“STUDY OF SERUM MAGNESIUM IN TYPE-2 DIABETES MELLITUS”

By

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Dissertation submitted to BLDE University, Vijayapur

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IN

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Dr. SHIVARAJ N PATIL

LIST OF ABBREVIATIONS USED

AAS: Atomic Absorption Spectrometry

ACE: Angiotensin Converting Enzyme

AER: Albumin Excretion Rate

AGE: Advanced Glycosylation Products

BMI: Body Mass Index

GAG: Glycosaminoglycans

GFR: Glomerular Filtration Rate

HDL: High Density Lipoproteins

IDDM: Insulin Dependent Diabetes Mellitus

Ig: Immunoglobulin

IL: Interleukin

IGF: Insulin like Growth Factor

IHD: Ischemic Heart Disease

LDL: Low Density Lipoprotein

NIDDM: Non Insulin Dependent Diabetes Mellitus

PPBS: Post Prandial Blood Sugar

PVD: Peripheral Vascular Disease

PN: Peripheral Neuropathy

VLDL: Very Low Density Lipoprotein

SIG: Significant

Sr: Serum

ABSTRACT

Background:

Magnesium deficiency has been proposed as a novel factor implicated in the pathogenesis of diabetic complications. Hypomagnesemia can be both a consequence and a cause of diabetic complications.

Objective :

The aim of our study was to know the relationship between magnesium levels and diabetes and also note its association with the level of control of diabetes.

Methodology:

This study was undertaken in patients admitted to B.L.D.E.U's ShriB.M.Patil Medical College Hospital and Research Centre, Vijayapurbetween January 2015 to June 2016. A total of 70 cases of type-2 diabetes mellitus were taken for the study after satisfying the inclusion and exclusion criteria. 70 non diabetic patients were taken as controls. All the patients were evaluated in detail and serum magnesium levels were estimated using calmagite method.

Results :

There is significant difference between levels of serum magnesium levels among diabetics and controls. The mean serum magnesium levels in cases and controls are 1.8± 0.3 mg/dl and 1.9±0.2 mg/dl respectively. Cases are 7.2 times significantly more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Controls with P<0.001(significant).

There was significant difference between magnesium levels among controlled and uncontrolled diabetics. The mean serum magnesium levels among controlled and uncontrolled diabetics were 2.0± 0.3 mg/dl and 1.7± 0.2 mg/dl respectively. With p value <0.001.Uncontrolled DM Cases are 10.1 times significantly more likely to have

less Serum magnesium (<1.7 mg/dl) when compared to Controlled DM Cases with P= 0.004

Conclusion:

Serum magnesium levels were lower in type 2 diabetes mellitus patients compared with non diabetic controls. Levels of serum magnesium in uncontrolled type 2 diabetic patients were further lower than those in whom diabetes was under control.

Hypomagnesemia is an important factor in type 2 diabetes mellitus patients, leading to various complication. Hence hypomagnesemia should be corrected by supplementation**.**

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INTRODUCTION

The term diabetes mellitus, derived from Greek words meaning siphon and sweet, refers to group of metabolic disorders characterized by elevated blood glucose resulting from inadequate insulin secretion or insulin action. In some cases the primary defect is the synthesis, release or action of insulin; in other instances a metabolic defect beyond insulin is responsible. The chronic hyperglycemia that results may eventually lead to dysfunction, especially the heart, kidneys, blood vessels, nerves and eyes.[1]

Hypomagnesemia is a common feature in patients with type 2 diabetes. Although diabetes can induce hypomagnesemia, magnesium deficiency has also been proposed as a risk factor for type 2 diabetes. Magnesium is a necessary cofactor for several enzymes that play an important role in glucose metabolism. Animal studies have shown that magnesium deficiency has a negative effect on the post-receptor signaling of insulin. On the post-receptor signaling of insulin. Some short-term metabolic studies suggest that magnesium supplementation has a beneficial effect on insulin action and glucose metabolism.[2]

Hypomagnesemia has long been known to be associated with diabetes mellitus. Low serum magnesium level has been reported in children with insulin dependent diabetes mellitus and through the entire spectrum of adult type1 and type2 diabetes mellitus regardless of the type of therapy.[3]

Initially the cause of hypomagnesemia was attributed to (1) osmotic renal losses from glycosuria (2) decreased intestinal magnesium absorption and redistribution of magnesium from plasma into red blood cells caused by insulin effect. Recently a specific tubular magnesium defect in diabetes has been postulated.

Hypermagnesuria results specifically from a reduction in tubular absorption of magnesium.[4]

Magnesium is involved on multiple levels in insulin secretion, binding and activity. Cellular magnesium deficiency can alter the membrane bound sodium-potassium-adenosine triphospatase which is involved in the maintenance of gradients of sodium and potassium and in glucose transport.[5]

In diabetics there is a direct relationship between serum magnesium level and cellular glucose disposal that is independent of insulin secretion. This change in glucose disposal has been shown to be related to increased sensitivity of the tissues to insulin in the presence of adequate magnesium levels.[6]

Magnesium deficiency has been found to be associated with diabetic microvascular disease. Low serum magnesium level correlated positively with the velocity of regaining basal vascular tone after hyperemia. Hypomagnesaemia has been demonstrated in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe diabetic retinopathy.[7]

Magnesium depletion has been associated with multiple cardiovascular implications: arrhythmogenesis, vasospasm, and hypertension and platelet activity.[8]

In this study estimation of serum magnesium was carried out in patients of type2 diabetes mellitus and a correlation of these values with the metabolic control and variations in the levels with reference to the treatment was also studied.

OBJECTIVES

1. To compare the levels of serum magnesium in patients with type 2 DiabetesMellitus and normal healthy individuals.
2. To study levels of serum magnesium in controlled and uncontrolled diabetics.

REVIEW OF LITERATURE

Diabetes Mellitus is the single most important metabolic disease recognized worldwide as one of the leading cause of death and disability. The problem has reached pandemic proportions. Type2 diabetes is the commonest form of diabetes constituting almost 90% of diabetes population. Prevalence of diabetes worldwide was estimated to be 4% in 1995 and expected to be 5.4% by the year 2025. Today India leads in the world with its largest number of diabetes subjects as compared with any other given country It has been estimated that presently 19.4 million individuals are affected by diabetes and these numbers are expected to increase to 57.2 million by the year 2025 ($1/6^{th}$ of world total)[62]

It has been centuries since this syndrome was first recognized. The term diabetes which is from the Ionian Greek meaning to pass through, was first used by Aretaeus of Caappadocia in the second century AD as a generic description for conditions causing increased urine output. The association of polyuria with a sweet tasting substance in the urine was first reported in Sanskrit literature dating from the 5^{th} and 6^{th} century AD at the time of two notable physicians, Sushruta and Charaka. The urine of certain polyuric patients was described as tasting like honey (madhumeha), being sticky to touch and strongly attracting ants'. Indian descriptions of this appears to distinguish two forms of diabetes, one associated with emaciation, dehydration, polyuria and lassitude. The other form associated with stout build, obesity and sleepiness[64]

The word Magnesium is derived from the name of ancient gracian town of Magnesia. In 1808, Sir Humphrey Devy investigated the alkaline earth metal and earned the white magnesia stone by its modern name of Magnesium.[4]

Magnesium is not a trace element. It is the fourth most abundant cation in the body and within the cell is second only to potassium .The adult human body (70kg) contains 21 to 28 grams of magnesium, approximately 1 mole of this, about 60% is in bone. 20% in skeletal muscle, I9% in other cells and about I% in extra cellular fluid[66]

About 45% of the body's magnesium is intracellular. The concentration of magnesium in the cells is approximately 1to3 mmol/L. In general, the higher the metabolic activity of a cell, the higher is its magnesium content within the cell, Magnesium is compartmentalized and most of it is bound to proteins and negatively charged molecules ;80% of cytosolic magnesium is bound to ATP.Significant amount of magnesium is found in the nucleus, mitochondria and endoplasmic reticulum. Free magnesium accounts for 0.5 to 5.0% of the total cellular magnesium and it is this fraction that is probably important for the support of 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 the plasma membrane is quite impermeable to magnesium. Extracellular magnesium accounts for about 1% of the total body magnesium content. The normal serum magnesium concentration is approximately 1.7 to 2.4 mg/dL (0.70-0.99mmol/L).About 55% of magnesium is free, 30% associated with proteins (primarily albumin) and 15% complexed with phosphate, citrate and other anions.[12,67]

Magnesium is the fourth most common cat-ion in the body and second most common intracellularcat-ion after Potassium. Magnesium has a role in carbohydrate metabolism in general and also has an action on the insulin in particular Magnesium increases the cellular ability to utilize calcium, phosphorous, sodium, potassium, vitamin C, E and B-eomplex.[68,69]

The link between magnesium (Mg) deficiency and type 2 diabetes mellitus is well known. Type 2 diabetes is frequently associated with both extracellular and intracellular Mg deficits. A chronic latent Mg deficit or an overt clinical hypomagnesaemia is common in subjects with type 2 diabetes, especially in those with poorly controlled glycemic profiles. Insulin and glucose are important regulators of Mg metabolism. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. A low Mg intake and an increased Mg urinary loss appear the most important mechanisms that may favor Mg depletion in patients with type 2 diabetes. Low dietary Mg intake has been related to the development of type 2 diabetes and metabolic syndrome. Benefits of Mg supplementation on metabolic profile in diabetic subjects have been found in most, but not all clinical studies and larger prospective studies are needed to support the potential role of dietary Mg supplementation as a possible public health strategy in diabetes risk.[16]

Dasgupta et al. in 2012 studied magnesium levels in 150 non critically ill diabetic patietns.Hypomagnesemia (Se magnesium < 1.6 mg/dl) was documented in 11.33%. Mean HbA1c was 11.9% in the hypomagnesemic patients compared with 9.8% in controls..Microvascular complications and coronary artery disease was present more in patients with hypomagnesemia.In their study there was positive correlation between hypomagnesemiaand poorer glycemic control, retinopathy, nephropathy, and foot ulcers in diabetics.[61]

Mc Nair Petal in 1978 The measured serum magnesium concentration in 71 insulin-treated diabetic outpatients who had had the disease for 10 to 20 years. The

patients were divided into two subgroups according to the severity of their retinopathy. As a whole the patients exhibited a definite hypomagnesemia that was most pronounced in the subgroup having the severest degree of retinopathy. The subgroups were comparable regarding known risk factors implicated in diabetic retinopathy. Thus, hypomagnesemia appears to be an additional risk factor in the development and progress of this complication.[7]

Seyoum B et al. studied magnesium levels in diabetics in tertiary hospital in Ethiopia in 2008.The study were done in 159 patients with 113 cases and 46 controls. The mean magnesium level was significantly lower in patients with diabetes than in controls. The levels in type 1 and type 2 patients were similar.The overall prevalence of hypomagnesemia was 65% in patients with diabetes. The duration of diabetes, sex, and lipid profile of the patients with diabetes were similar in the different categories of magnesium levels. They found a high rate of hypomagnesemia among patients with diabetes and concluded that diabetes mellitus is one of the most common causes of magnesium deficiency.[8]

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 diabetics.[29]

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 levels.[30]

Mc Nair Petal (1982) indicated that the net tubular reabsorption of magnesium is decreased in diabetic patients in presence of hyperglycaemia, leading to hypermagnesuria and hypomagnesemia.[31]

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 sensitivitiy in maturity onset diabetes.[6]

HatwalA,Gujral AS, Bhatia RP, Agarwal JK, Bajpai HS. (1989) provided data which seem to point towards association between hypomagnesemia and diabetic retinopathy.[7]

Gillian Grafton, Bunce M, Sheppard MC, Brown G, Baxter MA (1992) demonstrated that magnesium is a positive effector of inositol transport and is capable of promoting a 25 fold increase in the affinity of the transporter for inositol. They suggested that hypomagnesemia may be linked to the development of diabetic complications via reduction in the rate of inositol transport and subsequent intracellular inositol depletion.[32]

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 retinopathy.[33]

Rude RK (1992) suggested that 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 condition.[34]

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 diabetes.[35]

Betrelloni S (1992) showed that the deranged parathyroid hormone-vitamin D axis in IDDM is reversed after normalization of magnesium serum levels by oral magnesium. He also suggested that hypomagnesaemia is involved in the genesis of the altered mineral metabolism in children with IDDM.[36]

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 individuals.[37]

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 state.[38]

White JR Jr, Campbell – RK (1993) in their conclusion suggested a link between hypomagnesemia and hyperglycemia, as well as an association between hypomagnesemia and the complications of DM .[39]

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 NIDDM. They suggested that oral supplementation of magnesium may be useful in the treatment of hyperlipidemia in patients with NIDDM.[40]

Isbir T, TamerL, Taylor A, Isbir M.(1994) stated that the concentrations of copper were higher and the magnesium levels were lower in IDDM patients than in control subjects. They also said these changes 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 therapy.[41]

MaJ, 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 atherosclerosis.[42]

Alzaid AA, Dinnean SF, Moyer TP, Rizza RA. (1995) sought to determine whether insulin-induced stimulation of magnesium uptake is impaired in NIDDM and enhanced by acute hyperglycaemia and concluded that insulin resistance in subjects with NIDDM impairs the ability of insulin to stimulate magnesium as well as glucose uptake.[43]

Nagase N (1996) investigated interrelations between hypertension, ischemic heart disease (IHD) and diabetes mellitus in diabetic subjects and showed that serum Mg level of poorly controlled diabetic patients is lower than that of well controlled

diabetic patients. It also suggested that Mg deficient states is one of the cause of insulin resistancy.[44]

Corica F Allegra A, Buemi MJ, et al (1996) their studied 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 magnesium.[45]

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. Hypomagnesemia has been correlated with both poor diabetic control and insulin resistance in non diabetic elderly patients.[46]

Corica F, Allegra A, Buemi MJ et al. (1996) evaluated magnesium concentrations in plasma erythrocyte and platelet and plasma and urine levels of the soluble form of intercellular adhesion molecule-1 (SICAM-1) in subjects and concluded that the reduced intraplatelet magnesium content may contribute to the progression on the vascular complications in IDDM subjects with microalbuminuria.[47]

Husmann MJW, Fuchs P, Truttman AC, et al (1997) confirmed findings of reduced circulating ionized magnesium but normal circulating total magnesium in adults with non-insulin dependant diabetes mellitus.[48]

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 linkhelping to explain the epidemiological association between NIDDM and hypertension.[49]

Ewis SA, Abdel Rahman MS (1997) showed a state of low levels of magnesium and glutathione (GSH) in both blood and liver of diabetic animals. Treatment with atenolol alone did not change these levels significantly; however administration metformin or atenolol/metformin increased significantly the GSH levels in both liver and blood, andreturned the liver Mg content take to normal values.[50]

De Leeuw I, Engelen W, VertommenJ,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 test.[51]

Jacomella V, Sauser A, TruttmanAC, 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 glucose.[52]

De ValkHW,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 concentration.[53]

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 complications.[54]

