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SERUM MAGNESIUM AS AN EFFECTIVE TOOL IN MONITORING THE CONTROL OF TYPE II DIABETES MELLITUS

By

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Dissertation submitted to the

Tamil Nadu Dr. M.G.R Medical university, Chennai

In partial fulfilment of the requirements for the degree of

Doctor of Medicine in General Medicine

Under the guidance of

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This is to certify that the dissertation entitled, **"SERUM MAGNESIUM AS AN EFFECTIVE TOOL IN MONITORING THE CONTROL OF TYPE II DIABETES MELLITUS**" is the bonafide original work of **Dr. SANJEEV V.K** in partial fulfilment of the requirements for the degree of Doctor of Medicine in General Medicine.

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I hereby declare that this dissertation entitled **"SERUM MAGNESIUM AS AN EFFECTIVE TOOL IN MONITORING THE CONTROL OF TYPE II DIABETES MELLITUS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. L.S.Somasundaram M.D,** Professor of Medicine, P.S.G IMSR, Coimbatore.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University in fulfilment of the University regulations for the award of MD degree in General Medicine. This dissertation has not been submitted for award of any other degree or diploma.

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April 4, 2014

To
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The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on March 14, 2014 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your study proposal entitled:

"Serum magnesium as an effective tool in monitoring the control of type II diabetes mellitus"

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent Forms (ver 1.1)
4. Data Collection Tool
5. CV
6. Budget

After due consideration, the Committee has decided to approve the study.

The members who attended the meeting at which your study proposal was discussed are as follows:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member - Secretary	Female	Yes	Yes
Dr Y S Sivan	Ph D	Member –Social Scientist	Male	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

The approval is valid for one year.

We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

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This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

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INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member - Secretary
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ABSTRACT

Background & Objectives:

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. 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.

Methods:

This study was undertaken in PSG institute of medical research and hospital Research in coimbatore from May 2014 to September 2014. A total of 50 cases of type-2 diabetes mellitus were taken for the study after satisfying the inclusion and exclusion criteria. 50 non diabetic patients were taken as controls. All the patients were evaluated in detail and serum magnesium levels were estimated using calmagite method.

Results:

The serum magnesium levels among cases and controls were 1.47 ± 0.20 mg/dl and 1.67 ± 0.20 mg/dl respectively. The serum magnesium levels in controlled and uncontrolled were 1.57 ± 0.20 mg/dl and 1.41 ± 0.20 mg/dl respectively.

Interpretation and Conclusion:

There was significant reduction in serum magnesium levels in diabetics compared to the controls. There was a significant correlation between magnesium levels and the level of control of diabetes. The levels of magnesium were found to be lower in uncontrolled diabetics.

INTRODUCTION

Diabetes mellitus is a common metabolic disorder that is characterised by hyperglycemia. Diabetes mellitus etiology is based on factors which leads to persistent hyperglycemia are decreased insulin production from beta cells , tissue utilizing glucose getting decreased and increase in synthesis of glucose . This persisting hyperglycemia can cause multiorgan dysfunction like retina, kidney, peripheral nerve, heart and atherosclerotic changes.

The most of cases of diabetes mellitus were broadly classified in to two categories. Insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM). Both these types of diabetes mellitus are usually proceeded by a phase where there is a impairment in maintenance of blood glucose level is considered as a progression in pathogenic process. Type 1 diabetes mellitus usually occurs due to insulin deficiency which can either be complete or partial deficiency. Whereas type 2 diabetes mellitus is due to both due to sensitization of tissue to insulin action is decreased and inability of beta cells to compensate there by resulting in inadequate insulin secretion. Several pathological features are seen in persons developing diabetes mellitus and long term complications. Persons who have type 1 diabetes mellitus , always have a immunological trigger which is mediated through genetic factors which initiates an autoimmune response, which decreases gradually the beta cell mass. This decline in beta cell mass usually varies depending on individuals as it may not be similar in every one. This progressive and prolonged impairment in insulin secretion causes diabetes where around 80% of beta cell mass would be destroyed. In type 2 diabetes mellitus, the individual becomes more resistant to insulin thereby insulin level increases . Thereby failure to

compensate insulin secretion results initially in impaired glucose tolerance and utimately in type 2 diabetes mellitus.

Most common acute complications in type 1 diabetes mellitus is diabetic ketoacidosis and hyperglycemic hyperosmolar state which is more common in type 2 . Chronic complications of diabetes mellitus include microvascular complications and macrovascular complications. The microvascular complications are diabetic retinopathy, macular edema, diabetic neuropathy and diabetes related renal involvement. The macrovascular complications include cardiovascular disease like coronary artery disease and neurological disease like cerebrovascular accident other macrovasular complications include are peripheral vascular disease. Because of insufficient action of insulin on target tissues carbohydrate metabolism is mostly affected. Fat and protein are also affected in diabetes . Several vitamins and minerals act as a cofactor in the enzyme reaction regulated by insulin . These vitamins and minerals deficiencies such as vitamin E, potassium, zinc , chromium and magnesium can aggravate carbohydrate intolerance. Among these persons either potassium or magnesium replacement can be detected easily based on low serum levels.

Magnesium is widely distributed and it’s concentration can be particularly seen in the Bone, myocardium and muscle tissue. This acts as a cofactor for enzymes that could be even 300 enzymes particularly in enzymes where ATP and energy production are concerned with Magnesium is also required for cells to perform normal functions thereby regulation of cellular permeability and improving neuromuscular functions. It is necessary because both the production and function of the parathyroid harmone depend on magnesium level. It also causes formation of 25-OH D3. Hypomagnesaemia often seen in in diabetic patients, mostly seen in those with uncontrolled blood sugar levels. There is also evidence that Increased magnesium

supplements can cause improvement in insulin secretion and action, dyslipidemia, decrease thrombotic tendency thereby prevention of endothelial dysfunction and vascular contractility. There is a relation between Hypomagnesemia and insulin resistance, where it enhances insulin resistance thereby hyperglycemia keeps persisting, and when it is chronic it leads to macrovascular and microvascular complications, thereby decrease in magnesium level also getting worsened.

The exact pathology process between the DM and decreased magnesium was still unclear but there are some studies which proved that magnesium supplementation has shown some improvement in the insulin action and also in the carbohydrate metabolism. Since Magnesium also takes part in carbohydrate metabolism, it's deficiency can be seen in diabetes mellitus where the both inadequate nutritional requirement and low serum magnesium levels contribute . Infact studies have shown that low magnesium levels are recently considered as risk factor for hypertension and acute coronary syndrome. With all these evidence in order to study about the correlation between the diabetes and achievement of glycemic control and also to study about the alteration in serum magnesium levels in those with diabetes mellitus who are healthy controls also to compare the levels of magnesium in a controlled and in uncontrolled glycemic status in diabetic patients. It also helps to correlate the relation of magnesium to microvascular and macrovascular complications in patients with diabetes.

AIMS AND OBJECTIVES

1. To compare the levels of magnesium in patients with type 2 diabetes mellitus and in non-diabetic individuals.
2. To study levels of serum magnesium in controlled and uncontrolled diabetics.

REVIEW OF LITERATURE

Type 2 diabetes mellitus is a chronic metabolic disorder it becomes on of the major health challenge in 21st century [1]. So many modalities of prevention of diabetes and it's complication has been under trial.

Hypomagnesemia is now become a common feature in diabetes mellitus particularly type 2. Magnesium deficiency was accepted as a risk factor for type 2 diabetes mellitus in recent studies , diabetes itself can cause hypomagnesemia[2]. In some animal study, it shows that magnesium has a negative effect on insulin signaling especially in the post receptor signaling. Even there are studies which shows that magnesium supplementation usually gives a Improvement in insulin action and also regulates metabolism of carbohydrates[2]. In some studies. There is a evidence that magnesium plays a important role in glucose metabolism[3].

MAGNESIUM

In our body magnesium is one of the most abundant cation and where it is largely seen intracellularly like potassium. Human body contains 21 to 28 gm of magnesium[4] (approximately 1 mol.) in a average 70 kg of body weight. Of this 60% are seen in bone, skeletal muscle comprises about 20% , 19% of magnesium is found in other cells and 1% of magnesium found in extracellular fluid. It is a eleventh most abundant element in human body mass. serum magnesium levels can be normal even if there is a underlying deficiency , even though there are no proven mechanism to maintain a homeostatic level in blood and also by renal excretion of high blood levels.

BIOCHEMISTRY

Since it is an alkaline earth metal, it has chemical properties different from other other transition metals. When compared with other transition component and has a relative preference for oxygen over nitrogen atoms[5]. There are two major roles for magnesium in bilogical system .

- Magnesium can interact with calcium binding sites on protein and membranes
- It has the capacity to form chelates due to most important ligands, which is present intracellularly like Adenosine Triphosphate (ATP).

It can catalyse more than 300 enzymes in our human body. It also act as an coenzyme which gain it's essential in concerning with cell respiration, pathway of glycolysis and also take part in transport of other cations such as calcium and sodium across transmembrane[6] . Even the activity of Na-K ATPase can depend on serum magnesium level for it's action .The active site of the enzyme like pyruvate kinase and Enolase activity are affected where the magnesium causes conformational changes especially during the catalytic process (Na-K ATPase) through by ligand binding (ATP-requiring enzymes) and also it promotes aggregation of multi enzyme complexes. The magnesium also can affect the permeability characteristics and electric properties of membrane. It has a strongly intense 2+ charge, magnesium ions which is predicted to engage primarily in electronstatic bonding with negative ions in which charge is a primary determinant of bonding strength.[7] In general there are very few instances in biology can engage in covalent bonding. The most notable example is covalently-bound magnesium in the ring structure of chlorophyll.

There are some other biochemical processes that of magnesium which are used for the synthesis of cholesterol, where Magnesium ions not only assist in forming the pyrophosphate

bond from Magnesium-ATP in cholesterol precursors. It can also used in subsequent condensations reaction that give rise to the familiar ring structure of cholesterol[8]. It is a prominent element in the nucleus and cytosol where it serves as a crosslinking ion that stabilizes DNA and RNA. Magnesium due to overall architecture of its cell membrane, a property it shares with calcium and to a lesser extent zinc. Stabilization is brought about by acting as a bridging ion between phosphorylated and carboxylated molecules.

DISTRIBUTION

Magnesium is considered as the fourth most abundant cation seen in our body and is also the second commonest amongst elements which is present intracellularly. The total body content of magnesium in human is approximately 25 g (1.03 mmol)[9], of which about 55% resides in the skeleton. Around 35% of skeletal magnesium are released through channels for maintaining a normal level of magnesium both intra and extracellularly[10]. About 45% of the magnesium in our body is intracellular. The magnesium concentration in cells is approximately 1 to 3 mmol/lit. In general, when the cell has higher metabolic activity then we can expect it's magnesium content will also to be higher . Most of the magnesium seen in our body is bounded to proteins and some of the negatively charged molecules;at the sametime 80% of cytosolic magnesium is bounded to ATP[11]. Significant amount of magnesium were found in the nucleus, cytoplasm, mitochondria and endoplasmic reticulum. Freely available magnesium accounts for only 0.5% to 5.0% of total magnesium levels in our body and in this fraction it is important for enzyme activity[12]. This free level of magnesium concentration is maintained by a cotransport system which changes the rate of magnesium to be extruded and intruded by the cell as magnesium cannot enter the plasma membrane . Extracellular magnesium levels account for only about 1% of the total magnesium concentration in our body. The magnesium normal concentration in our body is around 1.7 to

2.4 mg/dl (0.70-0.99mmol/d)[13]. in that about half of magnesium is available as free ion , 1/3rd is associated with proteins (primarily albumin) and 15% complexed with phosphate, citrate and other anions.

TISSUE DISTRIBUTION AND METABOLISM:

The content of magnesium at birth is around 760mg and during 4-5 months of age it is approximately 5 g . During adult the magnesium requirement is high so around 25 gram is found . Among the total body magnesium, muscles and soft tissues comprises about 30-40 %, remaining 1 percent is found in extracellular fluid[14], and some of it is found in the skeleton, where it accounts for up to 1 percent of bone ash. Magnesium levels are seen abundantly in plant, animal foods, geochemical and other variables [12]. Plants which are rich in magnesium are legume seeds, peas, green leafy vegetables beans, and nuts .magnesium contents are much rich in food stuff like some shellfish, spices, and soya flour, where the they contain magnesium of more than 500 mg/kg fresh weight[14].

Reasonable sources for magnesium are unrefined cereal grains are many highly refined flours, tubers, fruits, and fungi and most oils and fats which contribute to the magnesium dietary requirement (<100 mg/kg fresh weight) . other vegetables which have low magnesium content are polished rice flour, Corn flour, cassava and sago flour[15] . The recommended dietary allowance for magnesium in adult is 270-350 mg/day. Normally 1/3rd of ingested magnesium is absorbed through the gastrointestinal tract. But sometimes this may be changing because intestinal absorption of magnesium is opposite to amount of intake of magnesium.

The malabsorption syndromes can affect intestinal absorption of magnesium which can be affected by factors like things that can affect transit time, calcium, phosphate, protein, lactose

or ingested alcohol. There is no evidence regarding Vitamin D affecting magnesium absorption. Now the kidney plays the major excretory pathway for magnesium so it is considered that kidney maintain magnesium homeostasis thereby maintaining plasma concentrations. When there is a magnesium depletion occurs renal system tries to compensate by decreasing magnesium excretion[16]. Kidney excretes only 3 to 6% of the filtered magnesium . whereas Around 1/4th of the filtered magnesium is getting reabsorbed in the proximal convoluted tubule and one half of ingested magnesium level are absorbed in the ascending limb of loop of henle where as in the distal convoluted tubule magnesium absorption is usually depending on quantity of intake . The renal clearance and plasma concentrations can be often compared to those of calcium, phosphate, sodium and potassium. The hormonal regulation which plays in the renal clearance of potassium the same hormonal regulation was seen in magnesium.

The most part of magnesium is that in plasma (about 60-70%) usually seen as free ions whereas sometimes it is seen in the form of various diffusible complexes; especially like protein. In children under these ages of six mother's milk is a only source of magnesium[17]. Infact there is insufficient information to establish an RDA for infants. Gender differences are not seen until early adulthood. In Pregnancy and lactation period there should be a modest increase in the recommended dietary allowance for magnesium. The intake of magnesium tends to increase as a person grows older.

The homeostasis of magnesium is maintained by three important organ like intestine which plays in absorption, the bone it's also plays in absorption and the Kidneys which causes excretion of magnesium levels. Like calcium it gets absorbed in the intestine and usually stored in bone material. When there is excess magnesium in our body then kidney and faces tries to release by maintaining homeostasis[18] . Most of the magnesium is absorbed in small intestine and

also some is absorbed in large intestine. The absorption of magnesium is through small intestine is due to a passive process , which can process either by an gradient which is active and solvent drag. Other mechanism is through transcellular transporter transient receptor potential channel melastatin member (TRPM) 6 and TRPM7[19]—these are related to persisting transient potentially activated receptor channel[19] family— they also have an role in absorption of calcium through intestinal tract.

Table 1:

DAILY REQUIREMENTS OF MAGNESIUM:

LIFE STAGE	AGE (in years)	RECOMMENDED DIETARY ALLOWANCE	
		MALES (mg/day)	FEMALES (mg/day)
CHILDREN	1 - 3	80	80
CHILDREN	4 - 8	130	130
CHILDREN	9 - 13	240	240
ADOLESCENT	14 - 18	410	380
ADULT	19 - 30	400	310
ADULT	30 - 50	420	320
ADULT	>51	420	350
PREGNANCY	19 - 30	---	350
PREGNANCY	30 - 50	---	360
LACTATING	19 - 30	---	310
LACTATING	30 - 50	---	320

CLINICAL SIGNIFICANCE:

The prevalence of hypomagnesaemia is one of the common entity seen in Patients who are admitted , with a range between 9 to 65% with highest incidence is observed in intensive care units[16]. Recent studies shown that there is a strong association of hypomagnesaemia in patients undergone esophageal surgery. Generally critical care patients, magnesium supplemented for patient is insufficient. Drugs were also found to have been associated with depletion of magnesium in our body therefore , making the patients at an very much severe risk for clinical manifestation . It also have been proposed that in patients who are admitted with very low magnesium levels , there is a increase in mortality rate[11]. So magnesium assessment is required in critically ill patients. One of the best defined manifestation of magnesium deficiency is impairment of neuromuscular junction which can present as hyperirritability, tetany, convulsions and electrocardiographic changes.[2] Magnesium deprivation has also shown to be associated with cardiovascular disease through so many studies which showed epidemiologically related evidence that relation between low magnesium intake to a high incidence of cardiac deaths, particularly seen in soft water areas where there is a lowwaterborne magnesium content and a very minimal incidence of cardiac deaths is noticed in hard water areas in which the content of magnesium is high. Magnesium depletion also have been linked to hypertension, myocardial infarction, cardiac dysrhythmias, coronary vasospasm and premature atherosclerosis.

Usually reduced magnesium levels is associated with either normal or reduced serum calcium concentrations. Hypomagnesemia also may play a role in secondary affect in hypocalcemia or calcium deficient tetany[20]. When a case present with hypomagnesemic normocalcemic tetany has been described only magnesium supplementation can be given alone. There are some cases which present as tetany with normal serum calcium levels and decreased

serum magnesium levels.[14] So only calcium administration in tetany will not be given alone if there is a evidence of magnesium deficiency then magnesium supplementation should also be given. There is a association between decreased serum potassium concentrations (hypokalemia) and magnesium deprivation.[21] Even in unexplained hypokalemia and also in unexplained hypocalcemia serum magnesium deficiency to be suspected.

There are so many condition that have been associated with hypomagnesemia that includes acute pancreatitis, chronic alcoholism, hypothyroidism, malabsorption, chronic glomerulonephritis, aldosteronism, childhood maturation, lactation, digitalis intoxication and prolonged intravenous feeding.[22] If there is any disrupt in normal renal conservation of magnesium like renal tubular reabsorption defects, those taking drugs like chlorothiazides, diuretics for congestive heart failure and ammonium chloride also results in hypomagnesemia.

Hypomagnesemia can also be triggered by conditions which trigger the increased excretion of magnesium in conditions like diabetes mellitus, hyperthyroidism, renal tubular disorders, another major cause like hypercalcemia, or aldosteronism or in persons with excessive lactation and acute pancreatitis due to Compartmental redistribution of magnesium will be seen in patients with pancreatitis patients[18]. Diagnosis of chronic hypomagnesaemia will be difficult because there will be always maintenance of magnesium with negative balance overtime. There is a equilibrium which is mostly seen in most of tissue pools that serum concentration of magnesium is usually maintained by magnesium available from bone.

