serum magnesium levels showed a low normal values.



Mean Serum Magnesium and duration of diabetes



Among diabetics OHA treated patients were 36%, insulin requiring patients were 42% and those on both insulin and OHA were around 16%. The mean serum magnesium in OHA treated patients were 1.53mg/dl. The mean serum magnesium in insulin treated diabetics was 1.78mg/dl. The mean serum magnesium levels in both insulin and OHA treated diabetics were 1.69mg/dl.

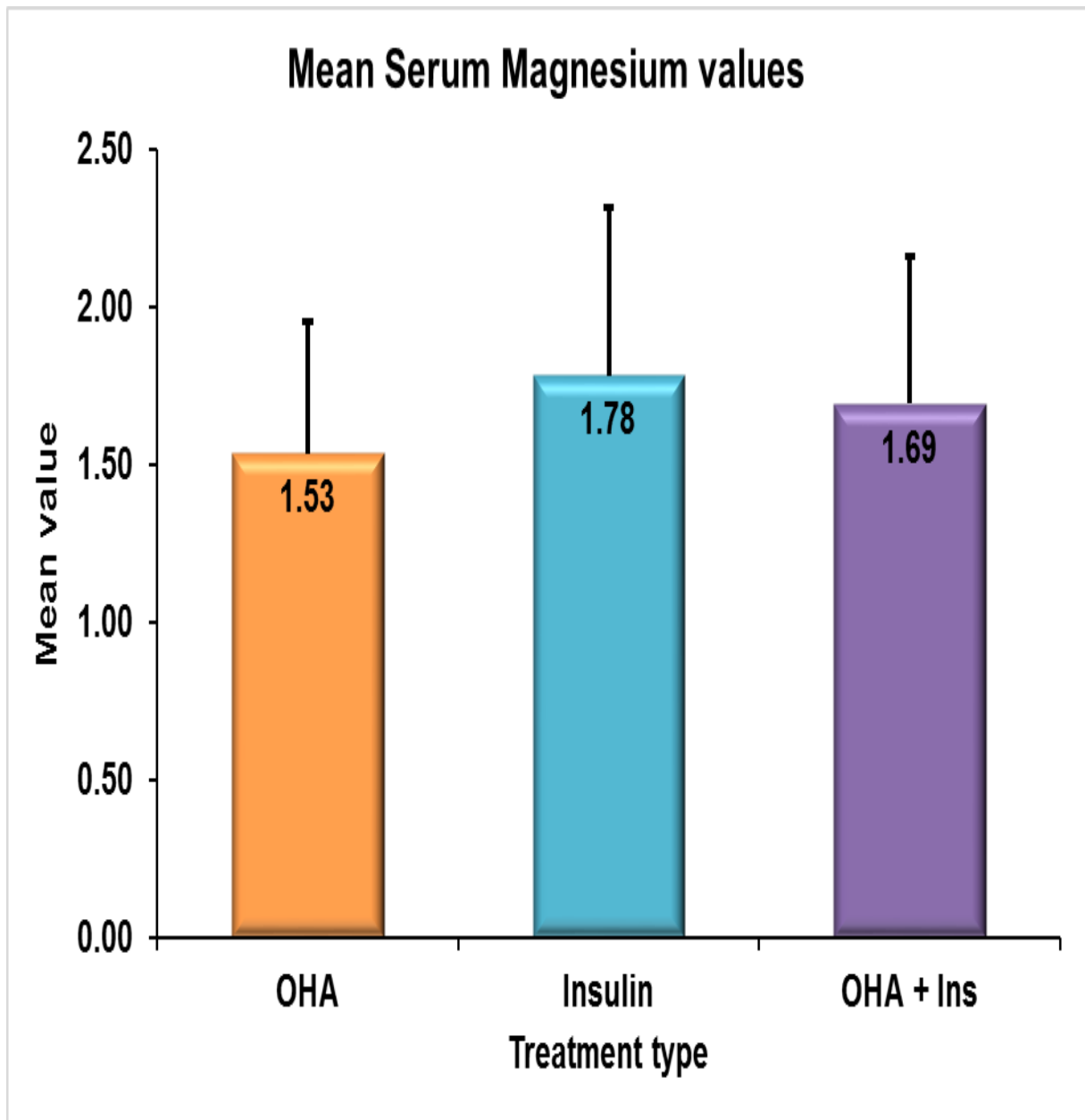


Table 8 One way ANOVA to compare mean Mg values between type of treatments

Treatment type	N	Mean Mg	Std. Dev	95% CI for Mean		Min	Max	F-Value	P-Value
				LL	UL				
OHA	18	1.533	.4173	1.326	1.741	1.0	2.2	1.299	0.282
Insulin	21	1.781	.5335	1.538	2.024	1.0	2.6		
OHA + Ins	11	1.691	.4679	1.377	2.005	1.0	2.4		
Total	50	1.672	.4832	1.535	1.809	1.0	2.6		

There was no significant difference between the type of treatment and serum magnesium levels on statistical assessment p value <0.282

Table 9: Pattern of distribution of newly detected diabetes among cases and control

New DM	Group					
	Case		Control		Total	
	N	%	N	%	N	%
Yes	3	6.0	1	2.0	4	4.0
No	47	94.0	49	98.0	96	96.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square Test	Value	P-Value
Fishers Exact Test	-	0.617

Table 10. Mean Mg among new DM

New DM	N	Mean Mg ²⁺	Std. Dev	95% CI for Mean		Min	Max
				LL	UL		
Yes	4	1.500	.3559	.934	2.066	1.2	2.0

Around 4% of patients among cases were newly detected Type 2 Diabetes Mellitus. The mean serum magnesium level in these newly detected Type 2 Diabetes mellitus was also observed and was found to be low normal value of 1.500mg/dl

Table 11: Associaton of hypomanesemia and glycemic control.

Independent samples T-Test to compare mean Mg Values

Group	HbA1c level	N	Mean Mg	Std. Dev	t-Value	P-Value
Case	Under control (≤ 8.5)	20	1.835	.5923	1.831	0.077
	No in control (> 8.5)	30	1.563	.3662		
Control	Under control (≤ 8.5)	50	1.930	.3112	-	-
	No in control (> 8.5)	0	.	.		
Total	Under control (≤ 8.5)	70	1.903	.4089	3.921	<0.001
	No in control (> 8.5)	30	1.563	.3662		

A negative correlation was obtained between S.Mg and HbA1C, i.e. as HbA1C increases serum magnesium decreases. These findings were found to be significant. The scatter plot below proves the same.

