A STUDY ON CORRELATION OF SERUM MAGNESIUM IN DIABETIC PATIENTS WITH PROTEINURIA

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BONAFIDE CERTIFICATE

This is to certify that dissertation named **"A STUDY ON CORRELATION OF SERUM MAGNESIUM IN DIABETIC PATIENTS WITH PROTEINURIA"** is a bonafide work performed by **Dr.V.AMALAN CHRISTUDHAS**, post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfillment of regulations of the Tamilnadu Dr. M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2010 to April 2013.

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DECLARATION

I solemnly declare that this dissertation **"A STUDY ON CORRELATION OF SERUM MAGNESIUM IN DIABETIC PATIENTS WITH PROTEINURIA"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr.N.GUNASEKARAN M.D.**, **DTCD.** Director & Superintendent Institute of Non Communicable Diseases, Government Royapettah Hospital, Chennai, Professor and Head of the Department of Internal Medicine, Kilpauk Medical College, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

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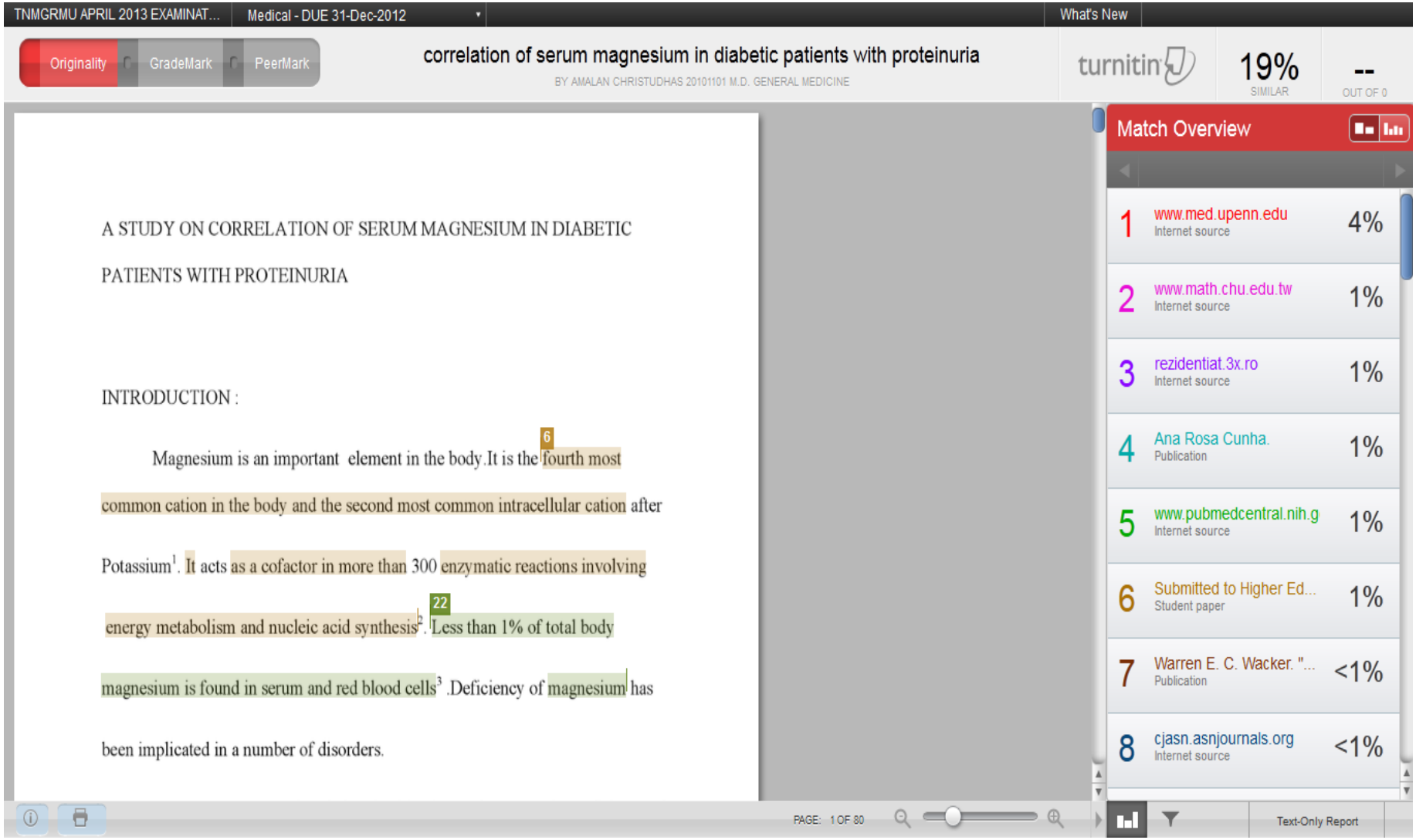
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INTRODUCTION :
Magnesium is an important element in the body.It is the fourth most
common cation in the body and the second most common intracellular cation after
Potassium[1]. It acts as a cofactor in more than 300 enzymatic reactions involving
energy metabolism and nucleic acid synthesis[2]. Less than 1% of total body
magnesium is found in serum and red blood cells[3] .Deficiency of magnesium has
been implicated in a number of disorders.
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ABSTRACT

INTRDUCTION:

Magnesium is the second most important intracellular cation in the body next only to potassium. It acts as a cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis. Magnesium deficiency inhibits the acute phase of insulin release in response to glucose challenge. Magnesium deficiency is associated with insulin resistance; conversely insulin resistance is associated with low serum magnesium. Hypomagnesemia in patients with diabetes results from poor oral intake, poor gastrointestinal absorption and enhanced renal magnesium excretion. Microalbuminuria and overt proteinuria in patients with diabetes contribute to renal magnesium wasting due to protein bound magnesium loss. There exists an inverse correlation between serum magnesium level and diabetic patients with proteinuria. More the proteinuria , more the magnesium loss, lesser the serum magnesium level.

AIMS AND OBJECTIVES:

To study the correlation of serum magnesium in diabetic patients with proteinuria.

MATERIALS AND METHODS:

This was an observational study done in Government Royapettah Hospital.The study recruited 50 patients ,who were admitted in the department of medicine and who attended diabetology department as out patients.Those who fulfilled the inclusion and exclusion criteria were included in the study.Serum Magnesium level and 24hours urinary protein were estimated.

Observation and results:

Out of 50 patients recruited in the study 12 patients were type 1 and 38 were type 2.Out of 50 patients 25 patients had microalbuminuria and 25 patients had macroalbuminuria.Those patients who had macroalbuminuria had lower magnesium level compared to patients who had microalbuminuria.Patients who had more proteinuria had the lowest magnesium level.

CONCLUSION:

The study concluded that there is an inverse correlation between serum magnesium level and proteinuria.As deficiencyof magnesium is involved in many complications of diabetes ,supplementing oral magnesium can reduce morbidity and mortality.

CONTENTS

INTRODUCTION

Magnesium is an important element in the body. It is the fourth most common cation in the body and the second most common intracellular cation after potassium[1]. It acts as a cofactor in more than 300 enzymatic reactions involving energy metabolism and nucleic acid synthesis[2]. Less than 1% of total body Magnesium is found in serum and red blood cells[3]. Deficiency of magnesium has been implicated in a number of disorders.

Magnesium is involved in glucose homeostasis. Deficiency of magnesium gives rise to alterations in glucose metabolism. Magnesium affects insulin secretion as well as glucose uptake by cells. Magnesium deficiency inhibits the acute phase of insulin release in response to glucose challenge. Magnesium deficiency is associated with insulin resistance; conversely insulin resistance is associated with low serum magnesium[4].

Hypomagnesemia in patients with diabetes results from poor oral intake, poor gastrointestinal absorption and enhanced renal magnesium excretion[5]. In diabetes, ultra filterable magnesium load may be enhanced by glomerular hyper filtration, recurrent excessive volume depletion due to hyperglycemia induced osmotic diuresis, recurrent metabolic acidosis

associated with diabetic ketoacidosis and hypoalbuminemia. Microalbuminuria and overt proteinuria in patients with diabetes contribute to renal magnesium wasting due to protein bound magnesium loss.

There is an inverse correlation between serum magnesium and serum cholesterol, triglyceride, low density lipoprotein level[6]. In patients with hypomagnesemia these lipids are at a higher level. Magnesium deficiency increases angiotensin II induced plasma aldosterone concentration and production of thromboxane and vasoconstrictor prostaglandin. These changes lead to increase in vascular tone. Magnesium deficiency leads to progression of atherosclerosis by its effect on lipid metabolism, platelet aggregation and blood pressure[7]. Thus it can lead to increase in cardiovascular related mortality.

There exists an inverse correlation between serum magnesium level and diabetic patients with proteinuria. More the proteinuria , more the magnesium loss, lesser the serum magnesium level[8].

Thus by treating these patients with oral magnesium, we can improve glycemic control and can prevent other vascular complication related to diabetes[9].

REVIEW OF LITERATURE

DEMOGRAPHY:

India is having the world's largest number of diabetic patients. Type 2 diabetes accounts for more than 90% of cases and Type 1 diabetes is on the increasing trend. International Diabetes Federation (IDF) said that total number of diabetics in India was around 40.9million in the year 2006, and it projected that it will become 69.9million by the year 2025[10].Study done in1998 in Chennai population showed a prevalence of 8.2% in urban and 2.4%in rural areas[11].A study done after 5 years in the same urban area showed a prevalence of 11.6%[12].

Chennai Urban Rural Epidemiology study (CURES), showed that the prevalence of diabetes in Chennai was 15.5% and that of impaired glucose tolerance was10.6%.The prevalence of diabetes in Chennai increased by 39.8% from 1989 to1995.It increased by 16.5% from the year 1995 to 2000 and by 6% between 2000 to 2004.Thus the prevalence of diabetes increased significantly by 72.3% within the span of 14years[13].

Diabetic nephropathy develops in one third of the patients with diabetes. The incidence is increasing worldwide and the Asia pacific region being the most affected. According to statistical prediction, in India diabetic nephropathy is expected to develop in 6.6million people

out of 30million people with diabetes[14]. Studies in south India have shown that the prevalence of microalbuminuria is 26.9% and overt proteinuria is 2.2%[15].Prevalence of diabetic nephropathy in Asia in Vellore (India) was 8.9%, and Asians in Leicester, United Kingdom was 22.3% and Caucasians in Leicester, in United Kingdom was 12.6%[16]. 25to 39% of patients with diabetes will have low serum magnesium level.

Diabetes mellitus is a group of common metabolic disorders that share the phenotype of hyperglycemia. Several types of diabetes mellitus are caused by complex interaction of environmental and genetic factors. Based on the etiology of the DM, factors contributing to increased blood sugar are decreased insulin secretion, reduced glucose utilization, and increased production of glucose. One of the most important causes of end stage renal disease in United States is diabetes mellitus. Because of the increasing incidence of diabetes mellitus it will be the most common cause of morbidity and mortality in the future [17].

CLASSIFICATION OF DIABETES

Diabetes has been broadly classified into two types:

TYPE 1: It is due to near total or complete lack of insulin.

TYPE 2: It is due to insulin resistance, reduced insulin secretion and increased production of glucose. Impaired fasting glucose or impaired glucose tolerance precedes the development of diabetes.

Criteria for the diagnosis of Diabetes[17]:

1. Random blood glucose > 200mg/dl, plus symptoms of diabetes or
2. Fasting plasma glucose > 126mg/dl or
3. Hb A1C > 6.5% or
4. Two hour plasma glucose during an oral glucose tolerance test more than 200mg/dl

Pathogenesis of Type 1 diabetes:

Type 1 diabetes mellitus is the result of interaction of environmental, genetic and immunological factors that ultimately causes pancreatic β cell destruction and insulin deficiency. The rate of decline in β cells varies with individual, some patients' progress slowly and others rapidly to clinical diabetes. Features of diabetes occur only when 70-80% of β cells are destroyed. At this stage residual β cell function exists, but are not sufficient to maintain glucose tolerance. Once the requirement of insulin increases as with any infection or puberty, they manifest as frank

diabetes. After the initial clinical presentation of type 1 DM, a "honeymoon" phase may ensue during which time glycemic control is achieved with modest doses of insulin or, rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears as the autoimmune process destroys remaining beta cells, and the individual becomes insulin deficient[17].

GENETIC CONSIDERATION:

Susceptibility to Type 1 DM involves multiple genes. Concordance in identical twin ranges between 40-60%.The susceptibility gene is located in the HLA region in chromosome 6.Most individual have HLA DR3 and or HLA DR4 haplotypes. The haplotypes DQA1*0301, DQB1*0302, and DQB1*0201 are strongly associated with type 1 DM[18]. However, most individuals with these haplotypes do not develop diabetes. The presence of haplotype DQA1*0102, DQB1*0602 gives protection against the development of Type 1 DM.

PATHOPHYSIOLOGY:

There is infiltration of pancreatic islet cells with lymphocytes (termed insulitis).After the destruction of β cells the inflammatory process stops and the islet cells become atrophic and the immunological

markers will disappear. The following abnormalities of cellular humoral immune response was found in patients with Type 1 DM

1. Islet cell auto antibodies
2. Proliferation of T Lymphocyte when stimulated with islet proteins
3. Release of cytokines within the insulitis
4. Activated lymphocytes in the islets and systemic circulation.

Insulin, glutamic acid decarboxylase, and a beta cell specific zinc transporter are the pancreatic islet cell molecule targeted by autoimmune process.

Metabolic disturbances of Type 1 diabetes

Carbohydrate metabolism:

Basal hyperglycemia is due to increased production of glucose by the liver and is increased after eating because glucose is not cleared in the periphery. Hepatic glucose output is increased because of increased gluconeogenesis and supply of gluconeogenic precursor is increased. Postprandial glucose uptake into fat and muscle mediated by insulin is decreased.

Fat metabolism:

Severe insulin deficiency stimulates lipolysis thereby generating glycerol and free fattyacids,which are substrates for ketone formation. Ketogenesis is particularly increased by glucagon excess. Weight loss in untreated type 1 diabetics is due to mobilization of body fat.

Protein metabolism:

Anabolic effect of insulin is lost, catabolism of proteins are increased through proteosome mediated pathway and generates aminoacids such as alanine and glutamine which are precursors of gluconeogenesis. Muscle wasting may be prominent[17].

TYPE 2 DIABETES:

Central to the development of type 2 diabetes are insulin resistance and abnormal insulin secretion. The primary defect in diabetes mellitus is controversial, most studies support insulin resistance precedes the development of insulin secretory defect but diabetes occurs only when insulin secretions are not adequate.

Genetic consideration:

Type 2 diabetes mellitus has a strong genetic basis. The concordance of Type 2DM is between 70% and 90% in identical twins.

Sibling of parent with type 2DM has an increased risk of getting diabetes. The risk approaches 40% if both parents are type 2 diabetic. The disease is multifactorial and polygenic in addition to genetic susceptibility; environment factors such as nutrition, obesity and physical activity also have a role. A variant of transcription factor 7 like 2 genes is associated with type 2 diabetes[17].

Pathophysiology:

Type 2 diabetes is characterized by insulin resistance, reduced insulin secretion, abnormal fat metabolism and increased glucose production from the liver[19].Visceral or central obesity is more common in type 2 diabetics. In the early stage of disease glucose tolerance remains near normal inspite of insulin resistance, because the pancreatic beta cells compensate by augmenting insulin output. Impaired glucose tolerance which is characterized by increase in postprandial blood sugar develops because of sustained hyperinsulinemic state due to insulin resistance and compensatory hyperinsulinemia. Once the insulin secretion declines further overt diabetes ensues with fasting hyperglycemia due to increased hepatic glucose production.