Gurlek A, Bayratkar M, Ozaltin N. (1998) suggested that intracellular Mg depletion without significant hypomagnesemia is related to increased urinary Mg loss in patients with type 1 diabetes. The urinary Mg loss is not correlated with the degree of metabolic control.[55]

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 retinopathy.[56]

Mikhail N, Ehsanipoor K (1999) concluded that their data do not support routine Mg supplementation or monitoring in type 2 diabetes.[57]

Kao WH, Aoron 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 diabetics.[58]

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. Magnesium intake was evaluated every 2-4 yrs. Significant inverse relationship between magnesium intake and diabetes risk was found. This study recommends the increased consumption of foods rich in magnesium.[2]

Huerta MG, Holmes V F, Roemenich J N, et al. studied 24 obese non diabetic children and 24 sex and puberty matched lean control subjects. Serum magnesium, indices of insulin sensitivity, dietary magnesium intake and body composition were

measured. Association between magnesium deficiency and insulin resistance was present during childhood. Serum magnesium deficiency may be secondary to decreased dietary magnesium intake.[3]

Martha Rodríguez-Morán, and Fernando Guerrero-Romero. This study was 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 levels.[59]

Yokota K, Kato M, Lister F, et al.(2004) Effects of magnesium (Mg) supplementation on nine mild type 2 diabetic patients with stable glycemic control were investigated. Water from a salt lake with a high natural Mg content (7.1%) (MAG21) was used for supplementation after dilution with distilled water to 100mg/100mL; 300mL/day was given for 30 days. Fasting serum immunoreactive insulin level decreased significantly, as did HOMA squareR (both $p < 0.05$). There was also a marked decrease of the mean triglyceride level after supplementation. The patients with hypertension showed significant reduction of systolic ($p < 0.01$), diastolic ($p = 0.0038$), and mean ($p < 0.01$) blood pressure. The salt lake water supplement, MAG21, exerted clinical benefit as a Mg supplement in patients with mild type 2 diabetes mellitus.[60]

Fujii et al observed that a marked depletion in plasma and erythrocyte Magnesium levels was particularly evident in diabetic patients with advanced retinopathy and poor diabetic control.[70]

Nadler JL et al in their study of 20 subjects in the year 1992 concluded that magnesium depletion has negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes, as well as on the evolution of complication such as retinopathy, thrombosis and hypertension.[35]

Grafton Baxter et al during 1992 suggested that hypomagnesaemia leads to reduction of inositol transport and subsequent inositol depletion that might enhance the development of diabetic complications.[71]

Nadler JL et al in their study concluded that the diet, induced magnesium deficiency increases the thromboxane urinary concentration and enhances angiotensin induced aldosterone synthesis. These effects are associated with a decrease in insulin action suggesting that magnesium deficiency may be a common factor associated with insulin resistance and vascular disease.[72]

Barbagallo et al in 1993, concluded in their study that glucose itself has a crucial role in cellular ion homeostasis and causes increase in intracellular calcium and decrease in intracellular magnesium.[73]

Lefebvre and scheen et al in 1995, concluded that magnesium deficiency results in impaired insulin secretion, while magnesium replacement restores insulin secretion.[74]

Eibl N.L et al in study of 40 patients in the year 1995 found that Oral Magnesium replacement therapy is important for prevention of late diabetic complications.[75]

Devalk et al in this study of 61 patients in the year 1999, concluded an association between plasma concentration of magnesium and development of progression of retinopathy in insulin using patients.[76]

Corsonello A et al in their study of 60 patients concluded that, microalbuminuria, clinical proteinuria as well as poor glycometabolic control and hypertriglyceridemia are associated to relevant alteration in magnesium metabolism.[77]

Rodriguez-Moran M et al in their study of 33 patients in the year 2001 concluded that, serum magnesium depletion is present and shows a strong relationship with foot ulcers in subjects with Type 2 diabetes mellitus.[78]

Moniker K et al in their study of 109 patients in the year 2003 concluded that lower plasma magnesium and poor magnesium status are common in Type2 diabetes mellitus.[79]

Only 1% of total magnesium is in extra cellular fluid and of this about 25% is in the plasma, rest is in the red blood cells. Around 50% of serum magnesium is free, 32% is protein bound and rest 18% is accounted for Magnesium phosphate, citrate and other unidentified complexes. Since the vascular space represents only a fractional portion of the body involved in Magnesium homeostasis, it is evident that the demonstration of serum Magnesium does not always give true indication of total body Magnesium stores.[80]

Nevertheless, in contrast to complex balance studies on tissue determination, measurement of serum magnesium is the quickest, simplest and most effective first approach to as evaluation of magnesium deficiency states. This procedure has wide spread success in identification of clinical syndromes that have responded to replacement therapy with magnesium salts,[81] Indeed hypomagnesaemia can occur

when cellular content of magnesium is normal and cellular depletion may exist without a concomitant lowering of serum magnesium valuves.[82]

DIABETES MELLITUS

Introduction :

Diabetes mellitusis emerging as the chronic non-communicable diseaseof concern in developing countries with changing environs, urbanization and altered life-styles, diabetes is also increasingly identified as a major cause of morbidity and mortality.

Furthermore, 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.

Definition:

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

Pathogenic process 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 in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action.

Long term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputation, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary and cardiovascular symptoms and sexual dysfunction.

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

Diabetes is worldwide in distribution and the incidence of both types of primary diabetes, i.e. type1 and type2 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 mellitus[26]

I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)

a. Immune mediated

b. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)

a Other specific types:

1. Genetic defects of beta cell function
2. Chromosome 12 HNF – 1 α (MODY – 3)
3. Chromosome 7, glucokinase (MODY – 2)
4. Chromosome 20, HNF – 4 α (MODY – 1)
5. Mitochondrial DNA
6. Others

b Genetic defects in insulin action

1. Type A insulin resistance

2. Leprechaunism

3. Rabson – mendenhall syndrome

4. Lipoatropic diabetes

5. Others

c Disease of the exocrine pancreas

1. Pancreatitis

2. Trauma/Pancreatectomy

3. Neoplasia

4. Cystic fibrosis

5. Hemochromatosis

6. Fibrocalculouspancreatopathy

7. Others

d. Endocrinopathies

1. Acromegaly

2. Cushing's syndrome

3. Glucagonoma

4. Pheochromocytoma

5. Hyperthyroidism

6. Somatostatinoma

7. Aldosteronoma

8. Others.

e. Drug or Chemical related

1. Pentamidine

2. Nicotinic acid

3. Glucocorticoids

4. Thyroid hormones
5. Diazoxide
6. Beta-adrenergic agonists
7. Thiazides
8. Dilantin
9. Alpha- interferon
10. Others

f. Infections

1. Congenital Rubella
2. Cytomegalovirus
3. Others

g. Uncommon factors of immune mediated diabetes

1. Stiff Man syndrome
2. Anti – insulin receptor antibodies
3. Others

h. Other genetic syndromes sometimes associated with diabetes

1. Down’s syndrome
2. Klinefelter’s syndrome
3. Turner’s syndrome
4. Wolfram’s syndrome
5. Friendrich’s ataxia
6. Huntington’s chorea
7. Laurence- Moon Biedl syndrome
8. Myotonic dystrophy
9. Porphyria

10. Prader- willi syndrome

11. Others

IV. Gestational Diabetes mellitus (GDM)

TYPE-2 DIABETES:

This form of diabetes is characterized by insulin resistance and usually relative (rather than absolute) insulin deficiency. Most patients with this form of diabetes are obese. Ketoacidosis seldom occurs 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:

Life Style:

Overeating, especially when combined with obesity and under activity isassociated with the development of type 2 diabetes. Obesity probably acts as a diabetogenic factor (through increasing resistance to the action of insulin) in those genetically predisposed to develop type 2 diabetes.

Malnutrition in Utero:

It is proposed that malnutrition in utero and in infancy may damage beta cell development at a crucial period, predisposing to type 2 diabetes later in life.

Age :

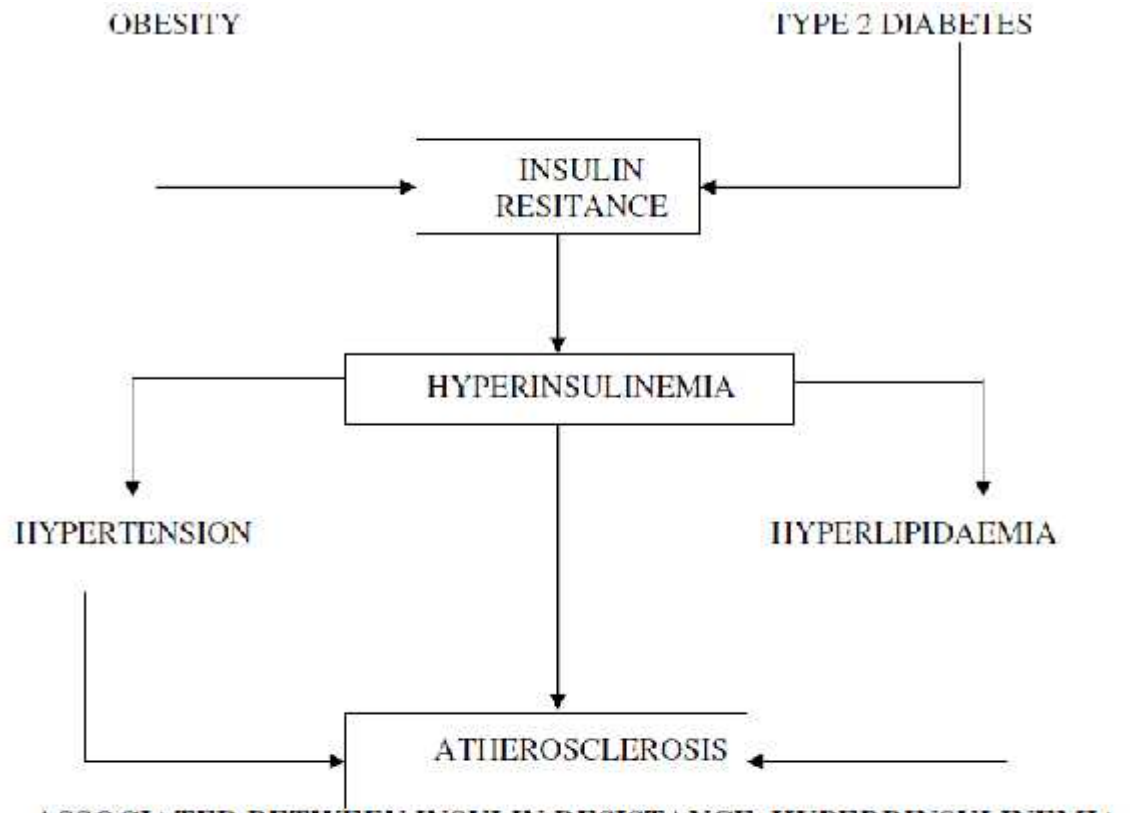
Type 2 diabetes is principally a disease of the middle aged and elderly affecting10% of the population over the age of 65.

PATHOGENESIS OF TYPE 2 DIABETES

Insulin Resistance:

Increased hepatic production of glucose and resistance to the action of insulin in muscle are invariable in obese and non-obese patients with type 2 diabetes. Insulin resistance may be due to any one of the three general causes: an abnormal insulin molecule, and excessive amount of circulating antagonists or target tissue defects.

The characteristic feature of type 2 diabetes is that it is often associated with other medical disorders including 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.



ASSOCIATED BETWEEN INSULIN RESISTANCE, HYPERRINSULINEMIA, AND PROMOTION OF ATHEROSCLEROSIS [27]

PANCREATIC BETA CELL FAILURE

In type 2 diabetes there is only moderate reduction in the total mass of pancreatic islet tissue. Deposition of amyloid, accompanied by atrophy of the normal tissue, particularly islet epithelial cells are typical of type 2 diabetes. Deposition of amyloid reflects a pathologic process which is increased in type 2 diabetes.

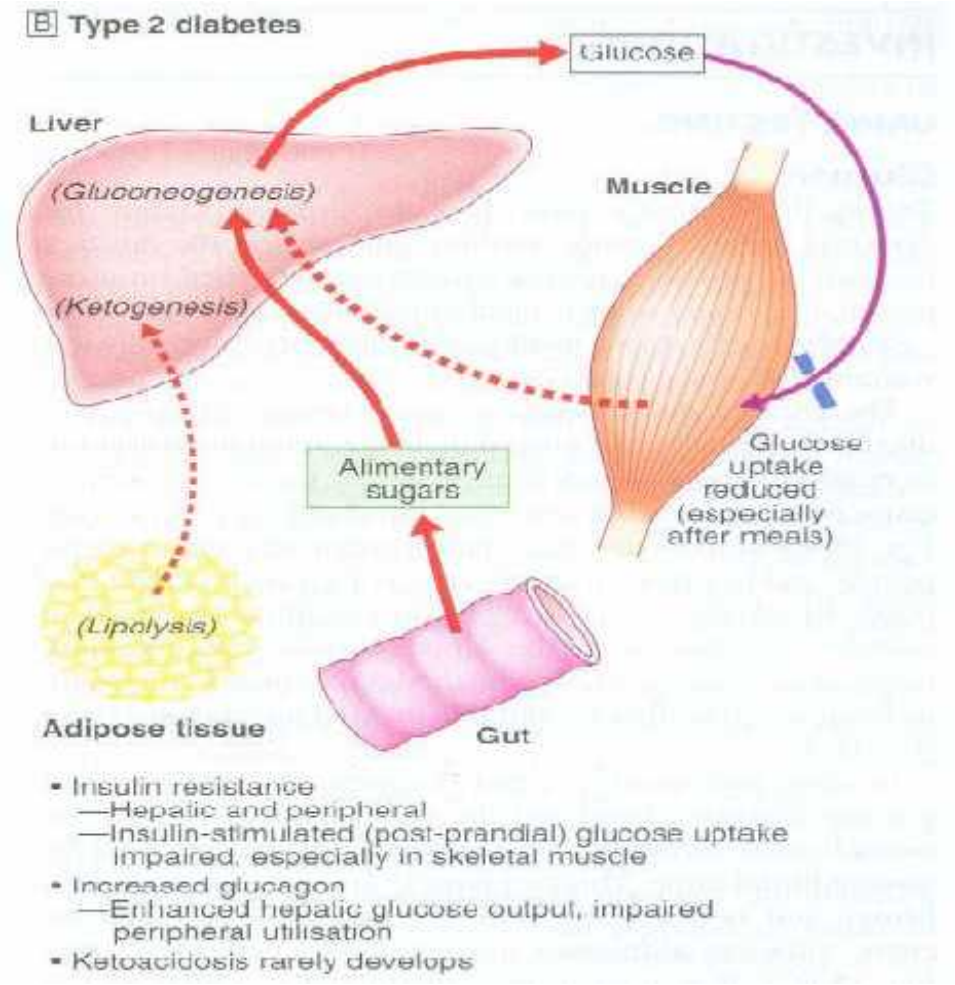
Alpha cell mass is unchanged and glucagons secretion is increased and this may contribute to the hyperglycaemia. Insulin resistance tends to raise blood glucose and stimulate insulin secretion to prevent hyperglycaemia. When the maximal insulin secretory capacity has been exceeded, any further increase fasting blood glucose levels causes a decline in insulin generation.