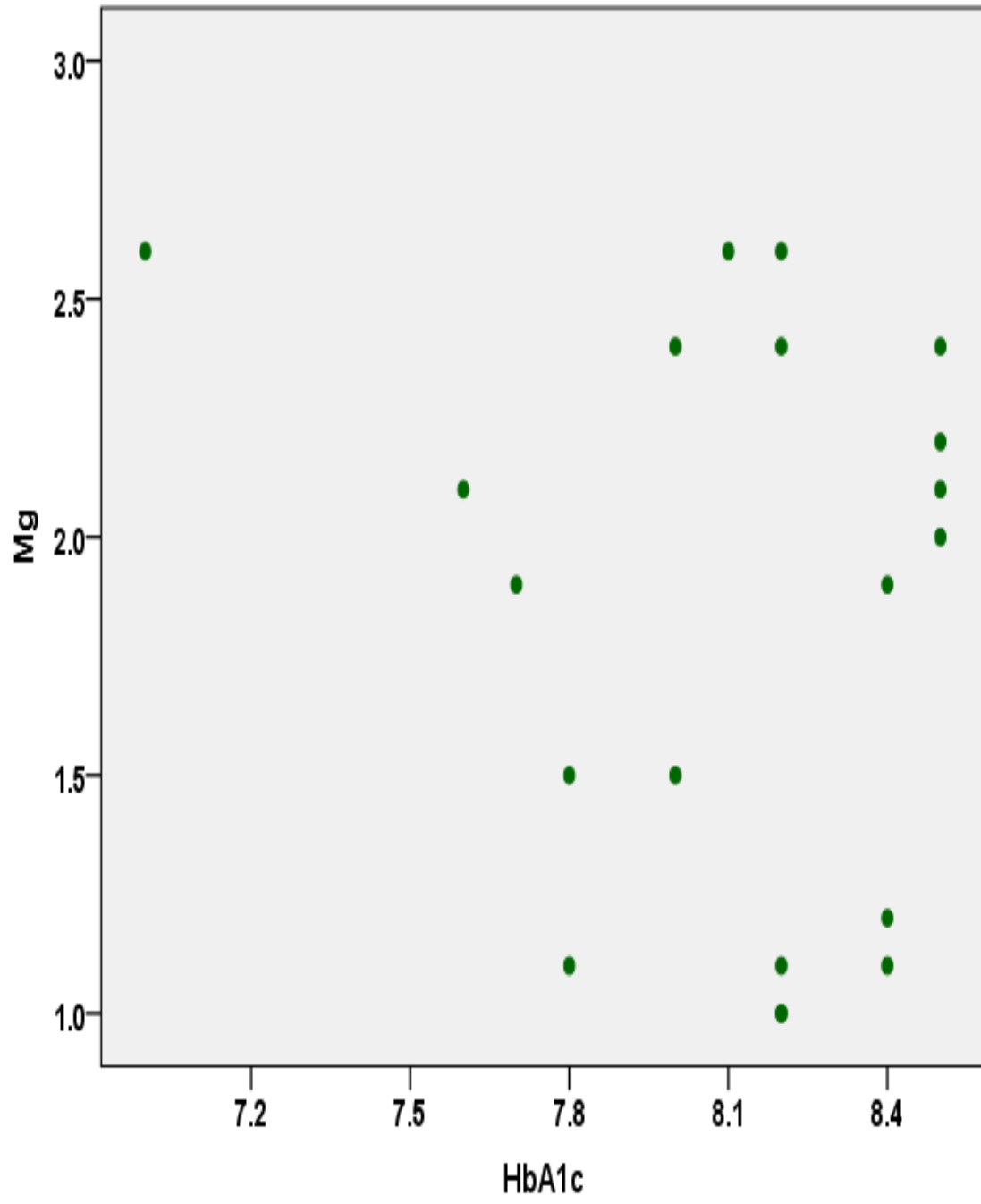


Table12: pattern of distribution of microvascular complication among cases and control

Retinopathy	Group					
	Case		Control		Total	
	N	%	N	%	N	%
Yes	20	40.0	0	.0	20	20.0
No	30	60.0	50	100.0	80	80.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square Test	Value	P-Value
Pearson Chi-Square	25.000	<0.001

Neuropathy	Group					
	Case		Control		Total	
	N	%	N	%	N	%
Yes	11	22.0	0	.0	11	11.0
No	39	78.0	50	100.0	89	89.0
Total	50	100.0	50	100.0	100	100.0