Metabolic abnormalities:

Muscle and fat metabolism:

The prominent feature in type 2 DM is insulin resistance, which is mainly contributed by genetic susceptibility and obesity. Because of insulin resistance the activity of insulin in target tissues such as muscle, liver and fat is reduced. Insulin resistance in type 2 DM is relative, since there is circulating supra normal levels of insulin will normalize the blood sugar. Insulin resistance has two consequences

1. It reduces the utilization of glucose by insulin sensitive tissues and
2. It increases the output of glucose from the liver. These effects contributes to increase in plasma sugar level .Increased fasting plasma sugar is mainly due to increased hepatic glucose production and postprandial hyperglycemia is due to increased insulin resistance. In type 2 DM glucose metabolism in insulin independent tissue is unaffected.

The exact mechanism of insulin resistance is not known, but there is evidence to say that insulin at the receptor level and tyrosine kinase activity level are reduced in skeletal muscle. These changes are mainly secondary to hyperinsulinemia and not a primary defect. The important role in insulin resistance is played by the postreceptor defect in insulin

regulated phosphorylation/ dephosphorylation[19].Lipids gets accumulated within skeletal muscles and impairs mitochondrial oxidative phosphorylation, which in turn reduces insulin stimulated mitochondrial ATP production. Reactive oxygen species such as lipid peroxides gets accumulated within the skeletal muscles due to lipid accumulation and impaired fatty acid oxidation.

Impaired insulin secretion:

Insulin secretion increases initially in response to hyperglycemia to maintain normal glucose tolerance. Insulin secretary defect is mild initially and only glucose stimulated insulin secretion is affected. There is abnormalities of proinsulin processing which is seen as increased in proinsulin level.The exact reason for insulin secretary defect is not known.The probable reason will be, there is a genetic defect superimposed upon insulin resistance and leads to β cell failure. In long standing cases of type 2 DM β cells secrete amyloid polypeptide or amylin which forms the amyloid fibrillar deposits in the islet cells[20].

Hepatic glucose and lipid production

Increased Insulin resistance in liver cells results in fasting hyperglycemia because of failure of suppression of gluconeogenesis by hyperinsulinemia. Because of insulin resistance in adipose tissue flux of

free fatty acids and lipolysis from adipocytes are increased, leads to increased hepatic synthesis of lipids. This lipid steatosis in the liver leads to non alcoholic fatty liver disease. The dyslipidemia found in type2 DM are elevated triglyceride, reduced high density lipoprotein, and increased small dense low density lipoprotein particles[17].

Insulin resistance syndrome:

The syndrome X or the insulin resistance syndrome is characterized by dyslipidemia, hypertension, visceral or central obesity, insulin resistance, type 2 diabetes or impaired fasting glucose or impaired glucose tolerance and accelerated cardiovascular disease. There are two types of severe insulin resistance in adults, 1.type A which occurs in young women and the features are obesity, severe hyperinsulinemia and hyperandrogenism.It is due to an undefined defect in insulin signaling pathway. 2. type 2 which occurs in middle aged women and the features are severe hyperinsulinemia, hyperandrogenism and autoimmune disorder.These individuals have autoantibodies directed against insulin receptor[21].

COMPLICATIONS OF DIABETES:

Acute metabolic complications are

1. Diabetic ketoacidodis

2. Hyperglycemic hyperosmolar state

3. Hypoglycemia.

DIABETIC KETOACIDOSIS:

Diabetic ketoacidosis is more common in type 1 diabetes. Sometimes it may be the presenting feature in type 1 diabetes. It is less common in type 2 diabetes, but it can occur in type 2 diabetes. It is associated with relative or absolute insulin deficiency, volume depletion and acid base abnormalities. Counter regulatory hormones such as glucagon, cortisol, growth hormone and catecholamine play an important role in diabetic ketoacidosis[22].Glucgon excess and insulin deficiency is necessary for diabetic ketoacidosis to develop. Decrease in insulin level augments the activity of phosphoenol pyruvate carboxykinase, increase in glucagon level reduces the activity of pyruvate kinase. These changes cause pyruvate to get converted to glucose. Increases in catecholamine level causes glycogenolysis. Increased levels of counter regulatory hormones and decreased levels of insulin causes increase in lipolysis and release of free fatty acids.The increased free fatty acids causes increase in

triglyceride and very lowdensity lipoprotein level.In diabetic keto acidosis, increase in glucagon level alters liver metabolism infavour of ketone body formation by activating the enzyme carnitine palmitoyl transferase 1. At normal pH these ketone bodies exist as ketoacids and these are neutralized by bicarbonate.Once bicarbonate stores are depleted metabolic acidosis ensures.

CLINICAL FEATURES:

Patients usually presents with thirst, polyuria, abdominal pain, nausea, vomiting and breathlessness. Diabetic ketoacidosis is precipitated by infarction, infection, inadequate dose of insulin administration .Drugs such as cocaine can precipitate. Pregnancy itself can precipitate diabetic ketoacidosis. Physical signs include dehydration, hypotension, tachypnea, tachycardia, respiratory distress, kussmals breathing.In case of severe acidosis lethargy, cerebral edema and coma can occur.

LAB ABNORMALITIES AND DIAGNOSIS:

Blood glucose is only mildly elevated. Serum bicarbonate is <10 mmol/lit, the pH is in the range of 6.8 to 7.3 depending on the severity of acidosis. Hyperproteinemia, hypertriglyceridemia and leucocytosis can occur. Serum sodium, phosphorous, chloride and magnesium levels are reduced in ketoacidosis. There is mild elevation of blood urea nitrogen

and serum creatinine level. Serum levels of β hydroxybutyrate level are useful in diagnosis. Acetoacetate is the ketone body detected by keto stick.

HYPERGLYCEMIC HYPEROSMOLAR STATE:

It occurs as a result of decreased fluid intake and relative insulin deficiency. Insulin deficiency causes increased glucose output from the liver and decreased glucose utilization in skeletal muscle. Hyperglycemia causes osmotic diuresis and leads to intravascular volume loss which is further accentuated by decreased fluid intake. The absence of ketosis in hyperglycemic hyperosmolar state is not known. Studies have shown that the levels of counter regulator hormones and free fatty acids levels are low in hyperglycemic hyperosmolar state when compared to diabetic ketoacidosis.It is said that insulin/glucagon ratio doesn't favors ketogenesis[17].

CLINICAL FEATURES:

Typically patients present with weight loss, weeks history of polyuria and decreased oral intake which ultimately results in lethargy, mental confusion or coma. It is usually precipitated by sepsis, pneumonia, and concurrent illness such as stroke or myocardial infarction. Examination will reveal tachycardia, hypotension, profound dehydration,

hyperosmolality, and altered mental status. Absence of nausea, vomiting, abdominal pain and kussmaul breathing favour the diagnosis of hyperglycemic hyperosmolar state.

LAB ABNORMALITIES AND DIAGNOSIS:

Plasma glucose is usually in the range of 600-1000mg/dl. Other features hyperosmolality, prerenal azotemia. Potassium, magnesium, chloride and phosphate levels are well within normal range. Bicarbonate is within normal limits or slightly reduced. Secondary to starvation there can be mild ketonuria.

HYPOGLYCEMIA:

Hypoglycemia is one of the most important complications of diabetes. It occurs due to excess administration of insulin or oral hypoglycemic agent particularly in the setting of organ failure or sepsis. Hypoglycemia is documented by whipple′s triad.1. Reduced plasma blood sugar. 2. Symptoms of hypoglycemia.3.Relief of symptoms after giving glucose. Symptoms of hypoglycemia and blood sugar value less than 55mg/dl and improvement of symptoms after giving glucose documents hypoglycemia.

As the blood sugar falls below the physiological range counter regulatory hormones comes into action. First defense is reduced insulin

secretion. Second defense is the glucagon, which causes hepatic glycogenolysis. Third is the epinephrine which stimulates hepatic glycogenolysis and gluconeogenesis. When hypoglycemia is for more than 4 hours cortisol and growth hormone comes into action and promotes glucose production.

CLINICAL MANIFESTATION:

Neuroglycopenic symptoms are due to reduced sugar level in the brain. Symptoms are fatigue, behavioral changes, confusion, seizures, loss of consciousness and if severe and prolonged it may result in death. Signs of hypoglycemia are pallor and diaphoresis. Blood pressure and heart rate are increased, but may not be increased in patients with recurrent episodes of hypoglycemia.

Hypoglycemic unawareness:

The reduced sympatho adrenal response to hypoglycemia causes the syndrome of hypoglycemic unawareness. It is due to loss of warning adrenergic and cholinergic symptoms. Affected patients are at increased risk of iatrogenic hypoglycemia.

CHRONIC COMPLICATIONS OF DIABETES:

It can be classified into microvascular and macrovascular. Microvascular complications in the eye include retinopathy and macular edema, diabetic nephropathy, autonomic, sensory and motor mono and poly neuropathy. Macrovascular complications include cerebrovascular disease, peripheral arterial disease and coronary artery disease.

CORONARY ARTERY DISEASE:

Diabetes mellitus patients have many different forms of dyslipidemia. Common forms are reduced high density cholesterol, increased triglyceride level and the small dense lipoprotein particles found in patients with diabetes have more atherogenic potential and they are more easily glycated and susceptible to oxidation[23]. Somes of the risk factors for coronary artery disease in diabetic patients are cigarette smoking, reduced physical activity, obesity, dyslipidemia and hypertension. The association between insulin resistance and hypertension and the subsequent hyperinsulinemia is well established. Patients who were not on treatment for essential hypertension, have elevated levels of insulin level in the fasting and postprandial state when compared to the normotensive people regardless of bodymass index. Thus these statements say that hypertension is an insulin resistance state[24].

Some of the additional risk factors associated with diabetes are macroalbuminuria, microalbuminuria, abnormal platelet function and increased serum creatinine level. Patients with diabetes and insulin resistance have elevated levels of fibrinogen and plasminogen activator inhibitors. These substances augments the coagulation process and impairs fibrinolysis[25]. Thus leading to easy formation of thrombosis. Diabetic patients have impaired vascular smooth muscle and endothelial dysfunction, these also contributes to thrombus formation, thus increasing the cardiovascular morbidity and mortality .Diabetic patients have fourfold (in women) and two fold (in men) increase in mortality due to cardiovascular events[17].

Coronary artery disease occurs in Type1 diabetic patients usually in the third or fourth decade of life, regardless of the development of diabetes in the child hood or early adolescence. After the age of 40 years coronary artery disease risk increases rapidly and by 55 years 35% of women and men will die of coronary artery disease when compared to 8% without diabetes.

CEREBRO VASCULAR DISEASE:

Type 1 and Type 2 diabetic patients are more prone for stroke. Diabetes increases carotid atherosclerosis and mortality due to stroke is

about threefold high[26]. Studies have shown that using statin therapy was significantly associated with reduced incidence of stroke.

DIABETIC NEUROPATHY:

Studies have shown that the prevalence of diabetic peripheral neuropathy is from 5%to 100%.The most common form of diabetic neuropathy is predominantly sensory or sensory motor distal polyneuropathy. Classification is based on clinical presentation. Modified classification of diabetic neuropathy by Thomas is shown below[27]:

SYMMETRIC NEUROPATHY:

- ✓ Distal symmetric sensory motor polyneuropathy.
- ✓ Hyperglycemic neuropathy
- ✓ Autonomic neuropathy
- ✓ Acute painful neuropathy
- ✓ Treatment induced neuropathy
- ✓ Symmetric proximal lower extremity neuropathy

FOCAL AND MULTIFOCAL NEUROPATHY

- ✓ Diabetic amyotrophy
- ✓ Focal limb neuropathy
- ✓ Cranial neuropathy
- ✓ Thoraco abdominal neuropathy

Clinical Features:

Paresthesias and numbness starts in the toes and gradually ascends to involve the feet and lower legs. Sensory deficit usually occurs in a symmetric pattern but not infrequently asymmetric pattern of nerve distribution may superimpose on this symmetric distribution. The distal portions of the longer nerves of the lower extremities are affected first producing the typical stocking and glove pattern. These symptoms are often described as like walking on pebbles, having cotton bunched up under the toes. The positive symptoms are superficial burning, deep burning, parasthesia, dysesthesia, paroxysmal jabbing pain and contact induced discomfort .Sensory symptoms are commonly accompanied by mild distal motor weakness and autonomic neuropathy.

Involvement of myelinated large fibers and unmyelinated small fibers occurs In varying combination. Small fiber neuropathy produces defects in pain and temperature perception, dysesthesias, paresthesias, dysautonomia, defect in perception of visceral pain and predisposition to foot ulceration. Deep tendon reflexes and proprioception are relatively preserved. Nerve conduction studies are usually normal or minimally abnormal. Involvement of large fiber neuropathy cause loss of position and vibration position sense and absent deep tendon reflexes. Nerve conduction studies are abnormal.

OCULAR COMPLICATIONS OF DIABETES:

Diabetic retinopathy is one of the most important complications of diabetes. Other complications include, mononeuropathies involving the 3^{rd},4^{th} and 6^{th} nerve, decreased sensitivity and recurrent erosion in the cornea, neovascularisation of iris and neovascular glaucoma, refractive fluctuations, premature cataract and diabetic cataract.

In the United States diabetes is the leading cause of blindness in the age group 20 and 74 years[28]. Individuals with diabetes have 25 times more risk of becoming blind. Causes of blindness include clinically significant macular edema and diabetic retinopathy. Retinopathy can be classified into proliferative and non proliferative retinopathy. Non proliferative diabetic retinopathy occurs after 10 to 20 years of diabetes. Non proliferative diabetic retinopathy is characterized by vascular microaneurysm, cotton wool spots and blot hemorrhages. More extensive disease is characterized by more microaneurysm formation and hemorrhages, intra retinal microvascular abnormalities and change in venous vessel caliber[29].The pathophysiology involved in the formation of non proliferative diabetic retinopathy are abnormal retinal microvasculature, alteration in the retinal blood flow, loss of retinal pericytes and increased vascular permeability, all these leads to retinal ischemia.

The hall mark of proliferative diabetic retinopathy is neovascularization in response to retinal hypoxia[17].The new vessels usually appear near the macula or the optic nerve.The rupture of newly formed vessels leads to vitreous hemorrhages, fibrosis and ultimately leads to retinal detachment. The more severe the non proliferative retinopathy more the chance of getting proliferative diabetic retinopathy within 5 years. The best predictors for the development of the diabetic retinopathy are duration of diabetes and degree of glycemic control.Macular edema usually occurs only when there is non proliferative retinopathy.Fundus fluorescein angiography can detect macular edema and when it is present the chance of developing moderate visual loss in the next 3 years in 25%.

DIABETIC NEPHROPATHY:

Among diabetic patients only 30% develop diabetic nephropathy. The sibling of a diabetic patient with type 1 diabetes without nephropathy has a 25%risk of getting diabetic nephropathy. The sibling of a type 1 diabetic patient with nephropathy has a 72% risk of developing nephropathy[30]. Thus inherited factors play an important role in the development of diabetic nephropathy. Familial predisposition to raised blood pressure is an important determinant of susceptibility to renal disease in patients with diabetes. The risk of nephropathy is 3 times

higher in type 1 diabetic patients who have history of hypertension in atleast one parent[31]. The prevalence of proteinuria is higher in those parents who are hypertensive when compared to normotensive. Studies have shown that mean blood pressure levels are high in patients who progress to microalbuminura than those who do not[32].