METABOLIC DISTURBANCE IN DIAB ETES

The hyperglycaemia of diabetes develops because of an absolute (type 1 diabetes) or a relative (type 2 diabetes) deficiency of insulin, resulting in decreased anabolic and increased catabolic effects. In both type-1 and type- 2 diabetes, insulin's actions are also impaired by insensitivity of target tissues. While this is the fundamental defect in type-2 diabetes, hyperglycaemia can also induce insulin resistance through glucose toxicity.

PATHOPHYSIOLOGICAL PROCESSES IN DIABETES MELLITUS

Type 2 Diabetes



Glycosuria occurs 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. The severity of the classical osmotic symptoms of polyuria and polydypsia is related to the degree of glycosuria. If hyperglycaemia develops slowly over months or years, as in type 2 diabetes, the renal threshold for glucose rises, and the symptoms of diabetes are mild.

CRITERIA FOR TESTING FOR DIABETES IN ASYMPTOMATIC ADULT

INDIVIDUALS[27]

1. Testing for diabetes should be considered in all individuals at age 45 years and above,particularly in those with a BMI 25 kg/m^2, and, if normal, should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently inindividuals who are overweight (>BMI 25 kg/m^2) and have additional risk factors are:

- Habitually physically inactive have a first-degree relative with diabetes are members of a high-risk ethnic population (e.g, African American, Latino, Native American, Asian American, Pacific Islander) have delivered a baby weighing 9 lb or have been diagnosed with GDM are hypertensive (140/90 mmHg) have an HDL cholesterol level35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250 mg/dl (2.82 mmol/l)have PCOS on previous testing, had IGT or IFG have other clinical conditions associated with insulin resistance (e.g. PCOS or Acanthosisnigricans) have a history of vascular disease

Symptoms of Diabetes Mellitus

Symptoms of marked hyperglycaemia include polyuria, polydypsia, polyphagia and blurring of vision. Type 2 diabetes frequently goes undiagnosed for many years because the hyperglycaemia develops gradually.

DIAGONOSIS OF DIABETES MELLITUS

Criteria for the Diagnosis:

Normoglycaemia	IFG or IGT	Diabetes Mellitus
FPG < 110 mg/dl	FPG $\geq$ 110 and < 126	FPG $\geq$ 126 mg/dl
	mg/dl (IFG)	2- h PG $\geq$ 200 mg/dl
2-h PPG < 140 mg/dl	2h PPG $\geq$ 140 and < 200	Symptoms of DM and
	mg/dl (GIT)	random plasma glucose
		concentration > 200 mg/dl

A diagnosis of diabetes must be confirmed on a subsequent day by measurement of FPG, 2 hour PG or random plasma glucose (if symptoms are present). The FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients and lower cost. Fasting is defined as no caloric intake for at least 8 hours.

- 2-h PPG: 2-h post load glucose
- FPG: Fasting Plasma Glucose
- IFG: Impaired Fasting Glucose
- IGT: Impaired Glucose Tolerance

This test requires the use of glucose load containing the equivalent of 75g anhydrous dissolved in water.

COMPLICATIONS OF DIABETES

1. ACUTE:

1. **Hypoglycemia:** Occurs often in diabetic patients treated with insulin. Therisk of hypoglycemia is the most important single factor limiting the attainment of the therapeutic goal, namely near normal glycemia.
2. **Diabetic Ketoacidosis:** Is a major medical emergency and remains aserious

cause of morbidity, principally in patients with type 1 diabetes.

The cardinal biochemical features of diabetic Ketoacidosis are

- Hyperglycaemia
- Hyperketonaemia
- Metabolic acidosis

Complications:

- Cerebral edema
- ARDS
- Thromboembolism
- DIC
- Acute circulatory failure

3. Non Ketotic hyperosmolar diabetic coma: This condition is characterized by severe hyperglycaemia without significant hyperketonaemia or acidosis Thromboembolic complications are common.
4. Lactic Acidosis:High concentration of lactic acid (> 5.0 mmol/L) in the blood.

II. CHRONIC

Macrovascular Disease

- Diabetes mellitus is a major factor for morbidity and mortality through premature and accelerate atherosclerosis.
- Coronary and cerebrovascular disease is 2 to 4 times as common in a diabetic and the post-infarction mortality is higher.
- Peripheral vascular disease is a 4 to 6 times more common in diabetic; associated presence of neuropathy accentuates diabetic foot problems.
- The usual relative protection against atherosclerosis prior to menopause is lost in diabetic women.

Diabetic Neuropathy

- It is a major cause of morbidity and premature death in diabetic patients.
- It requires many years before becoming clinical overt.

Stages:

1. Incipient (sub clinical nephropathy)
2. Clinical (overt nephropathy)
3. Advanced nephropathy
4. End stage renal disease

Diabetic Retinopathy

- Sight threatening eye disease is serious complication of diabetes and often be present without visual symptoms
- Early detection and appropriate management can greatly reduce risk of visual loss.

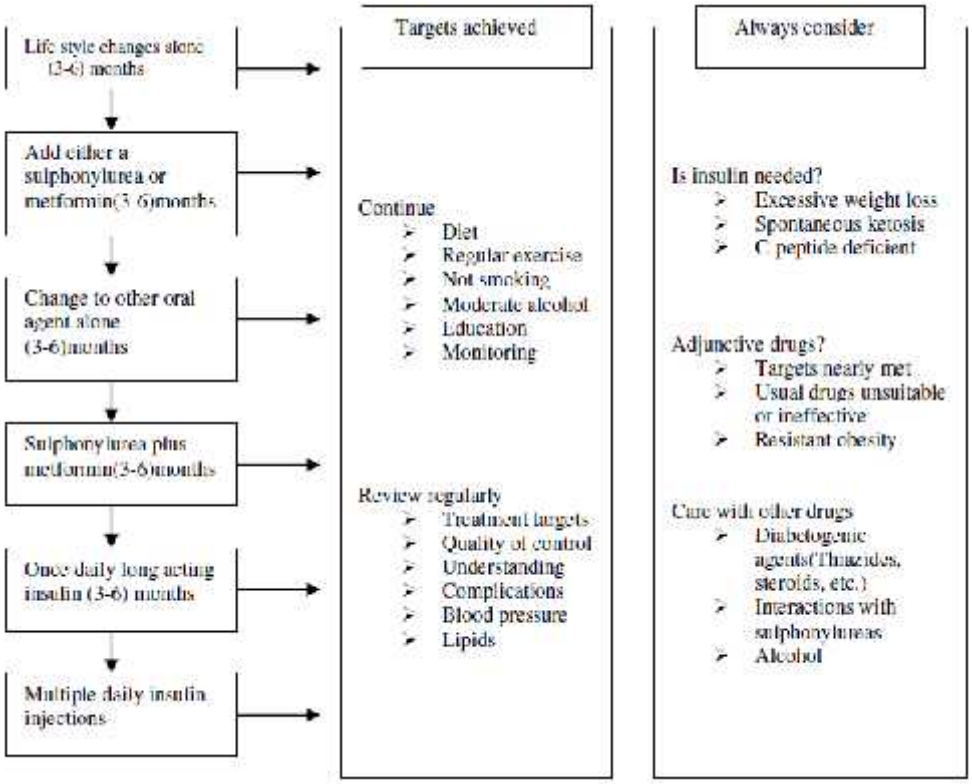
Diabetic foot:

- Foot ulcers and other foot problems are one of the commonest causes of morbidity, significant disability and even mortality, amongst diabetics.
- The frequency and severity of foot problems can be decreased with adequate foot evaluation and more importantly, good patient education about foot care.

ASSOCIATED PROBLEMS:

1. Lipid Disorders: Dyslipidemias contribute significantly towards the premature and accelerated atherosclerosis seen in diabetes and should be corrected more aggressively than in a non diabetic.
2. Hypertension: It is more commonly prevalent in a diabetic than in a non-diabetic. It is a major risk factor for the development of macro/micro vascular disease in diabetics.

Treatment Algorithm for Type-2 Diabetes Mellitus



MAGNESIUM

Introduction:

Magnesium is not a true trace element. 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 extra cellular fluid.[18]

Magnesium catalyses or activates more than 300 enzymes in the body. Magnesium 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. Magnesium 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 multi enzyme complexes.

The permeability characteristics and electric properties of membrane are affected by magnesium. Reduced extra cellular magnesium concentrations increase membrane excitability in tissues such as the heart. Magnesium also 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 anecessary prerequisite for the trigger function of calcium in several processes**.**

DISTRIBUTION

Magnesium is the fourth most abundant cation in the body and the second most prevalent intracellular cation. The total body magnesium content is approximately 25 g (1.03 mol), of which about 55% resides in the skeleton. One third of skeletal magnesium is exchangeable and probably serves as a reservoir for maintaining a normal extracellular magnesium concentration. About 45% of the body's magnesium is intracellular. The concentration of magnesium in the cells is approximately 1 to 3 mmol/lit. In general, higher the metabolic activity of a cell the higher is its magnesium content. Within the cell magnesium is compartmentalized 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. Free magnesium accounts for 0.5% to 5.0% 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 accounts for about 1% of the total body magnesium content. The normal magnesium concentration is approximately 1.7 to 2.4 mg/dl (0.70-0.99). About 55% of magnesium is free, 30% associated with proteins (primarily albumin) and 15% complexed with phosphate, citrate and other anions.[19]

METABOLISM OF MAGNESIUM

Magnesium intakes vary appreciably an approximate range for US and Western European population being 140 to 180 mg/d. The recommended dietary allowance (RDA) for magnesium is listed in table 1 and is 270 – 350 mg/d for adults. The magnesium content of food varies widely. Vegetables containing chlorophyll, seafood, nuts and grains contain appreciable amounts, whereas oils, fats and sugars contain very little. In addition drinking water especially hard water may be major source of magnesium.[18]

About 20 to 30% of ingested magnesium is absorbed from the gastrointestinal tract in people consuming self selected diets. However this may vary widely because intestinal absorption is inversely related to magnesium intake. Magnesium absorption is affected by malabsorption syndromes, factors that affect transit time, calcium, phosphate, protein, lactose or ingested alcohol. Vitamin D has not shown to affect magnesium absorption.

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 the filtered load in the kidney is excreted. 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 those of calcium, phosphate, sodium and potassium. There is evidence for hormonal regulation of the 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.[18]

Table1: Recommended dietary intakes of magnesium :[18]

	Recommended dietary allowances (RDA)			
	Age(Years)			Magnesium(mg/day)
Infants	0.0	-	0.5	40
	0.5	-	2.0	60
Children	1	-	3	80
	4	- 6		120
Males	7	- 10		170
	11	- 14		270
	15	- 18		400
	19	- 22		350
	23	- 50		350
	51 +			350
Females	11	- 14		280
	15	- 18		300
	19	- 22		280
	23	- 50		280
	51+			280
Pregnant				320
Lactating				355

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 higher. Hypertension, myocardial infarction, cardiac dysrhythmias, coronary vasospasm and premature atherosclerosis also have been linkedto magnesium depletion.[20]

Human magnesium deficiency as indicated by reduced serum magnesium amounts (hypomagnesemia) occurs with either normal or reduced serum calcium concentrations. Hypomagnesemia may be secondary affect in hypocalcemia or calcium deficient tetany. Yet a hypomagnesemicnormocalcemictetany 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.

Conditions that have been associated with hypomagnesemia include chronic alcoholism, childhood malnutrition, lactation, malabsorption acute pancreatitis, hypothyroidism, chronic glomerulonephritis, aldosteronism, digitalis intoxication and

prolonged intravenous feeding. 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 failure.

Increased serum magnesium concentrations have been observed in dehydration, severe diabetic acidosis and Addison's disease. Conditions that interfere with glomerular filtration, for example uremia results in retention of magnesium and hence elevation of serum concentrations.Hypermagnesemia leads to an increase in atrioventricular time of the electrocardiogram.

Magnesium retention after acute administration

Oral and intravenous magnesium loading tests have been described and are more widely used in clinical practice for diagnostic purpose than intracellular measurements. Normal individuals in magnesium balance excrete essentially all injected magnesium in urine within 24 to 48 hours after administration, whereas individuals with a magnesium deficit retain a significant proportion of the injected magnesium. In this procedure 30 mmol of magnesium in 500 ml of 5% dextrose is administered intravenously over 12 hours. A 24 hour urine collection is started at the beginning of the infusion. Retention of less than 30% of infused magnesium suggests magnesium depletion is unlikely. Patients who are to undergo this test should have normal kidney, not be taking medication that affects renal excretion of magnesium and not have disturbances in cardiac conduction or advanced respiratory insufficiency.

DETERMINATION OF MAGNESIUM

Methods

Serum magnesium has been measured using a wide variety of techniques including precipitation, titration,fluorometry, photometry, flame emission spectroscopy and AAS.[21]

Early methods used ammonium phosphate to quantitatively precipitate magnesium which could then be determined gravimetrically or by analysis of phosphate in the precipitate. The precipitation of magnesium by 8-hydroxyquinolone is the basis for the measurement of magnesium by various techniques. Titrimetric methods have been reported using EDTA with an indicator eriochrome black T in a manner analogous to the titrimetric method described for calcium. Flame emission spectroscopy has been used despite the fact that magnesium is a poor emitter at low temperature and the large quantity of sodium, potassium and phosphate interfere. A number of flourometric methods have been used. Enzymatic methods have now been developed with hexokinase or other enzymes that use Mg-ATP as substrate.[22] The rate of this reaction is dependent on the concentration of magnesium in the sample. Coupling hexokinase glucose-6-phosphate-dehydrogenase allows the reaction to be monitored at 340 nm with the formation of NADPH.[23] Today photometric methods are more commonly used by clinical laboratories, although AAS considered the reference method is also used by some

laboratories.[24]

Free magnesium

Free magnesium has been determined in whole blood, plasma, or serum by ion selectiveelectrode neutral carrier ionophores.[25] Further improvements in ion selective formagnesium are required in order to increase the availability of free magnesiumdeterminations.

Specimen

Serum is the preferred specimen but heparinised plasma may also be used. Other anticoagulants such as citrate, oxalate and EDTA are not acceptable because they form complexes with magnesium. Magnesium is considered to be stable in serum for days at 4^0 C and for months when frozen, provided evaporation and lyophilization are avoided.

Serum or plasma must be separated from the clot or red blood cells as soon as possible to avoid increased levels due to cell leakage. Because erythrocytes contain higher levels of magnesium than plasma or serum hemolysed samples are unacceptable. Interference by icterus or lipemia depends on the methods and use of dialysis, bichromate analysis or blanking. Lipemic specimens should be ultracentrifuged. Interference in photometric methods may be overcome with EDTA blanking.