Table 2:

CAUSES FOR HYPOMAGNESEMIA

PRIMARY NUTRITIONAL DISTURBANCES	➢ Inadequate intake ➢ Total parenteral nutrition ➢ Refeeding syndrome
GASTROINTESTINAL DISORDERS	➢ Intestinal absorbtion defects ➢ Malabsorption syndromes ➢ Chronic diarrhoea ➢ Chronic nasogastric suction ➢ Acute Pancreatitis ➢ Ingestion phosphate cellulose
HORMONE RELATED DISORDERS	➢ Hyperparathyroidism ➢ Hypoparathyroidism ➢ Grave's disease ➢ Aldosteronism-primary ➢ Bartter's syndrome ➢ Diabetes acute complications ➢ Alcoholic with dehydration
CATABOLIC CONDITION	➢ Epinephrine excess ➢ Acute necrotising pancreatitis ➢ After correction of respiratory acidosis ➢ Multiple blood transfusion
CHRONIC ETHANOL CONSUMPTION	➢ Alcohol withdrawl syndrome ➢ Alcohol dependent syndrome

INCREASED RENAL EXCRETION	➢ Idiopathic ➢ Post renal transplantation ➢ Cyclosporine administration ➢ Amikacin (Aminoglycoside) theraphy ➢ SIADH ➢ Diuretic administration - Loop diuretics - Ethacrynic acid administration - Acetazolamide theraphy - Hydrochloro thiazides - Recovery from acute tubular necrosis ➢ Theophylline toxicity
OTHER CAUSES	➢ Stress ➢ Increased period of lactation, heat, exercise ➢ Burns with high grade ➢ Bypass surgery ➢ Iatrogenic

Table 3:

CLINICAL SIGNS OF HYPOMAGNESAEMIA:

NEUROMUSCULAR	➢ Weakness ➢ Tremor ➢ Muscle fasciculation ➢ Positive Chvostek's sign ➢ Positive Trousseau's sign ➢ Dysphagia
CARDIAC	➢ Arrhythmias ➢ ECG changes: Depression of ST segment Flattening of T waves QT/QTc prolongation Enhanced atrial and ventricular excitability
CENTRAL NERVOUS SYSTEM	➢ Depression ➢ Agitation ➢ Psychosis ➢ Nystagmus ➢ Seizures
METABOLIC	➢ Hypokalaemia ➢ Hypocalcaemia

LABORATORY ASSESMENT OF MAGNESIUM NUTRITION:

Serum or plasma magnesium concentration

Plasma level of magnesium monitoring can provide an appropriate support for diagnosing magnesium deficiency. [2] Hypomagnesemia in serum level can predict whether there is a evidence of low magnesium levels, but sometimes it's normal report will not always exclude magnesium deficiency always. The serum level of magnesium level shows found correlation only with interstitial fluid when compared to any other tissue pools of magnesium.

Magnesium concentration in muscle:

Muscle usually contains approximately 27% of total magnesium. Thus tissue plays a important role for magnesium status assessment[5]. Needle biopsy is done to determine the magnesium concentration in muscle, but this procedure is invasive so requires special skills and the assay is tedious.

Mononucleated white cell magnesium concentration:

Intracellular magnesium is usually measured by using index of mononucleated white cell (MNC) magnesium concentration which has been proposed as a possible index[7] . In humans magnesium concentrations in MNCs there is no correlation between serum or erythrocyte concentrations but there are some studies which showed a positive correlation between the magnesium concentration of MNC and muscle[23]. The magnesium content of MNCs is reportedly a better indicator of cardiac arrhythmias associated with magnesium deficiency than that of serum magnesium level.

Magnesium retention after acute administration:

There are oral and intravenous magnesium preparation available in which loading tests have been described and they are mostly used in clinical practice for diagnostic purpose rather than intracellular measurements[3]. In normal individuals within 24 to 48 hours after administration magnesium balance is maintained by excretion of essentially all injected magnesium in urine, whereas persons with a magnesium deficit the kidney tries to retain a significant proportion of the administered magnesium. In this procedure 30 mmol of magnesium in 500 ml of 5% dextrose is administered intravenously over 12 hours[24]. A 24 hour urine is collected before starting the magnesium infusion.when there is a retention of less than 30% of infused magnesium suggests magnesium depletion is unlikely. Patients who are undergoing this test should have normal functioning kidney, there should not be any intake of medication that affects renal excretion of magnesium and also does not have disturbances in cardiac conduction or advanced respiratory insufficiency.

DITERMINATION OF MAGNESIUM

Methods

Measurement of Serum magnesium has been done by a wide variety of techniques including precipitation, titrtration, fluorometry, photometry, flame emission spectroscopy and AAS.[25] Methods used earlier are 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[4]. 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. 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. Today photometric methods are more commonly used by clinical laboratories, although AAS considered the reference method is also used by some laboratories.

Photometric methods

A metallochromatic indicators or dyes which changes colours that are selectively considered as binding site for magnesium and have been proposed to measure magnesium it in biological samples. Eriochrome black T, chrome fast blue G and titan yellow are of historical interest they are not widely used today[17]. According to the American college pathologists where they did the comprehensive chemistry survey on 1991, Where calmagite was considered and used by 43% laboratories for magnesium determinations, followed by methylthymol blue and a formazan dye, each with 24% magon at 7% and AAS ay 1%. Calmagite a metallochromatic indicator which forms a coloured complex when combined with magnesium in alkaline solution which is measured at 530-550nm[26]. A specific calcium chelating agent, EGTA (ethylene glycol-O,O-bis(2-aminoethyl)-N,N-tetra acetic acid, is added to prevent interference by calcium. Potassium cyanide is added to avoid formation of heavy metal complexes. Polyvinylpyrrolidone and surfactants are included to reduce interference from protein and lipemia. Methylthymol blue

forms a blue complex with magnesium which is measured around 600 nm. EGTA is generally added to avoid interference by calcium.

Magon, or xylidyl blue (1-azo-hydroxy-3-[2,4-dimethylcarboxanilideo]-naphthalene-1-[2-hydroxybenzene], binds magnesium in alkaline solution causing a spectral shift and forming a red complex. Calcium and protein interference is eliminated by EGTA and dimethyl sulfoxide respectively.[27] A formazan dye (1, 5-bis[3,5-dichloro-2-hydroxyphenyl]-3-formazan carbonitrile) forms a complex with magnesium at alkaline Ph which has been measured at 630 nm by thin film reflectance photometry. The thin film reflectance method is unaffected by icteric, lipemic and hemolysed specimens. Elevated calcium levels cause a small but measurable overestimation.

Atomic absorption spectrometry

Although neutron activation with magnesium is the definitive method for magnesium analysis, clinical laboratories use AAS as the reference method. Even though AAS can provide greater accuracy and precision it is not frequently used by most clinical laboratories for routine determination of magnesium[16]. Magnesium done here determined by AAS which is obtained by diluting the specimen collected in a standard solution which contains lanthanum hydrochloride is added inorder to stop any anionic disturbance including phosphate and some other include metal[28]. The viscosity is reduced by dilution and it is important thereby confirming that absorptive capacity for aqueous calibrators and other things to be compared. The specimen is usually aspirated and aspirated one is sent into an flame which contains airacetylene because so that magnesium ions which were grounded can absorb light from a magnesium hollow lamp (285.2nm)[19] placed within the calibrator . Absorption of light at particular nanometer is considered as a directly proportional to the magnesium atoms which were grounded in the flame.

Free magnesium

Free magnesium has been determined in whole blood, plasma, or serum by ion selective electrode neutral carrier ionophores. 25 Further improvements in ion selective for magnesium are required in order to increase the availability of free magnesium determinations.

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 C and for months when frozen, provided evaporation and lyophilization are avoided. As soon as Serum or plasma is collected it should be separated from the clot or red blood cells all these to be done to avoid increased levels due to cell leakage. Because erythrocytes used to contain higher levels of magnesium when compared to 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[12]

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 considered as 1.7 to 2.2 mg/dL (0.70 - 0.99 mmol/L). serum Erythrocytes have been tend to have magnesium levels probably three times when compared to those of serum. There are some Interconversion factors used to determine the units and also to show levels of serum magnesium are :

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

TREATMENT

- Underlying cause to be treated
- In healthy individuals with mild hypomagnesemia oral supplementation of magnesium is indicated
- Oral supplementation is also indicated in persons with inadequate intake or disorders of intestine and excess urinary excretion of magnesium[29]

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
- In persons with cardiac arrythymia and severe hypomagnesemia intravenous administration of magnesium sulphate is indicated.

- In Cardiac arrhythmias patients with nausea and vomiting – IV Magnesium therapy 4.2 mmol Mg SO_4 (1 gm) every 6 hours.
- In torsade de pointes or ventricular arrhythmias – 8 mmol of Mg SO_4 over 1 to 2 minutes followed by infusions (8 to 12 mmol/hour for 4 to 8 hours and smaller doses thereafter).

HYPERMAGNESEMIA

The renal system plays a important role in maintaining magnesium homeostasis, so in case of patients with advanced chronic kidney disease[11], here the compensation becomes impaired and there by hypermagnesaemia may develop. In Symptomatic hypermagnesaemia causes could be due to increased oral intake of either could be magnesium salts or rapid use of magnesium-containing drugs like liquid paraffin, lactulose and alluminium hydroxide, these occur when particularly when used in combination especially in the aged persons[16] . In eclampsia hypermagnesaemia can be iatrogenic, when high doses of magnesium sulphate is routinely used for treating seizure even as an infusion and also as a prophylaxis in eclampsia.

Other causes for hypermagnesemia

1) Rhabdomyolysis
2) Adrenal insufficiency
3) Familial benign hypocalciuric hypercalcemia
4) Near drowning in the dead sea (in Jordon)

Clinical features:

- Facial parasthesia
- Sedation
- Hypoventilation with respiratory acidosis
- Diminished deep tendon reflexes
- Weakness of muscle
- Low blood pressure
- Bradycardia
- Areflexia, coma and respiratory paralysis occurs at higher levels

TREATMENT:

- Symptomatic hypermagnesemia can be reversed by calcium gluconate infusion
- Normal saline and furosemide helps in renal excretion of magnesium
- Hemodialysis is indicated in severe symptomatic hypermagnesemia

Table 4:

SERUM MAGNESIUM LEVELS (mmol/L)	CLINICAL MANIFESTATION AND ECG CHANGES
2.1–2.4	GIT MANIFESTATION : Paralytic ileus ECG CHANGES: Bradycardia
2.5–4.0	NEUROLOGICAL MANIFESTATION: Absent or diminished reflexes , weakness of muscle , Slurring of speech, tiredness CIRCULATORY-RESPIRATORY-GIT MANIFESTATION: Low blood pressure, nausea, decreased uterine tone upon magnesium infusion ,periodic bowel paralysis ECG CHANGES: Tachycardia, T-wave abnormalities , prolonged QT-time
3.7–4.9	NEUROLOGICAL MANIFESTATION: Drowsiness, absent reflexes, quadriparesis. CIRCULATORY MANIFESTATION: Hypotension
5.0–6.95	NEUROLOGICAL MANIFESTATION: Complete tiredness , slurring of speech, worsening muscle weakness CIRCULATORY-RESPIRATORY- MANIFESTATION: Hypotension , increased respiratory rate, respiratory arrest ECG CHANGES: Atrial fibrillation , QT prolongation, sinus tachycardia, 1st degreeAV-block, bradycardia

Up to < 7.65 and 7.3	NEUROLOGICAL MANIFESTATION: Paralysis of the limbs CIRCULATORY-RESPIRATORY- MANIFESTATION: No respiratory arrest, slight decrease of blood pressure ECG CHANGES: Sinus arrhythmia, slight alterations in ventricular action (T-wave, ST, R abnormalities, prolonged PR interval)
>8.9–10.65	NEUROLOGICAL MANIFESTATION: Coma, pseudocomatose state, central brain-stem herniation syndrome, non-fatal neuromuscular blockade CIRCULATORY-RESPIRATORY- MANIFESTATION: Profound hypotension, cardiopulmonary non-fatal arrest cardiovascular collapse at 25 mg/dL ECG CHANGES: Prolonged QT interval, bradycardia
Up to 13. 5	CIRCULATORY-RESPIRATORY- MANIFESTATION: Respiratory depression, apnoe, cardiopulmonary arrest ECG CHANGES: Non-fatal refractory bradycardia

DIABETES MELLITUS

It is a common metabolic disorder encountered in India which sharing the same phenotyping of serum hyperglycemia. There are several different types of diabetes mellitus which are caused by complex features of both genetics and environmental factors.Diabetes is becoming one of the most epidemic of the 21st century.[29] Type 2 diabetes mellitus , which is more prevalent (more than 90% of all diabetes cases) among all diabetes and it is usually considered as a the main driver of the diabetes epidemiology ,which now at present usually affects approximately 5.9% of the world's adult population and in this population among 80% of

the diabetes are total in developing countries. Now diabetes epidemic is more pronounced in India as per World Health Organization (WHO) reports which shows information that around 32 million people had been diagnosed as diabetes in the year 2000[30].

The International Diabetes Federation (IDF) has estimated that number of diabetic subjects to be around 40.9 million in India and this can further set to rise to as much 69.9 million by the year 2025

DEFINITION

It is a variable disorder in which the carbohydrate metabolism is altered which can be caused by a combination of hereditary and environmental factors[8]. But it is usually characterized by inadequate production or impaired utilization of insulin by l tissues, by excessive urinary excretion , by increased levels of sugar in the blood and urine, and all these can cause thirst, hunger, and weight loss.

There are some independent factors which contribute to hyperglycemia is inadequate insulin Production , impairment in utilization of glucose and increased glucose production in body[7] . All these contributing factors are formed depending on specific etiology of diabetes mellitus. The metabolic dysregulation usually starts occurring gradually in diabetes mellitus finally which causes secondary pathophysiological changes in multiple organ systems there by resulting in both macrovascular and microvascular complications, including diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy.

Pathology behind diabetes ranges from auto-immune destruction of the beta cells of the pancreas due to which there is a consequent insulin deficiency to abnormalities in metabolism of carbohydrate, fat and protein resulting in diabetes and in some patient there is a deficient action

of insulin on target tissues[28] since there is a deficient insulin action which usually results from insufficient insulin secretion and/or decreased tissue responses to insulin at one or more points resulting in the complex pathways of hormone action.

Long term complications of diabetes include retinopathy along with Gradual loss of vision, nephropathy which can eventually lead to renal failure(ESRD – end stage renal disease), peripheral neuropathy associated with risk of foot ulcers which can progress to amputation, and also Charcot joints can be seen [31]; and autonomic neuropathy causing orthostatic hypotension, gastrointestinal paresis, genitourinary symptoms, cardiovascular symptoms(chest pain) and sexual dysfunction (impotence). Patients with diabetes have an increased incidence of atherosclerotic either involving cardiovascular, peripheral vascular and cerebrovascular disease[32]. Hypertension abnormalities due to lipoprotein metabolism and periodontal disease are often found in people with disease.

The classification of diabetes is based on pathogenic process. It is generally classified in to two broad categories type 1 DM and type 2 DM[8]. Other than these two etiologies of DM include specific genetic effects, insulin production / action, metabolic abnormalities that can impair insulin secretion, mitochondrial abnormalities and a number of conditions that impair glucose tolerance.

ETIOLOGICAL CLASSIFICATION OF DIABETES:

Reference American Diabetes Association (2011)

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)

III. Other specific types:

A. Genetic defects of beta cell function

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)

2. Chromosome 7, glucokinase (MODY – 2)

3. Chromosome 12 HNF – 1 α (MODY – 3)

4. Insulin promoter factor-1 (IPF-1 : MODY-4)

5. HNF-1 (MODY-5)
6. NeuroD1 (MODY-6)
7. Mitochondrial – DNA
8. Subunits of ATP – sensitive potassium channel.
9. Proinsulin or insulin
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson – mendenhall syndrome
4. Lipodystrophy syndrome
C. Disease of the exocrine pancreas
1. Pancreatitis
2. Trauma
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. mutations in carboxyl ester lipase
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. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormones
6. Diazoxide
7. Beta-adrenergic agonists
8. Thiazides
9. Dilantin
10. Alpha- interferon
11. Others
F. Infections
1. Congenital
Cytomegalovirus

1. Coxsackie virus
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 1 DIABETES MELLITUS

This is a form of diabetes where there is a autoimmune pancreatic β- cell destruction and is characterized by absolute insulin deficiency. American diabetes association has differentiated type 1 diabetes mellitus as type 1A and type 1B.[13] It is mostly seen in children. Type 1 is immune mediated and type 1 are other forms of diabetes associated with insulin deficiency. The current best criteria for diagnosis of type 1A diabetes is the presence of anti-islet auto antibodies which can be measured with highly specific (and reasonably sensitive) autoantibody radio assays. [33]The presence of auto antibodies with assays is usually defined as positive if fewer than 1 of 100 control subjects where specificity ≥99% is reasonably diagnostic tool for type 1A diabetes.

More than 90% of children who are presenting with diabetes express one of four measured anti-islet auto antibodies. In contrast, some half of black or Latin American children lack any autoantibody[34]. But these children most of them appear to have an early age at onset of type 2 diabetes mellitus and some other have attendant risk factors like obesity, and many lack human leukocyte antigen (HLA) alleles associated with type 1A diabetes.