PATHOGENESIS OF DIABETIC NEPHROPATHY:

The main mechanisms involved in the pathogenesis of diabetic nephropathy are,

1. Metabolic insults
2. Hemodynamic insults
3. Inflammatory mediators
4. Signalling pathways.

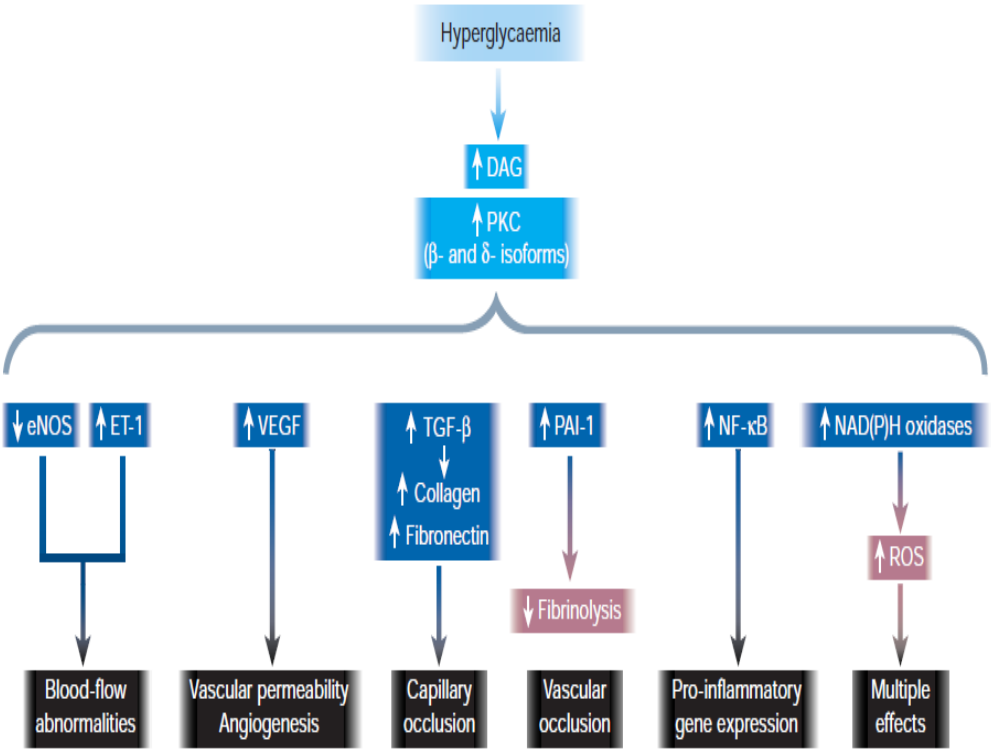
METABOLIC INSULTS:

HYPERGLYCEMIA:

Poor glycemic control is associated with diabetic nephropathy. HbA1c levels are higher in patients with micro and macro albuminuria, when compared to normoalbuminuria[33].High blood sugar levels induces hypertrophy of mesangial cells and protein secretion of extracellular

matrix components such as collagen, laminin and fibronectin. Hyperglycemia reduces the activity of metalloproteases,which is an enzyme responsible for degradation of extracellular matrix. The four hypothesis by which hyperglycemia induces renal damage are,

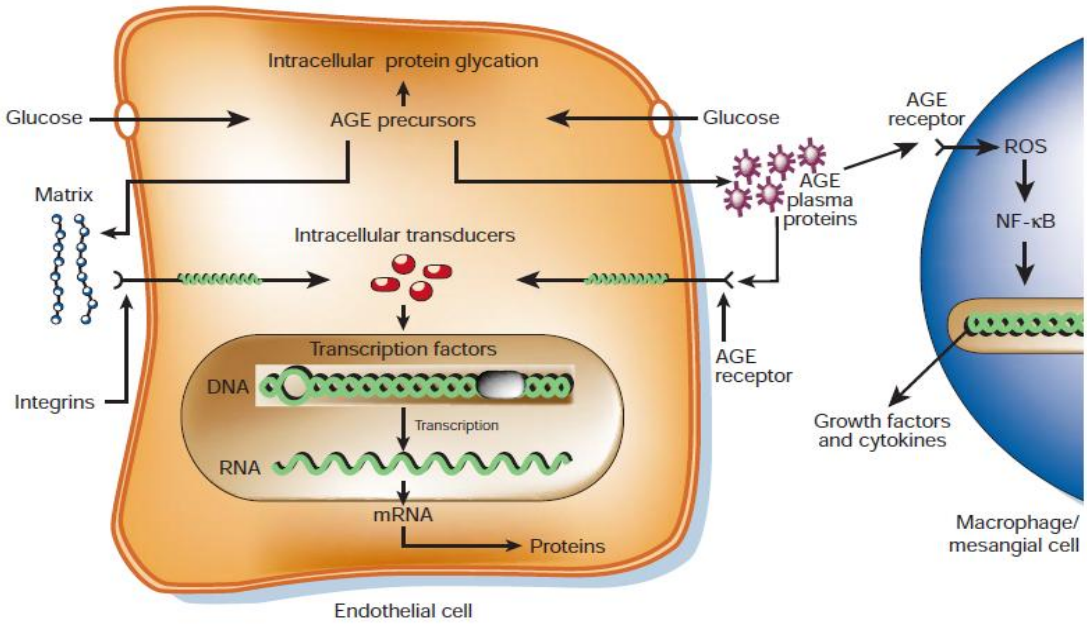
1. Formation of advanced glycated end products.
2. Increased polyol pathway flux
3. Activation of protein kinase
4. Increased hexosaminase pathway flux.



FORMATION OF ADVANCED GLYCATION END PRODUCTS:

Non enzymatic glycation of proteins is a physiological reaction which is enhanced in the presence of hyperglycemia. The glycated proteins undergo progressive dehydration, cyclization, oxidation and rearrangement to form advanced glycation end products. Once these products are formed the reaction is irreversible and they gradually accumulate over the life time of protein[34].AGEs accumulate in the glomeruli and tubules and leads to albuminuria ,mesangial expansion and thickening of glomerular basement membrane. Interaction of AGE-modified proteins with its receptors degrades AGE proteins but also stimulates the synthesis and release of cytokines such as platelet derived growth factor, transforming growth factor β and insulin like growth factor, these results in increased production of fibronectin, collagen and laminin[35,36].Overexpression of AGE receptors rapidly develops glomerular lesion similar to diabetic nephropathy.It is also expressed in tubular epithelial cells and upon activation induce tubular epithelial cell trans differentiation to myofibroblast which leads to the development of interstitial fibrosis[37].

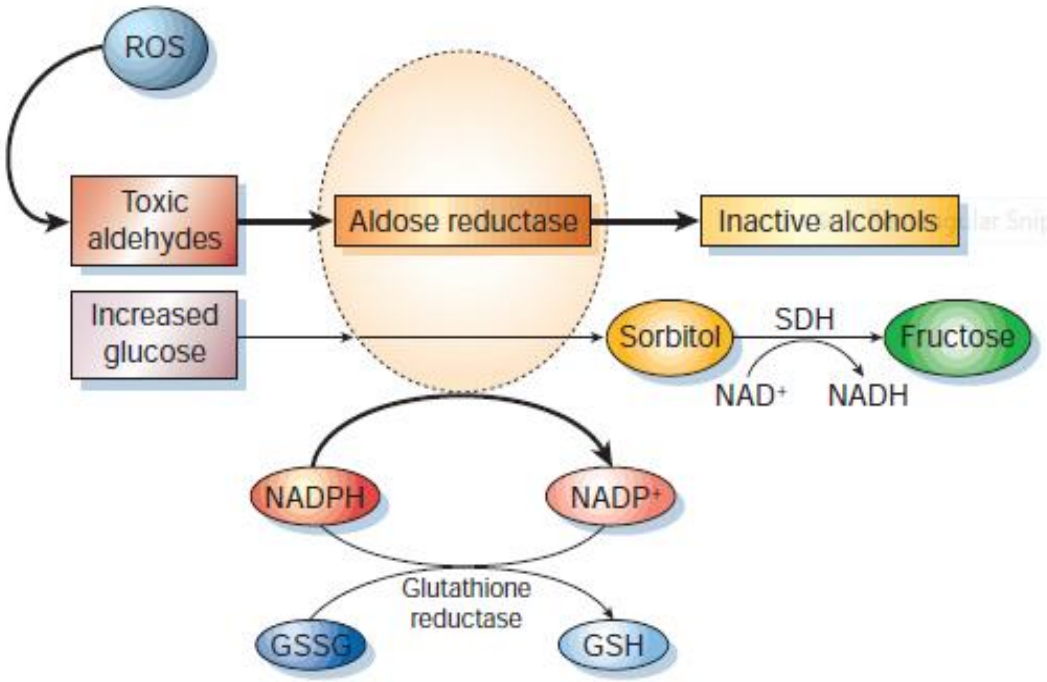
Figure showing : Formation of advanced glycated end products



THE POLYOL PATHWAY:

Intracellular glucose is predominantly metabolized by phosphorylation and glycolysis and when there is hyperglycemia, the excess glucose is converted to sorbitol by the enzyme aldose reductase, excess sorbitol is oxidized to fructose by the enzyme fructose dehydrogenase .Increased activity of polyol pathway was demonstrated in diabetic patients[38].Fructose is a reactive sugar that leads to the formation of advanced glycated end products. The increased ratio of NADH/NAD and in addition of oxidation of sorbitol to fructose results in the formatin of reactive oxygen species[39].

Figure showing : Formation of Sorbitol



HEXOSAMINE BIOSYNTHETIC PATHWAY:

Small amount of glucose entering into the cell is metabolized by the hexosamine biosynthetic pathway, which converts glucose 6 phosphate into hexosamine 6 phosphate.The rate limiting enzyme in this reaction is the glutamine: fructose 6 phosphate aminotransferase. In patients with diabetic nephropathy there is overexpression of this enzyme. This leads to increased formation of transforming growth factor β and fibronectin[40].

HEMODYNAMIC INSULTS:

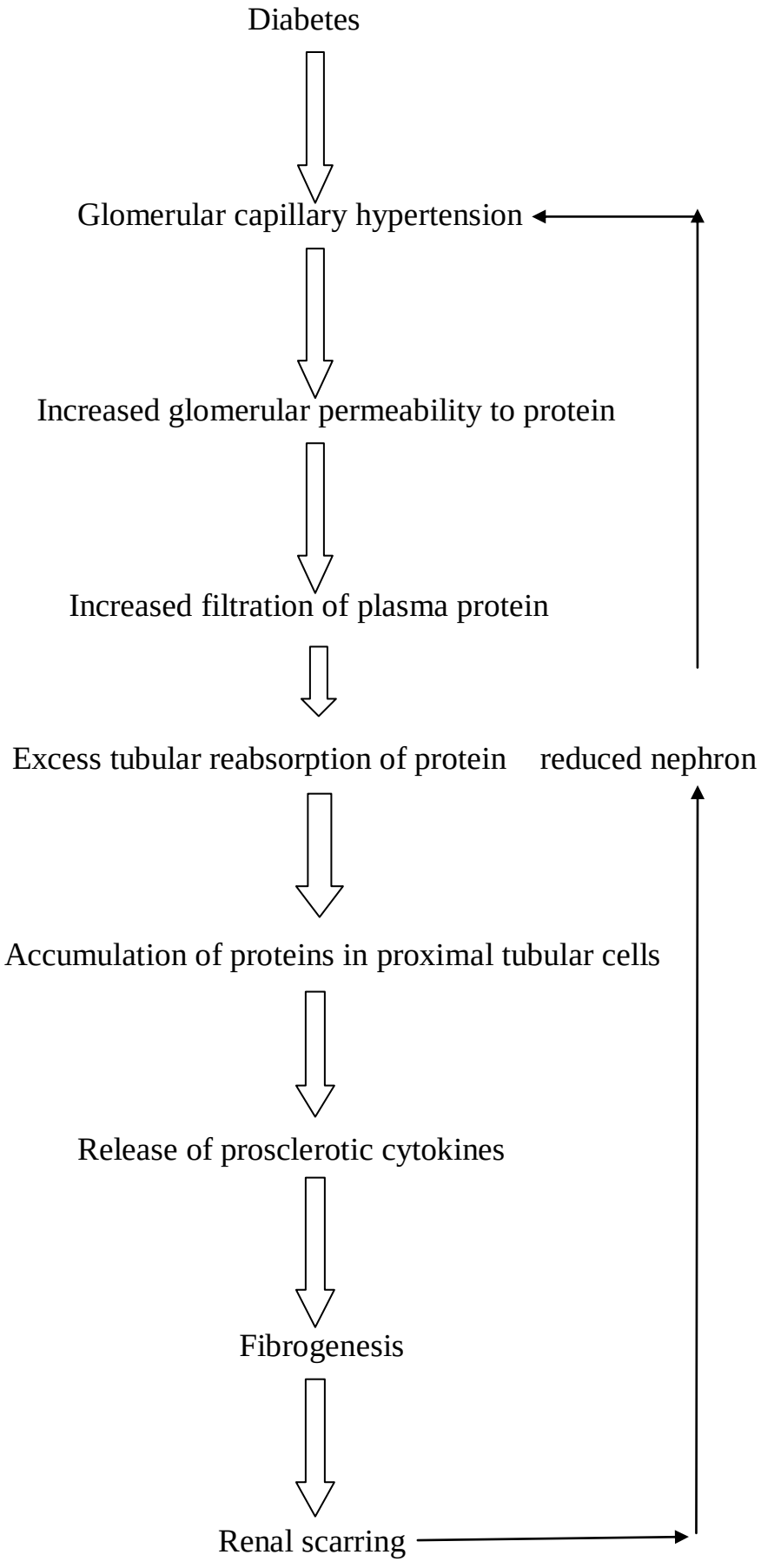
These are due to systemic hypertension and glomerular hypertension. Hypertension plays an important role in the development of diabetic nephropathy. Proteinuria correlates well with the gradual rise in the systemic blood pressure. There is a significant correlation between the blood pressure levels and rate of decline in glomerular filtration rate[41]. Studies have shown that patients with type1 and type 2 diabetes with normal albumin excretion with higher mean arterial blood pressure progress to microalbuminuria, when compared to those with normal mean arterial pressure[42].

Intra glomerular pressure is regulated by the precise adjustment of the afferent and efferent arteriolar resistance.In diabetic patients there is loss of autoregulation of glomerular capillary pressure. Hyperglycemia causes vasodilation and in diabetic patients there is a marked reduction in the afferent and lesser reduction in the efferent arteriolar resistance.This leads to elevated glomerular pressure[43].When there is any change in the systemic pressure it gets reflected in the glomerular pressure.The mechanism by which increased glomerular capillary pressure leads to kidney damage is due to the unique elastic properties of the glomerular structure and the response of the mesangial cells to mechanical stretch.

When the glomerular pressure increases, the glomerular volume increases by about 30%.These volume change reach their maximum in 3to 4 seconds following alteration in the intraglomerular pressure.Thus it responds for a transient variation in the glomerular pressure. Mesangial cells are exposed to mechanical stretch in response to increase in glomerular pressure. Cyclical stretch stimulates the synthesis of deposition of matrix components such as fibronectin, laminin and collagen in proportion to the intensity of the stretch[44].