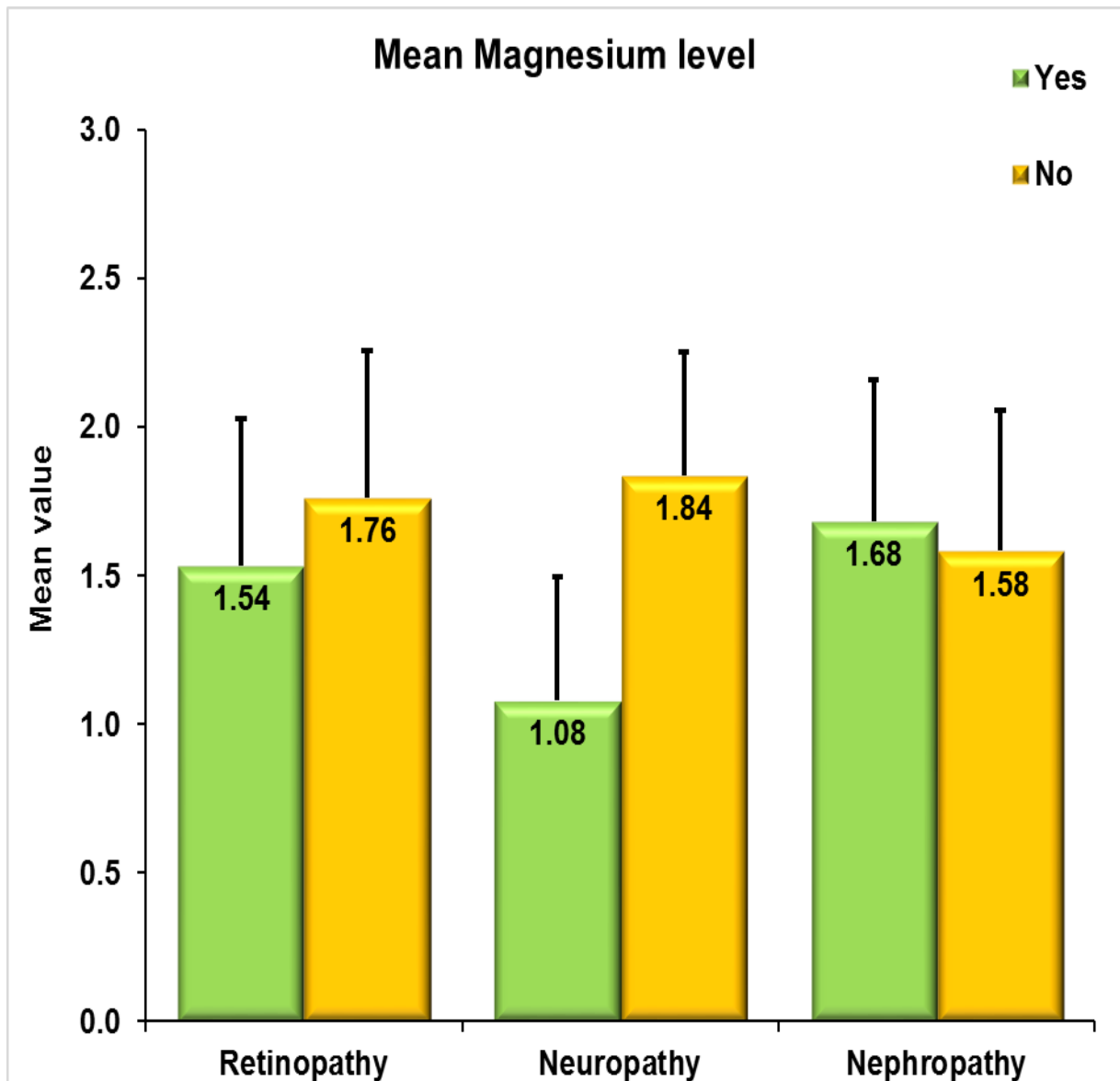
Chi-Square Test	Value	P-Value
Pearson Chi-Square	12.360	<0.001

Nephropathy	Group					
	Case		Control		Total	
	N	%	N	%	N	%
Yes	44	88.0	0	.0	44	44.0
No	6	12.0	50	100.0	56	56.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square Test	Value	P-Value
Pearson Chi-Square	78.571	<0.001

Table13: Mean magnesium values in diabetic patients with microvascular complications

Variables	Group	N	Mean Mg	Std. Dev	t-Value	P-Value
Retinopathy	Yes	20	1.535	.4464	1.666	0.102
	No	30	1.763	.4923		
Neuropathy	Yes	11	1.082	.0751	10.832	<0.001
	No	39	1.838	.4127		
Nephropathy	Yes	44	1.684	.4884	0.475	0.637
	No	6	1.583	.4750		



The mean serum magnesium in each vascular complications of diabetes was estimated and was analyzed statistically for significance with ANOVA .

The mean serum magnesium was lowest in patients with diabetic neuropathy which was 1.08mg/dl. Next lowest mean serum magnesium value was in patients with diabetic retinopathy which was 1.54mg/dl. The mean serum magnesium in patients with diabetic nephropathy was 1.68mg/dl .

In those patients without any microvascular complications of diabetes the mean serum magnesium was 1.726mg/dl.

The above observations suggested that serum magnesium levels were in the low normal side in patients with microvascular complications of Type 2 Diabetes Mellitus, it was lowest with diabetic neuropathy.

TABLE14: Distribution of habit of smoking among cases and control

Smoking	Group					
	Case		Control		Total	
	N	%	N	%	N	%
Yes	28	56.0	16	32.0	44	44.0
No	22	44.0	34	68.0	56	56.0
Total	50	100.0	50	100.0	100	100.0

Chi-Square Test	Value	P-Value
Pearson Chi-Square	5.844	0.016

T ABLE 15: Independent sample T test to compare mean magnesium values

	Group	N	Mean Mg	Standard Deviation	t-Value	p-Value
Smoking	Yes	28	1.593	.4537	1.316	0.194
	No	22	1.773	.5110		

There is no significant difference in serum magnesium values between smokers and non smokers (among cases)

Statistical methods: Chi-square and Fisher Exact test has been used to find the significance of proportion of serum magnesium levels between cases and controls.

Student t test has been used to find the significance of mean pattern of serum magnesium between cases/controls, Insulin/OHA. Statistical significance was assigned at a p value<0.05.

ANOVA was used to find statistical significance in duration of diabetes/serum magnesium and serum magnesium/various microvascular complications of diabetes mellitus.

Statistical software: The statistical software namely SPSS version 13.000 was used for the analysis of data and Microsoft word and Excel have been used to generate graphs, tables etc..

DISCUSSION

Hypomagnesemia is a common feature in patients with Type 2 Diabetes Mellitus. It may be a cause or consequence of diabetes. This study was designed to find out the serum magnesium levels and its influence on Type 2 diabetics and how it is associated with duration, treatment modalities and complication of the disease.

The present study included 50 Type 2 Diabetes Mellitus patients with microvascular complications and 50 diabetic individuals without microvascular complications.

I. Age and Sex distribution

The present study had diabetic patients ranging from 35-85years. The mean age of diabetics in the present study was 61.52 years. The mean age of controls was 52.84years. There was no significant difference between the mean age of cases and controls after statistical analysis.

Majority of patients with diabetes were in the 4th to 6th decade of their life. In the present study sex distribution showed male preponderance for Type 2 Diabetes Mellitus with 58% being males and 42% being females.

In recent studies conducted by Mishra S *et al*⁵⁹, Nasri H *et al*⁵⁸ and earlier studies by Yajnik CS *et al*⁷⁹ also had similar findings.

II. Age and Serum Magnesium level

In the present study a borderline significant inverse correlation was observed between age of the cases and serum magnesium levels as estimated by Pearson correlation ($p=0.057$) but there was no significant correlation between them among the control group.

Previous studies by Mishra S *et al*⁵⁹ and Nasri H *et al*⁵⁸ also noted significant negative correlation both in cases as well as in controls depicting as the age advances plasma magnesium level decreases.