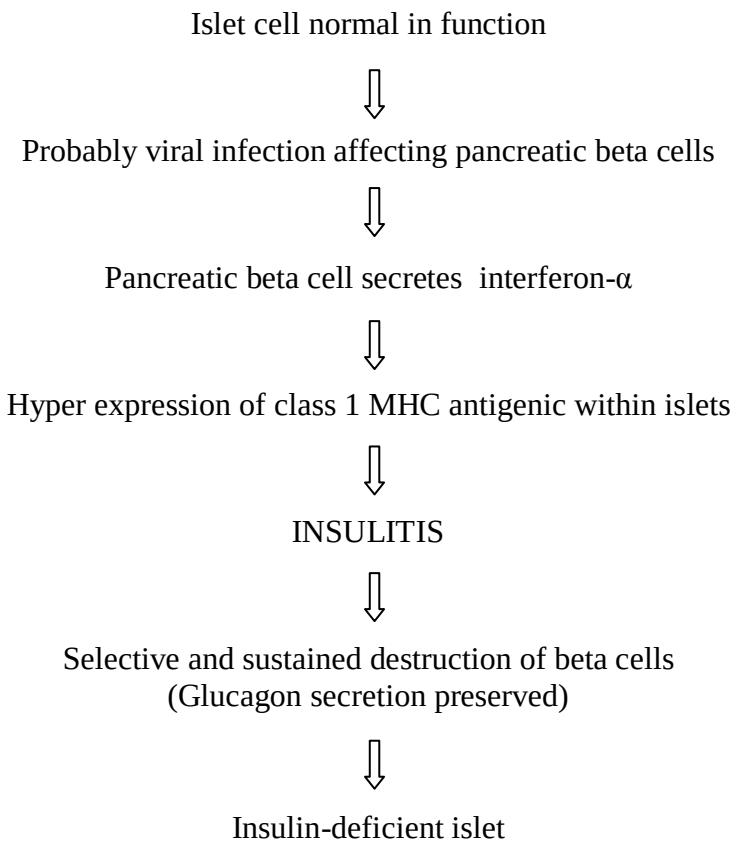
Table 5:

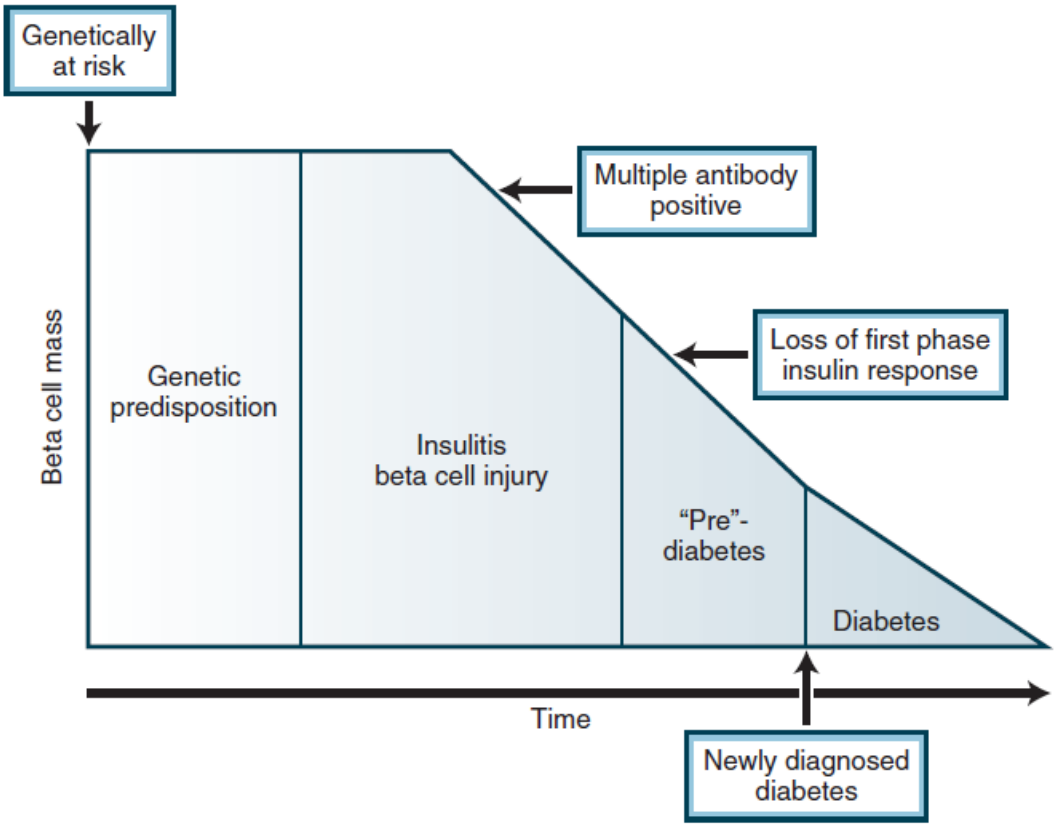
Differential diagnosis of type 1 A diabetes [34]:

Types of diabetes	Anti-Islet Auto antibodies	Genetics	Comments
TYPE 1A	Positive >90%	HLA 30-50% DR3 and DR4 HLA 90% DR3 or DR4 HLA < 3% DQBI*0602	90% non-Hispanic white children 50% black children 50% Latin American children
TYPE 1B	Negative	Unknown	Rare in whites
TYPE 2	Negative	Unknown	If Ab+ , likely LADA, and HLA is similar to type 1A
OTHER	Negative	MODY mutation and Other syndromes	

Reference: Williams book of endocrinology

Pathogenesis of type 1 diabetes mellitus





Reference: William's text book of endocrinology

Hypothetical stages in development of type 1A diabetes mellitus as beginning with genetic susceptility and they ending in complete beta cell destruction.

Type 1 diabetes mellitus are previously referred as juvenile-onset diabetes. It is usually diagnosed in childhood, sometimes in adolescence age group, or now cases in early adulthood are seen[34] . Eventhough the onset of type 1 DM is seen in much earlier life (childhood life), some 50% of patients with new-onset type 1 DM are seen in age older than 20 years of age. Usually the onset of type 1 diabetes mellitus starts in children probably around 4 years of age or older with the peak incidence at 11-13 years of age. Now a day's incidence is relatively high in people of around 30s and early 40s, but in these people the disease tends to be less aggressively[33] . This type of slower-onset adult form of type 1 DM is referred to as latent autoimmune diabetes of the adult (LADA). In this condition there is a risk of development of antibodies (anti-islet) in relatives of patients with type 1 DM generally decreases with increasing age[29]. This gives guidance for annual screening for antibodies in relatives who are younger than 10 years who have positive family history of diabetes and 1 additional screening should be done during adolescence[35]. Type 1 DM is more commonly seen in males when compared to females. It is comparatively uncommon among Asians.

The classical symptoms of type 1 diabetes mellitus include increased thirst, increased frequency of micturition , polyphagia and unexplained weight loss[36] Others include fatigue, nausea ,blurring of vision. Rarely some patients initially present with diabetic ketoacidosis. All these symptoms could be sudden in onset. Type 1 diabetes mellitus patients will lose weight, despite normal or increased appetite it is due to water depletion and a majority of catabolic state occurring in the body with reduced glycogen storage , proteins, and triglycerides. This Weight

loss is usually once treatment is initiated. Since type 1A diabetes mellitus patients are immune mediated they are sometimes associated with some auto immune disease also.

Table 6:

Disease	Auto antibody		Disease prevalence (%)
	Type	Percentage (%)	
Addison's disease	21-Hydroxylase	1.5	0.5
Celiac disease	Transglutaminase	12	6
Pernicious anemia	Parietal	21	2.6
Thyroiditis or Grave's disease	Peroxidase or thyroglobulin	25	4

WHO CRITERIA:	
Fasting blood glucose	≥7.0mmol/l (126mg/dl)
Post prandial glucose	≥11.1mmol/l (200mg/dl)
(2 hrs after meal)	
Impaired Glucose Tolerance (IGT):	
Fasting plasma glucose	<7.0mmol/l (126mg/dl)
Post prandial glucose	≥7.8 and <11.1mmol/l
(2 hrs after meal)	(140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG) :	
Fasting plasma glucose	6.1 to 6.9mmol/l
	(110mg/dl to 125mg/dl)
Post prandial glucose	<7.8mmol/l (140mg/dl)
(2 hrs after meal)	
AMERICAN DIABETES ASSOCIATION CRITERIA:	
Fasting blood glucose	≥7.0mmol/l (126mg/dl)
Post prandial glucose	≥11.1mmol/l (200mg/dl)
(2 hrs after meal)	
HBA1C	≥6.5%
Random blood glucose	≥11.1 mmol/L (200 mg/dL)

Table 7:

DIFFERENTIATION BETWEEN TYPE 1 DM AND TYPE 2 DM:

	TYPE 1 DM	**TYPE 2 DM**
Etiology	Auto immune destruction of pancreatic beta cells	Insulin resistance with Inadequate beta cell function to compensate
Insulin levels	Absent or negligible	Typically higher than normal
Insulin actions	Absent or negligible	Decreased
Insulin resistance	Not part of syndrome but may be present (eg: in obese patients)	Yes
Age of onset	Typically < 30 years	>40 years
Acute complications	Diabetic ketoacidosis Wasting	Hyperglycemic non ketotic hyperglycemia, coma
Chronic complications	Diabetic neuropathy Diabetic retinopathy Diabetic nephropathy Peripheral vascular disease Coronary artery disease	Same as type 1 DM
Pharmological interventions	Insulin	No. of drug classes are available including insulin if other therapies fall
Prognosis		

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus is a mostly predominant form in worldwide comprising about 90% globally[29]. It has become one of the most important world health problems. It usually begins in middle age or after 40 years of age. It is mostly seen in obese patients and now onset of type 2 diabetes mellitus is rising dramatically. Sex, age and ethnic plays a most important risk factors in onset of diabetes mellitus. Insulin resistance is a most pathophysiology of type 2 diabetes mellitus, that is usually seen in liver and peripheral tissue primarily muscle and adipose tissue[16]. Due to insulin resistance there will be increased amount of insulin may be needed to keep normoglycemic status. In type 2 diabetes mellitus, the pancreas initially will be able to produce increased amount of insulin quantity there by resulting in hyperinsulinemia condition. This hyperinsulinemia condition will be able to compensate the insulin resistance initially so these patients may not able to meet diagnostic criteria for diabetes mellitus. After some period the beta cells started declining and increased insulin levels will not be sufficient to compensate the insulin resistance thereby resulting in clinical diabetes.

Thus insulin production in type 2 diabetes mellitus patients are considered as "relative " insulin insufficiency. Another confounding factors include inability to suppress the glucagon production particularly in postprandial state which further increases glucose production from muscle and liver[5]. The pathophysiology abnormalities include ranging from predominantly predominant insulin resistance and insufficiency of relative insulin secretion to predominant insulin secretory insufficiency there by resulting in absolute reduction in insulin production. Type 2 diabetes mellitus should not be seen only from it's impact on glucose metabolism[37] it is also a part of constellation of other conditions like hypertension, dyslipidemia, abdominal obesity and hypercoagulability are generally reffered to as " metabolic syndrome"[22]. Obesity

itself contributes to risk factor for insulin resistance in type 2 diabetes mellitus and the distribution of obesity is abdominal.

MAJOR RISK FACTORS FOR TYPE 2 DIABETES MELLTUS
➢ Overweight (BMI ≥25 kg/m_2)
➢ Physical inactivity
➢ First-degree relative with diabetes
➢ Member of a high-risk ethnic population (e.g., African American, Latino, Native American)
➢ Female with a history of delivering a baby weighing >9 lb or diagnosis of GDM
➢ Hypertension (≥140/90 mm Hg or on therapy for hypertension)
➢ HDL cholesterol level <35 mg/dL (0.90 mmol/L) or triglyceride level >250 mg/dL (2.82 mmol/L)
➢ Female with polycystic ovary syndrome
➢ Hemoglobin A_{1c}≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
➢ Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
➢ History of cardiovascular disease

ENVIRONMENTAL FACTORS

LIFE STYLE

Overeating, especially when combined with obesity are more associated with risk of Developing type 2 diabetes[18]. Obesity probably acts as a diabetogenic factor (through which there is a increasing resistance of tissues to the action of insulin) in those person who are genetically predisposed to develop type 2 diabetes[18]. Most distribution pattern of obesity is abdominal where there will be additional pounds of adipose tissue thereby increasing insulin resistance. In recent years young people with obesity are more prone for development of type 2 diabetes mellitus.

AGING

Type 2 diabetes mellitus is more common after 40 years of age. In most of the people glucose tolerance decreases with age.

NUTRTION

There is a change in diets of many ethnic groups which have become westernized nowadays can contribute to increased incidence of type 2 diabetes mellitus. High calorie intake and increased fat content of meals are most etiologic factors. Reduced fiber intake has also been suggested as a risk factor as high fiber diets reduces the incidence of diabetes.

PATHOPHYSIOLOGY AND HISTORY RELATED TO TYPE 2 DIABETES MELLITUS

In type 2 diabetes mellitus there will be a gradual increase in insulin resistance. At this time pancreas will increase insulin output and normoglycemia is maintained. Over time the capacity of pancreas to secrete enough additional insulin started decreasing. This decline usually begin as many years prior to the diagnosis of type 2 diabetes[16]. There is also a reduced suppression of glucagon in postprandial state which causes increase in endogenous glucose production that's further contributing to postprandial hyperglycemia.

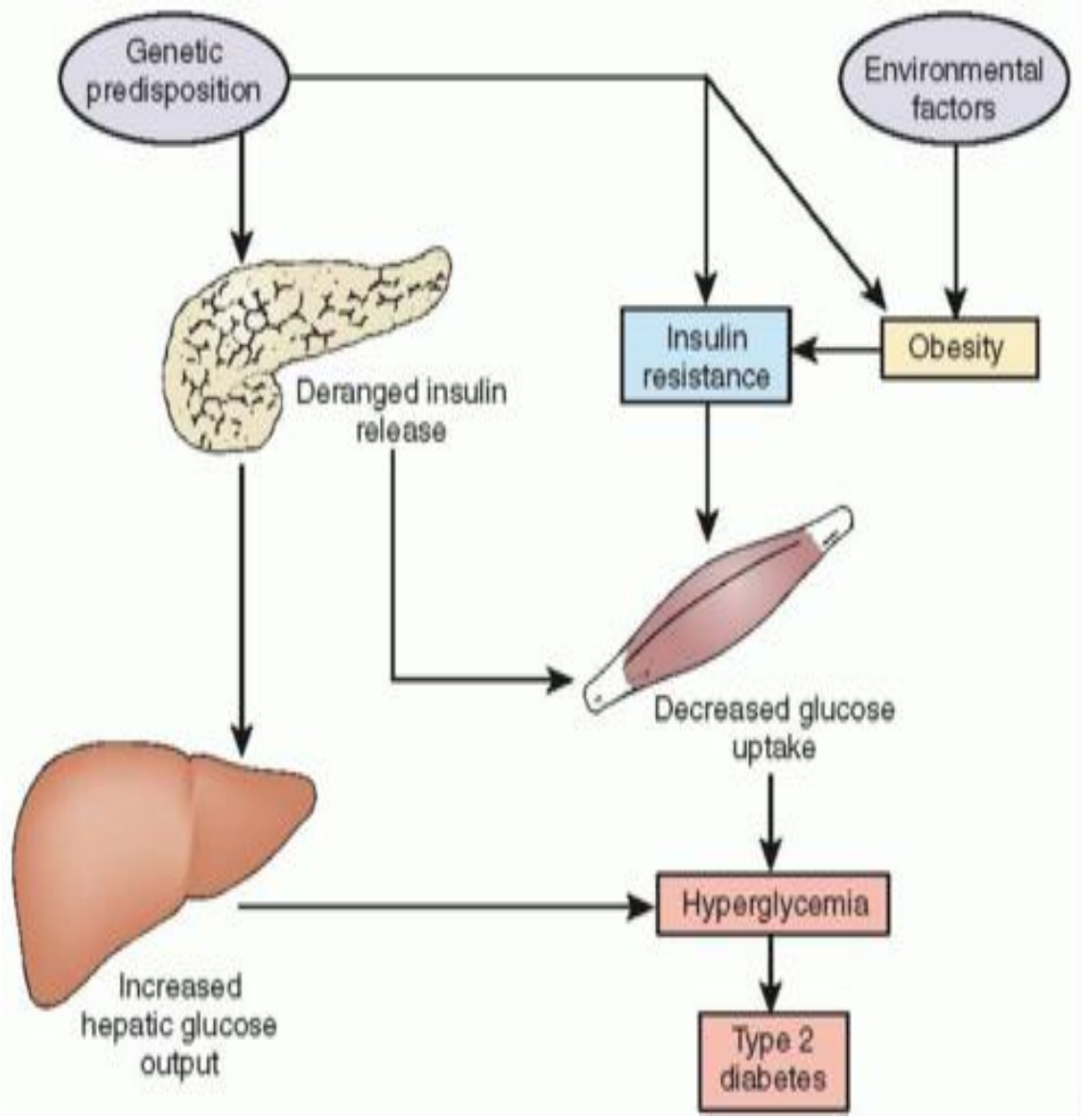
When the insulin secretion is enough to maintain the insulin resistance normoglycemia is maintained. If excess insulin secretory capacity started declining, mild hyperglycemia develop[29]. Even though when mild hyperglycemia develops diabetes is diagnosed but due to the lack of symptoms there is a delay in discovery of disease. If the diagnosis is made during this time then life style intervene can be done to prevent the diabetes and it's progression.

When diabetes is diagnosed initially there will be insulin resistance which is more peripheral where adipose tissue and muscle is involved. Thereby reflecting the decrease in postprandial glucose uptake. At the same time in beta cell there will be loss of first insulin phase release. Generally first phase release of insulin occurs after 15 minutes of carbohydrate intake. Where as second phase of insulin release represented as a newly manufactured insulin which begins after first phase subsided. This second phase last longer and gives sustained carbohydrate coverage for remainder.

Due to the loss of first phase of insulin release, postprandial glucose rises significantly. Lack of glucagon suppression also promotes production of endogenous glucose. In these patients

second phase insulin release is maintained which leads to greater amount of insulin release after a high postprandial glucose level[31]. This is because muscle is the main source of glucose uptake after meals. During this period more insulin is needed to drive the glucose in to muscle cell and fat cell. Insulin also suppress the liver output of glucose by inhibiting gluconeogenesis. This higher insulin level can cause drop in blood glucose level 3 to 5 hours after a meal and hypoglycemia symptoms can occur. As the glucose level increases, glucose toxicity can occur[2]. The glucose toxicity is due to paradoxical effect of hyperglycemia even on insulin production and action. Overtime insulin secretary capacity is blunted, elevation of glucagon levels occur and insulin resistance also increases.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS



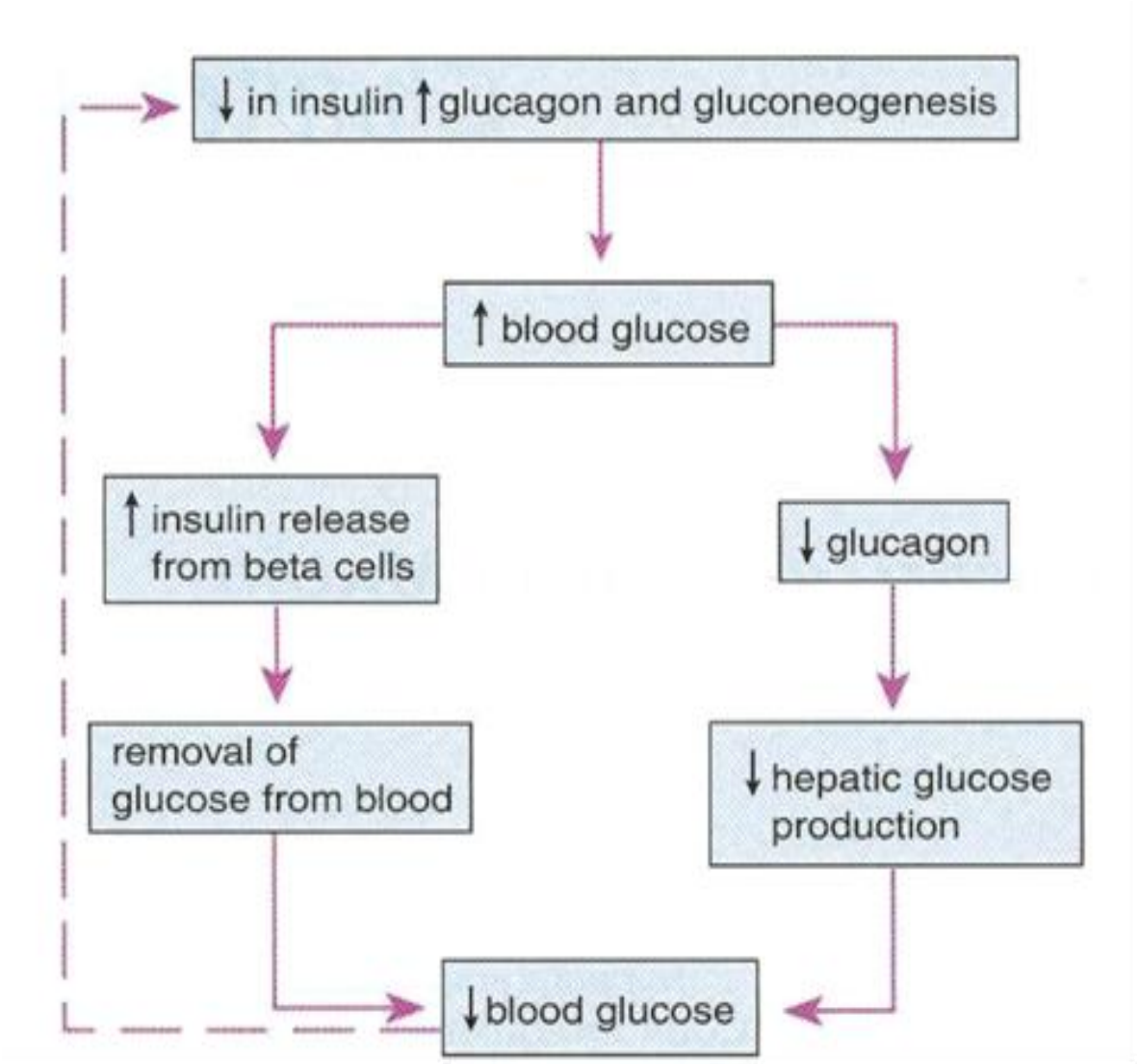
INSULIN RESISTANCE

- Hepatic and peripheral
- Insulin stimulated (post-prandial) glucose uptake impaired, especially in skeletal muscle.