PROTEINURIA:

Proteinuria is an independent predictor of decline in renal function in diabetic Nephropathy[45]. Proteinuria leads to excessive tubular reabsorption of proteins and leads to accumulation of proteins in the tubular epithelial cells. These causes release of vasoactive and inflammatory cytokines such as osteopontin, monocyte chemo attractant protein1,and endothelin 1.These factors leads to over expression of proinflammatory and fibrotic cytokines and which causes injury to the tubulointerstitium and finally leads to renal scarring and renal failure[46]


Diabetes
Glomerular capillary hypertension
Increased glomerular permeability to protein
Increased filtration of plasma protein
Excess tubular reabsorption of protein
reduced nephron
Accumulation of proteins in proximal tubular cells
Release of prosclerotic cytokines
Fibrogenesis
Renal scarring

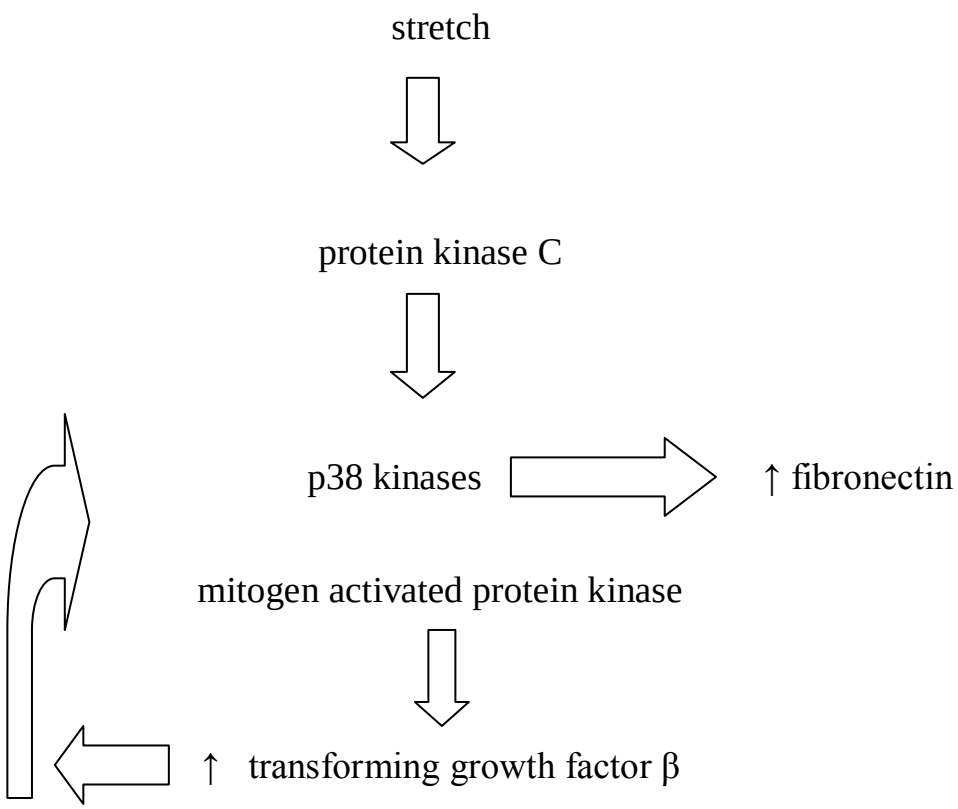
INFLAMMATORY MEDIATORS:

Molecular mediators such as transforming growth factor 1β,connective tissue growth factor, growth hormone and insulin like growth factor, vascular endothelial growth factor and angiotension 2 plays an important role in the pathogenesis of diabetic nephropathy

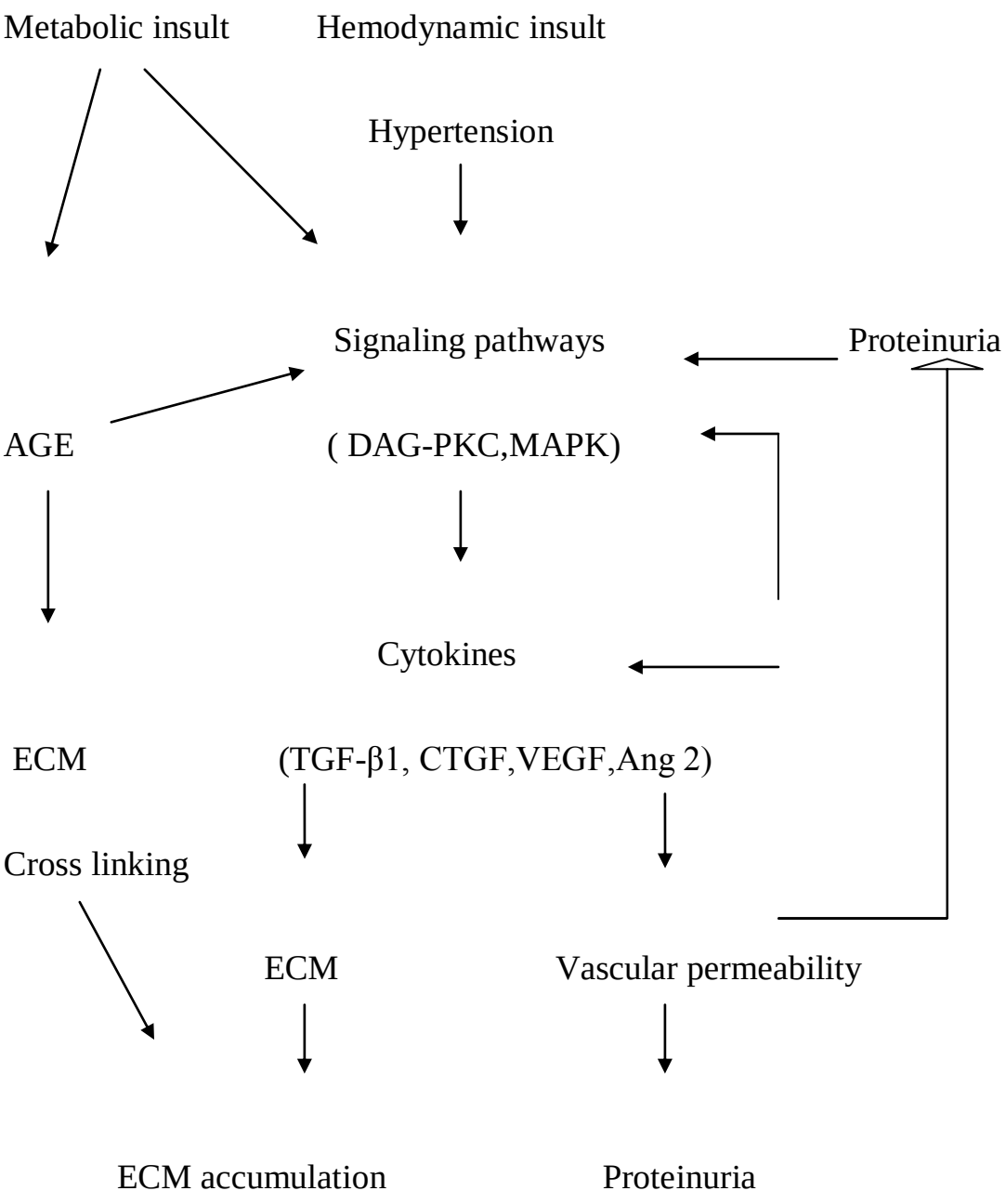
TRANSCRIPTION FACTORS AND INTRCELLULAR SIGNALLING PATHWAYS:

Transcription factors such as nuclear factor-k B, fos, jun and the AP 1transcription factors play a key role in the pathogenesis of diabetic nephropathy.

In diabetes diacyl glycerol levels are increased and protein kinase C is activated in variety of tissue including kidneys. Protein kinase C is a crucial downstream mediators of angiotensin 2, transforming growth factor β, vascular endothelial growth factor and cyclic stretch signaling. Thus showing that protein kinase C activation is the key intracellular target in both metabolic and hemodynamic insults. Mitogen activated protein kinases such as extracellular signal related kinases, p38 kinases and stress activated protein kinases plays an important role[47].



This is the schematic representation of stretch induced activation of protein kinase C and p38 kinase plays an important role in the production of fibronectin and transforming growth factor β.



This is the schematic representation of the interaction at the cellular and intracellular level in diabetic nephropathy.

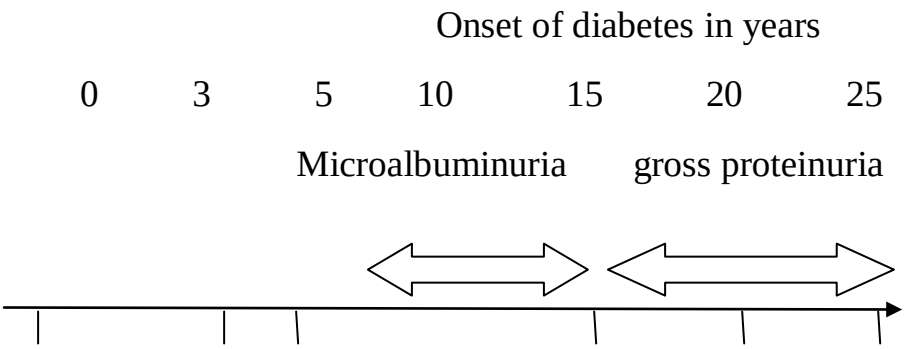
NATURAL HISTORYAND CLINICAL MANIFESTATION OF DIABETIC NEPHROPATHY:

It takes years to develop kidney disease in diabetic patients. In type 1 Diabetics it takes about 5 to15 years to develop diabetic nephropathy .In type 2 diabetics nephropathy can be present at the time of diagnosis, because most patients are asymptomatic or have only mild symptoms for quite long time before the diagnosis is made. Therefore the screening for diabetic nephropathy should be done at the time of diagnosis in type 2 diabetes and 5 years after the diagnosis in type 1 diabetes.

The earliest manifestation of diabetic nephropathy is the presence of albumin in Urine[48] .Microalbuminuria is the excretion of 30 to 299mg of albumin in 24 hours urine. Microalbuminuria has also been called as incipient nephropathy or early diabetic nephropathy. Macroalbuminuria is the excretion of more than 300mg of albumin in 24 hour urine.One year after the onset of diabetes there will be glomerular hyperperfusion and renal hypertrophy, which is associated with an increase in the GFR. GFR returns to normal during the first 5 years and the pathological changes include glomerular hypertrophy, thickening of glomerular basement membrane and mesangial volume expansion. In type 1 diabetes after 5 to 10 years 40% will have microalbuminuria and only 50% will progress to macroalbuminuria. Once microalbuminuria sets in, there is steady decline

in glomerular filtration rate and about 50% will reach end stage renal disease in the next 7to 10 years[17].When microalbuminuria develops the pathological changes are irreversible and the blood pressure rises. In type 2 diabetics microalbuminuria or macroalbuminuria may be present at the time of diagnosis and hypertension more commonly accompanies micro or macroalbuminuria and microalbuminuria may be less predictive of diabetic nephropathy. Most of the time diabetic nephropathy correlates well with diabetic retinopathy.

Onset of diabetes in years



GFR ml/min	120	150	150	120	60	10<
Serumcreatinine Mg/dl	1.0	0.8	0.8	1.0	2.0	>5

This picture shows the time course of development of diabetic nephropathy.The relationship of time from onset of diabetes, glomerular filtration rate and serum creatinine are shown in the figure.

Creatinine clearance should be estimated in all patients with nephropathy to accurately assess the renal function.

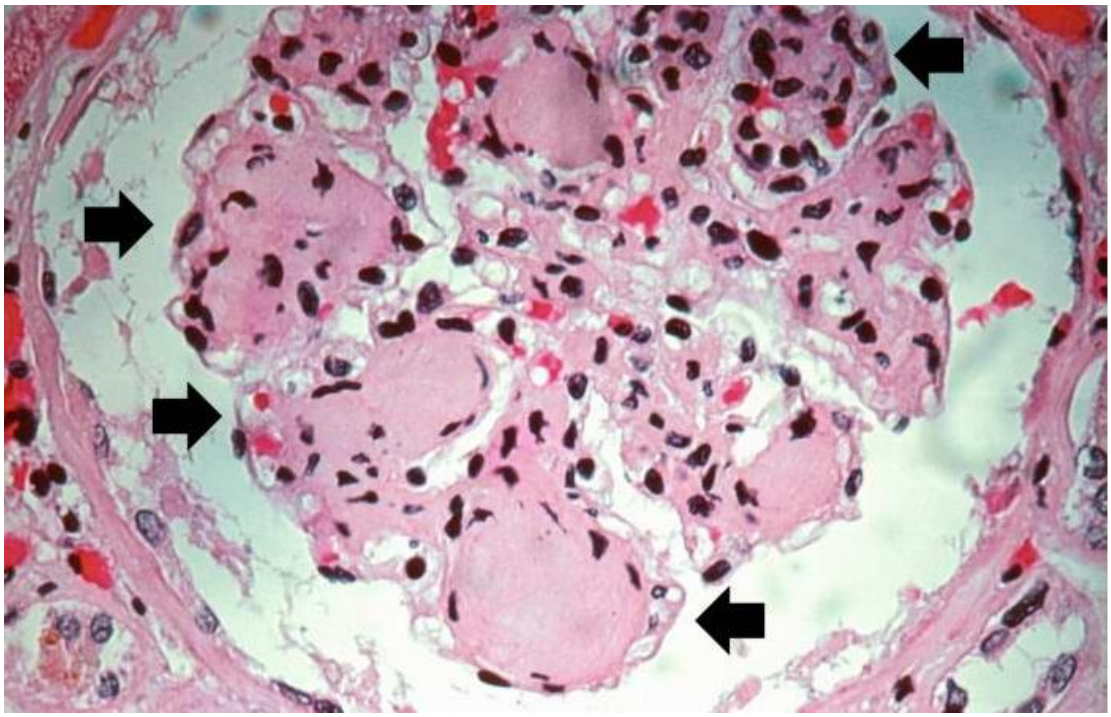
STAGES OF DIABETIC NEPHROPATHY:

1. Stage of hyperfunction and hypertrophy
2. Silent stage – which is characterized by normal blood pressure and normal urine albumin excretion. Structural lesions such as increased thickening of glomerular basement membrane and mesangial expansion can be present.
3. Stage of incipient diabetic nephropathy – characterized by persistent microalbuminuria and hypertension.
4. Stage of overt diabetic nephropathy – characterized by proteinuria,hypertension and fall in glomerular filtration rate.
5. Stage of end stage renal disease – characterized by uremia and very low glomerular filtration rate.

GLOMERULAR LESIONS:

- Glomerular capillary basement membrane thickening
- Diffuse mesangial sclerosis
- Nodular glomerular sclerosis - this is also known as intercapillary glomerular sclerosis or kimmelstiel –wilson disease. This is the characteristic histological finding in diabetic nephropathy.

This is the microscopic picture of nodular glomerular sclerosis- shown by arrow marks.



Kimmelstiel Wilson lesion

MAGNESIUM:

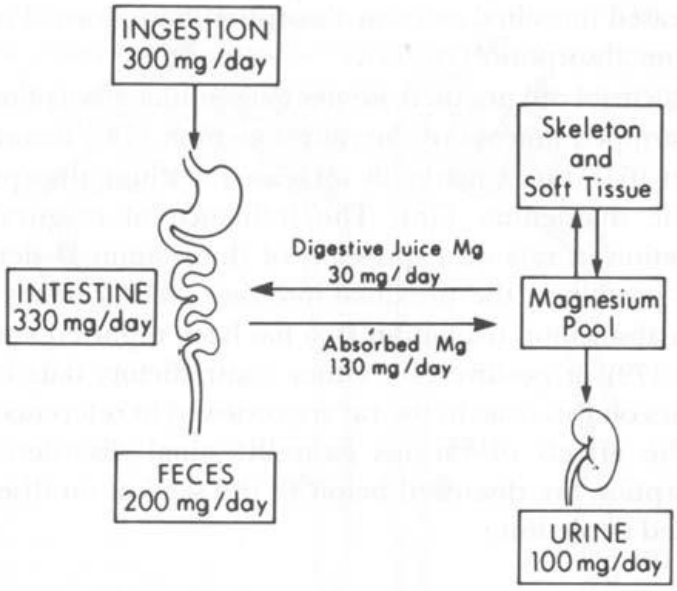
Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation next only to potassium[1].Normal adult human body contains 21 to 28 grams of magnesium which is approximately equal to 2000meq. 53% of total body magnesium is located in the bone and 27%is located in the muscle,19% in soft tissue and 1% is located in the extracellular fluid[3]. Most of the intracellular magnesium occurs in bound form and only 0.25 to 1mmol occurs as free magnesium[49].