Urine specimens should be collected in HCl, 20 to 30 ml of 6 mol/L for 24 hours specimen, to prevent precipitation of magnesium complexes. As with calcium, if acid must be added after collection, the entire specimen must be acidified and heated. Collection of the specimen in acid to prevent precipitation is recommended.

Reference Interval

The reference interval for serum magnesium is approximately 1.7 to 2.4 mg/dL (0.70 - 0.99 mmol/L).[25] Erythrocytes have magnesium levels approximately three times those of serum. Interconversion factors for the units used to express magnesium concentration are as follows:

- mmol/L= mEq/L X 0.5 = mg/dL X 0.14
- mEq/L = mmol/L X 2 = mg/dL X 0.82
- mg/dL = mEq/L X 1.22 = mmol/L X 2.43

MAGNESIUM DEFICIENCY:

Causes:

I. PRIMARY NUTRITIONAL DISTURBANCES

a) Inadequate intake

b) Total parenteral nutrition

c) Refeeding syndrome

GASTROINTESTINAL DISORDERS

a) Specific absorptive defects

b) Malabsorption syndromes

c) Prolonged diarrhoea

d) Prolonged nasogastric suction

e) Pancreatitis

f) Cellulose phosphate ingestion

II. ENDOCRINE DISORDERS

a) Hyperparathyroidism

b) Hypoparathyroidism

c) Hyperthyroidism

d) Primary hyperaldosteronism

e) Bartter's syndrome

f) Diabetic Ketoacidosis

g) Alcoholic Ketoacidosis

IV. CELLULAR UPTAKE OR REDISTRIBUTION

a) Administration of epinephrine

b) Acute pancreatitis

c) Following correction of respiratory acidosis

d) Massive blood transfusion

V. CHRONIC ALCOHOLISM, ALCOHOL WITHDRAWAL

VI. INCREASED RENAL EXCRETION

a) Ethanol ingestion

b) Idiopathic

c) Following renal transplantation

d) Cyclosporine therapy

e) Aminoglycoside therapy

f) SIADH

g) Diuretic administration

- Furosemide
- Ethacrynic acid
- Bumetanide
- Acetazolamide
- Thiazides

h) Recovery from acute tubular necrosis

i) Theophylline toxicity

Reasons for low Magnesium status in Diabetes

- Diets tend to be low in magnesium.
- Renal excreation of magnesium is high.
- Insensitivity to insulin affects magnesium transport as well as glucose metabolism.
- Use of loop and thiazide diuretics promotes magnesium wasting.

CLINICAL FEATURES

- Anorexia
- Nausea
- Vomiting
- Weakness

If Severe,

- Parasthesia
- Muscular cramps
- Irritability
- Decreased attention span
- Mental confusion
- Fasciculations
- Athetoid
- Tetany
- Convulsions
- Positive Trousseau and chvostek signs
- Cardiac arrhythmias, disturbances of conduction, ventricular fibrillation and cardiac arrest.

Treatment

- Should focus on correcting the cause.
- Those due to inadequate intake or to disorders that reduce intestinal absorption or cause excessive losses into the urine **–** Oral supplementation

- 2 ml of 50% magnesium sulfate heptahydrate every 6^{th} hourly- 1^{st} day
- 1 ml of 50% $MgSO_4$ $7H_2O$ for following 3 – 4 days

- Cardiac arrhythmias patients with nausea and vomiting – IV Magnesium therapy4.2mmol Mg SO_4 (1 gm) every 6 hours.
- In treatment of torsade de pointes or ventricular arrhythmias – 8 mmol of Mg SO_4 over 1 to 2 minutes followed by infusions of 8 to 12 mmol/hour for 4 to 8 hours and smaller doses thereafter.

HYPERMAGNESEMIA

Causes:

- End stage renal disease
- Ingestion of magnesium containing compounds like antacids
- Rhabdomyolysis
- Adrenal insufficiency
- Familial benign hypocalciurichypercalcemia
- Near drowning in the dead sea (in Jordon)

Clinical Features:

- Nausea
- Facial parasthesia
- Sedation
- Hypoventilation with respiratory acidosis
- Decreased deep tendon reflexes
- Muscle weakness
- Hypotension
- Bradycardia
- Areflexia, coma and respiratory paralysis occurs at higher levels .

Treatment:

Symptoms and findings can reverse by infusion of calcium salts.Administration of saline and furosemide may help promote excretions of magnesium and Haemodialysis.

MATERIALS AND METHODS

SOURCE OF DATA:

Patients admitted to B.L.D.E.U's ShriB.M.Patil Medical College Hospital and Research Centre, Vijayapurbetween January 2015 to June 2016.

METHOD OF COLLECTION OF DATA:

Information was collected through prepared proforma from each patient. All patients wasinterviewed as per the prepared proforma and then complete clinical examination was done.

Patients were considered to be diabetic based on WHO criteria for diagnosis of diabetes mellitus which is

1. Symptoms of diabetes mellitus plus a random glucose concentration>200mg/dl(11.1mmol/l). The classic symptoms of diabetes mellitus include polyuria, polydypsia and unexplained weight loss

OR

2. Fasting blood glucose >126mg/dl(7.0mmol/l). Fasting is defined as no caloric intake for at least 8 hours.

OR

3. 2 hour post prandial glucose >200mg/dl. Among diabetics, the above criteria wereconsidered to be included for the study.

Inclusion Criteria for Case Selection:

Patients diagnosed as diabetes mellitus as per WHO criteria

Exclusion criteria for Case Selection:

Patients excluded from this study were those diabetics who had associated hypertension, gastrointestinal disorders, impaired renal function, alcoholism,

pancreatitis, other endocrinal disorders, those on diuretic therapy and aminoglycosides.

Those patients who had persistent FBS levels >126 mg% in spite of therapy during hospital stay and \or HbA1c >5.6 were grouped as uncontrolled diabetics.

Age and sex matched non diabetic patients admitted in the hospital were taken as controls after applying the same exclusion criteria which were applied for the cases.

Investigations required in this study are routine standardized procedures.

INVESTIGATIONS

- Complete haemogram
- Urine Examination
- Urine Ketone bodies
- Serum Electrolytes-Magnesium, Sodium & Potassium,
- FBS,PPBS
- Blood Urea
- Serum Creatinine
- ECG
- USG Abdomen
- HbA1c

Estimation of serum magnesium

Colorimetric method using calmagite dye:

Test principle:

Under alkaline conditions, magnesium ions react with calmagite to produce a redcomplex which is measured sphectrophotometrically at 530 nm. Intensity of the colour produced is directly proportional to magnesium concentration in the serum. To eliminate the interference of calcium during estimation, EGTA is included in the

reagent. Heavy metal interference is prevented by presence of cyanide and a surfactant system is included to remove protein interference.

Kit contents

Reagent 1: Magnesium colour reagent

Calmagite 0.006w/v

Stabilizer 1% w/v

Surfactant 0.03 w/v

Reagent 2: Magnesium buffer reagent

2-Ethylaminoethanol 6 %

EGTA 1.18Mm

Potassium cyanide 0.10 %

Reagent 3: Magnesium standard

Magnesium salt 2 mEq/L

Preparation of the working reagent:

Ten volumes of colour reagent (reagent 1) are mixed with one volume of bufferreagent (reagent 2). The working reagent was prepared as per requirement for the day.

Specimen:

Fresh unhemolysed serum was used. A hemolysed sample may falsely elevate theresults. Grossly icteric or lipemic specimens were not used.

Test procedure:

Pipette into test tubes	Blank	Standard	Test
Magnesium working reagent	1.0 ml	1.oml	1.0ml
Standard	-	10µL	-
Distilled water	10µL	-	-
Sample	-	-	10µL
Mix and incubate at room temperature (22-28 C) for 10 min. read the absorbance of the test(A_T), standard(A_S) and blank(A_B) against distilled water at 530 nm.			

Calculations:

Magnesium concentration (mEq/lit) = $\frac{(AT) - (AB) \times 2}{(AS) - (AB)}$

Interfering substances:

Hemolysed, grossly icteric or lipemic specimens are unsuitable for this method.

Linearity

4 mEq/L (4.86 mg/dl)

Normal values

Adults : 1.3-2.5 mEq/L

Children : 1.4-1.9 mEq/L

New borns : 1.5-2.3 mEq/L

STATISTICAL METHODS

Study Design:

One and half yearCross Sectional study.

Sample Size:

It is known that the hypomagnesemia has reported to occur in 13.5 to 47.7% of patients with type 2 diabetes compared with 2.5 to 15% among nondiabetic.[9]

Considering the average occurrence of hypomagnesemia 40% among type 2 diabetes and nondiabetic at 99% level of confidence and at 90% power in the study, the calculated sample size is 67

$$n = \frac{(Z\alpha + Z\beta)2 \times 2 \times p \times (100-p)}{d2}$$

Zα=Z value at the level of significance =99%

Zβ=Z value atthe level of significance =90%

p=Proportion of hypomagnesemia

d=difference between two proportion

hence 70 cases and 70 controls were included in the study.

Statistical Analysis:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square ($\chi 2$)/Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with the unpaired t-test. If the p-value was < 0.05, then the results will be considered to be significant. (Data were analyzed using SPSS software v.23.0.)

Statistical software:

Data were analyzed using SPSS software v.20.0.

RESULTS

A Cross Sectional study consisting of 70 Diabetic Mellitus patients and 70controls was undertaken to investigate the change pattern of serum magnesium in DMcases when compared to controls.

Table 1: Distribution of cases by Age between Cases and Control

Age (Yrs)	Case		Control		Total		p value
	N	%	N	%	N	%	
≤25	0	0.0%	2	2.9%	2	1.4%	
26-40	12	17.1%	13	18.6%	25	17.9%	
41-60	38	54.3%	37	52.9%	75	53.6%	0.763
>60	20	28.6%	18	25.7%	38	27.1%	
Total	70	100.0%	70	100.0%	140	100.0%	

Figure 2: Distribution of cases by Age between Cases and Control.

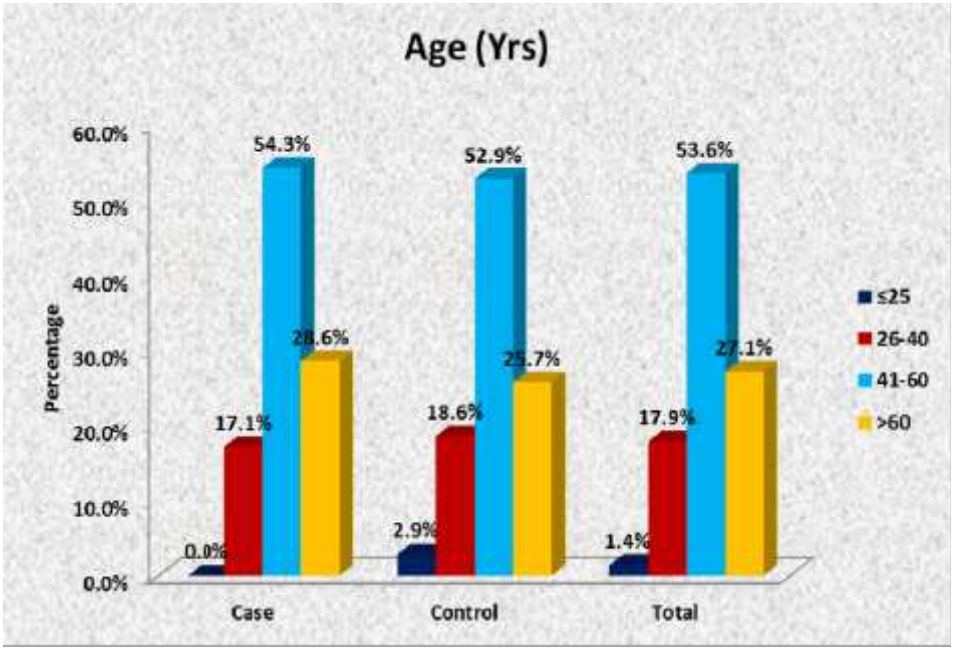
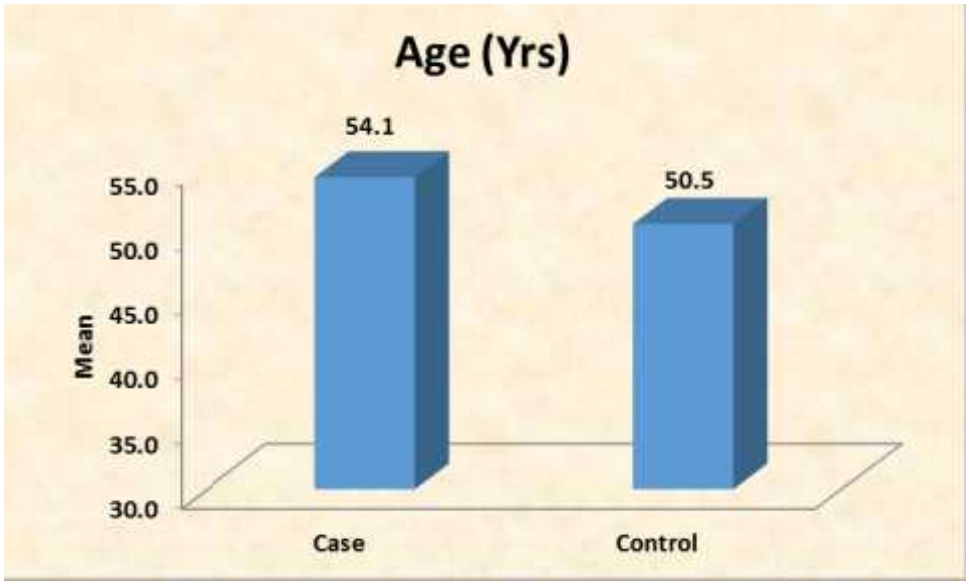


Table 2: Mean Age between Cases and Control

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
Age	54.1	11.4	50.5	13.6	0.091

Figure 3: Mean Age between Cases and Controls

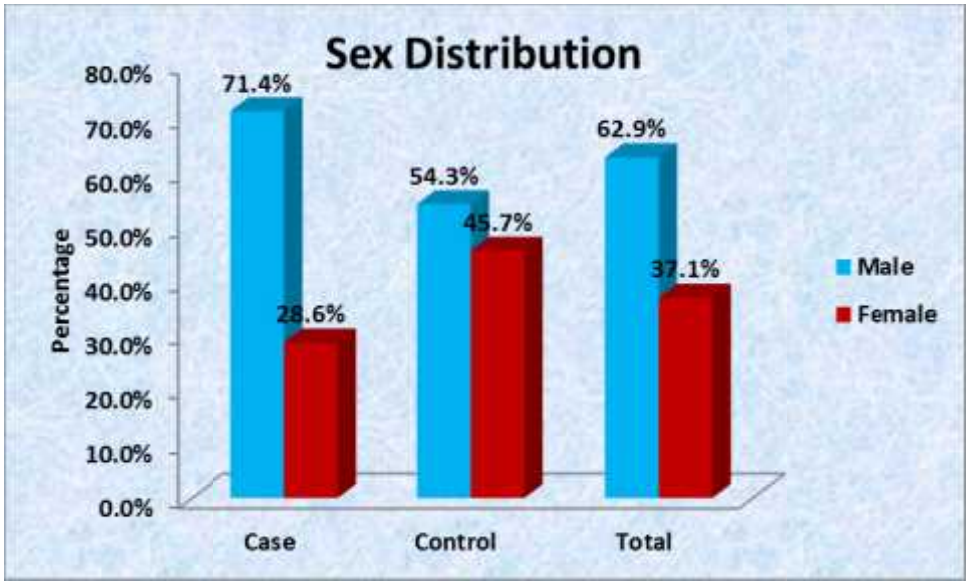


The mean age of the diabetics was 54.1 ± 11.4years whereas it was 50.5 ± 13.6year.The maximum number of patients were in the age group of 41-60 i.e. 53.6%. There was no significant difference in age between Case and Control.