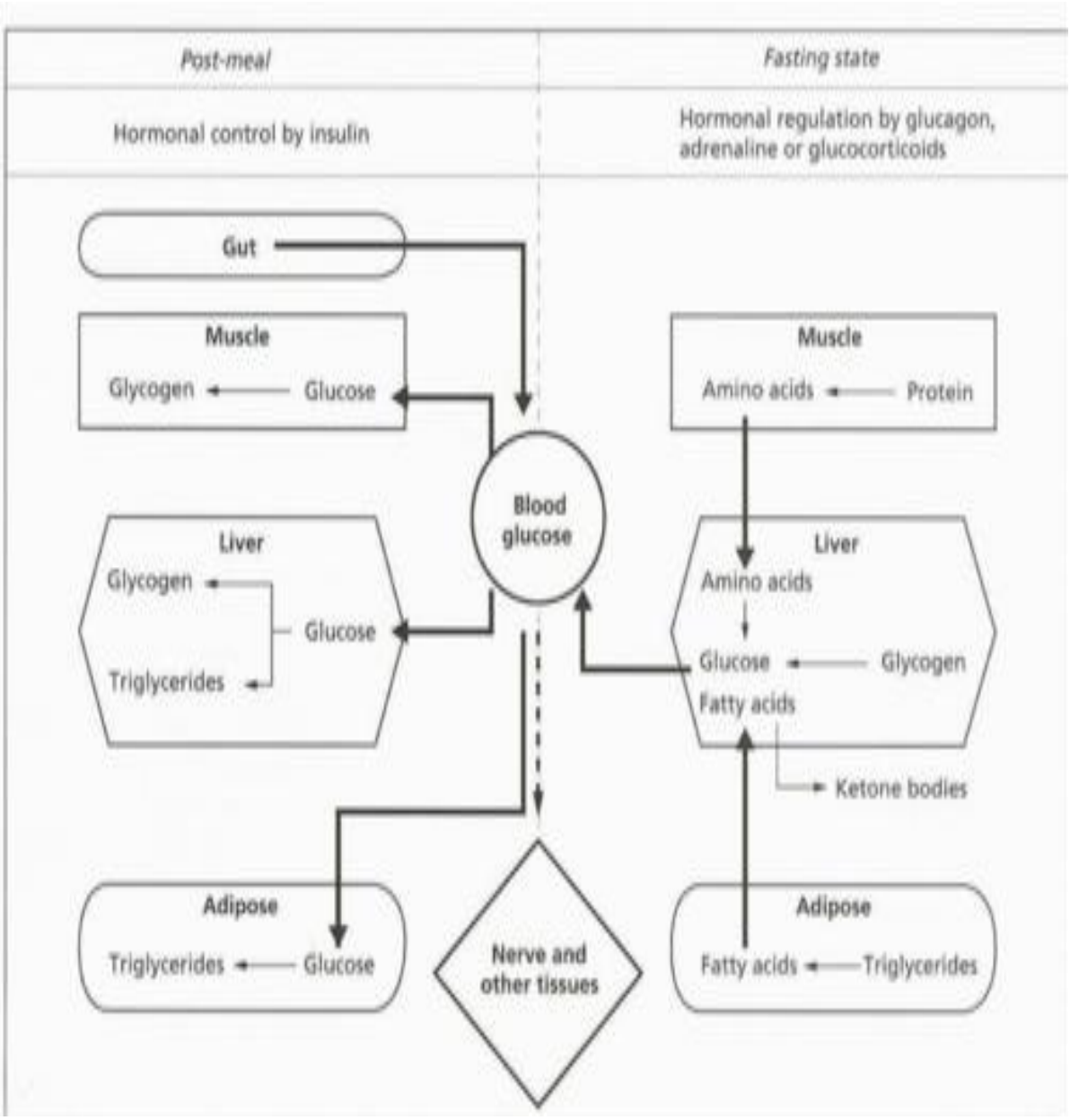
INCREASE GLUCOSE

- Enhanced hepatic glucose output, impaired peripheral utilization

PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS



COMPARISION OF NORMAL PHYSIOLOGICAL HORMONAL RESPONSE TO FASTING AND POSTPRANDIAL GLUCOSE:



When hyperglycemia begin to develop , the degree of insulin resistance reaches plateau. From this point most of the patients maintain a static degree of insulin resistance, sometimes it vary depending upon significant changes in food intake, physiological stress, glucose toxicity, activity level and glucose sensitizing medications[7]. From this point the further progression causes decline in beta cell function.

During early stages of beta cell dysfunction, abnormalities in postprandial glucose levels are seen. Fasting glucose can be more significantly elevated than postprandial because of multifactorial such as dawn phenomenon where there will be lack of eating to stimulate the insulin secretion by increasing hepatic insulin resistance and decreasing insulin secretion. Even though fasting glucose are elevated it is insufficient to normalize glucose levels. When preprandial (particularly fasting) glucose levels remain under 200mg/dl and also HbA1c levels also under 9% then oral anti-diabetic drugs can provide adequate glucose control targeting both pre and postprandial hyperglycemia[38]. Whereas when fasting glucose levels are at or above 00mg/dl then it indicates that endogenous insulin production is dropping down and glucose control can be sustained only with exogenous insulin supplementation. Longer duration of diabetes also suggest exogenous insulin supplementation may be needed.

FASTING HYPERGLCEMIA:

Elevated fasting glucose levels are due to one of the following

- Insufficient quantity of overnight insulin

The dawn phenomenon

There is a increase in amount of insulin requirement during latter part of sleep cycle and due to circadian changes in anti-insulin hormone levels (probably growth hormone)[6].

- There is a insufficient duration of overnight insulin action

The somogyi effect

Here the body tends to react to extremely low blood sugar (hypoglycemia) by overcompensating, thereby resulting in high blood sugar[39]. The Somogyi effect, also known as the "rebound" effect, which was named after the researcher Michael Somogyi, who first described it this phenomenon .When blood glucose levels drops, the body tries to compensate by releasing counter regulatory hormones such as glucagon and epinephrine[39]. All these hormones then goes to the liver where its glycogen stores in liver are converted into glucose, thereby raising serum blood glucose levels. After this compensation there is a period of high blood sugar during fasting following an episode of hypoglycemia occurred more commonly seen during 2am - 4 am.

The Somogyi effect usually occurs following an episode of untreated nighttime hypoglycemia[7], thereby resulting in high blood sugar levels in the morning due to compensatory mechanism by counter regulatory hormones. Patients who has a high blood sugar in fasting may need to check their blood glucose levels during the middle of the night (for example, around

3 AM). If there is a fall in blood sugar level at that time, then measures to be taken for increasing their food intake or lowering their insulin dose in the evening. For preventing the Somogyi effect The only way to avoid developing hypoglycemia in the first place.

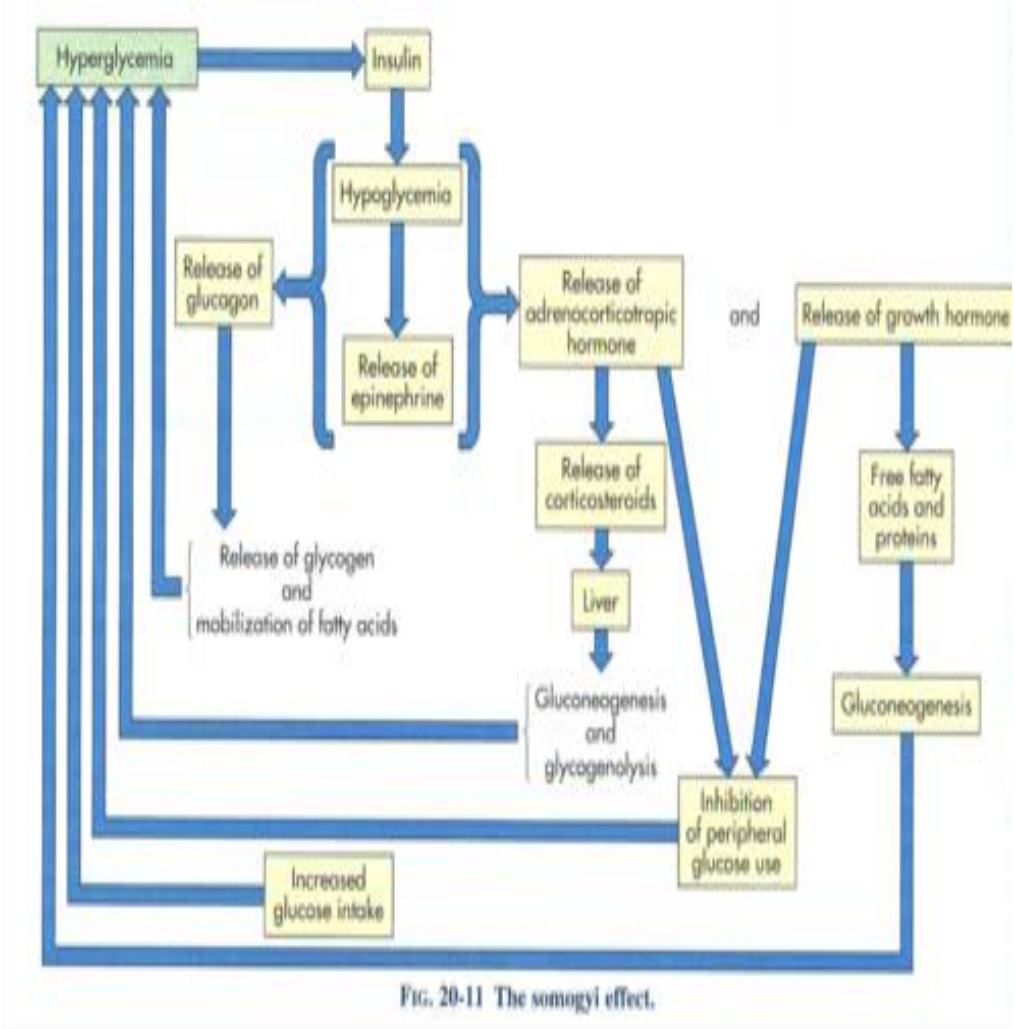


FIG. 20-11 The somogyi effect.

- Increased insulin resistance probably due to dietary fat in the supper meal
- Late intake of supper with glucose absorbtion after bedtime.

CRITERIA FOR TESTING FOR DIABETES IN ASYMPTOMATIC ADULT INDIVIDUALS

➢ Testing for diabetes should be considered in all individuals at age of 45 years and above,
particularly in those with a BMI more than 25 kg/m2*, and, if normal, should be repeated at
3-year intervals.
➢ Testing should be considered at a younger age or be carried out more frequently in
individuals who are overweight (BMI > 25 kg/m2*) and have additional risk factors:
• who are habitually physically inactive
• who have a first-degree relative with diabetes
• if persons are members of a high-risk ethnic population (e.g., African
American, Latino, Native American, Asian American, Pacific Islander)
• persons who have delivered a baby weighing more than 3.5 kg or who
have been diagnosed with GDM
• persons with history of hypertension
• persons with HDL cholesterol level >35 mg/dl (0.90 mmol/l) and/or a
triglyceride level >250 mg/dl (2.82 mmol/l)
• with history of Poly Cystic Ovarian Syndrome
• person who have Impaired Glucose Tolerance or Impaired Fasting
Glucose
• persons who have other clinical conditions associated with insulin

Resistance (e.g. Poly Cystic Ovarian Syndrome or Acanthosis nigricans)

TREAMENT

Clear treatment goals to be set by initial assessment of the patient. These are the list of goal parameters to be considered during treatment.

a. Glucose levels [fasting, before other meals, 2 hours after meals]
b. HbA1C
c. Weight change
d. Lipid levels
e. Blood pressure levels

LIFE STYLE ADJUSTMENT[33]

a. Patient should get adopted to new nutrition plan
b. Exercise activity program to be initiated (commensurate with cardiac and general medical status)

MONITORING

a. Self monitoring of blood glucose levels should be encouraged
b. Blood pressure monitoring
c. To monitor other metabolic parameters

TAKING MEDICATION OR INSULIN FOR DIABETES

Taking medications for other conditions[39] :

a. Dyslipidemia

b. Hypertension

c. Microalbuminuria

d. Hypercoagulability

e. Vascular protection

HEALTH CARE TEAM SUPPORTS

a. Diabetes educator

b. Dieticians

c. Exercise physiologist

FREQUENT CHECKUP WITH OTHER SPECIALIST[34] :

a. Ophthalmologist

b. Podiatrist

c. Vascular specialist

d. Mental health professionals

e. Cardiologist

f. Nephrologist

ORAL ANTIDIABETIC DRUGS

In type 2 diabetes mellitus patients when lifestyle changes are no longer sufficient for achieving treatment goals then antidiabetes medications are first line theraphy . The American diabetes association has recommended indications to start antidiabetes medications. They are

- Treatment goals have not met even after 3 months of medical nutrition theraphy and exercise programs.
- Symptomatic hyperglycemia
- Presentation of ketosis
- Imminent surgery

But in most of the cases it doesn't take 3 months to start antidiabetes drugs. American diabetes association made this point to say that there should be finite trial period to determine the effectiveness of life style. Infact the clinical trend was also to start antidiabetes medication earlier in both natural history of type 2 diabetes and progressive deterioration of sugar control. Monotherapy , combination therapy and combine with insulin are different mode of glycemic control available[40]. Type 2 diabetes treatment includes aggressive e glucose control. Because there are more risk of microvascular and macrovascular occlusion in type 2 diabetes mellitus. As diabetes mellitus is more important in metabolic syndrome and pathologically tied to it, also as a risk factor for cardiovascular related disorders it is important to optimize the glucose control so antidiabetic medications are initially tried along with lifestyle changes.[18]

Table 8:

ANTIDIABETIC MEDICATIONS	DOSAGE	EFFECT	ADVERSE EFFECTS
SULFONYLUREAS :			
FIRST GENERATION :		Increases insulin secretion in response to rising glucose levels	Anorexia ,Weight gain, nausea Symptomatic hypoglycaemia ,skin rahes Occasionally blood dyscarias
Tolbutamide	250 – 3000 mg		
Tolazamide	100 – 1000 mg		
Chlorpropamide	100 – 750 mg		
SECOND GENERATION:			
Glyburide	1.25 -20 mg	Increases insulin secretion response to hyperglycemia	
Glyburide (micronized formulation)	0.75 – 12 mg		
Glipizide	2.5 – 40 mg		
Glimipride	1 – 8 mg		
Gliclazide	5 – 40 mg		
Gliclazide ER	5 – 20 mg		
BIGUANIDES : Metformin	500 – 2000 mg	Reduces insulin resistance	Anorexia, abdominal discomfort and lactic acidosis .
ALPHA-GLUCOSIDASE INHIBITOR :			
Acarbose	25 – 150 mg if <60kg	Slows glucose absorption	Flatulence , abdominal bloating , Non response to carbohydrates other than glucose if hypoglycaemic , (Rare) liver abnormalities
Voglibose	25 – 300 mg if >60 kg		
Miglitol	25 – 100 mg		

THIAZOLIDINEDIONES Rosiglitazone Pioglitazone	2 – 8 mg 15 – 45 mg	Reduces insulin resistance	Increase in deposition of subcutaneous fat and/or fluid , Increases the risk of fractures in women , drop in haemoglobin levels Possible increases the risk of myocardial infarction in elderly (rosiglitazone) , Increased LDL-C (rosiglitazone
MEGLITINIDES : Repaglinide **D-PHENYLALANINE :** Netaglinide	2 – 16 mg 120 – 360 mg	Stimulates the glucose dependent postprandial insulin release from functioning beta-cells	Symptomatic hypoglycaemia , Nausea, diarrhoea, constipation , Skin rashes, abnormal LFT , (Rare) hepatitis and/or jaundice
GLP-1 AGONIST : Exenatide Liraglutide	Maximum 10 mcg/ dose BID Subcutaneously 0.6 mg – 1.8 mg Subcutaneously	Enhances glucose stimulated insulin secretion suppresses glucagon secretion, slows gastric emptying and reduces appetite	Constitutional symptoms , Reaction at Injection site, Possible pancreatitis
DPP-IV INHIBITORS : Sitagliptin Alogliptin Lingliptin Saxagliptin	25 – 100 mg 6.25 – 25 mg 5 – 20 mg 5 – 10 mg	Blocks the degradation of GLP-1, prolonging it's action time. Effects are stimulation of insulin secretion and suppression of glucagon suppresion	Upper respiratory tract symptoms , Headache , Nausea , occasionally pancreatitis

SGLT2 INHIBITORS : Dapagliflozin	2.5 – 10 mg	They inhibit glucose reabsorbtion in proximal renal tubulesproviding a insulin dependent mechanism to reduce glucose	

INSULIN

- Insulin is a peptide hormone which is produced by beta cells in pancreas.