Serum concentration of magnesium ranges from 0.7 to 1mmol/l or 1.7to 2.4mg/dl. The plasma concentration in healthy adults remain constant[50].The average daily intake of magnesium is about 140 to 360mg/day(25meq/day).Around 40% of dietary magnesium is absorbed in the small intestine particularly in the ileum. Elimination of magnesium occurs through the kidney and is about 100mg/day. The threshold for urinary excretion is the upper limit of normal range. When the serum magnesium level raise above the upper limit, excretion also increases to maintain the constant serum level. The main site for reabsorption of magnesium in the kidney is the thick ascending limb of loop of henle and in conditions of magnesium depletion, kidney has a strong capacity to reabsorb magnesium. Factors which impair renal reabsorption are volume

expansion, hypercalcemia and administration of diuretics such as thiazide, osmotic or loop diuretics. Magnesium acts as a cofactor in more than 300 enzymatic reaction involving protein and nucleic acid synthesis and energy metabolism. The active form of the element is the free ionized magnesium.

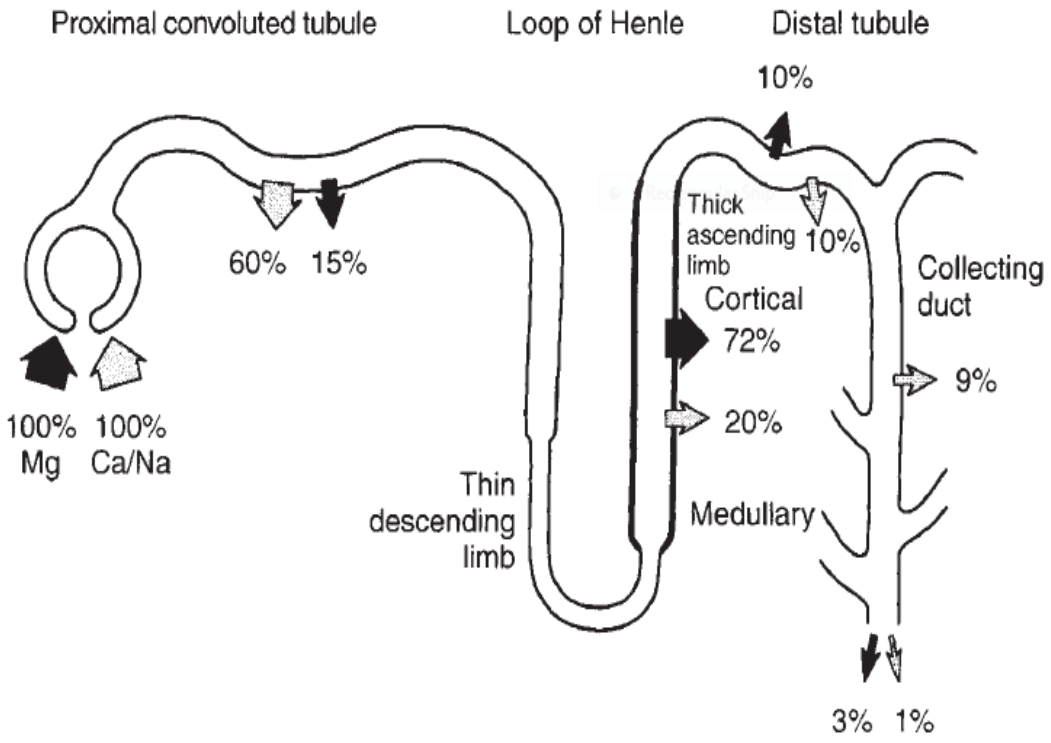
REGULATION OF MAGNESIUM:

Magnesium is absorbed from the gastrointestinal tract and excreted mainly by the kidneys. But a smaller amount is also excreted through the gastrointestinal secretion and a negligible amount through sweat and menstrual losses. The important sites of magnesium absorption are distal small intestine and colon[51]. Studies have shown that there is a direct correlation between magnesium absorption and dietary or luminal magnesium load. Absorption occurs through paracellular and transcellular pathway. Magnesium is re excreted into the intestine by bile ,pancreatic and other intestinal excretion and cell sloughing[52].The fractional absorption of ingested magnesium depends on the amount of magnesium in the food and the presence of enhancing or inhibiting substances in the food and the magnesium hemostasis[53].



Renal Excretion:

The kidney is the main organ that regulates magnesium homeostasis. Around 80% of the magnesium is filtered through the glomerulus. The important sites of magnesium reabsorption are the thick ascending limb of loop of henle(70-80%) ,the proximal tubule(5-15%),and the distal convoluted tubule (5-10%). 3% of filtered magnesium appears in the urine[54].The mechanism by which magnesium gets reabsorbed is mainly by paracellular pathway in the loop of henle and transcellular pathway in the proximal and distal tubules .Studies have shown that magnesium absorption increases in magnesium deficiency.



This is the schematic representation showing the renal handling of magnesium. Certain hormones play an important role in magnesium homeostasis. Hormones which **increase serum magnesium level are**[55]

- Parathyroid hormone
- Glucagon
- 1,25 dihydroxy cholecalciferol

Hormones which decreases serum magnesium level are,

- Aldosterone
- Vasopressin
- Calcitonin
- Thyroxine

FOOD SOURCES OF MAGNESIUM[61]

(Magnesium content in mg/100gm)

Legumes

- Split beans- 50
- Soyabean – 86

Nuts

- Peanuts -175
- Almonds -315
- Cashews -260

Dairy products

- Milk -24
- Butter -20
- Yoghurt -12

Fruits

- Dates -35
- Banana -30
- Oranges -10
- Apple -5

Cereals

- Shredded wheat – 110
- Rice -40

Meat and fish

- Pork -22
- Chicken -21
- Beef - 18
- Fish -22

Recommended dietary allowances of magnesium as developed by Food and Drug Administration[56]:

AGE	MALE	FEMALE	PREGNANCY	LACTATION
1 – 3	80	80	NA	NA
4 – 8	130	130	NA	NA
9 – 13	240	240	NA	NA
14 -18	410	360	400	360
19 - 30	400	310	350	310
31+	420	320	360	320

Magnesium values in mg/day.

BIOCHEMICAL IMPORTANCE OF MAGNESIUM:

Magnesium is an activator of our enzyme system which are particularly involved in cellular metabolism. Important enzymes are one which hydrolyze and transfer phosphate groups ,especially the reaction involving adenosine phosphate. As adenosine tri phosphate is required for fat, protein , glucose utilization ,nucleic acid and coenzyme synthesis ,muscle contraction and other reactions, by inference magnesium has an active role in the above reactions.

Magnesium is required as a cofactor in oxidative phosphorylation, which occurs in the mitochondria. The highly ordered organization of DNA, RNA and ribosome is stabilized by the presence of magnesium. Magnesium is involved in protein synthesis[58]. It helps in binding of the messenger RNA to the 70s ribosome.

The second messenger cyclic adenosine monophosphate is involved in many reaction including secretion of hormones such as parathyroid hormone. Cyclic adenosine monophosphate is formed from magnesium adenosine triphosphate and the enzyme adenylate cyclase, which is activated by magnesium by its two binding sites[57].Magnesium is also involved in membrane stabilization , ion transport and calcium channel activity[60].As magnesium takes part in many cellular activities ,it plays an important role in control of neuronal activity, cardiac excitability, muscle contraction, neuromuscular transmission, vasomotor tone , blood pressure and peripheral blood flow[59].

Causes of hypomagnesemia[62]:

- Impaired intestinal absorption
  - ✓ Primary infantile hypomagnesemia
  - ✓ Malabsorption syndrome
  - ✓ Vitamin D deficiency

- Increased intestinal loss
  - ✓ Intestinal drainage, fistula
  - ✓ Protracted vomiting, diarrhea
- Impaired renal tubular absorption

- Genetic magnesium wasting syndrome
  - ✓ Bartter syndrome
  - ✓ Gitelman syndrome
  - ✓ Na K ATP ase g-subunit mutation
- Acquired renal disease
  - ✓ Tubulointerstitial disease
  - ✓ Renal transplantation
  - ✓ Post obstruction/Acute tubular necrosis (diuretic phase)
- Drugs
  - ✓ Ethanol
  - ✓ Diuretics(osmotic, loop and thiazide)
  - ✓ Cisplatin, Cyclosporin
  - ✓ Aminoglycosides, Amphotericin B
- Metabolic causes
  - ✓ Diabetes mellitus
  - ✓ Metabolic acidosis
  - ✓ Hyperaldosteronisim

- ✓ Syndrome of inappropriate ADH secretion
- ✓ Hypercalcemia
- ✓ Hyperthyroidism

- Others
  - ✓ Pancreatitis
  - ✓ Excessive sweating
  - ✓ Osteoblastic metastasis

Clinical features of hypomagnesemia

Patient may present with non specific symptoms. Symptoms include weakness, muscle cramps, vertigo, ataxia, depression, seizure and altered mental status. Symptoms and signs occur only when serum magnesium concentration is less than 1.2mg/dl.

SIGNS[63]:

- ➢ Muscle cramps
- ➢ Hyperactive deep tendon reflexes
- ➢ Trousseau and chovstek sign
- ➢ Dysphagia due to esophageal dysmotility
- ➢ Irritability /disorientation
- ➢ Ataxia, nystagmus and seizure
- ➢ Tachycardia

ECG changes:

ECG changes in hypomagnesemia are non specific. Modest level of magnesium deficiency causes widening of the QRS complex and peaking of T wave. Severe magnesium deficiency causes prolongation of PR interval, progressive widening of QRS complex, flattening/inversion of T wave and U wave[64].

MAGNESIUM AND DIABETES:

Magnesium plays an important role in carbohydrate metabolism. Diabetes mellitus is one of the most common metabolic disorder associated with magnesium deficiency. The prevalence of magnesium deficiency in diabetes is around 25-39%[65].

Aetiology of hypomagnesemia in diabetes[66,67]:

- Diet tends to be low in magnesium
- Reduced intestinal absorption of magnesium
- Inceased renal magnesium loss due to glycosuria
- Insulin effect causes redistribution of magnesium from plasma to red blood cells.
- Insulin insensitivity affects magnesium transport and glucose metabolism
- Loop and thiazide diuretic use promotes magnesium loss.

A specific tubular defect has been postulated for magnesium deficiency in diabetes. The site of the defect is not yet defined. The proposed site of defect is the thick ascending limb of loop of henle or more distally. Reduced tubular magnesium absorption results in hypermagnesuria. Treatment with insulin will correct renal magnesium loss.

Role of Magnesium in Glucose homeostasis and insulin sensitivity:

In patients with diabetes magnesium deficiency have shown a negative impact on glucose homeostasis and insulin sensitivity[68]. In diabetics uptake of magnesium in erythrocytes in response to insulin is reduced. This change was associated with an increase in erythrocyte membrane microviscosity[69].Changes in the physical state of plasma membrane and insulin resistance were responsible for the lower erythrocyte magnesium level .Plasma membrane changes impair the interaction of insulin with its receptors and reduces glucose tolerance. The reduced insulin sensitivity is due to defective tyrosine kinase activity of the insulin receptor. Several enzymes are involved in glucose metabolism , which requires high energy phosphate bonds. Magnesium acts as a cofactor in these enzymatic reactions. Intracellular magnesium deficiency leads to worsening of insulin action and insulin resistance.

Thus low magnesium level contributes to insulin resistance ,which in turn reduces magnesium uptake in insulin sensitive tissues.

Magnesium and diabetic nephropathy:

Diabetic nephropathy is one of the most important micro vascular complication of diabetes. Na/K- ATPase plays an important role in the development of diabetic nephropathy. Na/K-ATP ase is involved in the maintenance of gradients of Na and K and in glucose transport. Magnesium acts as a cofactor in these reactions. Magnesium deficiency affects the activity of Na/K-ATPase. Studies have shown that the affinity of inositol transporter was increased by magnesium. Magnesium deficiency augments intracellular inositol depletion[70], which results in reduced activity of regulatory proteins and leads to diabetic nephropathy. Further more in worsening diabetic nephropathy, there is increase in vasoconstrictor prostaglandins and thromboxane A_2 [71], which leads to increase in filtration pressure and damage to the basal membrane which causes reduction in glomerular filtration rate and proteinuria. Elevated lipid levels and increase in Thromboxane A_2 synthesis plays an important role in progression of diabetic nephropathy[72].

Magnesium deficiency and other complications of diabetes:

Magnesium deficiency has also been implicated in some of the other complications of diabetes. Studies have shown that low serum magnesium was associated with severe background and proliferative diabetic retinopathy. Diabetic neuropathy and peripheral vascular disease contributes to the development of foot ulcers. Studies have shown that there is a strong association between low serum magnesium level and development of foot ulcers in diabetes[73].

Magnesium and Dyslipidemia:

Magnesium plays an important role in lipid metabolism. Dyslipidemia is strongly associated with magnesium deficiency. Magnesium modulates HMG-CoA reductase which is the rate limiting enzyme involved in cholesterol metabolism. Deficiency of magnesium is associated with decrease in HDL, inhibition of the enzyme lipoprotein lipase and elevation of triglyceride level.

Osteoporosis and Magnesium:

Deficiency of magnesium increases the risk of osteoporosis. Diabetics have reduced bone mass which is due to decreased parathormone. In diabetics reduced serum magnesium level and increase in serum ionized calcium level inhibits parathormone secretion[74].

Hypertension and Magnesium:

Magnesium is an activator of Na K- ATPase and it also acts as a calcium antagonist[75].Deficiency of magnesium causes increase in intracellular concentration of calcium and potassium which causes vasoconstriction and increase in peripheral vascular resistance. Studies have shown that there is an inverse correlation between blood pressure and serum magnesium level.

Magnesium and coronary artery disease:

Magnesium deficiency is a risk factor for coronary artery disease. Studies have shown that magnesium supplementation may have added antithrombotic effect with aspirin and improve exercise tolerance.

Magnesium and acute myocardial infarction:

Reduced magnesium is often found in acute myocardial infarction. In acute myocardial infarction , when there is mild hypomagnesemia the risk of ventricular arrhythmia in the first 24 hours is high. Studies have also shown that ventricular arrhythmias occurring in the second or third week after acute myocardial infarction is associated with low serum magnesium level[77].

Oral supplementation of magnesium:

Studies have shown that magnesium supplementation have shown to improve insulin secretion and increased insulin sensitivity[78]. Studies have also shown that magnesium supplementation may reduce platelet aggregation probably by decreasing Thromboxane A_2 level[79].Studies have also shown that magnesium supplementation has reduced low density lipoprotein and cholesterol[80]. Few studies have also shown that moderate decrease in systolic blood pressure after supplementation of magnesium[81].As magnesium deficiency has been implicated as an important reason in the development of complication of diabetes, supplementing oral magnesium can improve glycemic control and can prevent the complication of diabetes.

AIM OF THE STUDY

To study the correlation of serum magnesium in diabetic patients with proteinuria.

MATERIALS AND METHODS

This is an observational study, done at Government Royapettah Hospital in the department of Medicine. The study protocol was approved by the Ethical committee for research studies of Government Kilpauk Medical College and Hospital, Chennai.

The study period was between July 2012 – December 2012.The patients recruited in the study were patients admitted in the general medical ward for control of diabetes and patients attending diabetology department as outpatients in Government Royapettah Hospital.