III. Biochemical Parameters

a) Fasting Blood Sugar, HbA1c and Serum creatinine

In our study there was significant difference between diabetics with microvascular complications and diabetics without microvasculr complications with respect to FBS, HbA1c and serum creatinine ($p < 0.001$). The mean Fasting Plasma glucose levels among cases and controls were 181.84mg/dl and 112.54mg/dl respectively. The mean HbA1c levels among cases and controls were 9.616 and 6.056 respectively. The mean serum creatinine levels between cases and controls were 1.352mg/dl and 0.902mg/dl respectively.

The association of above said parameters and serum magnesium levels was statistically analyzed. A significant negative correlation existed as for Fasting blood sugar and HbA1c values with serum magnesium ($p < 0.001$). As the plasma fasting glucose levels and HbA1c increases the serum magnesium levels dropped.

Sharma A *et al*⁴, Mishra S *et al*⁵⁹ and few other recent studies also established the same i.e. there is a negative correlation between fasting blood sugars and HbA1c with plasma magnesium.

A significant positive correlation was not seen between serum creatinine and serum magnesium but a positive correlation between them was observed by Walti MK *et al*²⁹.

b) Serum cholesterol, Triglycerides and LDL

There was significant difference in the mean pattern of serum cholesterol, Triglycerides and LDL (all with $p < 0.001$) when compared with the controls. But a significant correlation could not be established with serum magnesium level when analyzed by Pearson correlation.

Recent studies conducted by Nasri H *et al*⁵⁸, Lal *et al*⁶⁰ observed a significant inverse correlation with serum cholesterol, LDL, Triglycerides and a positive correlation with HDL cholesterol. Corrica F *et al*⁵⁷ also supported that oral magnesium supplementation improved lipid levels in Type 2 Diabetes Mellitus but we could not establish in the present study.

IV. Effect of Type 2 Diabetes Mellitus on Serum Magnesium

In the present study we noticed a significant difference between levels of serum magnesium among diabetics with microvascular complications and control. The mean serum magnesium among diabetics with microvascular complications and control were 1.67mg/dl and 1.93mg/dl respectively with a p value <0.001 . Considering normal reference range of serum magnesium of 1.6-2.4mg/dl the observed mean value in the present study is a low normal value.

Our findings here substantiate various studies conducted worldwide recently by Albert Leucebe *et al* and in India by Sharma A *et al*⁴. Relatively earlier studies by Paolisso *et al*⁸⁶, Nadler J *et al*³⁹, Resnick L *et al*³⁴ also noted this in the level of serum magnesium among Type 2 Diabetics.

In our study we also observed that around 46% of diabetics had serum magnesium below the reference range. The study conducted by AP Jain *et al*⁷⁸ in 1986 had 32% diabetic subjects below the reference range.

V. Effect of Duration of Diabetes on Serum Magnesium levels

In the present study a significant association with duration of diabetes and serum magnesium levels was observed which was statistically analyzed with ANOVA and confirmed the same. Those patients with diabetic duration of 10-14 years had a mean serum magnesium level of 1.492mg/dl. It was noticed that as the duration of diabetes increases the serum magnesium values showed a low normal values.

Sharma A *et al*⁴, Mishra S *et al*⁵⁹, Walti MK *et al*²⁹ also had similar observations and came to a conclusion of an inverse correlation of duration of diabetes and serum magnesium.

VI. Effect of type of treatment on Serum Magnesium

In the present study among diabetics OHA treated diabetics accounted for around 36% of total number of cases. 42% of diabetics were on insulin and 22% of individuals received both OHA and insulin. The mean value in each group was calculated and found to be 1.781mg/dl in those patients on insulin; 1.533mg/dl in OHA treated diabetics and 1.691mg/dl in those patients receiving both OHA and insulin.

There was no significant difference noted when analyzed between OHA and insulin treated patients with serum magnesium levels (p value <0.27) which was against the observation obtained by previous studies by Yajnik CS *et al*⁷⁹ and AP Jain *et al*⁷⁸. But in our study it was observed that insulin treated diabetics had a higher mean value compared to OHA treated patients even though statistically insignificant.

VII. Effect of Serum Magnesium in patients with and without microvascular complications of Type 2 Diabetes Mellitus

In the present study among the 100 diabetic patient 50% were with microvascular complications of Type 2 Diabetes Mellitus and 50% were without any complications.

There was significant difference in the mean age of patients presenting with complications was 61.52years and without complications was 52.84 years with a p value <0.001. This could be explained on the basis that long duration of diabetes and delayed onset of presentation of complication resulted in this significant change.

We observed that maximum number of patients with complications of diabetes was in the age group 50-59years and patients without complications were in the age group 40-49 years with male preponderance in both group. The above said findings were similar to the observations made by Ghohal BK *et al*⁷⁷ in Indian diabetic population.

There was significant difference in the mean serum magnesium value between patients with complications and without complications (t -3.174, p=0.002). The mean value in diabetics with and without complications was 1.67mg/dl and 1.93 mg/dl respectively.

Earlier studies by Corrica *et al*⁵⁷, Nagase N *et al*⁸⁴ and Srivastava V *et al*⁸² observed correlation of vascular complications of diabetes and serum magnesium.

Recent studies by Sharma A *et al*⁴ also found that serum magnesium is significantly low in diabetics with and without vascular complications.

VIII. Miscellaneous

In the present study 8% of patients were newly detected type 2 diabetes mellitus whose mean serum magnesium was 1.5 mg/dl of which most of them presented with complications of diabetes requiring medical attention.

We also tried inferring certain other data from the control group

- a) Serum magnesium among controls with family history of diabetes was also observed. Here also we were unable to establish a significant reduction serum magnesium levels.

SUMMARY & CONCLUSION

Association of microvascular complications of Type 2 Diabetes Mellitus with serum magnesium levels was studied in 100 Type 2 Diabetic patients with and without microvascular complications.

The following conclusions were made:

- Maximum number of patients with Type 2 Diabetes Mellitus was noted from 4th decade to 6th decade.
- Male female ratio is 5.8:4.2 showing male preponderance.
- The mean age of diabetics with microvascular complications was 61.52years.
- Maximum number of patients presenting with microvascular complications of diabetes was from the 6th decade of life with male preponderance.
- The mean age of Type 2 Diabetes Mellitus patients presenting with and without complications were 61.52years and 52.84years.
- Among diabetics 36% patients were receiving Oral Hypoglycemic Agents (OHAs), 42% required insulin and 22% were receiving both OHA and insulin for therapy of diabetes.
- The mean fasting blood sugar, HbA1c and Serum creatinine were 181.18mg/dl, 9.62 and 1.35mg/dl respectively, whereas that of the controls was 112.5mg/dl, 6.05 and 0.90mg/dl respectively.
- The mean Total cholesterol, Triglycerides and LDL were 254.3mg/dl, 172.1mg/dl and 136.7mg/dl respectively, whereas that of the controls was 198.5mg/dl, 131.5mg/dl and 109.3mg/dl respectively.