ACTIONS

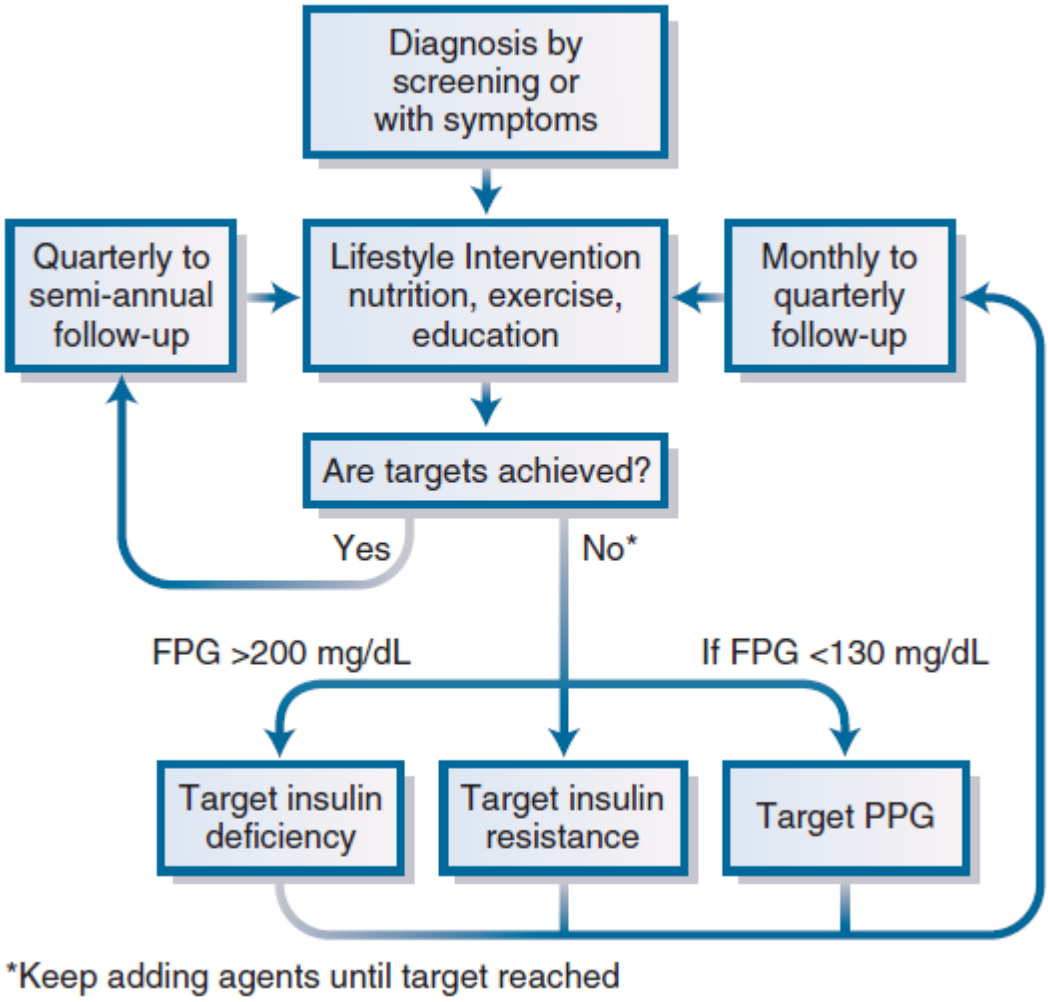
1. It regulates the metabolism of fats and carbohydrates .
2. It promotes glucose absorption from blood to skeletal muscle and fat tissue .
3. It inhibit the release of glucagon.

Type 2 diabetes mellitus:

Antidiabetes drugs are initially preffered in management of diabetes mellitus. As slowly beta cell declines requirement of exogenous insulin is required for maintaining glycemic control. Indications for insulin are

1) Glucose toxicity (marked hyperglycemia leading to decreased insulin sensitivity)
2) Decline in beta cell function and mass leading to insufficient endogenous insulin production
3) Needed for effective postprandial hyperglycemia control
4) Oral antidiabetes drugs contraindication .

TREATMENT ALGORITHM FOR TYPE 2 DIABETES MELLITUS



Reference: American diabetes association standards of medical care diabetes 2010

Reinforcement of lifestyle modification should be done at every visit, and glycosylated hemoglobin (HbA1c) should be checked periodically every 3 months until the HbA1c reaches less than 7% and should be repeated at least every 6 months. The interventions definitely should be changed if the HbA1c is 7% or higher.

GUIDE TO INSULIN THERAPHY[41]

Patients with type 2 diabetes who are receiving exogenous insulin can often be managed with a singledaily dose of either intermediate or long acting insulin which also can be added to their oral hypoglycaemic drugs . There is no need of every time for rapidly acting insulin. During starting the recommended dose for basal insulin is a single dose (for example: 10 units at bedtime or breakfast). The basal insulin can be either isophane or glargine. Glargine are prone to cause less hypoglycaemia when compared to isophane. In long term metformin can be continued or added as it reduces insulin resistance and also to help reduce weight gain.

STEP 1:

Check that diet, physical activity and oral medication that are appropriate and also that complicating medical conditions are not present

STEP 2:

Decide the timing and type of insulin

FASTING BLOOD GLUCOSE	EVENING BLOOD GLUCOSE	SCHEDULE
High	OK	Night-time basal
OK	High	Morning basal
High	High	Twice daily isophane/once daily glargine

STEP 3:

- Decide about dose either by starting at low dose and slowly increasing the dose.
- Single dose can be given either in morning or evening
- Low dose may be required in thin persons, elderly and active patients.
- High dose may be needed in over weight and underactive patients.

STEP 4:

- Adjustment of doses should be done in increments of 10 – 20% at intervals of 2 – 4 days
- Mixed insulin can be used.

SITES OF INSULIN INJECTION:

Abdominal wall: Generally fastest and the most uniform rate of absorption.

Legs: Slowest absorption (unless exercising). Acceptable site.

Arms: Not recommended

Activity Profiles of Different Types of Insulin

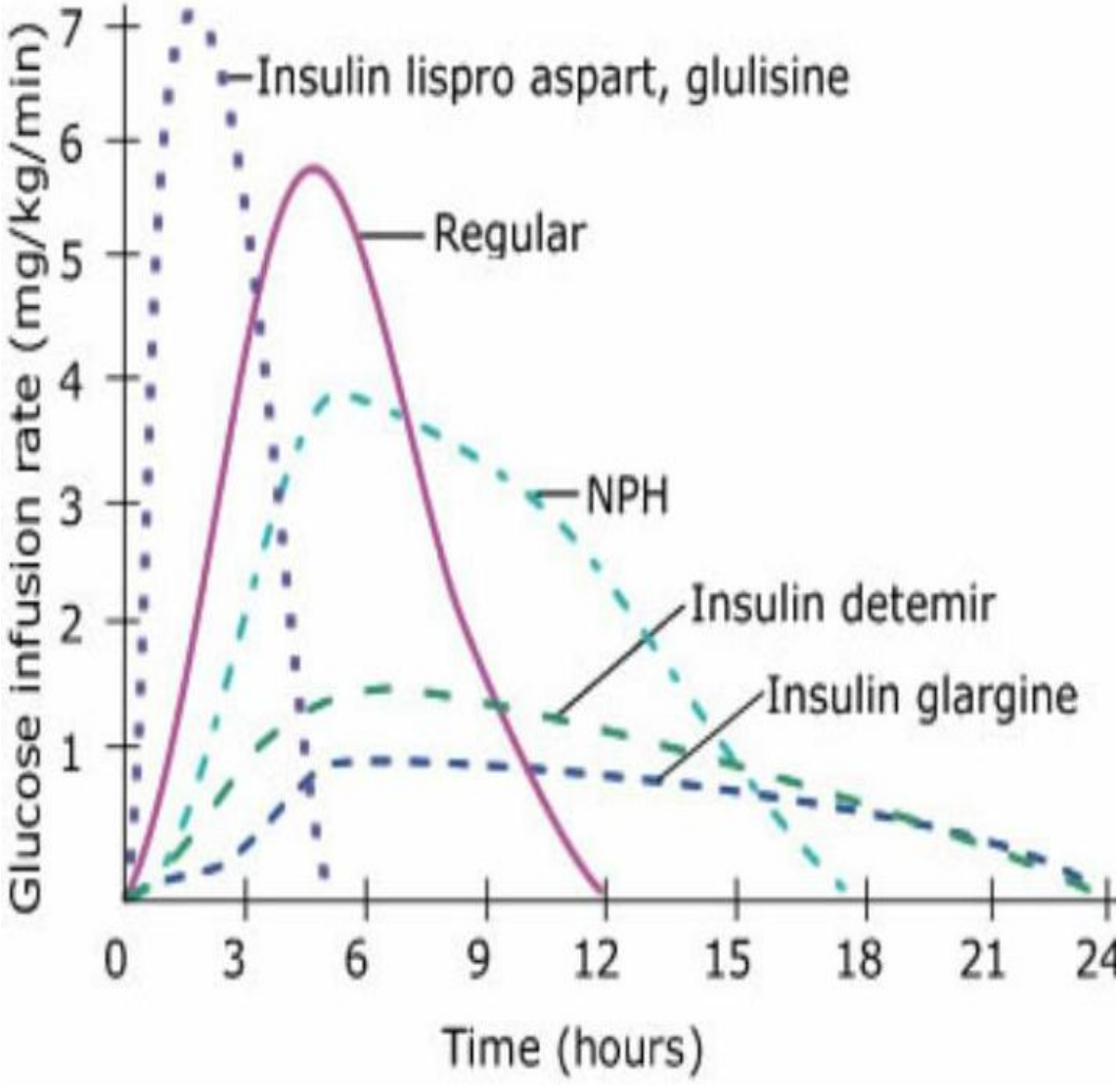


Table 9:

INSULIN TYPE	ONSET	PEAK	DURATION	NOTES FOR USE
RAPIDLY ACTING ANALOGUE:				
LISPRO	<15 minutes	0.5-1.5 hours	3-5 hours	If mixing with NPH rapid acting insulin should be drawn first. Mixture should be given immediately to avoid effect of peak action.
ASPART	<15 minutes	1-3 hours	3-5 hours	
GLULISINE	<15 minutes	1 hour	3-5 hours	
SHORT ACTING PRODUCTS :				
REGULAR	0.5-1 hours	2-4 hours	4-8 hours	May be mixed with NPH in same syringe. Mixed order should be the clear regular to be drawn first and then cloudy NPH
INTERMEDIATE ACTING PRODUCTS :				
NPH (NEUTRAL PROTAMINE HAGEDORN)	2-4 hours	4-8 hours	10-18 hours	
LONG ACTING ANALOGUE :				
GLARGINE	2-4 hours	Same action throughout the day	24 hours	Do not mix with any insulin. Available as a pen or vial with syringe.
DETEMIR	2-3 hours	6-8 hours	5.7-23.2 hours	
COMBINED PRODUCTS				
REGULAR/ NPH 30/70	0.5-1 hour	2-10 hours	10-18 hours	NPH 70% + REGULAR 30% .

				insulin action have two peaks.
REGULAR/NPH 50/50				NPH 50% + REGULAR 50%
ASPART/PROTAMINE 30/70 OR LISPRO/PROTAMINE 25/75 OR LISPRO/PROTAMINE 50/50	<15 minutes	1-2 hours	10-18 hours	ASPART PROTAMINE 70% + ASPART 30% LISPRO PROTAMINE 75% + LISPRO 25% LISPRO PROTAMINE 50% + LISPRO 50%

COMPLICATIONS OF DIABETES

I. ACUTE:

1. Hypoglycemia:

It is mostly seen in diabetic patients who are treated with insulin. The risk of hypoglycemia is the most important single factor as it is limiting the attainment of therapeutic goal, namely near normal glycemia[38].

Signs and symptoms of hypoglycemia :

Autonomic hyperactivity: Anxiety, Palpitation, Sweating, Tremors, Hunger, Nausea and Hyperactivity.

Neuroglycopaenia: Headache , Mental dullness[38] , Fatigue , Dizziness , Blurring of vision, seizure, amnesia, confusion and unconsciousness.

Risk factors for hypoglycemia:

1) If there is excessive doses of insulin or insulin secretagogues.
2) If the exogenous glucose delivery decreased
3) If utilization of glucose is increased (i.e during exercise)
4) If Endogenous glucose production is decreased (following alcohol ingestion)
5) Renal failure
6) If insulin sensitivity is decreased

2. Diabetic Ketoacidosis:

It is a major medical emergency and remains a serious cause of morbidity, principally in patients with type 1 diabetes. Symptoms of diabetic ketoacidosis are nausea, vomiting, excessive urination, thirst and abdominal pain. In severe acidosis laboured type of breathing is seen wich is characteristically reffered to as "kussmaul respiration"[33] on physical examination dehydration signs are present. Due to dehydration there will be decrease in blood volume which causes tachycardia and hypotension. Respiratory rate is increased if kussmaul breathing is present.

The cardinal biochemical features of diabetic Ketoacidosis are

- Hyperglycaemia
- Hyperketonaemia
- Metabolic acidosis

3) Hyperosmolar hyperglycemic state [39] :

This condition is usually characterized by marked hyperglycaemia without any significant hyperketonaemia or acidosis. Here Thromboembolic complications are common. It usually occurs in type 2 diabetes mellitus. Signs and symptoms are usually resemble like diabetic ketoacidosis.

DIFFERENCE BETWEEN DIABETIC KETOACIDOSIS AND HYPEROSMOLAR

HYPERGLYCAEMIC STATE:

Table 10:

	DKA	HHS
plasma glucose (mg/dl)	>250	>600
Arterial PH	<7.3	>7.3
Sodium bicarbonate	<15	>15
Serum or urine ketones	positive	Negative
Effective serum osmolality	Variable	>320
Anion gap	>12	<12
Mental status	Variable	Stupor or coma
Total water deficit	100	100 to 200
Sodium (mEq/kg)	7 to 10	5 to 13
Chloride (mEq/kg)	3 to 5	5 to 13
Potassium (mEq/kg)	3 to 5	4 to 6

Reference: associations of physician of india textbook of medicine

Pseudohyponatremia is present due to osmotic effect of hyperglycemia in which water moves from intravascular space to extravascular space. So correct serum sodium by approximately 1.6 mEq/l for 100 mg/dl of glucose. Hyperamylasemia can be seen in diabetic ketoacidosis and is of salivary origin.

II. CHRONIC COMPLICATIONS

Macrovascular Disease

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

Microvascular occlusion:

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 peripheral neuropathy [34] :

- Diabetes is a one of the most common cause for peripheral neuropathy in India.
- Diabetic peripheral neuropathy is most common complication in diabetes which increases the risk for foot ulcers and amputation. Due to significant nerve damage in their feet and toes, patients with diabetic peripheral neuropathy they often do not notice minor cuts, sores, or blisters in these areas. If these wounds were left untreated, they get infected, lead to gangrene, and may even require amputation of the affected area.

CLASSIFICATION OF DIABETIC NEUROPATHY:

- Distal symmetrical polyneuropathy
- Autonomic polyneuropathy
- Polyradiculopathies:
    - Diabetic amyotrophy (Diabetic lumbar polyradiculopathy)
    - Thoracic polyradiculopathy
    - Diabetic neuropathic cahexia
- Mononeuropathy:
    - Cranial mononeuropathy
    - Peripheral mononeuropathy
    - Mononeuropathy multiplex

Diabetic Retinopathy [42]

- 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.

CLASSIFICATION OF DIABETIC RETINOPATHY IN THE EARLY TREATMENT OF DIABETIC RETINOPATHY STUDY

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
Mild nonproliferative retinopathy	At least one microaneurysm, and definition not met for moderate nonproliferative retinopathy, severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Moderate nonproliferative retinopathy	Hemorrhages and/or microaneurysms ≥ standard photograph 2A*; and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present; and definition not met for severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy (see below)
Severe nonproliferative retinopathy	Soft exudates, venous beading, and intraretinal microvascular abnormalities all definitely present in at least two of fields four through seven; or two of the preceding three lesions present in at least two of fields four through seven and hemorrhages and microaneurysms present in these four fields, equaling or exceeding standard photo 2A in at least one of them; or intraretinal microvascular abnormalities present in each of fields four through seven and equaling or exceeding standard photograph 8A in at least two of them; and definition not met for early proliferative retinopathy or high-risk proliferative retinopathy (see below)
Early proliferative retinopathy (i.e., proliferative retinopathy without Diabetic Retinopathy Study high-risk characteristics)	New vessels; and definition not met for high-risk proliferative retinopathy (see below)
High-risk proliferative retinopathy (proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics)	New vessels on or within one disc diameter of the optic disc (NVD) ≥ standard photograph 10A* (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ one-quarter disc area

MATERIALS AND METHODS

Source of data

50 patients of type 2 diabetes mellitus admitted to PSG HOSPITAL between may 2014 and september 2014 were included in the study[43]. Also 50 non diabetic patients admitted during the same period were included in the study under the control group.

Method of collection of data [38]:(including sampling procedures if any)

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 were considered to be included for the study.

INCLUSION CRITERIA FOR CASE SELECTION:

- ✓ Patient diagnosed to be diabetic fitting in to the above criteria.