Table 3: Distribution of cases by Sex between Cases and Control

Sex	Case		Control		Total		p value
	N	%	N	%	N	%	
Male	50	71.4%	38	54.3%	88	62.9%	
Female	20	28.6%	32	45.7%	52	37.1%	0.056
Total	70	100.0%	70	100.0%	140	100.0%	

Figure 4: Distribution of cases by Sex between Cases and Control



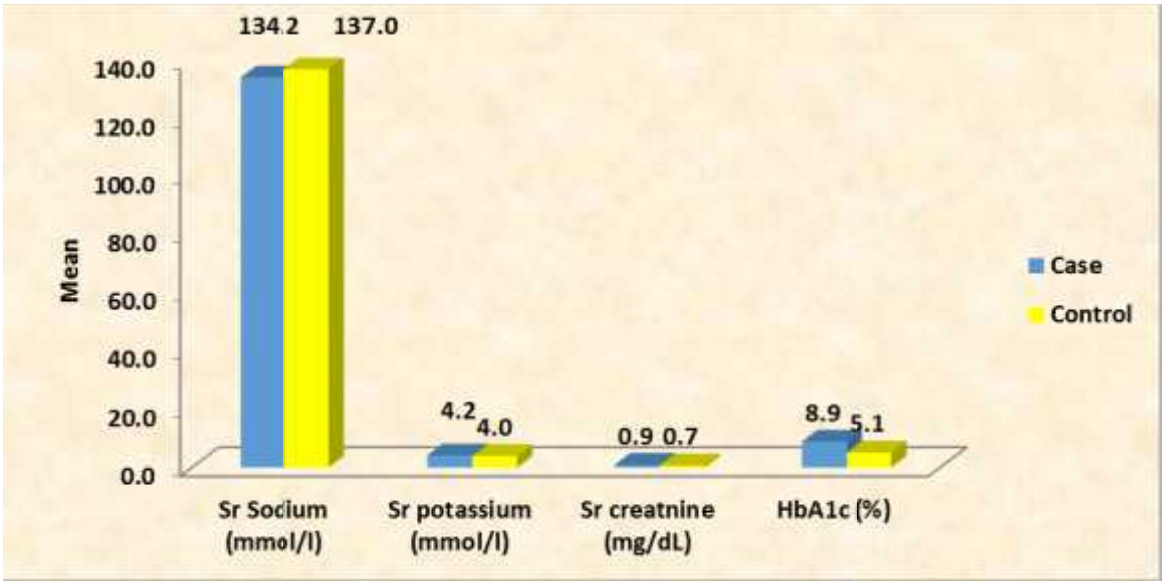
The above graph shows sex distribution in diabetic and control groups. In diabetic group 50 patients are males and 20 females. In control group 38 are males and 32 are females.

There was no significant differences in sex between Case and Control.

Table 4: Mean parameters between Cases and Control

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
Sr Sodium (mmol/l)	134.2	3.8	137.0	3.5	<0.001 (Sig)
Sr potassium (mmol/l)	4.2	0.7	4.0	0.5	0.047 (Sig)
Srcreatnine (mg/dL)	0.9	0.5	0.7	0.2	0.001 (Sig)
HbA1c (%)	8.9	2.4	5.1	0.6	<0.001 (Sig)

Figure 5: Mean parameters between Cases and Control



There was significant difference between cases and controls with respect to serum Sodium (134.2,137.0mmol/l), potassium (4.2,4.0mmol/l), creatinine (0.9,0.7mg/dl) and HbA1c (8.9,5.1%) levels. The mean serum creatinine levels among cases and controls were 0.9mg/dl and 0.7 mg/dl respectively.

Table 5: Distribution of cases by Serum magnesium (mg/dL) level between Cases and Control

Serum magnesium (mg/dL)	Case		Control		Total		p value
	N	%	N	%	N	%	
Hypo magnesium (<1.7)	31	44.3%	7	10.0%	38	27.1%	<0.001 (Sig)
Normal(1.7-2.4)	39	55.7%	60	85.7%	99	70.7%	
Hyper magnesium (>2.4)	0	0.0%	3	4.3%	3	2.1%	
Total	70	100.0%	70	100.0%	140	100.0%	

Figure 6: Distribution of cases by Serum magnesium(mg/dL) level between Cases and Control

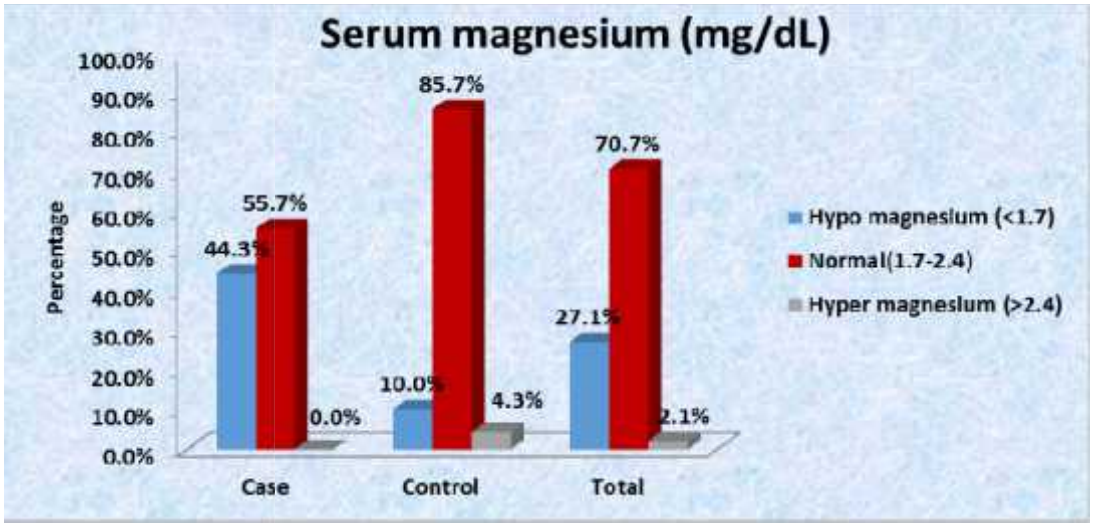
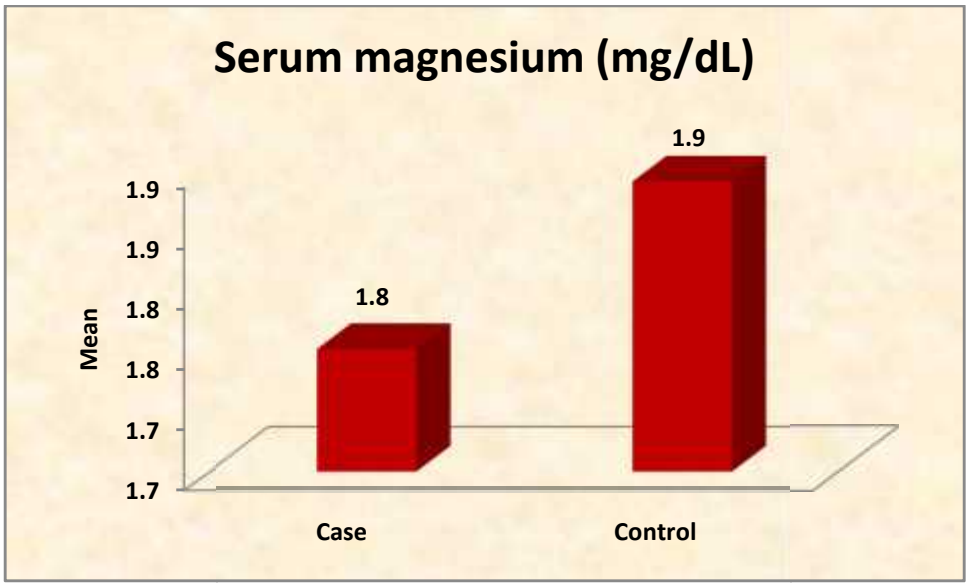


Table 6: Mean Serum magnesium (mg/dL) between Cases and Control

Serum magnesium (mg/dL)	Case		Control		p value
	Range	Mean± SD	Range	Mean± SD	
	1.3-2.4	1.8±0.3	1.5-2.5	1.9±0.2	0.001 (Sig)

Figure 7: Mean Serum magnesium (mg/dL) between Cases and Control



There is significant difference between levels of serum magnesium levels among

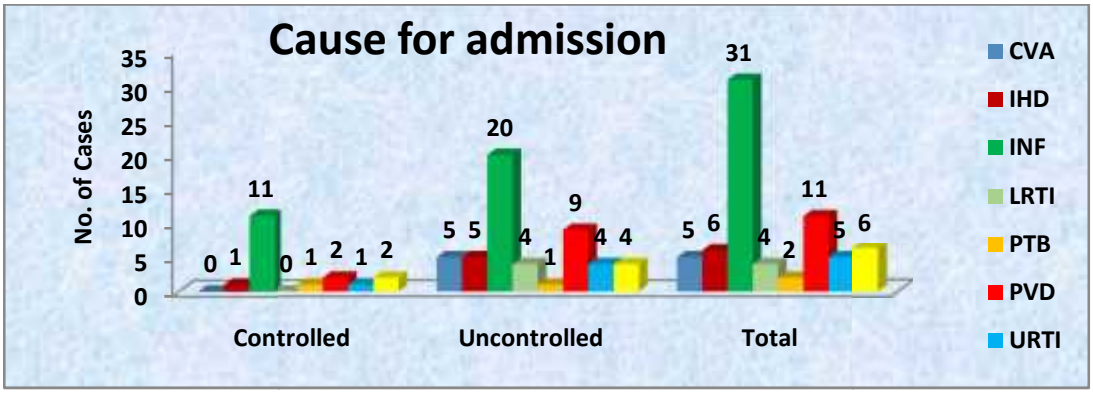
diabetics and controls. The mean serum magnesium levels in cases and controls are 1.8± 0.3 mg/dl and 1.9±0.2 mg/dl respectively.

Cases are **7.2 times** significantly more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Controls with P<0.001(significant).

Table 7: Distribution of cases by Cause for admission between Controlled and Uncontrolled DM

Cause for admission	Controlled		Uncontrolled		Total		p value
	N	%	N	%	N	%	
CVA	0	0.0%	5	9.6%	5	7.1%	
IHD	1	5.6%	5	9.6%	6	8.6%	
INF	11	61.1%	20	38.5%	31	44.3%	
LRTI	0	0.0%	4	7.7%	4	5.7%	
PTB	1	5.6%	1	1.9%	2	2.9%	0.524
PVD	2	11.1%	9	17.3%	11	15.7%	
URTI	1	5.6%	4	7.7%	5	7.1%	
UTI	2	11.1%	4	7.7%	6	8.6%	
Total	18	100.0%	52	100.0%	70	100.0%	

Figure 8: Distribution of cases by Cause for admission between Controlled and uncontrolled DM



Infections were the most common cause for admission accounting for 44.3% of theadmissions among diabetics.

The next commonest cause for admission was peripheral vascular disease whichaccounted for 15.7% of the admissions. 7 patients had ischemic signs in the limbs and 4 patients had gangrene.>80% of patients were admitted exclusively for poorly controlled diabetes.

Ischemic heart disease accounting for 8.6% Neurological problems accounted for 7.1% of admissions. 5 patients admitted for cerebrovascular accident. All are uncontrolled.

Table 8: Distribution of cases by Serum magnesium(mg/dL) level between Controlled and Uncontrolled DM

Serum magnesium (mg/dL)	Controlled		Uncontrolled		Total		p value
	N	%	N	%	N	%	
Hypo magnesium (<1.7)	2	11.1%	29	55.8%	31	44.3%	0.001 (Sig)
Normal(1.7-2.4)	16	88.9%	23	44.2%	39	55.7%	
Hyper magnesium (>2.4)	0	0.0%	0	0.0%	0	0.0%	
Total	18	100.0%	52	100.0%	70	100.0%	

Figure 9: Distribution of cases by Serum magnesium(mg/dL) level between Controlled and Uncontrolled

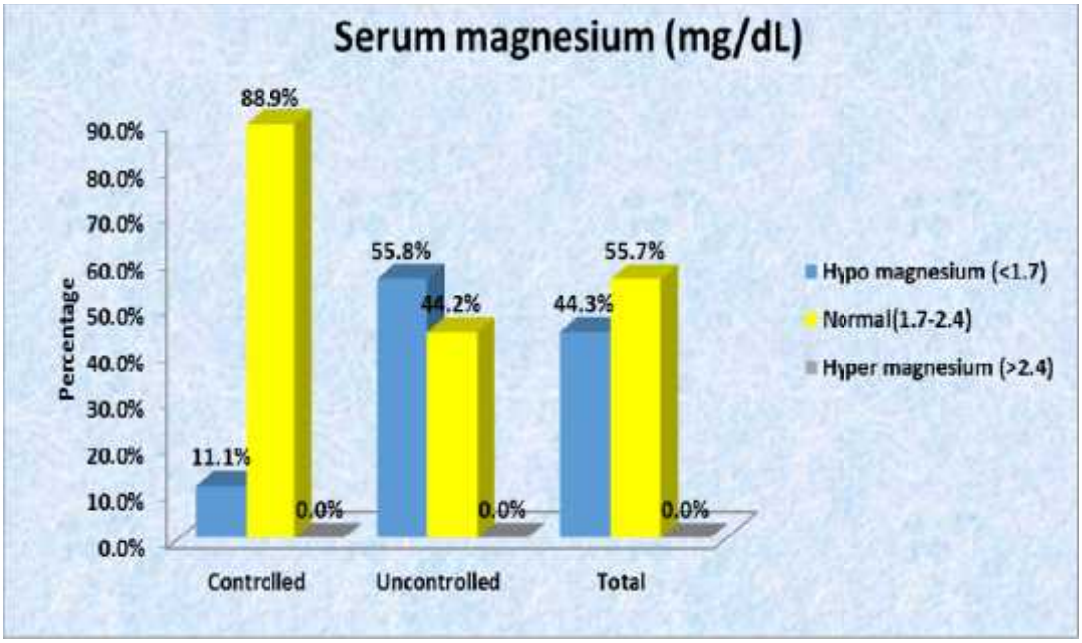
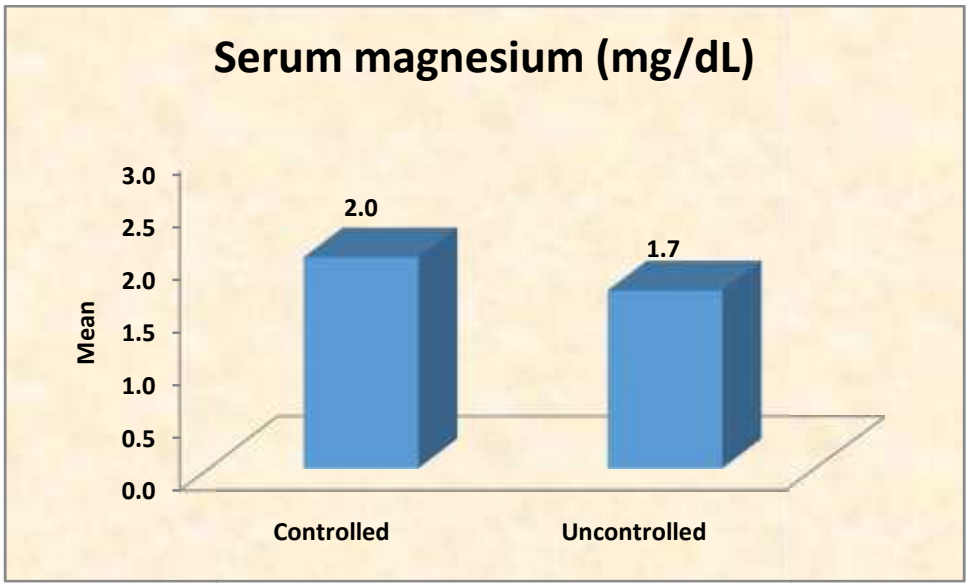