- The mean serum magnesium in diabetics with microvascular complications and diabetics without microvascular complications were 1.67mg/dl and 1.93mg/dl respectively.
- 29% of diabetics had serum magnesium in the below normal range of 1.0-1.6mg/dl.
- A significant inverse correlation was noted with HbA1c and serum magnesium.
- A significant negative correlation was present on duration of diabetes and serum magnesium.
- OHA treated diabetics had a low serum magnesium level compared to Insulin treated diabetics even though statistically insignificant.
- The mean serum magnesium in newly detected Type 2 Diabetes Mellitus was 1.5mg/dl.
- The mean serum magnesium in patients with Diabetic Neuropathy was 1.08mg/dl.
- The mean serum magnesium in patients with complications of Type 2 Diabetes was 1.67mg/dl, which was at lower level compared to those diabetics without complications i.e. 1.93mg/dl even though it was statistically insignificant.

In summary, we have demonstrated that low magnesium status is common in Type 2 Diabetics and there is a negative correlation between serum magnesium levels and duration of diabetes as well as diabetic control. Our study also found out the strong association between hypomagnesemia and diabetic neuropathy. Because magnesium depletion reduces insulin sensitivity and may increase risk of secondary complications, it may be prudent in clinical practice to periodically monitor plasma magnesium concentration in diabetic patients. If plasma magnesium is low an intervention to increase dietary intakes of magnesium may be beneficial. Henceforth our study substantiates the known importance of magnesium supplementation in diabetics to prevent complications.

LIMITATIONS

In the present study magnesium supplementation and its effects towards magnesium levels or metabolic control was not done in which can be taken as limitation of the present study.

There was no scope for follow up in the present study. Hence change in magnesium states with respect to improvement or worsening of diabetic state in the long run was not studied. This study focuses on magnesium levels in Type 2 Diabetes mellitus at a given point but not on therapeutically correcting hypomagnesemia or otherwise not correcting in the future course of the disease and its outcome.

Plasma magnesium is relatively an insensitive measurement of magnesium status of the body because major bulk of magnesium lies within the cell. Hence intra erythrocyte magnesium and urinary magnesium could not be done in the present study due to lack of facility and financial burden.

Isolation of patients with only one complication of Type 2 Diabetes Mellitus was difficult. Few patients had two or more complications of Type 2 Diabetes Mellitus at the same point of time.

The sample size of the study was small and the duration of study was short.

The study broadly studies treatment type with no mention to the specific type of OHA or insulin used.

RECOMMENDATIONS

- The study may be attempted on a larger population over a longer period of time including patients from varying socioeconomic backgrounds to look for variations.
- A magnesium supplementation trial may be attempted to see whether FBS and HbA1c levels improve post supplementation.
- A further study maybe done to look for relation between hypomagnesaemia and macro vascular complications of DM .

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**STUDY ON SERUM MAGNESIUM LEVELS IN DIABETIC PATIENTS WITH
MICROVASCULAR COMPLICATIONS**

PROFORMA

Sl. No: _____

Name: -----Age: -----Sex: -----

Address: -----

Occupation:-----Phone No:-----OP No:-----

IP No:-----DOA:-----DOS:-----DOD:-----

Marital Status:-----Educational Qualification:-----

=====

HISTORY (Tick the symptoms present):

Intense hunger	Increase d fatigue	Unusual weight loss	Numbness of limbs	Frequent urination	Disproportionate thirst	Irritability
Non Healing Ulcers	Others					

Past History:

Illness:	Hypertension	DIABETES	Kidney disorder	PVD	CVA	CAD	Thyroid disorder	Malabsorption syndromes
Y / N:								
Duration:								

Personal History:

Personal	Smoking	Alcoholism	Tobacco chewing

Drug History (tick whichever is applicable):

Drug:	PPIs	Amphotericin/diuretics	Magnesium supplements
Y / N			

Others(specify):

Family History:

	DIABETES	THYROID DISEASE	GASTROINTESTINAL DISEASES	CAD	HYPERTENSION
Illness:					
Duration:					

Examination:

Pallor	Icterus	Clubbing	Cyanosis	LNE	Edema	Thyroid
PR:	BP:	RR:	Temp:			

CVS:	
RS:	
Nervous System:	
GIT:	

Musculoskeletal:	
Others:	

Investigations:

Hb	TC	DC	Platelet	FBS	PPBS	HbA1C	
Na	K	Mg	Urea	Creatinine			
FLP	TOTAL CHOLESTROL	HDL	LDL	VLDL			
Urine:	Protein	Alb	RBC	WBC	Casts		
			Others				

URINE SPOT PCR:

CXR:

ECG:

FUNDOSCOPY:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

**STUDY ON SERUM MAGNESIUM LEVELS IN DIABETIC PATIENTS WITH
MICROVASCULAR COMPLICATIONS**

AT GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL, CHENNAI.

Place of study: Govt. Stanley medical college, Chennai

I have been informed about the details of the study in my own language.

I am aware that am suffering from decompensated disease of the liver and am willing to participate in this study where my serum sodium levels will be measured for further correlation with my health condition.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:

Name and address

Signature/thumb impression:

Date:

Investigator Signature and date

Witness:

Name and address

Signature/thumb impression

Date:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

STUDY ON SERUM MAGNESIUM LEVELS IN DIABETIC PATIENTS WITH MICROVASCULAR COMPLICATIONS

நான்இந்தஆராய்ச்சியில்விவரங்களைமுற்றிலும்புரிந்துகொண்டேன்.
ஆய்வில்பங்குஎடுத்துபோது,
சாத்தியமானஅபாயங்கள்மற்றும்பயன்களைபற்றிநான்அறிந்துள்ளேன்.