EXCLUSION CRITERIA FOR CASE SELECTION:

- ✓ Associated hypertension
- ✓ Gastrointestinal disorders
- ✓ Impaired renal function
- ✓ Alcoholism
- ✓ Pancreatitis
- ✓ Other endocrinal disorders
- ✓ Patient using diuretics, aminoglycosides
- ✓ Iatrogenic administration

INCLUSION CRITERIA FOR CONTROLS:

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

ESTIMATION OF SERUM MAGNESIUM:

Estimation of serum magnesium by chlorophosphonazo – 3

RESULTS

Study Design:

A Comparative study consisting of 50 Diabetic Mellitus patients and 50 controls was undertaken to investigate the change pattern of serum magnesium in DM cases when compared to controls[29]

Table-11:

Age distribution

Age	Gender		
	Male	**Female**	**Total**
<40	3	4	7
41-50	15	12	27
51-60	14	11	25
61-70	12	9	21
>70	15	5	20
Total	**59**	**41**	**100**

Table 12

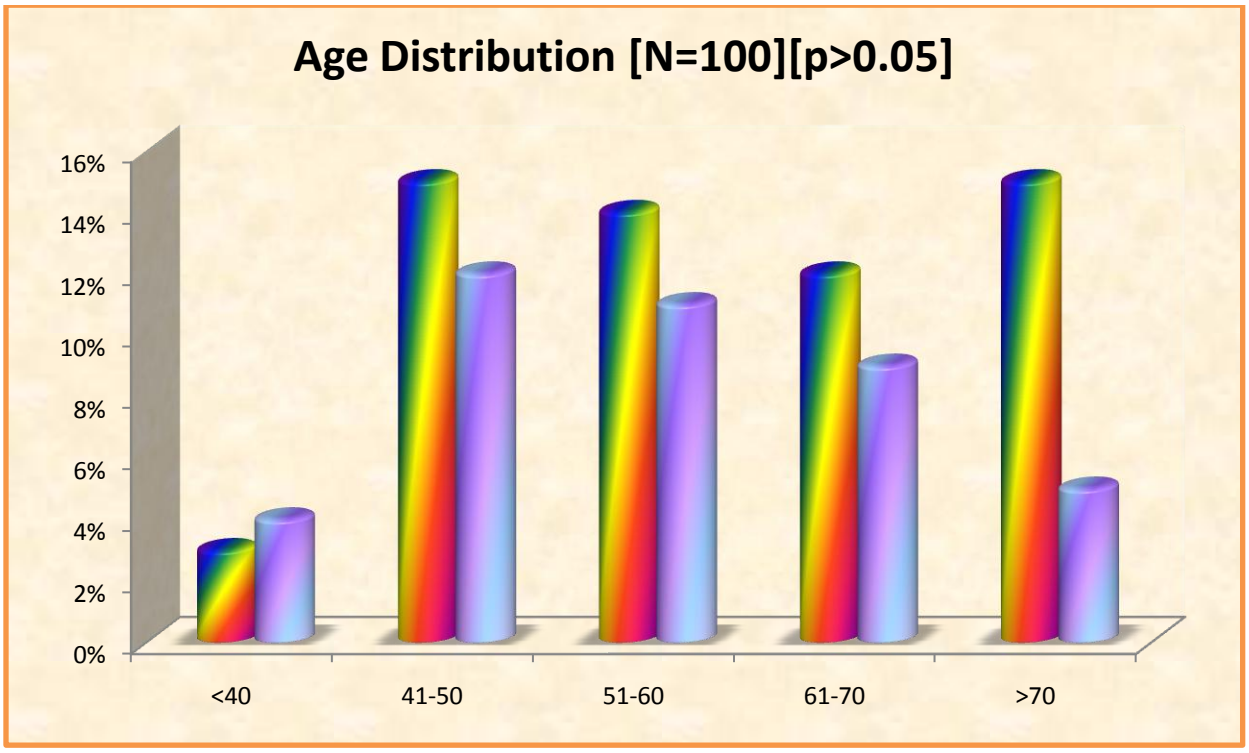
Sex distribution

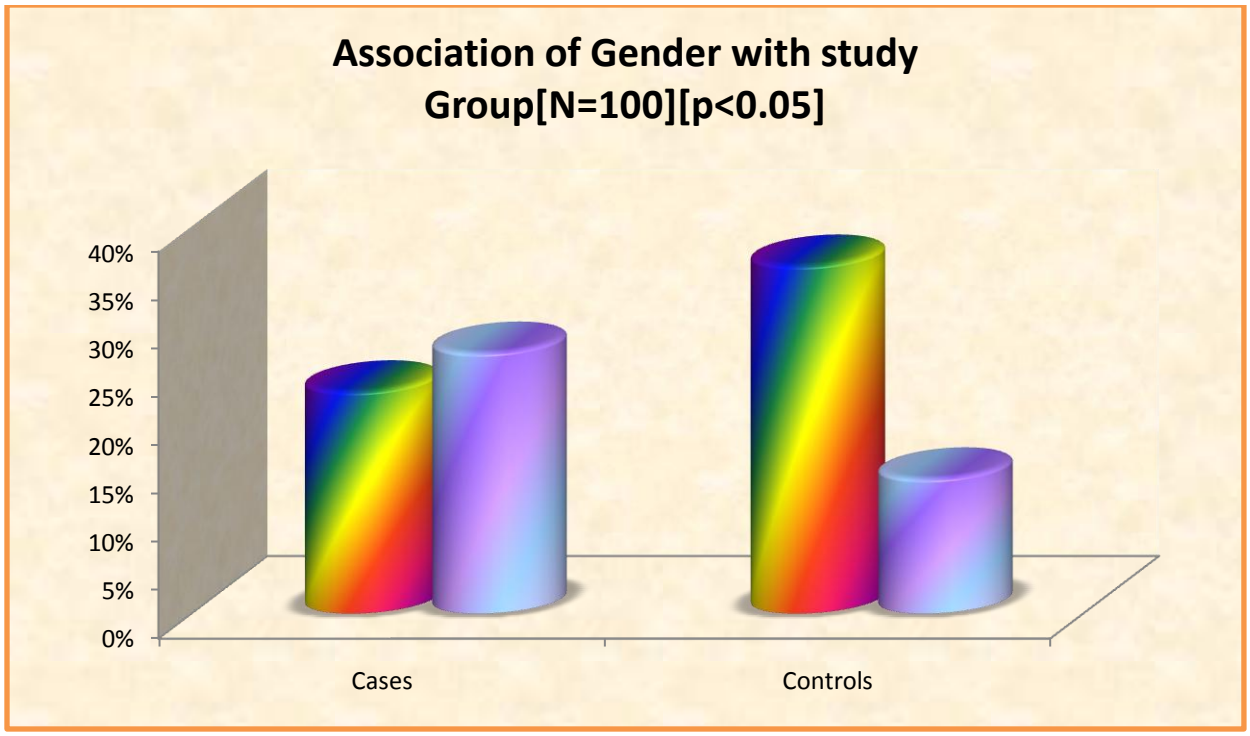
Gender	Group		
	Cases	**Controls**	**Total**
Male	23	36	59
Female	27	14	41
Total	50	50	100

Mean Clinical Variables

		Mean	SD	95% CI for Mean		Minimum	Maximum	'P' value
				Lower Bound	Upper Bound			
Age	**Male**	59	13	56	62	27	82	
	Female	55	12	52	59	32	80	>0.05
	Overall	58	12	55	60	27	82	

The mean age of patients (both control and cases) included in the study was 58 ± 12 he mean age For male include in this study was 59 ± 13and in female was 55 ± 12. There was no significant difference in the outcome among different age groups and gender (p value > 0.05).




Association of Gender with study Group[N=100][p<0.05]
40%
35%
30%
25%
20%
15%
10%
5%
0%
Cases
Controls

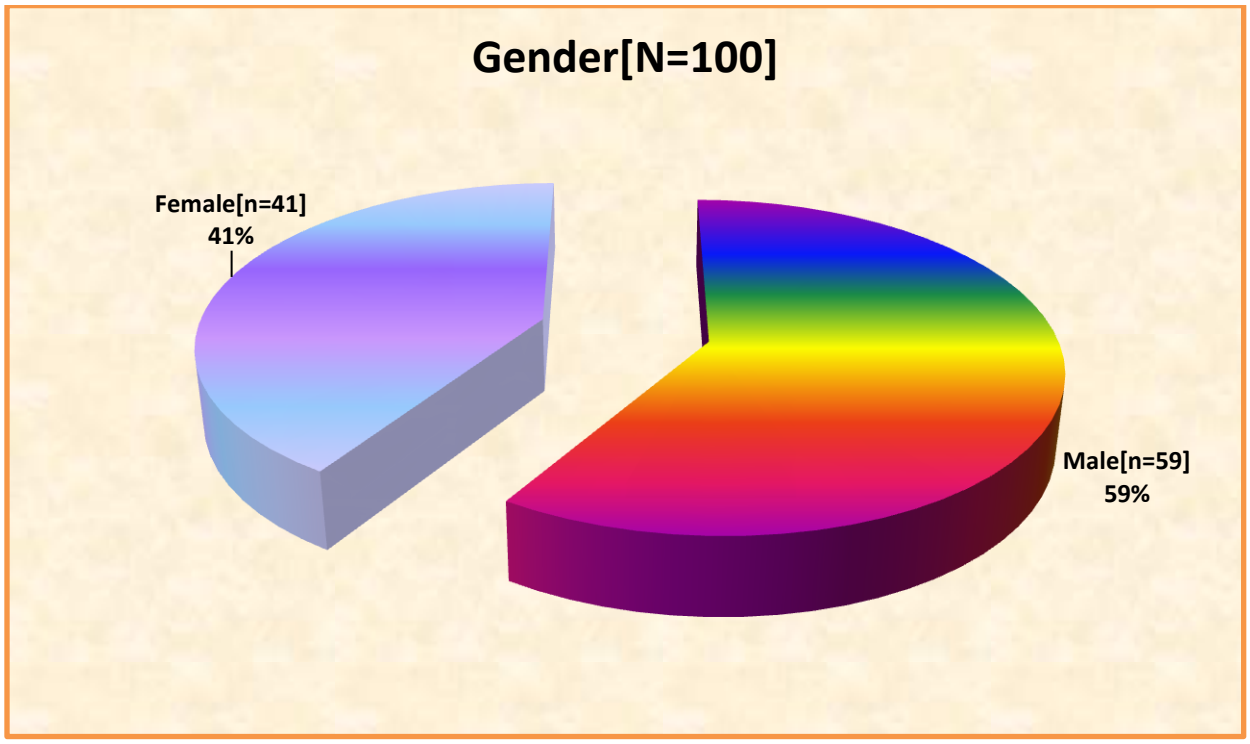

Gender[N=100]
Female[n=41]
41%
Male[n=59]
59%

Table 13:

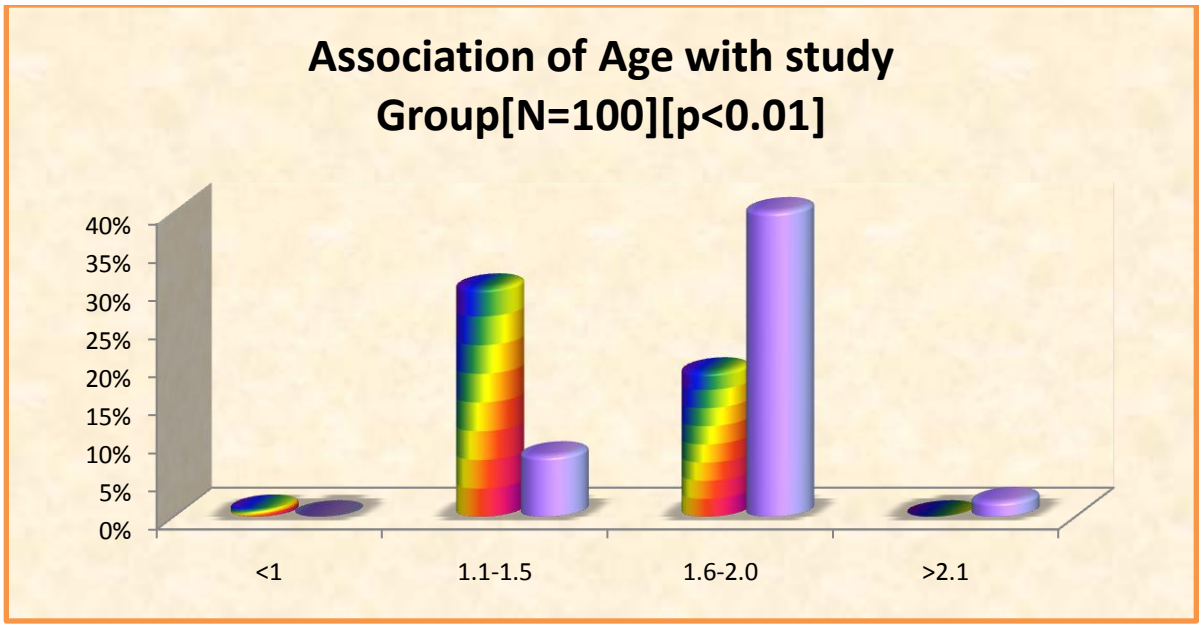
Comparison of serum magnesium levels between cases and controls:

Magnesium	Group		
	Cases	Controls	Total
<1	1	0	1
1.1-1.5	30	8	38
1.6-2.0	19	40	59
>2.1	0	2	2
Total	**50**	**50**	**100**

Mean Sr. Magnesium in study Groups

Clinical Variables		Mean	SD	95% CI for Mean		Minimum	Maximum	'P' value
				Lower Bound	Upper Bound			
MAGNESIUM	Cases	1.47	0.20	1.4	1.5	1.0	1.8	
	Controls	1.71	0.20	1.7	1.8	1.2	2.1	<0.001
	Total	1.59	0.23	1.5	1.6	1.0	2.1	

There is significant difference between levels of serum magnesium levels among diabetics and controls. The mean serum magnesium levels in cases and controls are 1.47 $\pm$ 0.2mg/dl and 1.71 $\pm$ 0.2 mg/dl respectively [45]. Cases are 24 times more likely to have less serum magnesium (<1.50mg/dl) when compared to controls with p<0.001[46].


Association of Age with study Group[N=100][p<0.01]
40%
35%
30%
25%
20%
15%
10%
5%
0%
<1
1.1-1.5
1.6-2.0
>2.1

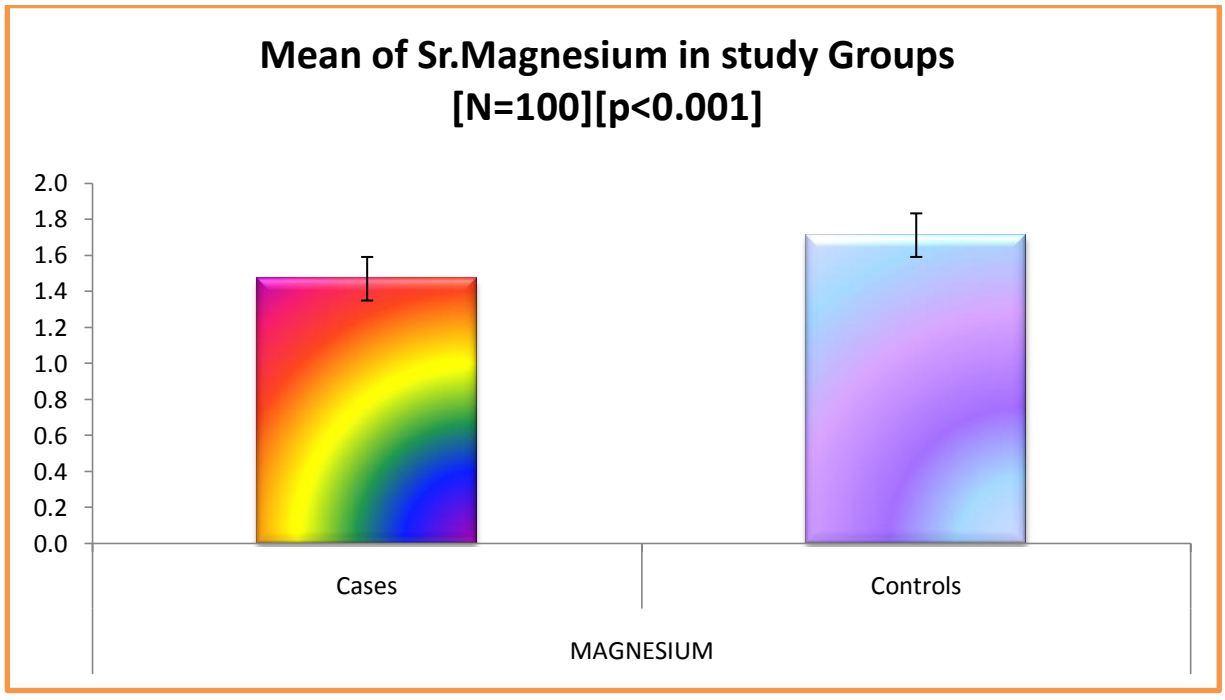

Mean of Sr.Magnesium in study Groups [N=100][p<0.001]
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Cases
Controls
MAGNESIUM

Table 14

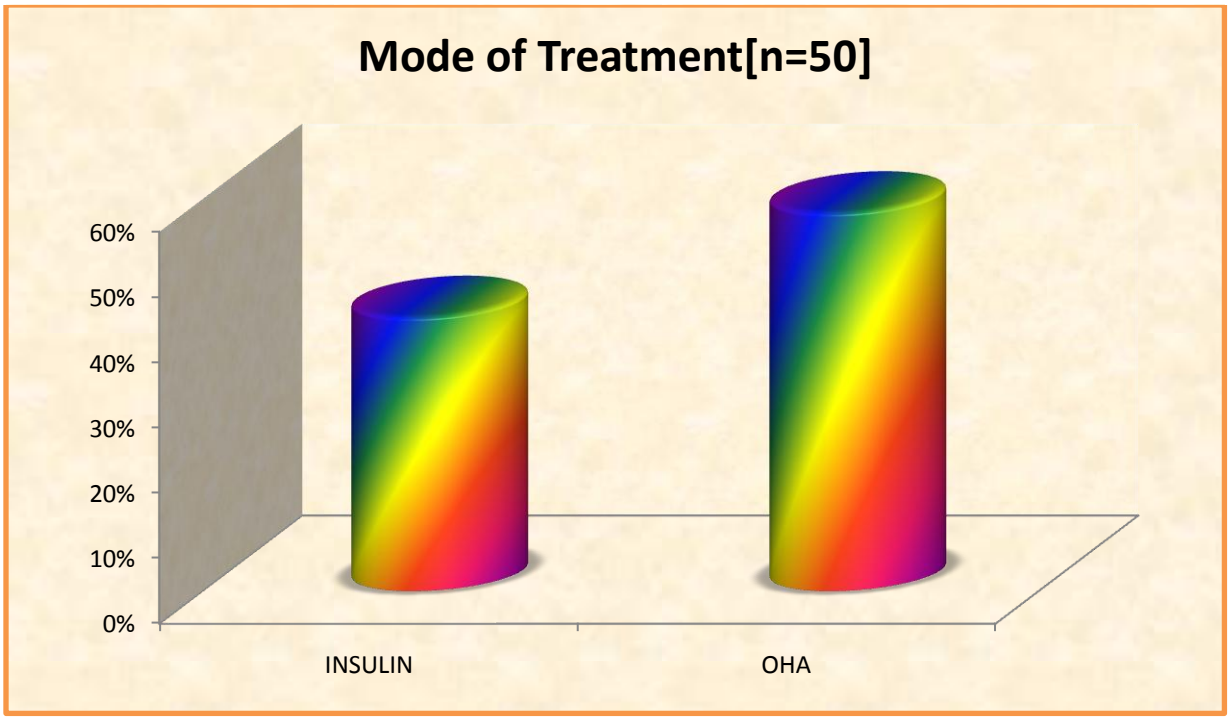
Effect of type of treatment on Serum magnesium

Mode of Treatment	Cases	(%)
INSULIN	21	42%
OHA	29	58%
Total	**50**	**100%**

Mean Sr.Magnesium with Treatment Group

MAGNESIUM	Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
			Lower Bound	Upper Bound			
INSULIN	1.44	0.2	1.3	1.5	1.0	1.8	
OHA	1.49	0.2	1.4	1.6	1.1	1.8	>0.05
Total	1.47	0.2	1.4	1.5	1.0	1.8	

The mean value for diabetic patients receiving insulin therapy was 1.44 ± 0.2 and in patients who are receiving OHA was 1.49 ± 0.2. There was no significant difference in the outcome among treatment groups (p value > 0.05) .