Table 9: Mean Serum magnesium(mg/dL) between Controlled and uncontrolled DM

Serum magnesium (mg/dL)	Controlled		Uncontrolled		p value
	Range	Mean± SD	Range	Mean± SD	
	1.5-2.4	2.0±0.3	1.3-2.3	1.7±0.2	<0.001 (Sig)

Figure 10: Mean Serum magnesium(mg/dL) between Controlled and Uncontrolled DM



There was significant difference between magnesium levels among controlled and uncontrolled diabetics. The mean serum magnesium levels among controlled and uncontrolled diabetics were 2.0± 0.3 mg/dl and 1.7± 0.2 mg/dl respectively. With p value <0.001.

Uncontrolled DM Cases are **10.1 times** significantly more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Controlled DM Cases with P= 0.004

Table 10: Distribution of cases by Treatment between Controlled and Uncontrolled DM

Treatment	Controlled		Uncontrolled		Total		p value
	N	%	N	%	N	%	
Insulin	0	0.0%	9	17.3%	9	12.9%	0.172
Newly Dignosed	3	16.7%	7	13.5%	10	14.3%	
Oral Hypoglycemic agent + Insulin	1	5.6%	7	13.5%	8	11.4%	
Oral Hypoglycemic agent	14	77.8%	29	55.8%	43	61.4%	
Total	18	100.0%	52	100.0%	70	100.0%	

Figure 11: Distribution of cases by Treatment between Controlled and Uncontrolled DM

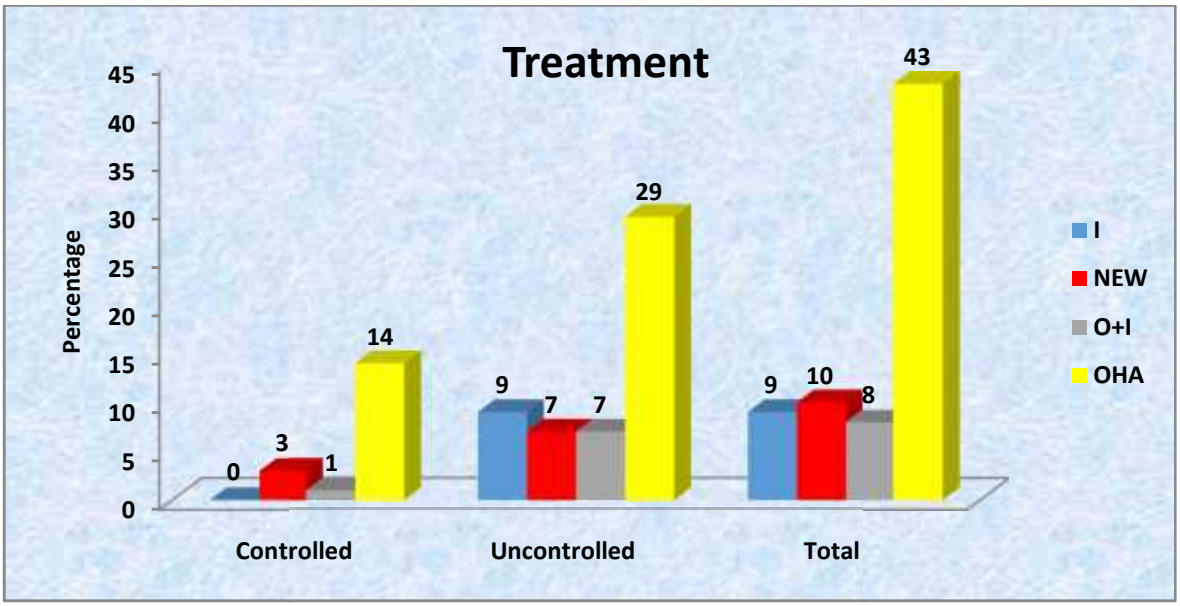
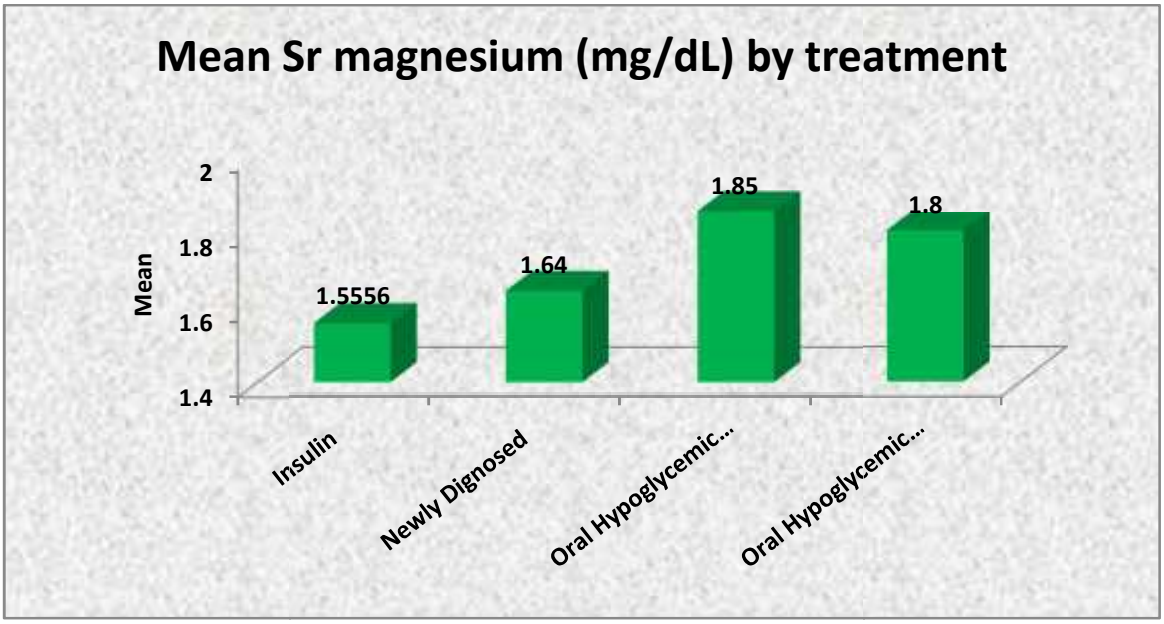


Table 11: Mean Serum magnesium(mg/dl) by treatment

Treatment	Insulin	Newly Dignosed	Oral Hypoglycemic agent + Insulin	Oral Hypoglycemic agent	ANOVA p value
Range	1.3-1.8	1.3-2.1	1.5-2.4	1.5-2.3	
Mean±SD	1.56±0.15	1.64±0.23	1.85±0.35	1.8±0.24	0.017 (Sig)

Figure 12: Mean Serum magnesium by treatment



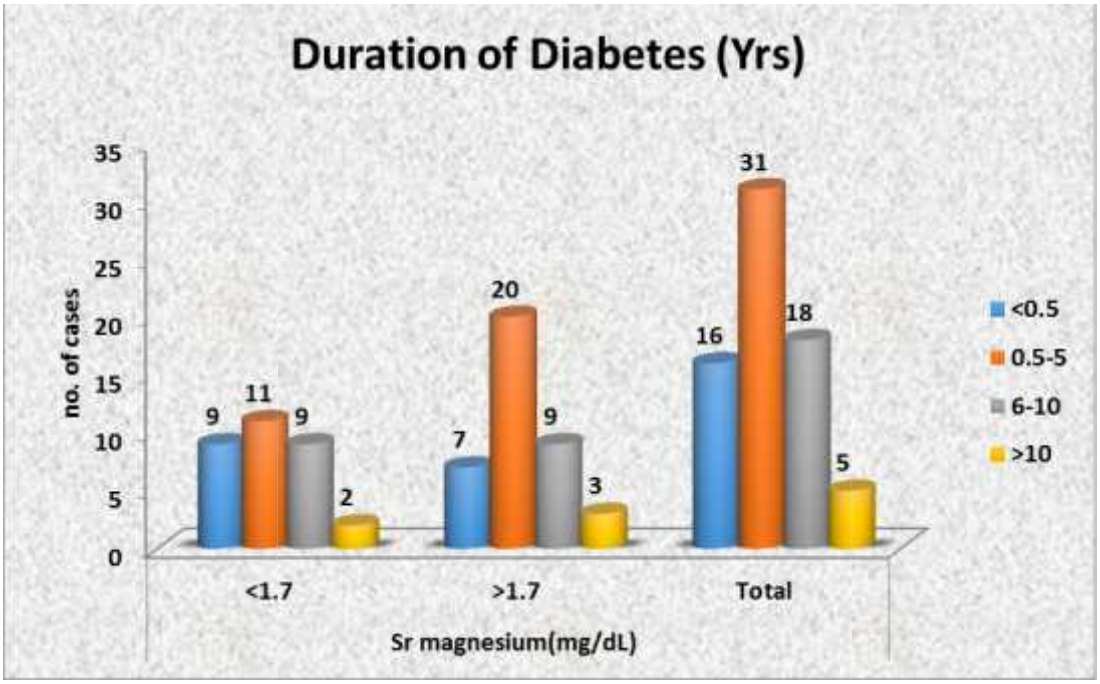
Of the total of 70 diabetic patients 9(12.9%) were on insulin alone, 43(61.4%) were on OHA'S and 8(11.4%) were on combination of OHA'S and insulin. The mean serum magnesium levels in the OHA group, insulin group and the insulin+ OHA group were 1.8 mg/dl,1.56mg/dl and 1.85 mg/dl respectively. The serum magnesium levels were significantly lower in the insulin treated group compared to the OHA treated group. Newly diagnosed patients accounts for 10(14.3%) in whom serum magnesium levels are significantly on lower side

Inference: Mean Serum magnesium is significantly different with different treatments (p=0.017). Cases with insulin are 2.3 times (p value=0.414), with Oral Hypoglycemic agent + Insulin, 0.4 times (p value=0.347), Oral Hypoglycemic agent, 0.36 times (p value= 0.150) more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Newly Dignosed cases.

Table 12: Relation between serum magnesium levels and duration of DM

Duration of Diabetes (Yrs)	Sr magnesium(mg/dL)			P value
	<1.7	>1.7	Total	
<0.5	9	7	16	0.536
0.5-5	11	20	31	
6-10	9	9	18	
>10	2	3	5	
Total	31	39	70	

Figure 13: Relation between serum magnesium levels and duration of DM



The above table shows that hypomagnesemia is not correlating with duration of diabetes mellitus.Hence there is no association between duration of DM and serum magnesium levels(p0.536. Not significant)

DISCUSSION

The present study included 70 type 2 diabetes mellitus patients and 70 non diabetic control subjects, their age were ranging from 25-70 years. In the diabetes group 71.4% of the patients were males and 28.6 % were female. In controls 54.3 % were males and 45.7 % were females. Serum magnesium levels were determined in all these subjects. Present study showed that 44.3 % of diabetic patients had low serum magnesium levels and 10.0% of non diabetic controls had low serum magnesium levels. The mean serum magnesium level was 1.8±0.3 mg/dL and 1.9±0.2 mg/dL in diabetics and controls respectively (p value0.001 significant).

Type 2 diabetic patients had higher incidence of lower serum magnesium levels when compared to their age/sex matched controls .

When this study parameters were compared with another study done by C.S. Yagnik et al, the average age of diabetic patients was 54.7 years and the mean age of controls was 46.5 years. Hypomagnesemia, defined by low serum Mg concentrations, has been reported to occur in 13.5 to 47.7% of non hospitalized patients with type 2 diabetes compared with 2.5 to 15% among their counterparts without diabetes.

This study is showing similar results as another study done at Zurich, Switzerland by Monika K et al. in the year 2002. In their study among 109 type 2 diabetic patients 37.6% had low plasma magnesium levels and among 156 age and sex matched controls 10.9 % had low plasma magnesium levels.

AP. Jain, N.N. Gupta and Abhay Kumar (1976) selected 85 cases, which included 20 comparable healthy adults and 65 diabetics of which 50 diabetics were without apparent renal involvement. They have studied simultaneously the intracellular (erytrocytic), extracellular (serum) and urinary magnesium levels in controls and

diabetics. An attempt to compare the findings in controlled and uncontrolled diabetics those getting insulin, with the group not getting insulin was made.

In the diabetic group low serum, normal erythrocytic and high urinary magnesium levels were recorded in comparison to controls. (2.10 ± 0.35mg/dL V/s 2.07 ± 0.27 mg/dL in controls and 1.72 ± 0.48 mg/dL V/s 1.8 ± 0.22 mg/dL in diabetics[30]

The diabetics getting insulin therapy had lower serum and higher urinary magnesium levels than those getting oral antidiabetics and dietic treatment (1.62 ± 0.41 V's 1.59 ± 0.13 mg/dL in the insulin treated and (1.94± 0,5 V/s 1.90 ± 0.18) in the OHA treated subjects.[30]

In the present study the serum magnesium level is compared between type 2 diabetic and age & sex matched non diabetic individuals. The effect of insulin and 0HA on serum magnesium level is also studied. In present study Of the total of 70 diabetic patients 9(12.9%) were on insulin alone, 43(61.4%) were on OHA'S and 8(11.4%) were on combination of OHA'S and insulin. The mean serum magnesium levels in the OHA group, insulin group and the insulin+ OHA group were 1.8 mg/dl,1.56mg/dl and 1.85 mg/dl respectively. The serum magnesium levels were significantly lower in the insulin treated group compared to the OHA treated group. Newly diagnosed patients accounts for 10(14.3) in whom serum magnesium levels are significantly on lower side

Nadler JL et al in the year 1992 evaluated the intracellular erythrocytic (RBC) Mg^{2+} concentration in 20 Type 2 diabetics. In addition, the effects of intravenous 3-h drip or 8 weeks of oral Mg supplementation on intracellular RBC Mg- levels and platelet reactivity was studied. The results showed intracellular RBC Mg2+ concentration of diabetic patients was significantly reduced compared with values innon diabetic control subjects.[35]

Magnesium levels were also reduced in the diabetic patients compared with the control subjects. Present study also shown similar results.