நான்எந்தவொருவேளையிலும்ஆய்வில்இருந்துதிரும்பமுடியும்,
அதன்பின்னர்,
நான்வழக்கம்போல்மருத்துவசிகிச்சைபெறமுடியும்என்றுபுரிந்துகொள்கிறேன்.

நான்ஆய்வில்பங்குஎடுத்துபணம்எதையும்பெறமுடியாதுஎன்றுஅறிந்துள்ளேன்.
இந்தஆய்வின்முடிவுகள்எந்தமெடிக்கல்ஜர்னலில்வெளியிடப்படஇருந்தால்நான்
எதிர்க்கவில்லை,
என்தனிப்பட்டஅடையாளத்தைவெளிப்படுத்தப்பட்டுஇருக்கக்கூடாது.

நான்இந்தஆய்வில்பங்கெடுப்பதன்மூலம்நான்என்னசெய்யபோகிறேன்என்றுதெரியும்.
நான்இந்தஆய்வில்என்முழுஓத்துழைப்பையும்கொடுப்பேன்என்றுஉறுதியளிக்கிறேன்.

தன்னார்வளர்

பெயர்மற்றும்முகவரி
கையொப்பம் / விரல்ரேகை:

சாட்சி _____

பெயர்மற்றும்முகவரி
கையொப்பம் / விரல்ரேகை:

ஆராய்ச்சியாளராக

LIST OF ABBREVIATIONS

DKA	-	Diabetic ketoacidosis
DM	-	Diabetes Mellitus
PPI	-	Proton Pump Inhibitor
SIADH	-	Syndrome of Inappropriate Antidiuretic Hormone secretion
DCCT	-	Diabetes Control and Complications Trial
NGSP	-	<i>National Glycohemoglobin Standardization Program</i>
<i>OGTT</i>	-	<i>Oral Glucose Tolerance Test</i>
TRPM6	-	Transient Receptor Potential Cation Channel, Subfamily M, Member 6
Mg	-	Magnesium
TAL	-	Thick Ascending Limb of the Loop of Henle
cAMP	-	Cyclic Adenosine Monophosphate
DCT	-	Distal Convolutated Tubule
PTH	-	<i>Parathyroid hormone</i>
DNA	-	Deoxyribonucleic acid
ROMK	-	Renal Outer Medullary Potassium <i>channel</i>

KEY TO MASTER CHART

OCCUPN	–	Occupation
F	–	Female
M	-	Male
Serum Mg	–	Serum magnesium
DURN	-	Duration
oha	–	Oral hypoglycemic agents
TRTMNT	-	Treatment
FAMILY HIS	–	Family history
HTN	-	Hypertension
PVD	–	Peripheral Vascular Disease
CVA	–	Cerebrovascular accident
CAD	-	Coronary Artery Disease
MAS	-	Malabsorption
SMKNG	-	Smoking
BP	–	Blood Pressure
ABS PERPULS	–	Absent Peripheral Pulses
FBS	–	Fasting Blood Sugar
NERVE	–	Altered nerve conduction study
R	–	Retinopathy present
+	-	Present
-	-	Absent
Y	-	Yes
N	-	No

1	patients		details			diabetic history			Personal history		Clinical ca			examination and investigations								
2	sl.no	case/com	id	age	sex	new DM	DOD	DUD	FHOD	smoking	alcoholis	Retinopa	Neuropat	Nephrop	FBS	PPBS	HbA1c	Mg	creatinine	TC	TGL	LDL
3	1	CASE	11019	48	MALE	Y	NA	INSULIN	Y	Y	NO	Y	NO	Y	210	356	10.1	1.2	1.2	240	200	146
4	2	CASE	12109	43	MALE	N	2	OHA	Y	Y	NO	N	N	Y	240	360	11.8	1.6	1	200	140	120
5	3	CASE	12211	57	F	N	5	INSULIN	Y	N	NO	N	N	Y	179	268	8.6	2	0.8	310	189	166
6	4	CASE	12218	63	F	N	18	OHA	Y	N	NO	Y	N	Y	150	190	8.4	1.9	1.9	290	170	140
7	5	CASE	13319	42	MALE	N	2	OHA	N	N	NO	N	N	Y	150	200	8.1	2.6	0.9	274	190	138
8	6	CASE	13869	70	F	N	18	INSULIN	Y	N	NO	Y	Y	Y	128	208	7.8	1.1	1.4	292	194	160
9	7	CASE	13970	40	F	N	2	OHA	Y	N	NO	Y	N	N	189	244	8.2	2.4	0.8	170	80	90
10	8	CASE	13982	61	F	N	13	OHA+INS	Y	N	NO	Y	N	Y	179	140	8.4	1.2	1	270	210	140
11	9	CASE	13990	70	F	N	20	INS	Y	N	NO	N	Y	Y	129	192	8.2	1.1	1.2	240	200	140
12	10	CASE	13998	45	MALE	N	5	OHA	N	N	NO	N	N	Y	263	348	10.2	1.8	1.4	276	205	154
13	11	CASE	14011	64	F	N	12	OHA+INS	N	Y	NO	N	N	Y	164	141	8	1.5	1.2	265	170	200
14	12	CASE	14112	82	F	N	>20	INS	Y	N	NO	Y	Y	Y	145	241	8.2	1	1.7	252	198	140
15	13	CASE	14431	60	MALE	N	15	OHA	N	Y	NO	N	N	Y	146	230	8.5	2.1	1.4	311	217	151
16	14	CASE	14578	46	MALE	Y	NA	INSULIN	N	Y	NO	N	N	Y	214	296	9.6	1.5	0.8	323	189	148
17	15	CASE	15087	70	F	N	10	INSULIN	N	Y	NO	Y	N	Y	180	278	9	1.6	0.8	310	220	158
18	16	CASE	15289	55	MALE	N	10	OHA+INS	Y	Y	NO	Y	N	Y	155	290	9.5	1.5	1.2	170	90	100
19	17	CASE	15351	62	F	N	20	OHA	Y	Y	NO	Y	N	Y	220	340	10.6	1.7	1.1	400	236	190
20	18	CASE	15467	65	MALE	N	15	INSULIN	Y	Y	NO	N	Y	Y	135	256	8.4	1.1	1.4	280	190	130
21	19	CASE	15567	68	MALE	N	18	OHA+INS	Y	Y	NO	N	N	Y	156	186	8.5	2	2.4	179	132	114
22	20	CASE	15860	42	F	N	7	INSULIN	Y	N	NO	N	N	Y	128	170	7.7	1.9	0.7	186	100	90
23	21	CASE	15967	68	MALE	N	13	INSULIN	Y	Y	NO	N	Y	Y	150	228	8.2	1	1.5	192	142	130
24	22	CASE	15991	63	MALE	N	15	INSULIN	Y	Y	NO	N	Y	Y	146	202	8.6	1.2	1.7	256	184	127
25	23	CASE	16011	57	MALE	N	11	INSULIN	Y	Y	NO	Y	N	Y	143	192	8.5	2.2	0.9	340	210	200
26	24	CASE	16098	74	MALE	N	>20	OHA	Y	Y	NO	N	N	Y	220	310	9.9	2.3	1.1	293	225	160
27	25	CASE	17031	45	MALE	N	5	INSULIN	Y	Y	NO	N	N	Y	121	192	7.6	2.1	0.8	286	170	136
28	26	CASE	17132	48	F	N	8	OHA	Y	N	NO	N	N	Y	211	310	10.4	1.7	0.9	156	86	97
29	27	CASE	17321	51	MALE	N	7	OHA	Y	Y	NO	N	N	Y	280	426	12.4	1.6	1.1	192	129	120
30	28	CASE	17451	53	MALE	N	13	INSULIN	N	Y	NO	N	N	Y	280	407	14	1.5	1.2	172	120	90
31	29	CASE	17552	64	MALE	N	>20	OHA	N	Y	NO	Y	Y	Y	178	242	10.8	1.1	1.8	220	164	100
32	30	CASE	17821	82	MALE	N	>20	INSULIN	Y	Y	NO	Y	N	Y	223	434	12.8	1.8	3.4	200	110	100
33	31	CASE	18011	60	F	N	15	OHA	Y	N	NO	N	N	Y	156	189	8.5	2.4	1.6	315	215	148
34	32	CASE	18092	48	F	N	4	OHA	Y	N	NO	N	N	Y	223	341	12.4	1.6	1	387	250	176
35	33	CASE	18321	47	MALE	N	3	OHA	Y	Y	NO	N	N	Y	120	176	7	2.6	0.8	362	240	210
36	34	CASE	18534	68	MALE	N	18	OHA	Y	Y	NO	Y	Y	Y	182	270	11.2	1	1.8	242	148	112
37	35	CASE	18689	58	MALE	N	10	INSULIN	Y	Y	NO	N	N	Y	289	430	13	1.4	1.1	323	284	190
38	36	CASE	18698	57	MALE	N	15	OHA+INS	Y	Y	NO	N	N	Y	140	178	8	2.4	1.9	356	254	148
39	37	CASE	18751	86	MALE	N	>20	OHA+INS	N	N	NO	Y	N	N	172	286	8.7	1.4	1	188	130	120
40	38	CASE	18761	52	MALE	Y	NA	OHA	Y	Y	NO	Y	N	Y	216	324	10	1.3	0.7	254	170	140
41	39	CASE	18831	74	F	N	15	OHA	N	N	NO	Y	N	Y	260	374	10.4	1.5	3	160	100	90
42	40	CASE	19011	73	F	N	13	OHA	Y	Y	NO	N	Y	N	180	220	11.4	1.2	1.1	182	140	126