Mode of Treatment[n=50]
60%
50%
40%
30%
20%
10%
0%
INSULIN
OHA

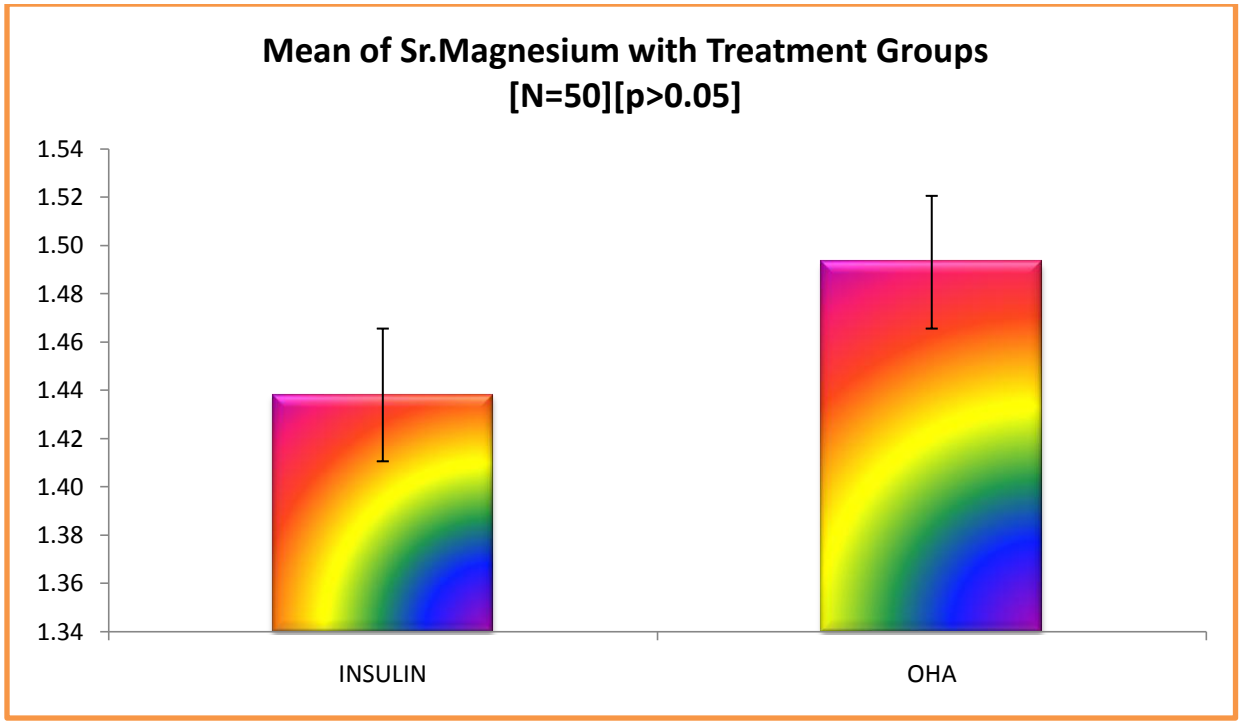

Mean of Sr.Magnesium with Treatment Groups
[N=50][p>0.05]
1.54
1.52
1.50
1.48
1.46
1.44
1.42
1.40
1.38
1.36
1.34
INSULIN
OHA

Table 15:

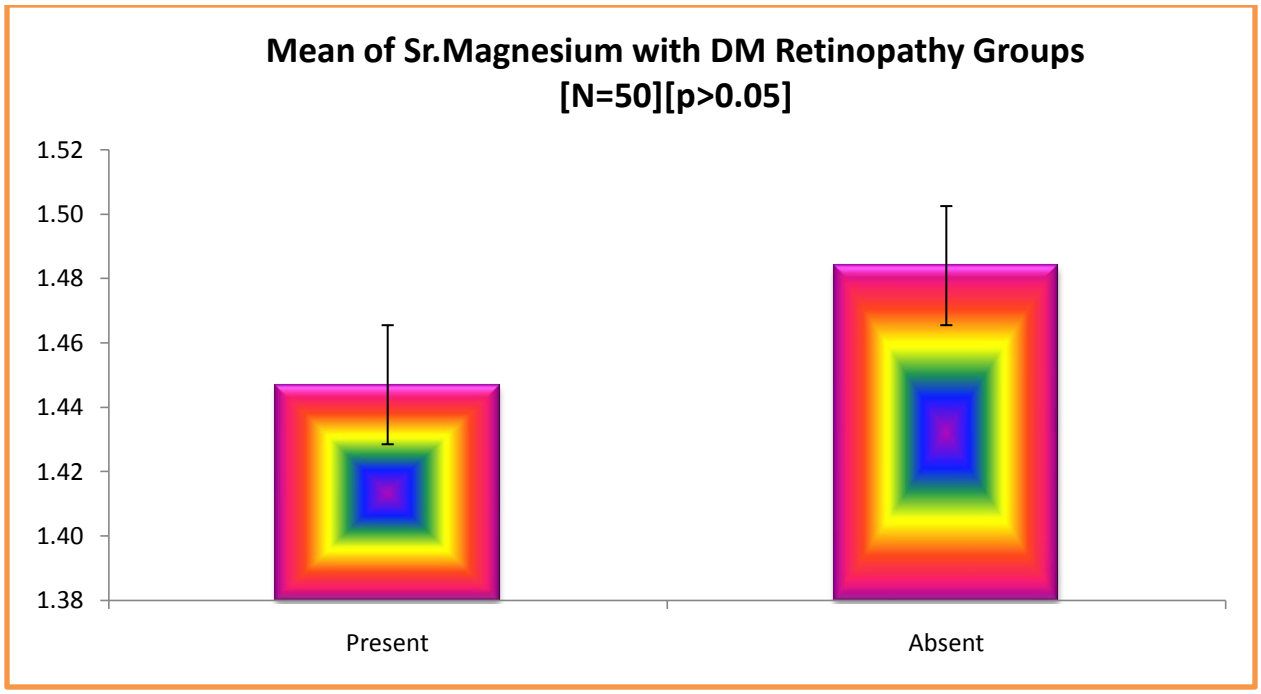
Effect of serum magnesium in Diabetic Retinopathy:

DM Retinopathy	Cases	(%)
Present	19	38%
Absent	31	62%
Total	**50**	100%

Mean Sr. Magnesium with DM Retinopathy

MAGNESIUM	Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
			Lower Bound	Upper Bound			
Present	1.45	0.19	1.4	1.5	1.20	1.80	
Absent	1.48	0.21	1.4	1.6	1.00	1.80	>0.05
Total	1.47	0.20	1.4	1.5	1.00	1.80	

The mean value for patients with diabetic retinopathy was 1.45 ± 0.19 and in patients without diabetic retinopathy was 1.48 ± 0.21. There was no significant difference in the outcome among treatment groups (p value > 0.05) .


Mean of Sr.Magnesium with DM Retinopathy Groups
[N=50][p>0.05]
1.52
1.50
1.48
1.46
1.44
1.42
1.40
1.38
Present
Absent

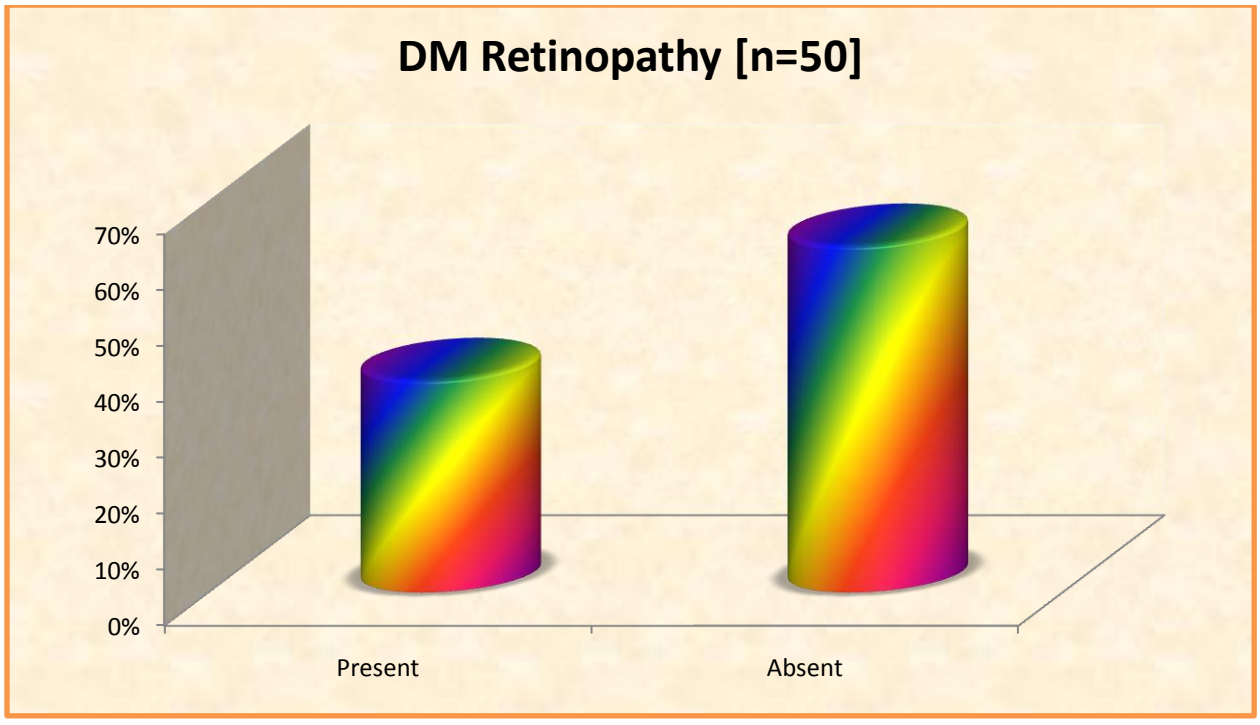

DM Retinopathy [n=50]
70%
60%
50%
40%
30%
20%
10%
0%
Present
Absent

Table 16:

Effect of level of Control of Diabetes Mellitus on Serum magnesium[47]

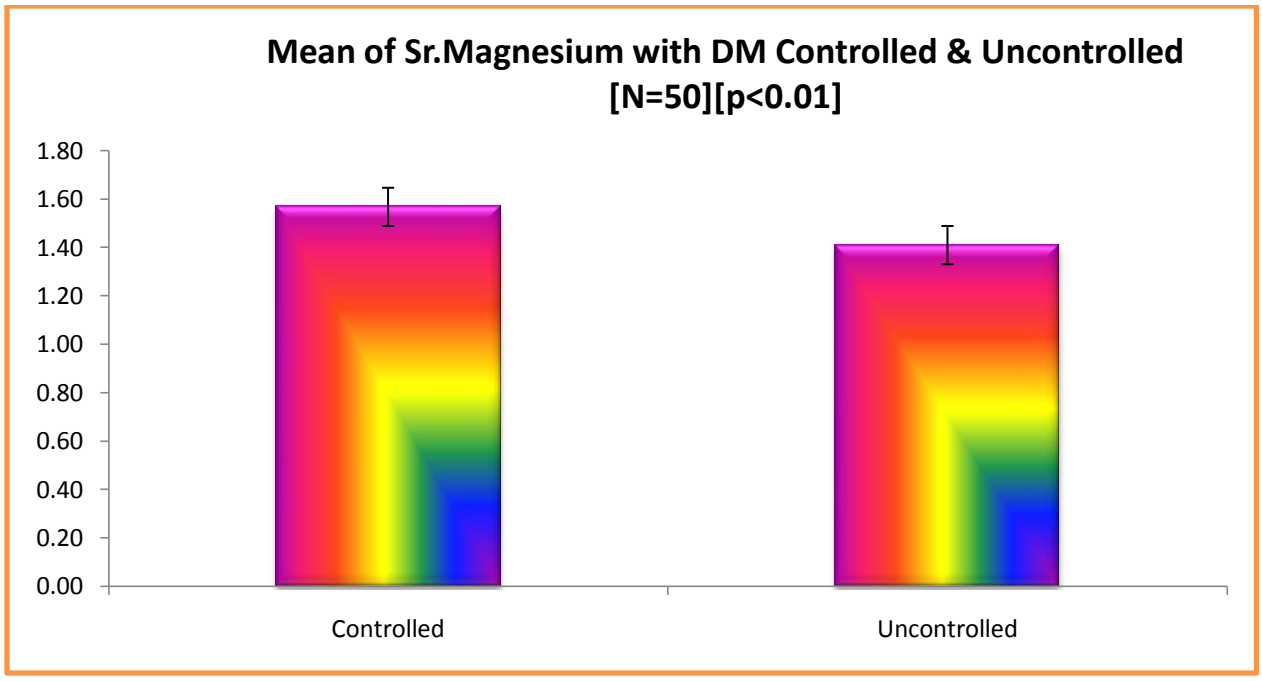
DM CONTROLLED/ UNCONTROLLED in the study Group

Controlled/Uncontrolled	Cases	(%)
Controlled	19	16%
Uncontrolled	31	26%
Total	**50**	43%

Mean Sr.Magnesium with DM Out come

MAGNESIUM	Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
			Lower Bound	Upper Bound			
Controlled	1.57	0.19	1.476	1.661	1.20	1.80	<0.01
Uncontrolled	1.41	0.19	1.34	1.479	1.00	1.70	
Total	1.47	0.20	1.412	1.528	1.00	1.80	

There was significant difference between magnesium levels among controlled and uncontrolled diabetics. The mean serum magnesium levels among controlled and uncontrolled diabetics were 1.57 mg/dl and 1.41 mg/dl respectively[48].


Mean of Sr.Magnesium with DM Controlled & Uncontrolled
[N=50][p<0.01]
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Controlled
Uncontrolled

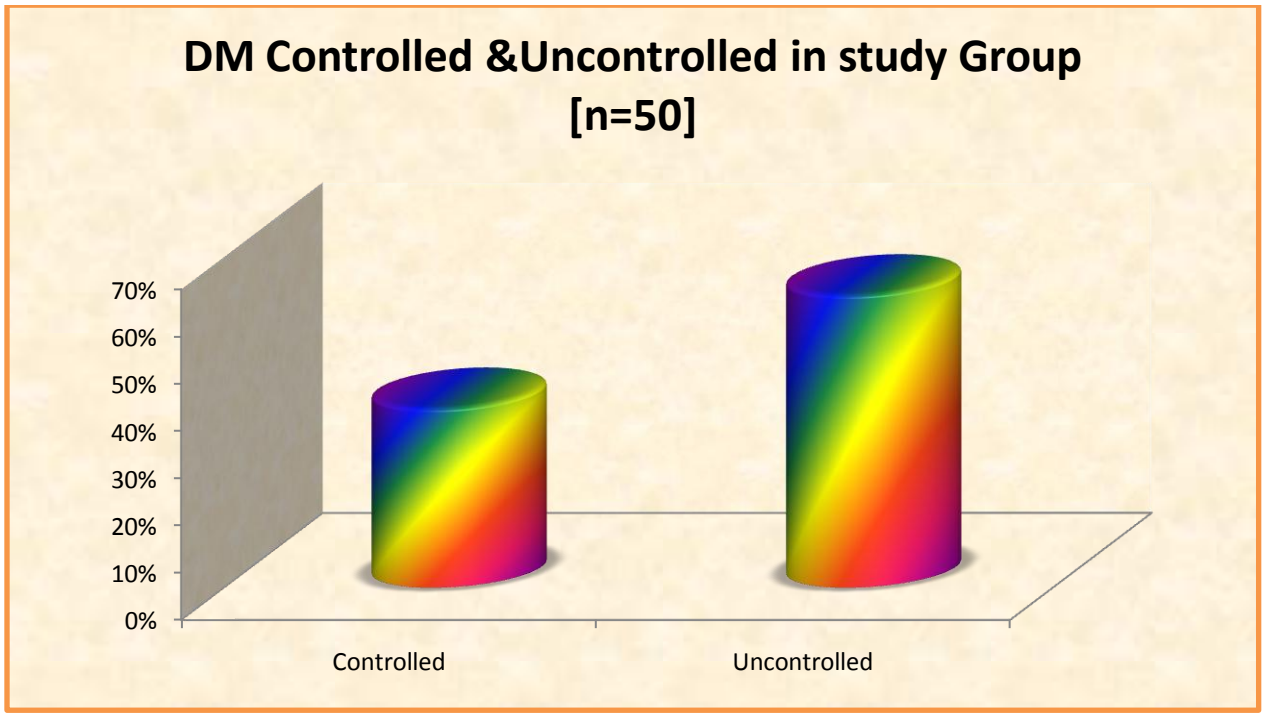

DM Controlled &Uncontrolled in study Group
[n=50]
70%
60%
50%
40%
30%
20%
10%
0%
Controlled
Uncontrolled

Table 17

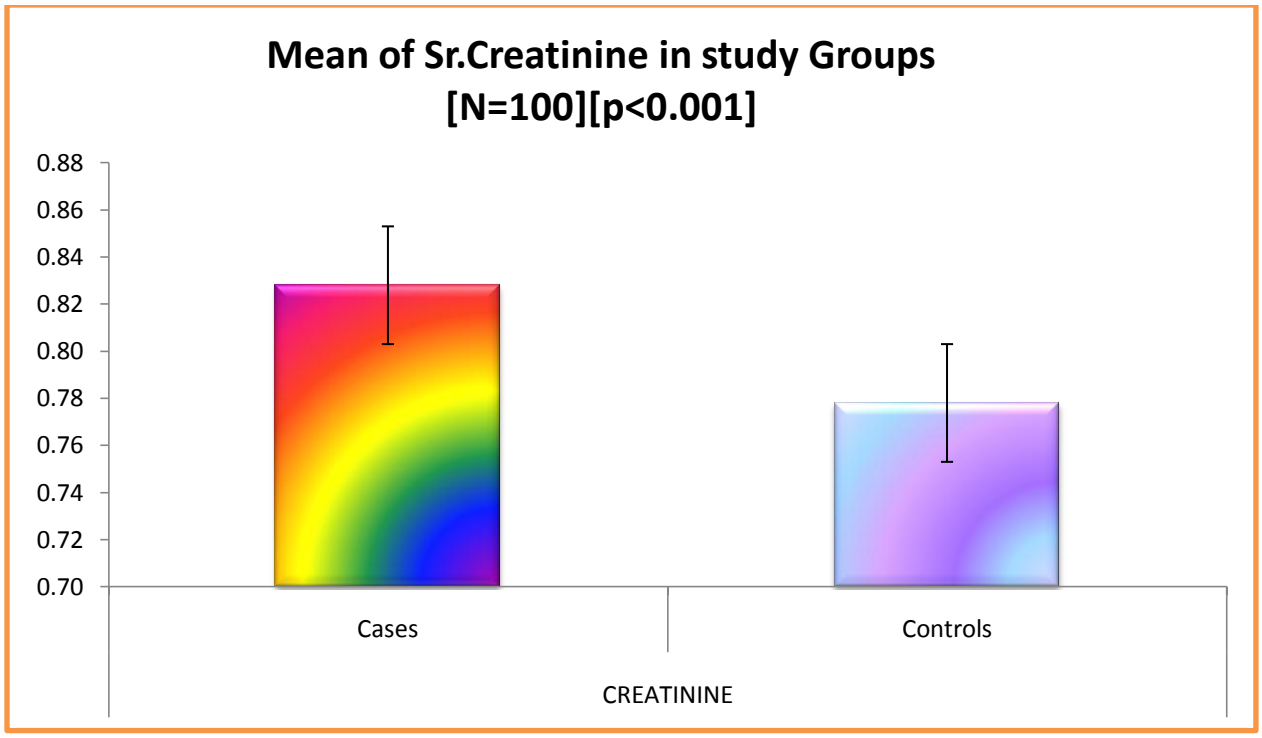
Effect of serum magnesium on creatinine, FBS, PPBS and Age

Mean of Clinical Variables

Clinical Variables		Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
				Lower Bound	Upper Bound			
AGE	Cases	57.16	11.5	53.9	60.4	27	82	
	Controls	57.96	13.3	54.2	61.7	38	82	>0.05
	Total	57.56	12.4	55.1	60.0	27	82	
CREATININE	Cases	0.828	0.3	0.8	0.9	0.4	1.2	
	Controls	0.778	0.2	0.7	0.8	0.2	1.2	>0.05
	Total	0.803	0.2	0.8	0.9	0.2	1.2	
FBS	Cases	188.74	92.9	162.3	215.1	69	485	
	Controls	102.32	7.5	100.2	104.5	85	119	<0.001
	Total	145.53	78.6	129.9	161.1	69	485	
PPBS	Cases	231.72	91.3	205.8	257.7	114	485	
	Controls	123.66	11.0	120.5	126.8	91	140	<0.001
	Total	177.69	84.5	160.9	194.5	91	485	

There is a significant difference between magnesium levels among fasting and postprandial blood glucose levels[49]. The mean value for fasting blood glucose among cases was 188.74and in controls was 102.32. The mean value for fasting blood glucose among cases was 231.72 and in controls were 123.66.