Nagase N et al in the year 1996 studied the interrelationships between hypertension (HTN), ischaemic heart disease (IHD) and Diabets Mellitus (DM) in the diabetic subjects without IHD (DM Group) or with IHD (DM+IHD Group) and subjects with IHD (IHD Group) which were not complicated with DM.

Their results showed serum magnesium levels of DM (1.9 ± 0.37 mg/dLwas significantly lower than that of normal controls (2.3 ± 0.32 mg/dL)[44].

Present study shown the mean serum magnesium level were 1.8 ± 0.3 mg/dL and 1.9 ± 0.2 mg/dL in diabetics and controls respectively. (p value 0.001 significant).The results were similar to the study done by Nagase N et al .

They also concluded that serum magnesium level of poorly controlled diabetic patients is lower than that of well controlled diabetic patients. These results suggested that magnesium deficient state is one of the cause of insulin resistance.

In the present study there was significant difference between magnesium levels among controlled and uncontrolled diabetics. The mean serum magnesium levels among controlled and uncontrolled diabetics were 2.0± 0.3 mg/dl and 1.7± 0.2 mg/dl respectively. With p value <0.001. Uncontrolled DM Cases are 10.1 times significantly more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Controlled DM Cases with P= 0.004. The results were similar to the study done by Nagase N et al.

Sharma A et al, in the year 2007 in their study among 50 diabetic patients and 40 non diabetic controls found that serum magnesium levels in diabetic population was significantly low (1.93 +1- 0.282 meq/L) in comparison to control (2.25 +/- 0.429

meq/L). Results are similar to present study (1.8 ± 0.3 mg/dL and 1.9 ± 0.2 mg/dL in diabetics and controls respectively)[89]

Lima Mde et al in their diabetic patients with metabolic syndrome and without metabolic syndrome showed that, serum and intracellular magnesium depletion were found in 75% and 30.8% patients with metabolic syndrome and without metabolic syndrome respectively. A negative correlation between intracellular magnesium levels (ICMg) and BMI and HbAl C was found[90]

Sales CH et al, in their study showed that hypomagnesemia is frequently present in diabetic patients and developing hypomagnesemia, which may be still directly related with some micro and macro vascular complications observed in diabetes, as cardiovascular disease, retinopathy and neuropathy. This way, the chronic complications of diabetes can appear precociously. Based on this, the supplementation with magnesium has been suggested in patients with diabetes mellitus who have proven hypomagnesemia and the presence of its complications[91].

Corica F et al in their study among 290 patients with type 2 diabetes mellitus, found that 49.3% of diabetics had hypomagnesemia. Hypomagnesemia is highly prevalent in diabetic patients. High plasma triglycerides, waist circumference and albuminuria are independent correlates of hypomagnesemia[92].

Matthias B et al, in their prospective study showed that high cereal fiber and magnesium intakes may decrease diabetes risk[95].

De Valk HW in a study found that 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 retinopathy.[56]

Oral magnesium supplementation for a 8 weeks (400 mg/day) restored RBC Mg-concentration to normal without significantly changing serum magnesium concentration. Both intravenous and oral magnesium supplementation markedly reduced platelet reactivity in response to the thromboxane A2 analogue, U46619.

The present study correlated with the study done by Nadler et al, with respect to the comparison of serum magnesium in diabetics and controls & Nagase N et al with respect to the comparison of serum magnesium in controlled and uncontrolled diabetics. However the present study did not include evaluating the effects of oral or IV magnesium supplementation which is out of scope of this study.

Garland H 0 in his study speculated on a potential link between the magnesium deficit in diabetes and several diabetic complications including cardiovascular problems and retionopathy.[32]

Rude R K suggested repletion of the deficiency or prophylactic supplementation with oral magnesium may help to avoid or ameliorate complications such as arrhythmias, hypertension and sudden cardiac death and may even improve the course of diabetic condition. However in the present study, the complications of diabetes in relation to hypomagnesemia was not studied. Also magnesium supplementation and supplementation and its effects towards magnesium levels or metabolic control was not done in this study which can be taken as limitations of the present study. There was no scope for follow up in the present study. Hence change in magnesium status with respect to improvement or worsening of diabetic status in the long run was not studied.

Possible Causes of Hypomagnesemia in Type 2 Diabetes

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

Gastroiniestinal Causes

Diabetic autonomic neuropathies that may reduce oral intake and gastrointestinal absorption include esophageal dysfunction, gastroparesis and diarrheas[83]. Whether gastrointestinal Mg absorption via TRPN16 is reduced in the patient with diabetes is not known.

Renal Causes

Enhanced Filtered Load**:**In the patient with diabetes, the ultrafilterable Mg load may be enhanced by glomerular hyperfiltration, recurrent excessive volume repletion after hyperglycemia-induced osmotic diuresis, recurrent metabolic acidosis associated with diabetic ketoacidosis and hypoalbuminemia[96]. 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 re-expansion and glomerular hyperfiltration also may induce renal Mg wasting at the proximal tubule and TAL, independent of the filtered load. Because Mg reabsorption parallels sodium reabsorption in the proximal tubules, volume expansion can decrease both sodium and Mg reabsorption at this level. Similarly a high tubular flow through the TAL may reduce Mg reabsorption at this segment[94].

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[41]. The expression of paracellin 1 in TAL, however, has not been shown to be increased in diabetic rats .[84]

In the same diabetic rat model, Lee et al 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 RPM6 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 .[85-86]

Hypokalemia.

At the TAL segment, hypokalemia may reduce Na+-K+-2C1— co-transport activity the associated potassium extrusion through the potassium channel ROMK, and resultant diminution of the favorable transmembrane voltage that is required for paracellular Mg reabsorption. In addition, there is evidence to suggest that Cellular potassium depletion may diminish Mg reabsorption at the DCT by yet unclear mechanisms .[85]

Hypophosphatemia.

Both micropuncture studies in phosphate-depleted dogs and in vitro studies involving phosphate-depleted mouse DCT cells have demonstrated reduced Mg^{2+} uptake [83-84]. Phosphate-induced reduction in cellular uptake of Mg is believed to be a posttranslational effect because the alteration in Mg uptake could be observed within 30 min of phosphate depletion.

Metabolic Acidosis.

In addition to its role in increasing serum ionized Mg concentration and hence ultrafilterable Mg load for renal excretion, metabolic acidosis has been suggested to enhance protonation of the Mg channel in the DCT and subsequent inhibition of

cellular Mg uptake. [85] More recently, Nijenhuis et al. showed reduced expression of TRPM6 with induced chronic metabolic acidosis in mice. [88]

Insulin Deficiency and/or Resistance.

As previously discussed, insulin deficiency or resistance may exacerbate renal Mg wasting because insulin has been shown to have antimagnesiuric effects in both the TAL and the DCT[95,93]

CONCLUSION

Serum magnesium levels were lower in type 2 diabetes mellitus patients compared with non diabetic controls.

Levels of serum magnesium in uncontrolled type 2 diabetic patients were further lower than those in whom diabetes was under control.

Hypomagnesemia is an important factor in type 2 diabetes mellitus patients, leading to various complication. Hence hypomagnesemia should be corrected by supplementation.

SUMMARY

This study was conducted at Shri B.M.Patil.medical college Hospital and research centre, Vijayapur. The present study included 70 diabetic patients and 70 non diabetic controls , in the age group ranging from 25 to 70 years. . In the diabetes group 71.4% of the patients were males and 28.6 % were female. In controls 54.3 % were males and 45.7 % were females

In this study 44.3% of diabetic patients and 10% of nondiabetic controls had hypomagnesemia. The results are correlating with other studies.

The mean serum magnesium level was 1.8±0.3 mg/dL and 1.9±0.2 mg/dL in diabetics and controls respectively (p value 0.001 significant). Cases are 7.2 times significantly more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Controls with P<0.001(significant)

There was significant difference between magnesium levels among controlled and uncontrolled diabetics. The mean serum magnesium levels among controlled and uncontrolled diabetics were 2.0± 0.3 mg/dl and 1.7± 0.2 mg/dl respectively. With pvalue <0.001. Uncontrolled DM Cases are 10.1 times significantly more likely to have less Serum magnesium (<1.7 mg/dl) when compared to Controlled DM Cases with P= 0.004

There is no association between duration of DM and serum magnesium levels.

This study demonstrated that, low magnesium status is common in type 2 diabetes mellitus patients compared to non diabetic controls and also in controlled and uncontrolled diabetes. Because Mg^{2+} depletion reduces insulin sensitivity and my increase risk of secondary complications, it may be prudent in clinical practice to periodically monitor plasma Mg2+ concentration in diabetic patients. If plasma Mg2+ is low, an intervention to increase dietary intake of magnesium may be beneficial.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E. UNIVERSITY'S

SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 at 3-30pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "Study of Serum magnesium in type-2 Diabetes Mellitus"

—— x —— x ——

Name of P.G. student Dr Shivaraj. N. patil

Dept of Medicine

Name of Guide/Co-investigator Dr S. M. Biradar.

Associate prof of Medicine

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

BLDE University's

Shri B M Patil Medical College, Hospital & R.C

Vijayapur, Karnataka

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that DrShivaraj N. Patil of Shri. B. M. PatilMdical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases. Further Doctor Shivaraj informed me that he/she is conducting dissertation/research titled "Study Of Serum Magnesium In Type-2 Diabetes Mellitus" under the guidance of Dr. S. M. Biradar requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place

PROFO RMA

BLDE'S Shri B.M. Patil Medical College Hospital and Research Centre, Vijayapur

"STUDY OF SERUM MAGNESIUM IN TYPE-2 DIABETES MELLITUS"

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Occupation:

Residence:

Presenting complaints with duration:

History of present complaints:

Past History:

History of hypertension

History of diabetes mellitus

Personal History:

Diet/appetite

Sleep

Bladder and bowel habits :

Smoking/Tobacco chewing/Snuff Inhalation

Duration

Number of cigarettes/beedis pack year smoked

Amount of tobacco chewed/snuff inhaled

Alcohol

Duration

Quantity/Frequency

Type

Sexual History

History of multiple sexual partners

Family History:

Treatment History :

General Physical Examination

Height :

Weight :

Body Mass Index :

Vitals

PR:

BP:

RR:

Temp:

Hair :

Eyes :

Nose :

Ears :

Oral Cavity :

Neck :

Upper Limbs :

Chest :

Abdomen :

Genetilia :

Lower Limbs :

Skin :

SYSTEMIC EXAMINATION.

- Respiratory System
- Cardiovascular System
- Central Nervous System
- Per abdomen

INVESTIGATIONS

HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

RBS/FBS/PPBS:

HbA1C:

U/Routine:

CXR-PA view:

RFT:

Blood urea	
Se Creatinine	
Se Electrolyte	
Na^+	
K^+	

SERUM MAGNESIUM:

<u>FINAL DIAGNOSIS</u>

KEY TO MASTER CHART

1. FBS- Fasting blood sugar
2. Mg- Serum magnesium
3. SC- Serum creatinine
4. C- Controlled
5. UC-Uncontrolled
6. T- Treatment
7. INF- Infection
8. URTI- Upper respiratory tract infection
9. LRTI- Lower respiratory tract infection
10. MEN- Meningitis
11. CVA- Cerebrovascular accident
12. IHD- Ischemic heart disease.
13. PTB- Pulmonary tuberculosis
14. APD- Acid peptic disease
15. AC- Acute cholecystitis
16. UTI-Urinary tract infection’
17. Insulin
18. OHA- Oral hypoglycemic agents

MASTER CHART

CASE

Sno	Grp	Ipno	Name	Age	Sex	Duration of DM (yrs)	Sr Sodium (mmol/l)	Sr potassium (mmol/l)	Srcreatnine (mg/dL)	HbA1c (%)	Sr magnesium (mEq/L)	Treatment	Cause for admission	Controlled /Uncontrolled	Diagnosis
1	1	1911	Lakkawwa	60	F	0	138	4.7	0.9	7.5	1.5	NEW	INF	C	Typhoid fever with type 2 DM
2	1	2255	Shivramappagouda	75	M	2	135	3.2	0.9	5.6	2.2	OHA	INF	C	COPD with DM
3	1	896	Jatteppa	42	M	5	130	4.5	0.8	5	1.8	OHA	INF	C	DM with septic shock
4	1	2492	Tavanu	67	M	1	135	4.5	0.9	5.6	2.4	O+I	PTB	C	Pulmonary tuberculosis with DM
5	1	2993	Basappa	60	M	5	137	3.4	0.8	5.4	1.9	OHA	PVD	C	Lt diabetic foot
6	1	5170	Basavantappa	65	M	10	136	4.6	0.7	5.2	1.6	OHA	INF	C	Type 2 DM URTI
7	1	20755	Siddaraya	54	M	12	125	3.2	0.7	5.7	1.8	OHA	INF	C	DM with Lt leg cellulitis
8	1	21800	Yallappa	60	M	0	140	4.3	1.3	6.3	1.8	NEW	IHD	C	DM with IHD
9	1	5291	Chandrabai	50	F	0	136	3.2	1.4	6.2	1.8	NEW	INF	C	Bronchial asthma with DM
10	1	7557	Shivasharanappa	65	M	6	134	4.1	1	6.3	2	OHA	UTI	C	Type 2 DM with rt eye cataract with UTI
11	1	5384	Basavaraj	39	M	0.16	135	3.2	0.6	5.5	2.3	OHA	INF	C	Type 2 DM with umbilical hernia
12	1	3549	Ambanna	35	M	2	136	3.5	0.7	5.7	1.9	OHA	INF	C	DM with submandibular abscess
13	1	5905	Shivappa	45	M	1	134	3.4	1.1	6	2.3	OHA	PVD	C	Rt diabetic foot
14	1	6911	Kashibai	70	M	2	130	4.3	0.7	6.4	2	OHA	INF	C	Type 2 DM with cystitis
15	1	6973	Revappa	53	M	2	133	3.9	0.8	6.2	2.1	OHA	UTI	C	Type 2 DM with diabetic nephropathy
16	1	2613	Shivakumar	51	M	8	140	3.9	0.6	6	2.2	OHA	INF	C	Type 2 DM with abscess over lt elbow
17	1	2754	Mallappa	65	M	6	136	4.1	1.2	5.8	2.2	OHA	INF	C	Type 2 DM with cellulitis over lt limb
18	1	44445	Sadashiv	32	M	2	138	4.2	0.8	5.6	1.9	OHA	URTI	C	Type 2 DM with pharyngitis
19	1	2123	Channabasappa	65	M	3	132	4.1	0.8	11.3	2	OHA	PVD	UC	Lt diabetic foot
20	1	2799	Jagadish	52	M	2.5	137	4.7	1	8	1.7	OHA	IHD	UC	Type 2 DM with inferior MI
21	1	2785	Ilabai	65	F	0	132	4.1	0.8	7	1.6	NEW	PVD	UC	Diabetic foot over Lt foot
22	1	3977	Kasturibai	70	F	8	130	3.2	0.8	9	1.6	OHA	IHD	UC	Type 2 DM with IHD