43	41	CASE	19023	78	MALE	N	>2	OHA+INS	N	N	NO	Y	N	N	270	365	12.4	1.6	1.1	156	82	74
44	42	CASE	19078	71	F	N	17	OHA	Y	N	NO	N	N	Y	168	146	8.2	2.6	2.6	270	210	136
45	43	CASE	19678	70	F	N	20	OHA+INS	Y	N	NO	Y	N	Y	210	360	10.8	2.4	2	180	146	113
46	44	CASE	19689	64	F	N	12	OHA	Y	N	NO	N	Y	N	140	220	10.3	1.1	1.2	258	200	140
47	45	CASE	19711	65	MALE	N	14	INSULIN	Y	Y	NO	Y	N	N	190	286	10	1.8	1	211	146	98
48	46	CASE	19845	58	F	N	6	OHA+INS	N	N	NO	N	N	Y	144	178	7.8	1.5	1	316	209	160
49	47	CASE	19878	77	F	N	>2	OHA+INS	Y	N	NO	N	N	Y	136	180	8.9	2.1	1.7	276	145	139
50	48	CASE	19931	82	MALE	N	13	OHA	Y	Y	NO	N	N	Y	164	272	8.8	1.3	1.4	294	158	160
51	49	CASE	19967	72	MALE	N	>2	OHA+INS	Y	Y	NO	Y	Y	Y	170	160	12	1	2.1	260	220	192
52	50	CASE	20012	58	MALE	N	10	INSULIN	Y	N	NO	N	N	Y	150	220	10	2.1	0.8	182	98	90
53	51	CONTRC	20089	49	MALE	N	4	OHA	N	N	NO	N	N	N	101	185	6.5	1.9	1.1	200	182	140
54	52	CONTRC	20131	52	MALE	N	2	OHA	Y	Y	NO	N	N	N	127	192	6	1.8	0.9	290	200	158
55	53	CONTRC	20341	51	MALE	N	3	OHA	Y	N	NO	N	N	N	101	169	6.2	2.1	0.7	158	87	112
56	54	CONTRC	20467	51	MALE	N	7	OHA	N	N	NO	N	N	N	107	146	6.5	1.9	0.9	275	200	140
57	55	CONTRC	20489	45	MALE	N	4	OHA	Y	Y	NO	N	N	N	98	139	5.9	2.1	0.7	380	211	164
58	56	CONTRC	20567	48	MALE	N	7	OHA	Y	Y	NO	N	N	N	131	182	6.1	2	1.2	160	120	140
59	57	CONTRC	20589	51	MALE	N	6	INSULIN	Y	N	NO	N	N	N	109	174	5.9	1.8	1	200	120	110
60	58	CONTRC	20598	59	MALE	N	9	OHA	Y	Y	NO	N	N	N	120	178	6.2	2.2	0.8	160	80	90
61	59	CONTRC	20875	53	MALE	N	5	OHA	N	N	NO	N	N	N	115	169	5.9	2.1	0.9	170	140	100
62	60	CONTRC	20942	48	MALE	N	7	OHA	N	Y	NO	N	N	N	121	190	5.7	2.1	0.8	185	97	90
63	61	CONTRC	20978	56	MALE	N	11	INSULIN	Y	Y	NO	N	N	N	126	191	7.2	2	0.9	156	90	80
64	62	CONTRC	21123	62	F	N	12	INSULIN	Y	N	NO	N	N	N	120	188	8	1.2	1	244	210	182
65	63	CONTRC	21341	60	MALE	N	8	OHA	N	N	NO	N	N	N	112	177	5.9	1.9	1	190	150	110
66	64	CONTRC	21451	48	F	N	3	OHA	N	N	NO	N	N	N	101	160	5.5	2	1.1	160	80	66
67	65	CONTRC	21551	55	F	N	5	OHA	Y	N	NO	N	N	N	101	165	5.9	1.5	0.8	178	96	90
68	66	CONTRC	21768	52	F	N	4	OHA	Y	N	NO	N	N	N	99	155	5.8	1.9	1.1	298	180	148
69	67	CONTRC	21983	47	MALE	N	2	OHA	Y	Y	NO	N	N	N	100	163	5.5	1.8	0.7	199	121	110
70	68	CONTRC	22051	65	MALE	N	7	INSULIN	Y	N	NO	N	N	N	120	178	7	1.2	0.9	165	140	94
71	69	CONTRC	22976	56	F	N	6	OHA	N	N	NO	N	N	N	125	162	6.8	2.2	1	174	97	100
72	70	CONTRC	23674	53	MALE	N	3	OHA	N	Y	NO	N	N	N	101	189	6.2	2.1	1.1	180	123	97
73	71	CONTRC	25438	48	MALE	N	8	OHA	N	N	NO	N	N	N	107	190	6.1	1.9	1	290	180	150
74	72	CONTRC	25798	61	F	N	7	OHA	Y	N	NO	N	N	N	134	180	5.8	2.3	0.8	201	130	126
75	73	CONTRC	25890	56	MALE	N	8	OHA	N	N	NO	N	N	N	98	156	5.4	2.1	0.9	160	78	86
76	74	CONTRC	26741	50	MALE	N	5	OHA	N	N	NO	N	N	N	116	159	6.1	2	0.7	211	100	96
77	75	CONTRC	27061	58	F	N	8	OHA	Y	N	NO	N	N	N	120	180	5.7	1.8	1	287	210	162
78	76	CONTRC	27141	55	F	N	6	OHA	Y	N	NO	N	N	N	103	156	5.5	2.1	1.1	156	81	97
79	77	CONTRC	27431	55	F	Y	1	OHA	N	N	NO	N	N	N	116	170	5.8	2	1	296	160	154
80	78	CONTRC	27561	50	MALE	N	3	OHA	N	N	NO	N	N	N	97	156	5.8	1.9	0.9	194	124	120
81	79	CONTRC	28975	52	MALE	N	2	OHA	N	N	NO	N	N	N	103	170	6	1.8	0.9	180	98	90
82	80	CONTRC	29864	49	MALE	N	4	OHA	Y	Y	NO	N	N	N	150	146	6.5	1.1	0.7	309	189	158
83	81	CONTRC	29880	50	F	N	3	OHA	N	N	NO	N	N	N	117	169	6.1	1.8	1	176	130	110
84	82	CONTRC	32171	48	F	N	3	OHA	N	N	NO	N	N	N	87	143	5.4	2.2	0.8	195	124	116