INCLUSION CRITERIA

- Patients with Type 2 Diabetes
- Type 1 Diabetes > 5yrs duration

EXCLUSION CRITERIA

- Systemic Hypertention
- Congestive cardiac failure
- Urinary tract infection
- Severe diarrhea
- Alcoholics
- Ketoacidosis

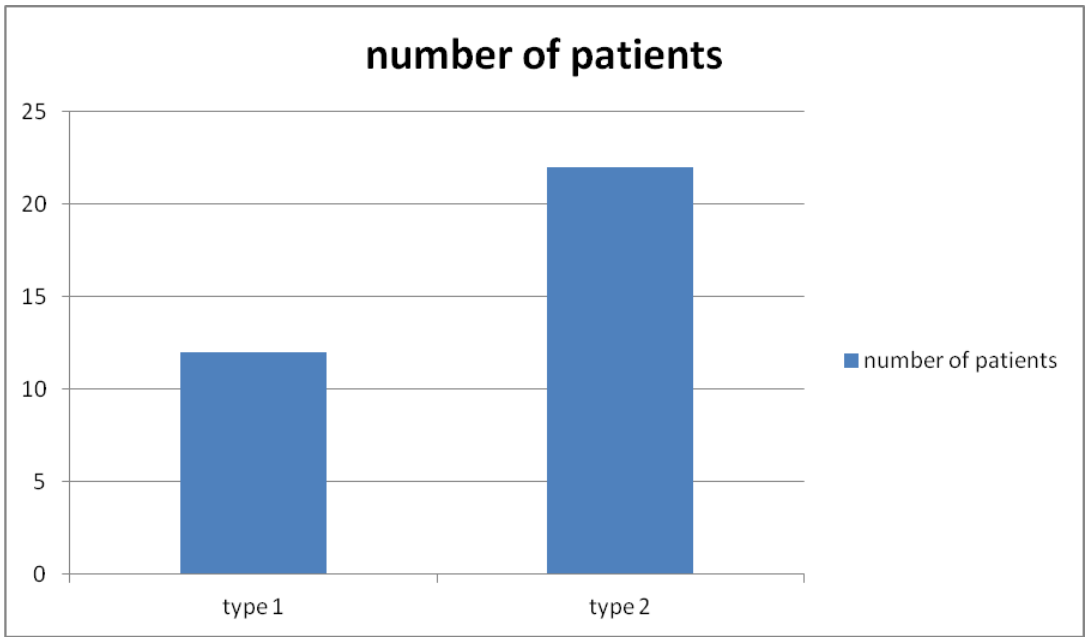
- Total parentral nutrition
- Drugs causing hypomagnesemia

Detailed clinical profile of each patient was noted and 24hrs urine protein was estimated, 2 – 5ml of blood was drawn from the patient. Blood was allowed to clot and serum was separated by centrifugation and serum magnesium was estimated by calorimetric method. Similarly blood was drawn to estimate blood sugar, lipid profile, HbA1c and serum creatinine.

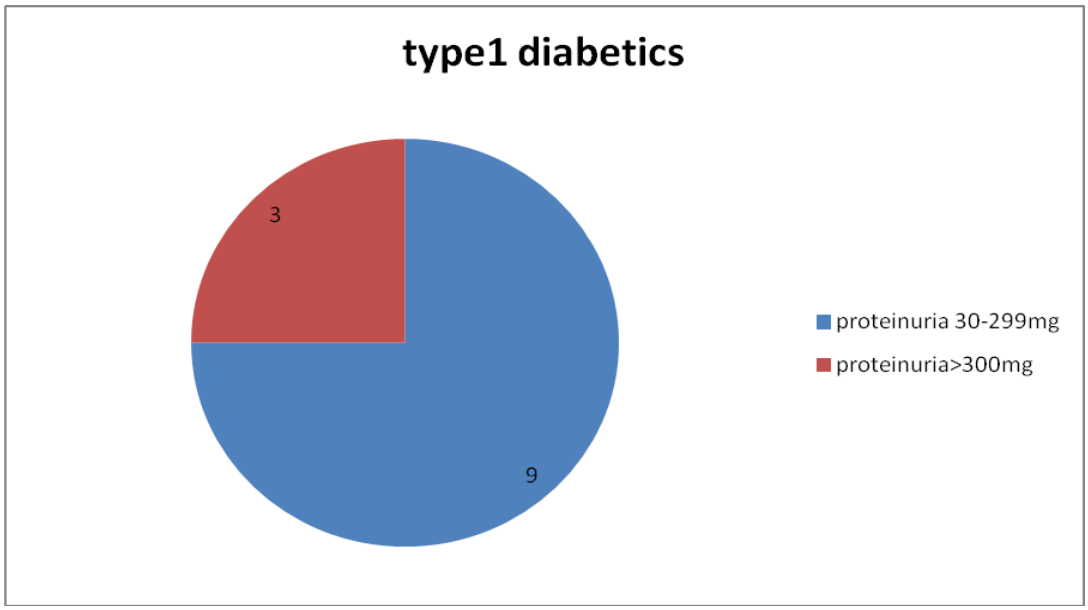
Statistical analysis was done to identify the significance of correlation between serum magnesium and proteinuria. Statistical analysis was done using Statistics Products Services Solution (SPSS) 15.Other variables used in the study were also correlated with serum magnesium.

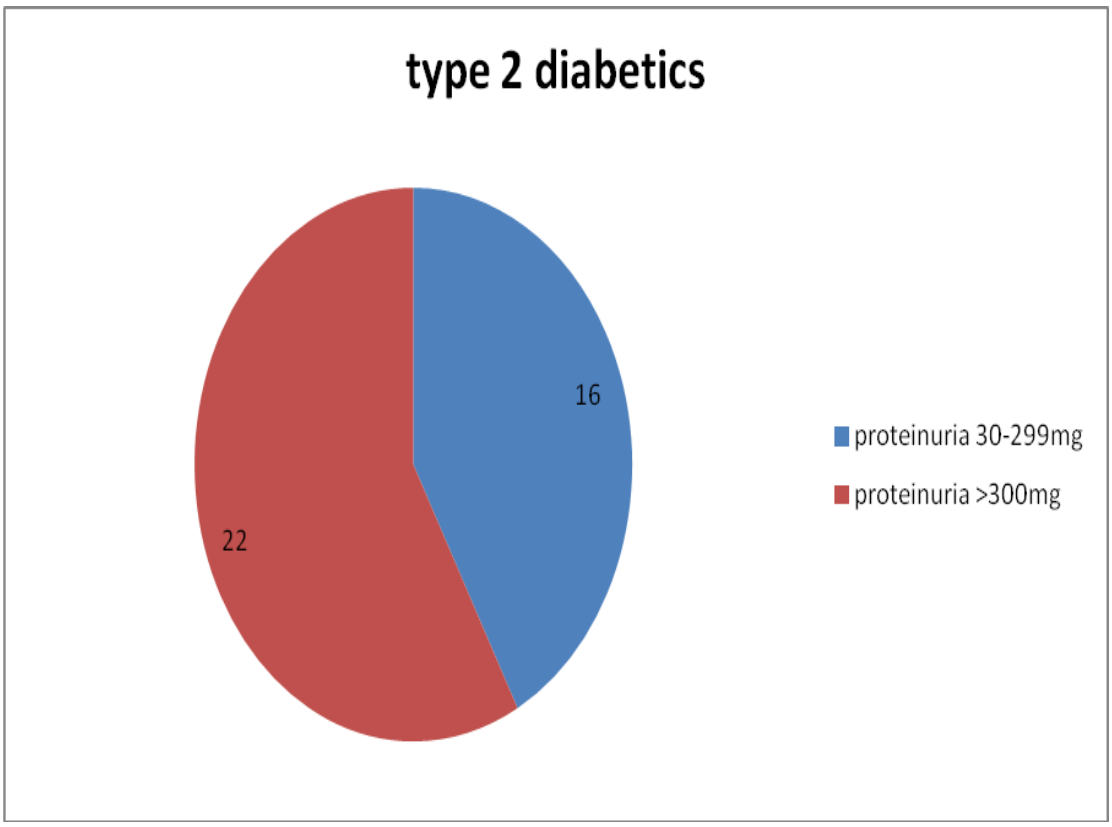
OBSERVATIONS AND RESULTS

Total numbers of patients included in the study were 50.Out of which 12 patients were type 1 diabetics and 38 were type 2 diabetics.



In type 1 diabetics 3 patients had macroalbuminuria and 9 patients had microalbuminuria.





In type 2 diabetics out of 38 patients 22 had macroalbuminuria and 16 had microalbuminuria.

VARIABLES ANALYSED

	N	Range	Minimum	Maximum	Mean	Std. Deviation
DURATION OF DIABETES	50	15	7	22	13.20	4.271
FASTING BLOOD SUGAR	50	164	125	289	184.74	34.723
POST PRANDIAL SUGAR	50	168	174	342	250.68	43.679
HbA1c	50	3.0	6.8	9.8	7.704	.7500
HDL	50	31	28	59	43.08	9.147
LDL	50	202	74	276	153.68	51.963
TOTAL CHOLESTEROL	50	56	200	256	222.78	14.063
TRIGLYCERIDE	50	169	116	285	216.08	34.457
SERUM CREATININE	50	1.2	.7	1.9	1.150	.2697
SERUM MAGNESIUM	50	.4	1.4	1.8	1.592	.1209
age	50	55	24	79	52.80	14.988
Valid N (listwise) 24 hours urinary protein	50 50		56	1698	467.26	368.166

The mean duration of diabetes in the study is 13.20 and mean serum magnesium concentration is around is 1.592.

Duration of diabetes and serum magnesium – correlation, Fasting blood sugar and serum magnesium- correlation.

Paired Samples Statistics

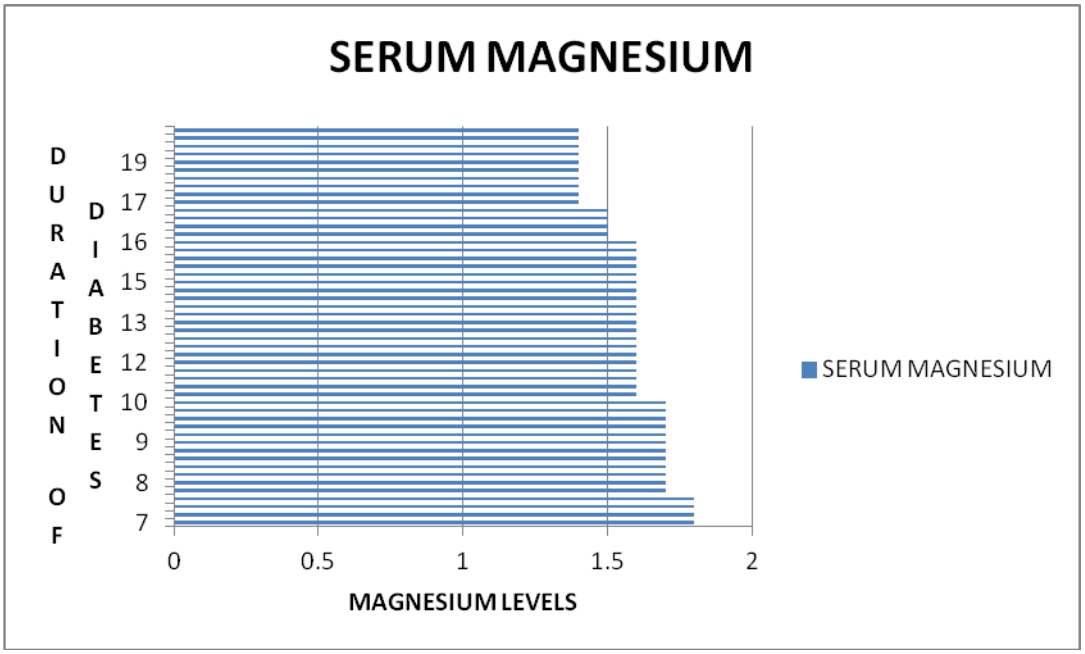
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	DURATION OF DIABETES	13.20	50	4.271	.604
	SERUM MAGNESIUM	1.592	50	.1209	.0171
Pair 2	FASTING BLOOD SUGAR	184.74	50	34.723	4.911
	SERUM MAGNESIUM	1.592	50	.1209	.0171

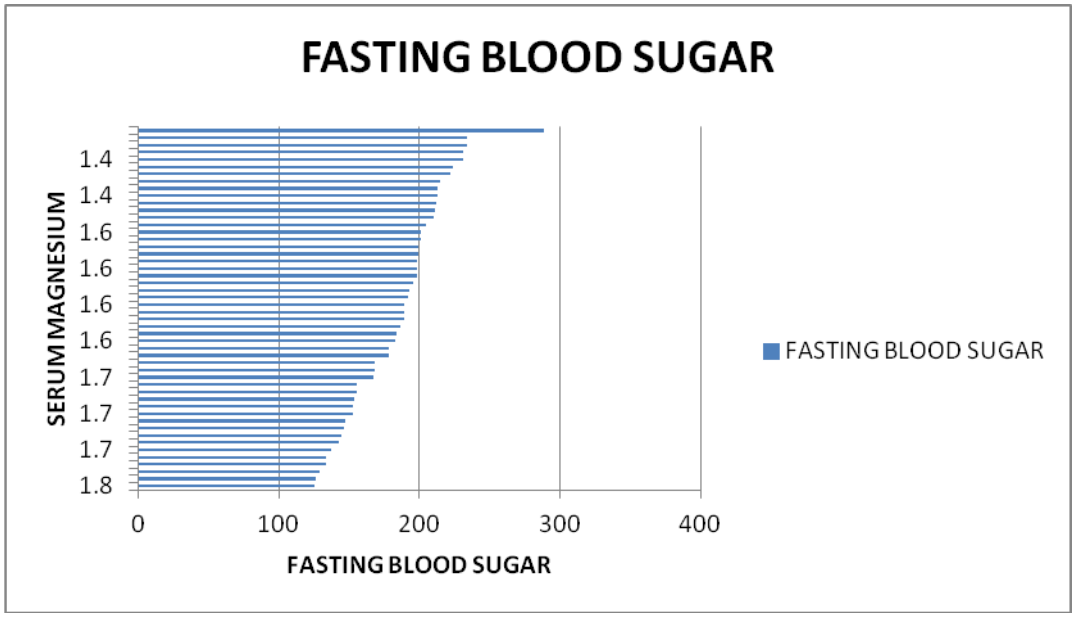
Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	DURATION OF DIABETES & SERUM MAGNESIUM	50	-.882	.000
Pair 2	FASTING BLOOD SUGAR & SERUM MAGNESIUM	50	-.720	.000

From the above observation it is clear that there is an inverse correlation between the duration of diabetes and serum magnesium and fasting blood sugar and serum magnesium level.

The chart below shows the correlation of serum magnesium levels and duration of diabetes. As the duration of diabetes increases serum magnesium level reduces.





The above chart shows the correlation of serum magnesium level with fasting blood sugar. Poor glycemic control reduces serum magnesium level.

HDL and serum magnesium – correlation. LDL and serum magnesium correlation.