23	1	4399	Basappa	62	M	10	132	5.4	3.8	9	1.5	O+I	PVD	UC	DM with ulcer foot lt
24	1	5270	Sunanda	35	F	1.5	129	4.3	0.9	10.2	1.4	I	INF	UC	DM with ketoacidosis
25	1	5370	Dundawwa	62	F	1	129	4.2	0.7	7.7	1.5	OHA	URTI	UC	DM with gastric varices with URTI
26	1	5390	Bhimanna	48	M	0	135	4	1.4	7.5	2.1	NEW	URTI	UC	DM with acute bronchitis
27	1	5674	Rudragouda	53	M	7	130	4.6	1.3	10	1.5	OH	IHD	UC	IHD with post CABG with DKA
28	1	6864	Mukund	30	M	4	135	4.8	0.8	8.5	1.6	O+I	UTI	UC	DM
29	1	7353	Sharanappa	60	M	0.5	136	4	1	10.8	1.6	OHA	INF	UC	DM with rt foot abscess
30	1	7944	Gangamma	70	F	10	135	4.1	0.9	7.1	1.5	OHA	CVA	UC	Type 2 DM with lt hemiplegia
31	1	8515	Ayyappa	38	M	8	131	4.3	0.8	10.4	1.5	I	PVD	UC	DM withpvd
32	1	9019	Tangawwa	55	F	0.5	132	4.3	0.6	9	1.6	OHA	IHD	UC	Type 2 DM with ACS with MI
33	1	9310	Shrankappa	65	M	0	136	4	0.9	13	1.5	NEW	PTB	UC	DM with PTB
34	1	9238	Jahirabi	69	F	0	131	4.8	0.7	8.4	1.5	NEW	UTI	UC	DM UTI
35	1	9290	Chikayya	53	M	12	135	4.2	1	8	1.5	I	INF	UC	DM with rt leg necrotizing fasciitis.
36	1	134301	Neelamma	68	F	0	133	4.8	0.7	11.4	1.6	I	INF	UC	DM
37	1	23874	Ramawwa	70	F	10	137	3.6	0.6	12.6	1.6	OHA	IHD	UC	IHD with DM
38	1	23991	Vithoba	60	M	0	130	4.3	0.8	9.5	1.5	NEW	LRTI	UC	Type 2 DM
39	1	24784	Mashak	52	M	10	138	4	1.2	9	1.6	OHA	URTI	UC	Lt diabetic foot
40	1	20355	Zubeda	35	F	6	138	4	0.6	7.7	1.7	OHA	INF	UC	Lt diabetic foot
41	1	20976	Dharmaraya	30	M	5	138	3.8	0.7	11	1.8	OHA	UTI	UC	DM
42	1	2403	Vijayakumar	31	M	4	135	3.7	0.7	14.3	1.6	OHA	INF	UC	Diabetic ketoacidosis
43	1	21265	Basappa	50	M	5	135	3.2	0.7	9.5	2	O+I	INF	UC	DM with non healing ulcer over lt foot
44	1	21695	kashiraya	60	M	6	129	5.7	2.3	10.1	1.8	O+I	INF	UC	DM with non healing ulcer over lt limb
45	1	21739	Tarabai	50	F	10	135	3.3	1	11	1.6	OHA	CVA	UC	Type 2 DM with parkinsons disease
46	1	22396	Shivasharan	45	M	1	135	4.1	0.9	13	1.7	OHA	INF	UC	Rt diabetic foot with non healing ulcer over Lt limb
47	1	22109	Karayappa	65	M	3	137	4.1	1.1	9.3	1.7	I	INF	UC	DM with RVD
48	1	22772	Hamanabai	75	F	5	140	4.8	0.7	13	1.8	OHA	LRTI	UC	Type 2 DM with rt lower lobe consolidation
49	1	22964	Ashok	50	M	0.08	130	4.9	0.7	8.7	1.6	I	PVD	UC	Lt diabetic foot with healing ulcer
50	1	19498	Lakshmi	40	F	8	140	6.2	1.3	7.5	1.9	OHA	PVD	UC	Lt diabetic foot
51	1	23171	Bhimanagouda	45	M	0	138	4.2	0.9	9.8	1.3	NEW	INF	UC	Type 2 DM with cholecystitis
52	1	23263	Hanamawwa	45	M	1	133	4.5	0.6	12	1.5	OHA	URTI	UC	Type 2 DM with non cardian chest pain
53	1	23920	Siddaraya	55	M	12	134	3.4	0.6	9.7	1.8	OHA	INF	UC	DM with cellulitis over lt limb
54	1	21399	Vadiraj	58	M	1	120	3.6	0.8	10.8	1.7	O+I	INF	UC	Diabetic ketoacidosis

55	1	24533	Bhimashi	55	M	6	140	3.5	0.9	13	1.7	OHA	PVD	UC	Lt diabetic foot
56	1	21815	Aravind	60	M	5	141	3.9	0.9	13	1.6	I	INF	UC	DM with febrillness
57	1	4838	Surekha	48	F	15	136	4.4	0.8	9.9	1.8	OHA	UTI	UC	Type 2 DM with UTI
58	1	7524	Mehaboob	62	M	0.5	134	3.3	0.6	10.5	2.1	OHA	INF	UC	Type 2 DM with Lt eye catract
59	1	3242	Dharmanna	56	M	10	131	4.3	0.8	10.8	2	OHA	PVD	UC	Diabetic foot with ulcer
60	1	2887	Basavaraj	47	M	5	135	5.4	0.6	10.7	1.8	I	CVA	UC	DM with CVA
61	1	5969	Hanamanth	56	M	1	137	2.7	0.6	8.6	1.5	OHA	INF	UC	Type 2 DM with lung abscess
62	1	7277	Mukthabai	55	F	0	136	4.2	0.6	11.7	1.8	NEW	CVA	UC	Type 2 DM with GTCS
63	1	7345	Gurappa	60	M	8	131	5.7	1.4	8.1	2.3	O+I	LRTI	UC	Type 2 DM with acute bronchitis
64	1	5734	Ambabai	50	F	0.08	134	4.1	0.9	9.4	1.7	OHA	INF	UC	Type 2 DM with leprosy
65	1	5184	Basavaraj	65	M	12	137	4.8	0.7	11.7	1.5	O+I	PVD	UC	Type 2 DM with bilateral cataract
66	1	2461	Ramangouda	45	M	1	137	3.4	0.9	9.2	1.3	I	LRTI	UC	Type 2 DM with LRTI
67	1	3216	Kanthabai	55	F	0.25	131	4.2	1	7.6	1.5	OHA	INF	UC	Type 2 DM with cellulitis lt foot
68	1	4689	Suresh	62	M	2	128	5.5	2	8.5	1.5	OHA	CVA	UC	Type 2 DM withRtHemparisis
69	1	3401	Sharanappa	40	M	5	132	5.7	1.4	10.8	2	OHA	INF	UC	Type 2 DM with DK
70	1	54103	Mahadevi	48	F	0	136	4.3	0.7	7.2	1.8	OHA	INF	UC	Type 2 DM

CONTROLS

1	2	11316	Somaning	80	M		133	4.1	0.8	6.1	1.8				Lt pleura effusion with
2	2	11333	Sangappa	60	M		135	4	0.9	5.1	1.6				COPD with emphysema
3	2	11485	Chandrashekar	45	M		139	4.5	0.8	4	1.7				COPD
4	2	11482	Ningappa	65	M		136	4.1	2.1	5.2	1.7				Viral fever
5	2	134199	Manjunath	23	M		139	4.6	0.8	5	1.7				UTI
6	2	11857	Girijabai	50	F		141	4.2	0.7	6.1	1.6				Pharyngitis
7	2	11832	Parvati	60	F		135	4.5	0.7	5.7	1.7				UTI
8	2	11896	Yamanawwa	45	F		131	4	0.7	4.6	1.9				RVD with URTI
9	2	11914	Mallamma	50	F		134	3.6	0.7	5	1.6				Clinica malaria
10	2	11795	Prabhu	60	M		135	4.8	0.6	5.6	2				Pulmonary TB
11	2	134077	Anuradha	34	M		142	4.6	0.6	5.1	1.7				Migraine
12	2	134455	Vijayalakshmi	80	F		141	4.1	0.9	5	2				Normal healthy individual
13	2	12349	Gopal	43	M		136	4.5	0.7	5.7	1.7				Lt lung fibrosis wit PT
14	2	12468	Ashok	50	M		145	4.4	0.6	6	1.6				Lt hemiplegia
15	2	12436	Babu	50	M		141	4.1	0.6	6.1	1.8				Chest pain decreased evaluation
16	2	134253	Yamunawwa	45	F		131	4	0.7	4.6	1.9				Frontal sinusitis
17	2	12662	Shantappa	42	M		137	4.6	1.1	5.7	2.5				UTI
18	2	12400	Vital	60	M		140	4.7	1	4.2	2.3				Atalatsis
19	2	43598	Mahadevi	30	F		138	4.7	0.6	4	1.7				Chronic headache
20	2	143597	Santosh	28	M		134	3.9	1.1	5.9	1.6				Acute febrile illness
21	2	142663	Siddaram	50	M		142	4.5	0.7	5	1.5				LRTR
22	2	143098	Neelakka	48	F		142	4.1	0.6	5.4	1.8				URTI
23	2	12542	Parasu	80	M		140	4.8	0.9	5.8	1.8				Gastritis
24	2	21191	Akshata	80	F		136	3.8	0.6	5.9	1.8				GTCS
25	2	22916	Parvati	45	F		145	4.1	0.6	5.5	2.5				GERD
26	2	22886	Mahadevi	50	F		138	3.4	0.7	6.2	1.8				Musculo skeletal chest pain
27	2	22910	Devendrappa	50	M		135	4.3	0.7	5.6	1.9				Musculo skeletal chest pain
28	2	22914	Chandamma	72	F		141	2.8	0.7	4.4	1.9				PTB
29	2	22915	Revenasiddappa	76	M		134	3.5	0.7	5.4	1.7				COPD
30	2	23773	Gouramma	52	F		140	5.4	0.7	5.4	1.8				Acute febrile illness with clinical malaria
31	2	23739	Ishwarappa	50	M		133	3.7	0.6	6.2	1.9				Gastritis

32	2	23777	Jayashree	35	F		140	3.5	0.7	5.1	1.8				Typhoid
33	2	23768	Mallabai	40	F		138	3.6	0.7	5.6	1.9				UTI
34	2	23763	Kamaleshwar	50	M		137	3.8	0.8	5.6	1.9				Acute febrile illness
35	2	23761	kantabai	45	F		136	3.5	0.6	4.6	1.7				UTI
36	2	5221	Savakka	70	F		139	3.7	0.7	4.6	1.7				Acute bronchitis
37	2	4645	Gouramma	35	F		129	3.7	0.6	5	1.8				Malaria
38	2	4700	Ravubai	50	F		137	4.4	0.6	4.4	1.7				Typhoid
39	2	6762	Bagamma	30	F		136	3.8	0.6	5.5	2.1				Dengue
40	2	2929	yamunappa	45	M		138	3.1	0.6	5.2	1.8				Acute bronchitis
41	2	3826	Dongarisab	50	M		140	3.6	0.6	4.6	2				OP
42	2	3787	Appu	35	M		137	3.9	0.6	5	1.9				Alcohol dependence
43	2	3720	Surabai	50	F		139	4.3	0.6	4.9	2				Microcytic hypochronic anemia
44	2	7530	Shantabai	65	F		133	3.6	0.6	5.6	1.7				Pulmonary TB
45	2	7360	Vital	35	M		134	4.5	0.8	4.6	2.2				Typhoid fever with UTI
46	2	7097	Iranna	40	M		140	3.6	0.9	5	2				Lt lower lobe consaladition
47	2	7131	Gopalappa	63	M		133	2.8	0.8	4.5	2.2				Malaria
48	2	7405	Arjunsingh	60	M		134	4	0.7	4	2.1				Pharyngitis
49	2	7437	Parutayya	52	M		136	3.9	0.6	5.2	2.2				COPD
50	2	6718	Mallappa	54	M		135	4.1	0.7	5	1.9				Acute gastritis
51	2	6585	Basavaraj	36	M		135	3.8	0.6	5.4	2				Megaloblastic anemia
52	2	6922	Neelamma	63	F		134	4.1	0.8	4.6	1.7				B/L Premature senil
53	2	6019	Gyanamma	35	F		134	3.6	0.8	5.4	1.6				White leukmatous
54	2	7380	Sunanda	60	F		137	3.8	0.6	5.6	1.8				Nasal bone fracture
55	2	3831	Maitia	63	F		140	4.2	0.6	5	1.7				Microcytic hypocytic anemia
56	2	3717	Bourawwa	60	F		142	3.4	0.6	4.4	1.8				NormaalMalingring
57	2	3832	Lakshmi	32	F		137	4.2	0.6	5	1.7				Microcytic hypocytic anemia
58	2	2164	Geeta	50	F		140	4.1	0.6	5	1.9				Severe anemia
59	2	2437	Kumar	45	M		128	3.5	0.7	5	1.9				RVD with pneumia
60	2	2112	Devaki	75	F		134	3.8	0.6	5.4	2				Lt pleural effusion
61	2	4972	Shivanand	63	M		140	3.4	0.6	4.6	2.1				Acute bronchitis
62	2	4615	Peerappa	60	M		137	3.3	0.7	5.5	2.2				COPD
63	2	4822	Vijayakumar	45	M		138	3.5	0.7	5	2.2				Acute bronchitis

64	2	3012	Parasappa	63	M		140	4.5	1	5.4	1.9				RHD with MI
65	2	8508	Basavaraj	63	M		136	3.5	0.6	4.6	2				Pulmonary tuberculosis
66	2	8875	Dhiru	60	M		136	3.9	0.6	4	1.9				Microcytic hypocytic anemia
67	2	9055	Santosh	50	M		129	3.7	1.2	5.3	2.1				Acute bronchitis with anemia
68	2	9091	Shivanand	63	M		136	4	0.8	4.4	2				Typhoid fever
69	2	8414	Shruthi	50	F		136	3.5	1.1	5	2.2				Dengue fever
70	2	8845	Deepali	25	F		140	4.9	0.6	4.6	2.5				Microcytic hypocytic anemia