83	81	CONTRQ	29880	50	F	N		3	OHA	N	N	NO	N	N	N	117	169	6.1	1.8	1	176	130	110
84	82	CONTRQ	32171	48	F	N		3	OHA	N	N	NO	N	N	N	87	143	5.4	2.2	0.8	195	124	116
85	83	CONTRQ	33421	55	MALE	N		5	OHA	Y	Y	NO	N	N	N	111	158	5.5	2.4	0.8	186	100	100
86	84	CONTRQ	33867	61	MALE	N		9	OHA	Y	N	NO	N	N	N	141	190	7.5	1.2	0.7	182	110	79
87	85	CONTRQ	35678	48	MALE	N		8	OHA	N	Y	NO	N	N	N	101	167	5.9	2.3	0.9	184	85	92
88	86	CONTRQ	36789	59	MALE	N		7	OHA	N	N	NO	N	N	N	115	178	5.2	1.9	0.9	187	122	86
89	87	CONTRQ	37821	49	MALE	N		9	OHA	Y	Y	NO	N	N	N	114	156	5.8	1.8	1	145	111	90
90	88	CONTRQ	39801	50	MALE	N		3	OHA	Y	N	NO	N	N	N	98	146	5.4	2.1	1.1	156	102	70
91	89	CONTRQ	40124	56	MALE	N		6	OHA	Y	N	NO	N	N	N	117	182	5.7	2.2	1	213	120	78
92	90	CONTRQ	41132	58	MALE	N		3	OHA	N	Y	NO	N	N	N	101	168	5.5	2.3	0.8	137	100	85
93	91	CONTRQ	42361	51	MALE	N		4	OHA	Y	N	NO	N	N	N	95	178	5.5	2.4	0.7	160	132	94
94	92	CONTRQ	42382	56	F	N		6	OHA	Y	N	NO	N	N	N	121	180	6.1	2.4	0.6	223	150	110
95	93	CONTRQ	43351	56	F	N		4	OHA	N	N	NO	N	N	N	120	182	6.7	2.1	0.7	155	130	112
96	94	CONTRQ	45367	49	MALE	N		7	OHA	Y	Y	NO	N	N	N	118	172	6	1.9	0.9	167	142	86
97	95	CONTRQ	46731	51	MALE	N		4	OHA	N	Y	NO	N	N	N	109	178	6.1	1.9	0.8	134	126	80
98	96	CONTRQ	47889	51	MALE	N		2	OHA	N	N	NO	N	N	N	120	182	6.8	1.3	1	175	133	100
99	97	CONTRQ	48821	49	MALE	N		3	OHA	Y	N	NO	N	N	N	108	167	7	2.1	0.9	209	160	125
100	98	CONTRQ	49841	48	MALE	N		4	OHA	Y	Y	NO	N	N	N	124	179	5.5	1.9	0.8	155	146	92
101	99	CONTRQ	49896	47	MALE	N		3	OHA	N	N	NO	N	N	N	111	167	5.3	1.8	1.1	168	138	80
102	100	CONTRQ	50018	55	F	N		5	OHA	Y	N	NO	N	N	N	120	157	6.1	1.7	1	210	142	121