Paired Samples Statistics

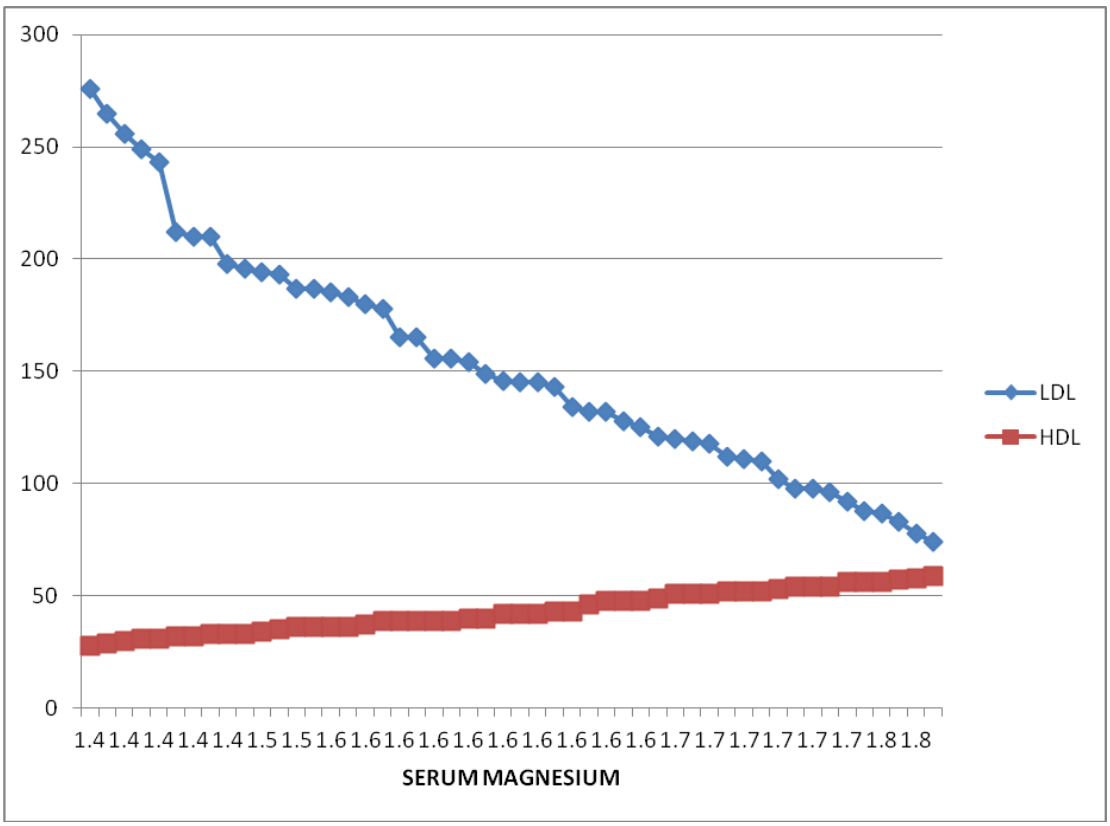
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HDL	43.08	50	9.147	1.294
	SERUM MAGNESIUM	1.592	50	.1209	.0171
Pair 2	LDL	153.68	50	51.963	7.349
	SERUM MAGNESIUM	1.592	50	.1209	.0171

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HDL & SERUM MAGNESIUM	50	.820	.000
Pair 2	LDL & SERUM MAGNESIUM	50	-.866	.000

Above table shows there is a positive correlation between serum magnesium level and HDL cholesterol and a negative correlation between serum magnesium level and LDL cholesterol.

The graph below shows that, when the LDL levels are high the serum magnesium levels are low and higher the HDL values higher the serum magnesium levels.



Total cholesterol and serum magnesium – correlation, Triglyceride and serum magnesium- correlation, 24hrs urinary protein and serum magnesium- correlation, Low density lipoprotein and serum magnesium- correlation

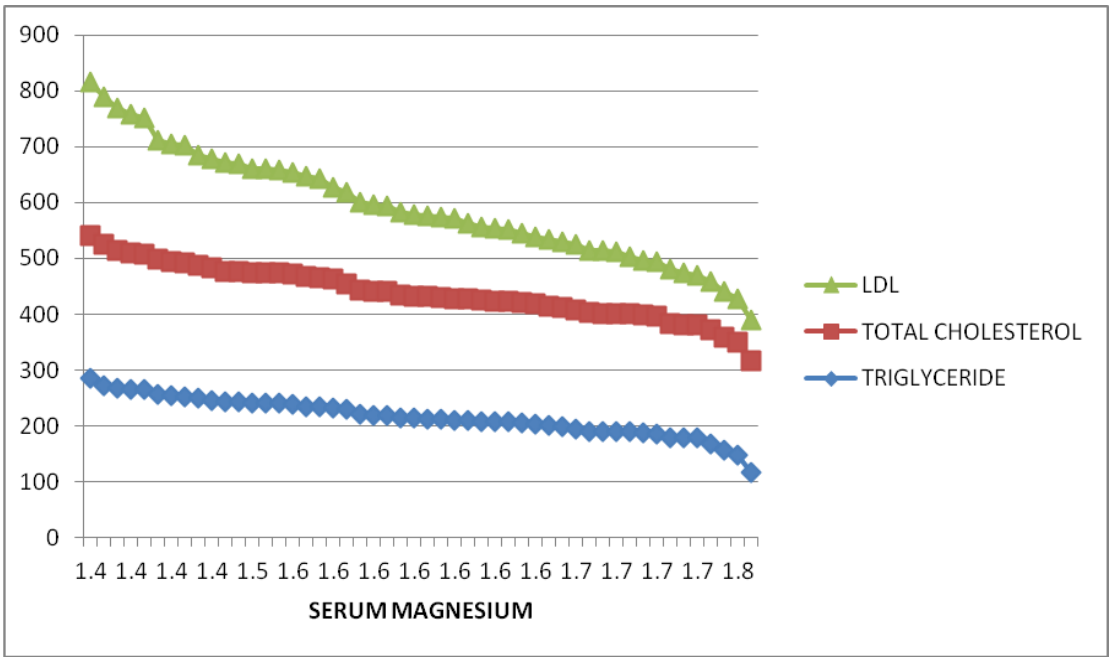
Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	TOTAL CHOLESTEROL	222.78	50	14.063	1.989
	SERUM MAGNESIUM	1.592	50	.1209	.0171
Pair 2	TRIGLYCERIDE	216.08	50	34.457	4.873
	SERUM MAGNESIUM	1.592	50	.1209	.0171
Pair 3	24 HRS URINARY PROTEIN	472.18	50	381.233	53.914
	SERUM MAGNESIUM	1.592	50	.1209	.0171
Pair 4	LDL	153.68	50	51.963	7.349
	SERUM MAGNESIUM	1.592	50	.1209	.0171

Paired Samples Correlations

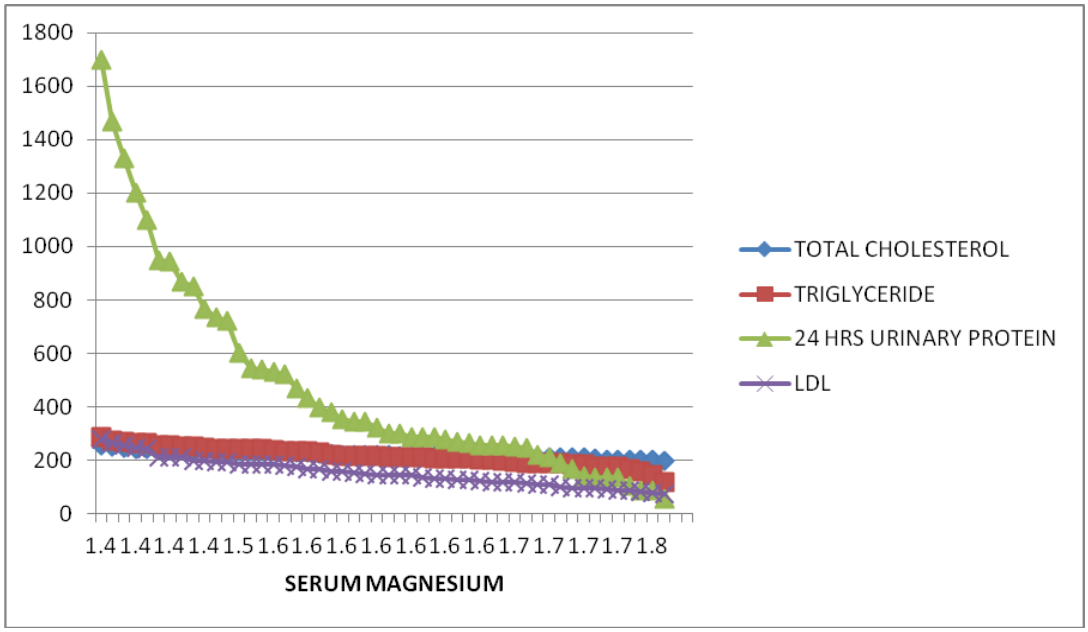
		N	Correlation	Sig.
Pair 1	TOTAL CHOLESTEROL & SERUM MAGNESIUM	50	-.621	.000
Pair 2	TRIGLYCERIDE & SERUM MAGNESIUM	50	-.847	.000
Pair 3	24 HRS URINARY PROTEIN & SERUM MAGNESIUM	50	-.869	.000
Pair 4	LDL & SERUM MAGNESIUM	50	-.866	.000

From the above observation it is clear that there is an inverse correlation between serum magnesium levels and cholesterol, triglyceride, 24hrs urinary protein and LDL levels.



The above graph shows that, when the serum cholesterol, triglyceride and LDL levels are high the serum magnesium levels are low.

The graph below shows that, the serum magnesium levels are low when there is increase in proteinuria, similarly higher the serum cholesterol, triglyceride and LDL lesser the serum magnesium level.



HbA1c and serum magnesium- correlation:

Paired Samples Statistics

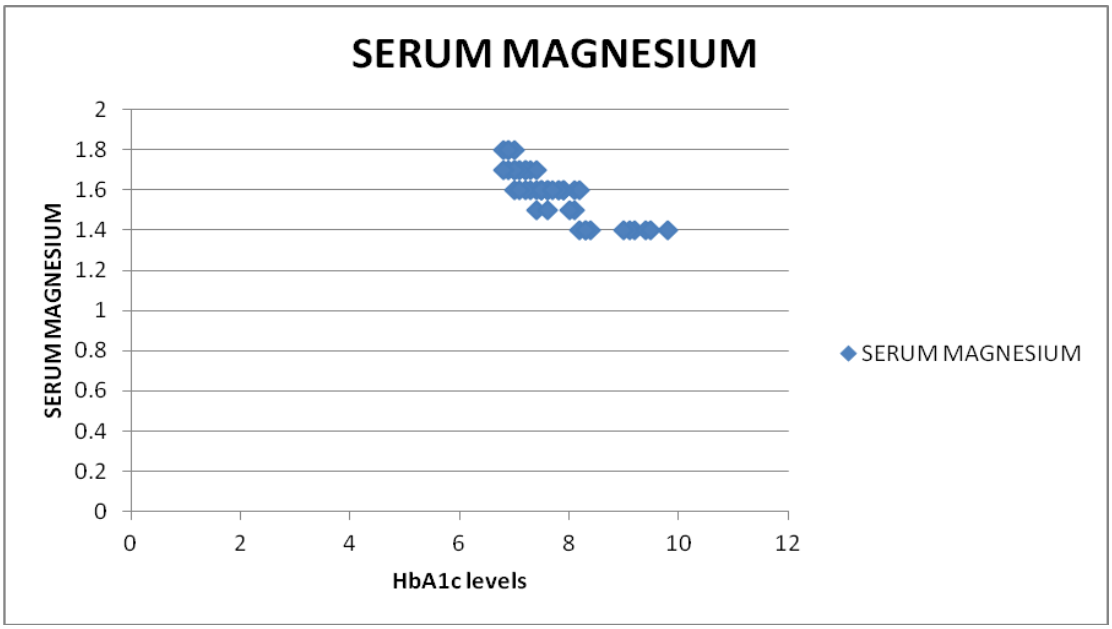
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HbA1c	7.704	50	.7500	.1061
	SERUM MAGNESIUM	1.592	50	.1209	.0171

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	HbA1c & SERUM MAGNESIUM	50	-.861	.000

The above table shows that there is an inverse correlation between serum magnesium level and HbA1c level.

The graph below shows that, as the HbA1c levels are on the higher side the serum magnesium are on the lower side.



Serum magnesium and serum creatinine- correlation:

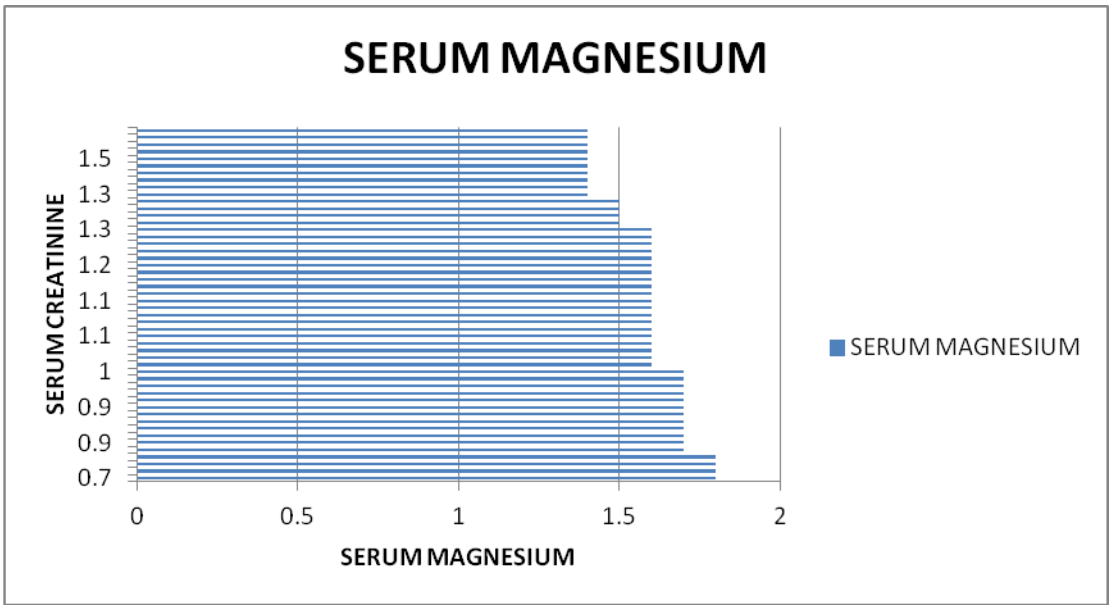
Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	SERUM CREATININE	1.150	50	.2697	.0381
	SERUM MAGNESIUM	1.592	50	.1209	.0171

Paired Samples Test

		df	Sig. (2-tailed)
Pair 1	SERUM CREATININE - SERUM MAGNESIUM	49	.000

From the above observation it is clear that there is an inverse correlation between serum magnesium and serum creatinine.



The above graph shows as the serum creatinine increases serum magnesium decreases.

Serum magnesium and 24 hrs urinary protein – correlation

Paired Samples Statistics

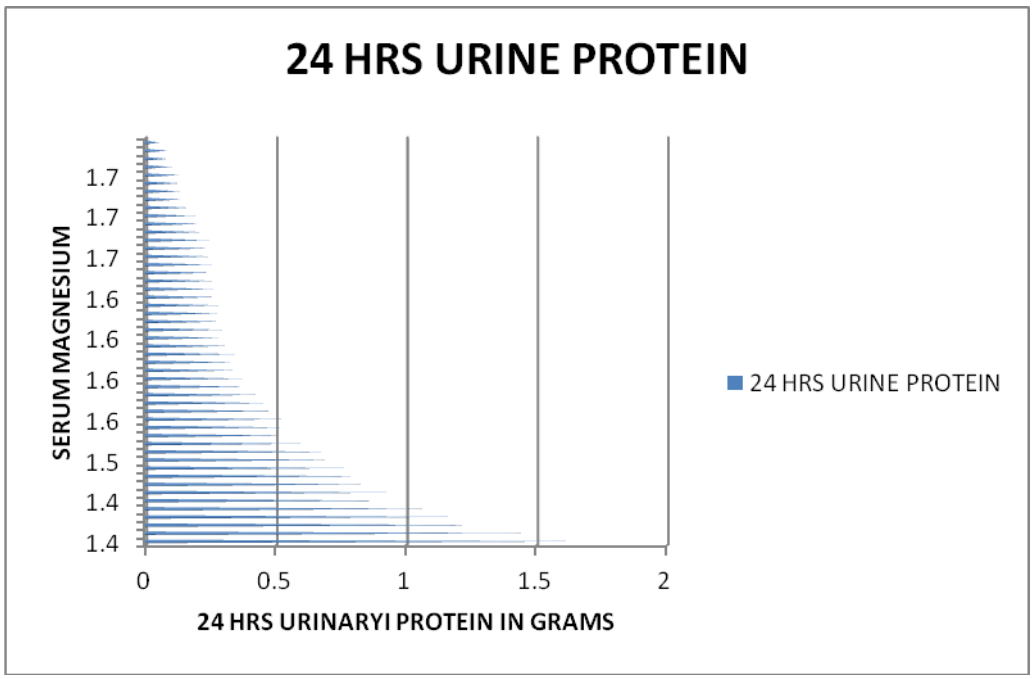
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	24 HRS URINARY PROTEIN	472.18	50	381.233	53.914
	SERUM MAGNESIUM	1.592	50	.1209	.0171

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	24 HRS URINARY PROTEIN & SERUM MAGNESIUM	50	-.869	.000

From the above table it is clear that , there is an inverse correlation between serum magnesium level and 24 hours urinary protein.

The graph below shows that, higher the proteinuria ,lesser the serum magnesium level.



Duration of diabetes and serum magnesium – correlation:

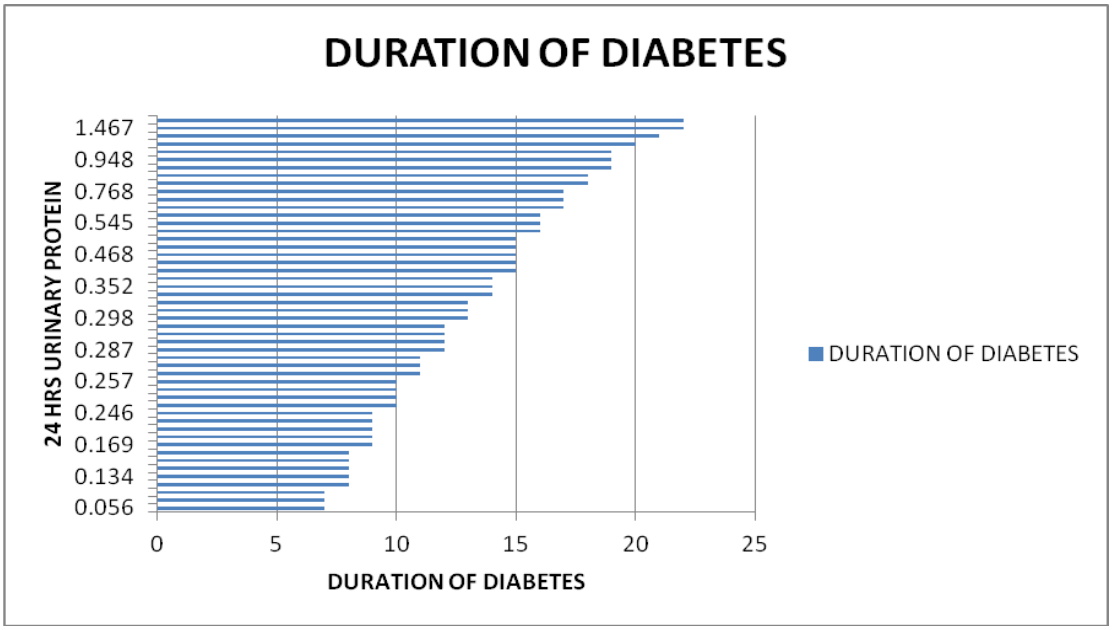
Correlations

		DURATION OF DIABETES	24 HRS URINARY PROTEIN
DURATION OF DIABETES		.000	.836**
	50	50	
	.836**	1	
24 HRS URINARY PROTEIN	.000		
	50	50	
	N		

**. Correlation is significant at the 0.01 level (2-tailed).

From the above observation it is clear that, there is a positive correlation between serum magnesium and 24 hrs urinary protein.

The graph below shows as the duration of diabetes increases, proteinuria increases. The mean duration of diabetes above which macroalbuminuria occurs is around 13years.



DISCUSSION

Our study enrolled 50 patients, out of which 12 were type 1 diabetics and 38 were type 2 diabetics. The mean duration of diabetes in our study is 13 years and mean serum magnesium level is 1.592 and mean proteinuria is 467.26

The important finding in our study was there is an inverse correlation between serum magnesium level and duration of diabetes .Similar finding was present in the study conducted by Nasri et al.

Serum levels of magnesium have been found by several investigators to correlate inversely with fasting blood sugar and HbA1c levels. Schlineger et al studied the significance of glycemic control on various trace elements and reported significantly reduced magnesium level in patients with poor control of diabetes. Our study shows a significant inverse correlation of serum magnesium and fasting blood sugar and HbA1c levels.

Hypomagnesemia is reported to be both the cause and result of poor glycemic control. Magnesium acts as a cofactor in both glucose transporting mechanism of cell membrane and enzymes involved in carbohydrate metabolism. Magnesium deficiency has been shown to promote insulin resistance in several studies. Several studies have shown

that daily oral magnesium supplementation improved insulin sensitivity by 10% and reduces blood sugar by 37%.

Several studies have shown that there is an inverse correlation of serum magnesium and cholesterol, triglyceride and low density lipoprotein. The present study also showed there is an inverse correlation between serum magnesium and cholesterol, triglyceride and low density lipoprotein level. The present study showed a positive correlation between serum magnesium and high density lipoprotein level.

Corsonello et al demonstrated significant low serum magnesium level in diabetic patients with micro or macroalbuminuria. Studies have also shown that there is a rapid decline in renal function which is associated with lower serum magnesium. It also shows that worse proteinuria was observed among patients belonging to lowest magnesium groups. The present study also shows there is an inverse correlation between serum magnesium level and serum creatinine. It also shows more proteinuria in patients with low serum magnesium and worsening serum creatinine. The present study also shows, proteinuria increases as the duration of diabetes increases and serum magnesium level decreases as the duration of diabetes increases.

Hyperglycemia enhances non enzymatic glycation of proteins. Glycated proteins transform into advanced glycated end products. These advanced glycated end products gets accumulated in the glomerulus and tubules and these products causes mesangial expansion, thickening of glomerular basement membrane and proteinuria. Proteinuria is an independent predictor of rapid decline in renal function. Proteinuria leads to excessive deposition of protein in tubuloepithelial cells, which causes release of inflammatory cytokines and finally leads to renal scarring and renal failure. Poor glycemic control and altered lipid metabolism are associated with increase in urine albumin excretion rate.

Several studies have shown that supplementing oral magnesium in diabetic patients can improve glycemic control, beneficial effect on lipid profile ,proteinuria and improvement in renal function. Diabetic nephropathy is one of the most common cause for end stage renal disease. Most common cause of death in diabetic nephropathy is cardiovascular event. By supplementing oral magnesium in diabetic patients can prevent diabetic nephropathy and reduce morbidity and mortality due to diabetes and its complications.

LIMITATIONS OF THE STUDY

- The sample size which we took in our study is only 50.Further studies need to be conducted in large population to study the correlation.
- Estimated glomerular filtration rate is usually used to assess renal function,but in our study we took only serum creatinine

CONCLUSION

- Our study has shown a negative correlation between serum magnesium level and proteinuria.
- There was a significant inverse correlation between serum magnesium and duration of diabetes.
- High Density Lipoprotein shows a positive correlation with serum magnesium.
- Serum cholesterol, triglyceride and Low Density Lipoprotein show a negative correlation with serum magnesium.
- Serum magnesium levels are low in patients with high fasting blood sugar and high HbA1C levels.
- Serum creatinine showed a negative correlation with serum magnesium.
- As the duration of diabetes increases, proteinuria also increases.

FUTURE TRENDS:

- As the deficiency of magnesium has been implicated in a number of important complications of diabetes, the study implies that the serum magnesium level should be checked in every patients with diabetes.
- Supplementing oral magnesium in diabetic patients, improves glycemic control and can prevent complications related to diabetes.

DISCLOSURE

The investigator had not received any form of support or grant from any institution or pharmaceutical company.

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ABBREVATIONS

IDF	-	International Diabetes Federation
CURES	-	Chennai Urban Epidemiology Study
DM	-	Diabetes Mellitus
ATP	-	Adenosine Tri Phosphate
DAG	-	Di Acyl Glycerol
PKC	-	Protein Kinase C
VEGF	-	Vascular Endothelial Growth Factors
ET	-	Endothelin
ROS	-	Reactive Oxygen Species
AGE	-	Advanced Glycation End Products
TGF β	-	Transforming Growth Factor β
CTGF	-	Connective Tissue Growth Factor
ECM	-	Extra Cellular Matrix
GFR	-	Glomerular Filtration Rate

PROFORMA

NAME:

AGE:

SEX:

OCCUPATION:

ADDRESS:

HISTORY:

- DURATION OF DIABETES,SYMPTOMS RELATED TO CARDIAC FAILURE,SYMPTOMS RELATED TO URINARY TRACT INFECTION.

PAST HISTORY:

- DIABETES MELLITUS , SYSTEMIC HYPERTENSION, CHRONIC DIARRHOEA,SEIZURES

PERSONAL HISTORY:

ALCOHOL- DURATION, AMOUNT,FREQUENCY.

DRUG HISTORY

- MAGNESIUM SUPPLEMENTATION
- ANTI DIABETIC , ANTI HYPERTENSIVE MEDICATIONS , CARDIAC DRUGS (DIURETICS)
- DRUGS AFFECTING SERUM MAGNESIUM LEVELS

O/E:

- **GENERAL EXAMINATION**
- **VITAL SIGNS - PULSE RATE, BLOOD PRESSURE, RESPIRATORY RATE**
- **SYSTEMIC EXAMINATION - CVS , RS , ABDOMEN , CNS**

INVESTIGATIONS

- **BLOOD SUGAR – FBS, PPBS**
- **LIPID PROFILE**
- **RENAL FUNCTION TESTS**
- **URINE EXAMINATION for 24 hrs urinary protein.**
- **SERUM MAGNESIUM**
- **HbA1c**

Sl. No.	name	age	sex	TYPE OF DIABETES	DURATION OF DIABETES	FASTING BLOOD SUGAR	POST PRANDIAL SUGAR	HbA 1c	HDL	LDL	TOTAL CHOLESTEROL	TRIGLYCERIDE	24 HRS URINARY PROTEIN	SERUM CREATININE	SERUM MAGNESIUM
1	muthkumar	56	male	type 2	18	224	338	8.3	32	196	220	221	600mg	1.2	1.4
2	palanivel	62	male	type 2	16	168	267	8.1	35	180	253	218	545mg	1.3	1.5
3	raj kumar	66	male	type 2	13	212	287	7.9	36	193	239	215	352mg	1.3	1.6
4	maariappan	65	male	type 2	15	187	292	8.1	33	178	223	246	380mg	1.1	1.6
5	kadar basha	59	male	type 2	14	193	256	7.8	32	185	236	239	322mg	1.2	1.6
6	mohammed ismail	71	male	type 2	19	231	298	8.4	33	194	234	251	850mg	1.4	1.4
7	kuppan	69	male	type 2	17	234	286	8	34	187	222	241	720mg	1.3	1.5
8	rajadurai	56	male	type 2	12	153	223	7.6	56	156	211	210	250mg	1.1	1.6
9	selvam	49	male	type 2	9	147	210	7.3	52	143	213	204	212mg	1	1.7
10	yasar rahim	79	male	type 2	22	213	276	8.2	37	212	240	254	1200mg	1.5	1.4
11	muthumari	65	male	type 2	19	289	312	8.3	39	210	232	266	948mg	1.3	1.4
12	bharathiar	49	male	type 2	8	154	195	7.2	57	112	212	189	134mg	0.9	1.7
13	aacharia	63	male	type 2	15	199	238	7.9	40	183	233	243	435mg	1.1	1.6
14	nagendran	54	male	type 2	10	210	256	7.5	46	149	215	208	298mg	1.2	1.6
15	selvaraj	64	male	type 2	14	196	234	7.5	36	165	204	230	521mg	1.1	1.6
16	abdullah	49	male	type 2	7	184	209	7	54	110	202	190	140mg	1.3	1.7
17	majeeth	48	male	type 2	13	211	245	7.6	36	154	231	241	530mg	1.1	1.6
18	narayanan	52	male	type 2	8	153	231	7.1	48	145	222	189	278mg	1	1.7
19	kalaiarasi	57	female	type 2	9	146	189	7	56	119	218	190	257mg	0.9	1.6
20	grace	50	female	type 2	11	178	256	7.4	42	156	213	212	346mg	0.9	1.6
21	vasanthi	48	female	type 2	7	198	247	7	54	111	217	178	256mg	1.4	1.7
22	lalitha bai	69	female	type 2	16	213	265	7.4	36	187	232	235	736mg	1.3	1.5
23	kamala	70	female	type 2	21	234	297	9.2	31	256	212	243	1100mg	1.4	1.4
24	mahaboobe e	71	female	type 2	19	199	301	9.1	30	265	234	265	1328mg	1.2	1.4
25	latha	40	female	type 2	8	125	204	7.3	51	121	233	201	287mg	1.1	1.6
26	prema	55	female	type 2	12	189	238	7.5	42	145	224	232	265mg	1.8	1.6
27	mary	62	female	type 2	15	192	287	7.6	39	165	218	241	768mg	1.6	1.5
28	kamala	60	female	type 2	18	201	318	9	33	198	237	253	867mg	1.5	1.4

29	varalakshmi	66	Female	type 2	9	183	245	7.2	54	118	218	195	298mg	1.1	1.7
30	mariamma	76	Female	type 2	17	222	312	9.4	31	243	245	272	1467mg	1.7	1.4
31	sumathi	56	Female	type 2	10	134	298	8.2	39	210	231	214	345mg	1.3	1.6
32	biju bee	49	Female	type 2	8	156	212	6.9	56	98	204	168	189mg	0.9	1.8
33	saroja	48	Female	type 2	7	137	196	7	58	96	219	156	104mg	0.8	1.8
34	anjalai	55	Female	type 2	11	201	287	7.6	42	132	233	218	289mg	1.1	1.6
35	kurshid bee	79	Female	type 2	22	231	313	9.8	28	276	256	285	1698mg	1.9	1.4
36	rahmat nisha	71	Female	type 2	20	215	342	9.5	29	249	243	268	946mg	1.3	1.4
37	shanti	54	Female	type 2	9	189	232	7.2	52	125	215	178	169mg	1	1.7
38	noor nisha	50	Female	type 2	8	134	203	7.1	48	83	203	208	220mg	0.9	1.7
39	kalaiselvi	26	Female	type 1	11	129	189	6.9	53	78	219	187	134mg	0.9	1.7
40	srinivasan28	28	Male	type 1	9	143	174	6.8	59	74	212	178	86mg	0.7	1.8
41	kudubasha	32	Male	type 1	12	126	217	7	51	92	206	147	56mg	0.9	1.7
42	muthulakshmi	35	Female	type 1	15	168	247	7.2	43	134	243	205	540mg	1.1	1.6
43	selvaraj	29	Male	type 1	10	156	187	7.4	52	87	212	186	136mg	0.8	1.7
44	bharathi	29	Female	type 1	13	198	206	7.5	48	98	215	208	267mg	1	1.6
45	sumathi	38	Female	type 1	17	205	287	7.9	40	132	243	256	468mg	1.2	1.6
46	vijaya	41	Female	type 1	16	189	245	7.8	39	146	202	234	398mg	0.9	1.6
47	palani	24	Male	type 1	10	167	199	6.9	49	88	200	116	87mg	0.8	1.8
48	nandagopal	30	Male	type 1	14	198	245	7.1	51	102	214	198	254mg	0.9	1.6
49	dhanalakshmi	27	Female	type 1	12	145	210	6.8	43	120	213	210	287mg	0.7	1.7
50	mala	39	Female	type 1	15	178	233	7.7	39	128	213	212	246mg	1.1	1.6