There was no significant difference between magnesium levels and creatinine in this study. The mean value for creatinine in cases was 0.828 ± 0.3 and in controls was 0.778 ± 0.2


Mean of Sr.Creatinine in study Groups
[N=100][p<0.001]
0.88
0.86
0.84
0.82
0.80
0.78
0.76
0.74
0.72
0.70
Cases
Controls
CREATININE

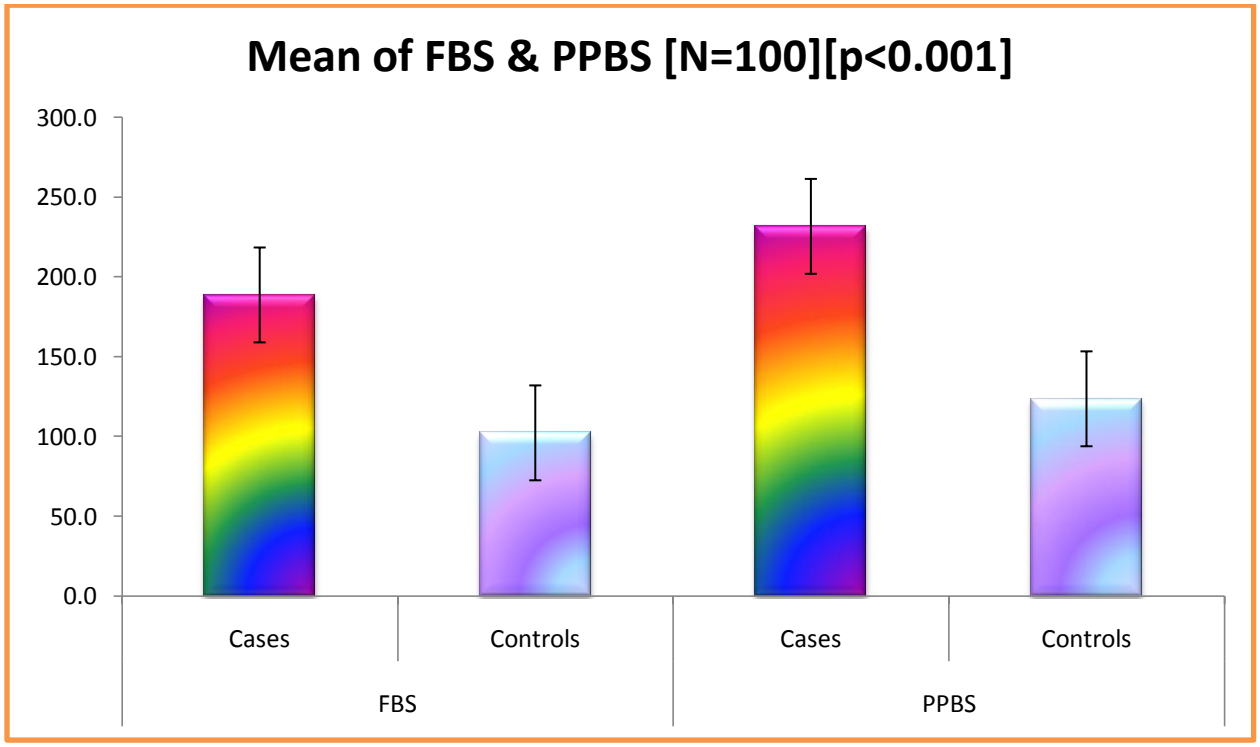

Mean of FBS & PPBS [N=100][p<0.001]
300.0
250.0
200.0
150.0
100.0
50.0
0.0
Cases
Controls
Cases
Controls
FBS
PPBS

Table 18:

Age Group with Magnesium level in the study Group

Group	AGE	Mean	SD	N
Cases	<40	1.55	0.07	2
	41-50	1.41	0.22	12
	51-60	1.47	0.21	16
	61-70	1.47	0.21	14
	>70	1.57	0.20	6
	Total	**1.47**	**0.20**	**50**
Control	<40	1.74	0.19	5
	41-50	1.83	0.19	15
	51-60	1.60	0.26	9
	61-70	1.73	0.05	7
	>70	1.64	0.16	14
	Total	**1.71**	**0.20**	**50**
Overall	<40	1.69	0.19	7
	41-50	1.64	0.29	27
	51-60	1.52	0.23	25
	61-70	1.56	0.21	21
	>70	1.62	0.17	20
	Total	**1.59**	**0.23**	**100**

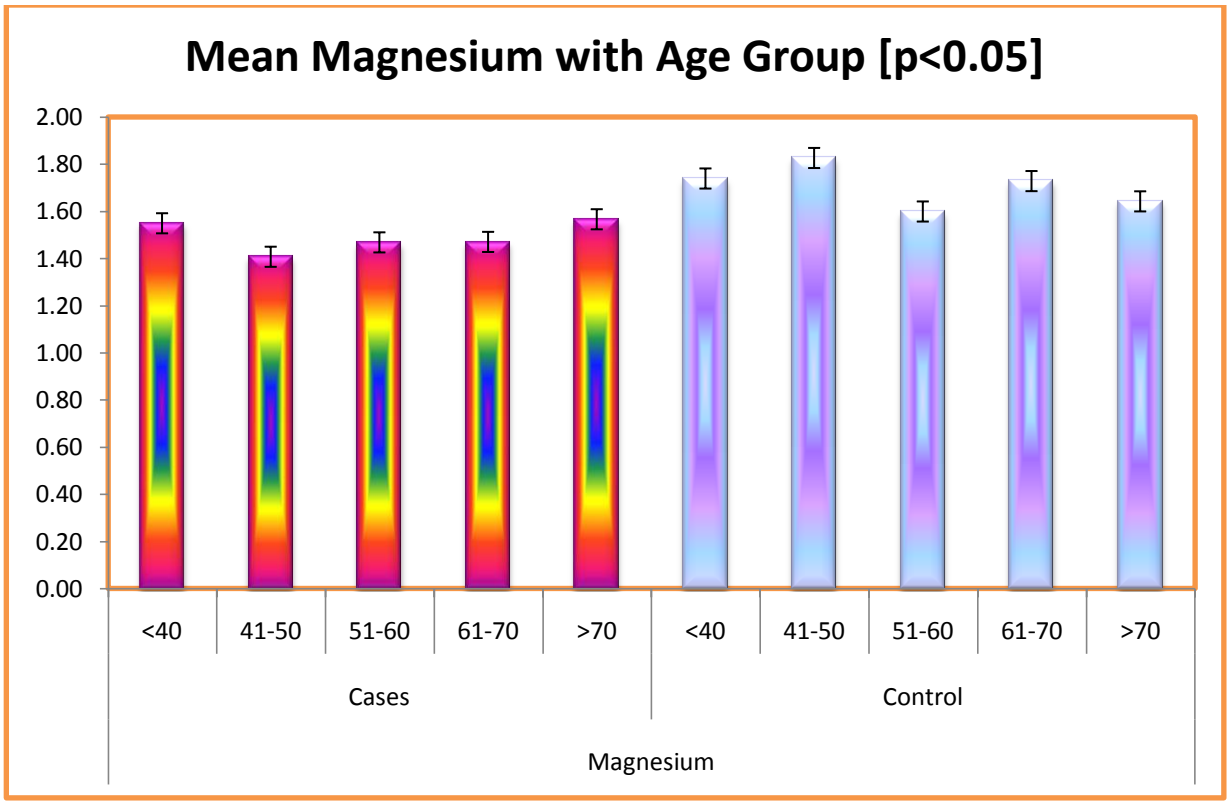

Mean Magnesium with Age Group [p<0.05]
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
<40
41-50
51-60
61-70
>70
<40
41-50
51-60
61-70
>70
Cases
Control
Magnesium

Table 19:

Causes in study Group

Causes	Group		Total
	Cases	Controls	
UTI	8	7	15
URTI	0	4	4
LRTI	5	5	10
FOLLOW UP	14	0	14
MYALGIA	0	9	9
VIRAL FEVER	1	9	10
GERD	0	5	5
OA KNEE	4	1	5
AGE	4	1	5
APD	0	3	3
PUO	3	0	3
MIGRAINE	3	0	3
GASTRITIS	2	0	2
CELLULITIS	1	1	2
PERIPHERAL NEUROPATHY	2	0	2
SINUSITIS	0	2	2
OTHERS	3	3	6
Total	**50**	**50**	**100**

Infections were the most common cause for admission in both diabetes and non diabetic patients (UTI 15% , URTI 4%, LRTI 10%, AGE 5%, CELLULITIS 2%, SINUSITIS 2% PUO 3% and VIRAL FEVER 10%)[50] .

The next most cause for admission is uncontrolled diabetes who came for regular follow up in diabetic individuals . other cause are fibromyalgia in control patients accounting for 9 % of admission ansd osteoarthritis of knee accounts for 5% of admission in both cases and controls. Gastroesophageal reflux disease account for 5% of admission in controls. Acid peptic disease other than GERD account for 3% of admission in controls. Migraine accounts for 3 % of admission in cases. Peripheral neuropathy account for 2 % of admission in cases. Other causes for admission are 6% in both cases and controls.

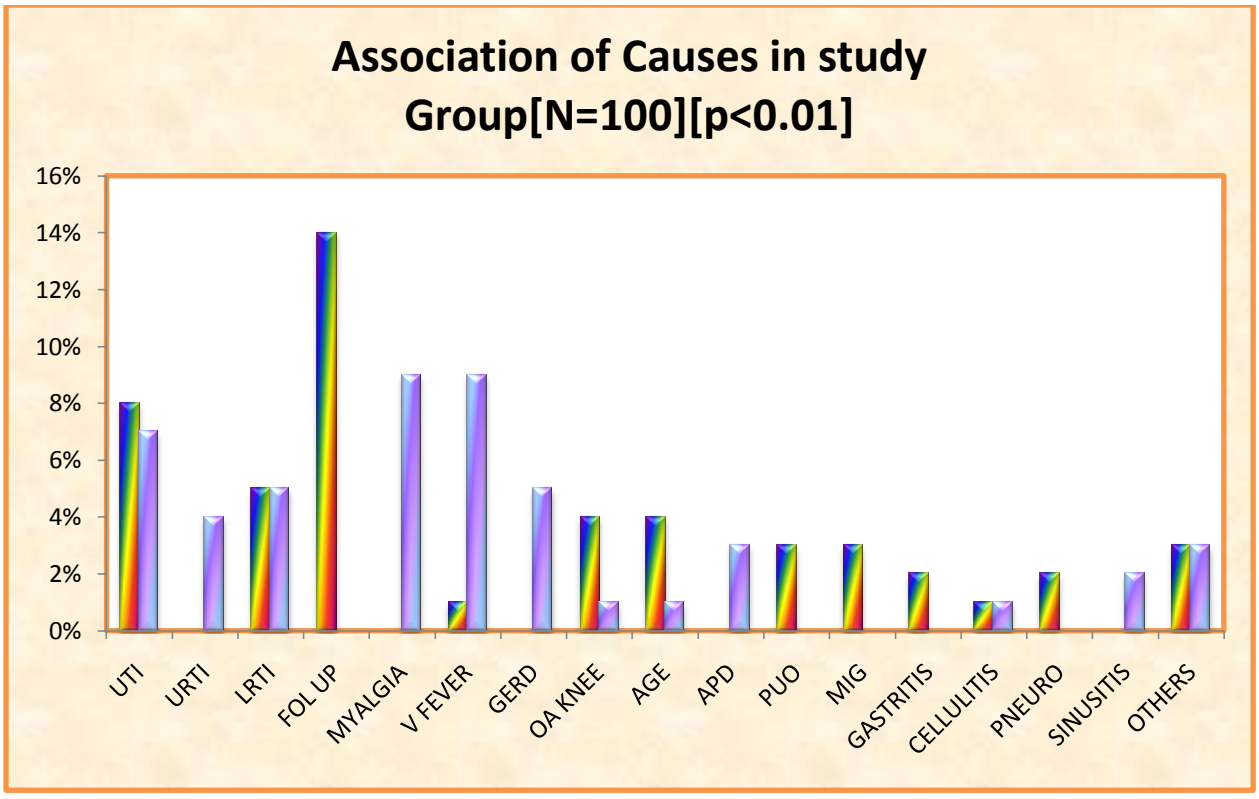


Table 20:

Mean Clinical Variables with Treatment Group

		Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
				Lower Bound	Upper Bound			
CREATININE	**INSULIN**	0.8	0.3	0.7	0.9	0.4	1.2	>0.05
	OHA	0.8	0.3	0.7	0.9	0.5	1.2	
	Total	**0.8**	**0.3**	**0.8**	**0.9**	**0.4**	**1.2**	
FBS	**INSULIN**	215.7	88.5	175.4	256.0	100	423	>0.05
	OHA	169.2	92.5	134.0	204.4	69	485	
	Total	**188.7**	**92.9**	**162.3**	**215.1**	**69**	**485**	
HbA1C	**INSULIN**	8.5	1.6	7.7	9.2	5.9	12.3	<0.05
	OHA	7.5	1.2	7.1	8.0	6.1	9.5	
	Total	**7.9**	**1.5**	**7.5**	**8.3**	**5.9**	**12.3**	
PPBS	**INSULIN**	258.5	92.0	216.7	300.4	135	485	>0.05
	OHA	212.3	87.3	179.1	245.5	114	415	
	Total	**231.7**	**91.3**	**205.8**	**257.7**	**114**	**485**	

There are no any significant difference between treatment group with relation to creatinine, fasting and post prandial blood sugar. Whereas there is a significant difference between treatment group and glycosylated hemoglobin level. The mean value for diabetic patients receiving insulin and OHA was 8.5 and 7.5 respectively.

Table 21:

Mean Clinical Variables with DM Retinopathy

		Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
				Lower Bound	Upper Bound			
CREATININE	**Present**	0.8	0.3	0.7	0.9	0 .4	1.2	>0.05
	Absent	0.8	0.3	0.7	0.9	0.4	1.2	
	Total	0.8	0.3	0.8	0.9	0.4	1.2	
FBS	**Present**	221.3	113.8	166.4	276.1	69	485	<0.05
	Absent	168.8	72.4	142.2	195.4	96	359	
	Total	188.7	92.9	162.3	215.1	69	485	
HbA1C	**Present**	8.1	1.4	7.5	8.8	5.9	11.2	>0.05
	Absent	7.8	1.5	7.2	8.4	6.1	12.3	
	Total	7.9	1.5	7.5	8.3	5.9	12.3	
PPBS	**Present**	253.3	82.8	213.4	293.2	142	389	>0.05
	Absent	218.5	95.1	183.6	253.4	114	485	
	Total	231.7	91.3	205.8	257.7	114	485	

There are no significant difference between diabetic retinopathy and glycosylated hemoglobin, post prandial sugar and creatinine. There is a significant difference between fasting blood sugar and diabetic retinopathy. The mean value for patient with diabetic retinopathy with fasting blood sugar is 221.3 and with out diabetic retinopathy the mean value for fasting blood sugar is 168.8.

Table 22:

Mean Clinical Variables with DM Out come

		Mean	SD	95% CI for Mean		Minimum	Maximum	'p' value
				Lower Bound	Upper Bound			
MAGNESIUM	**Controlled**	1.568	0.1916	1.476	1.661	1.2	1.8	<0.01
	Uncontrolled	1.41	0.1886	1.34	1.479	1	1.7	
	Total	1.47	0.2033	1.412	1.528	1	1.8	
CREATININE	**Controlled**	0.864	0.2726	0.732	0.995	0.5	1.2	>0.05
	Uncontrolled	0.806	0.2452	0.716	0.896	0.4	1.2	
	Total	**0.828**	**0.2548**	**0.755**	**0.9**	**0.4**	**1.2**	
FBS	**Controlled**	108.05	7.397	104.49	111.62	96	121	<0.001
	Uncontrolled	238.19	86.063	206.63	269.76	69	485	
	Total	**188.74**	**92.88**	**162.34**	**215.14**	**69**	**485**	
HbA1C	**Controlled**	6.447	0.2796	6.313	6.582	5.9	6.9	<0.001
	Uncontrolled	8.832	1.1053	8.427	9.238	7.3	12.3	
	Total	**7.926**	**1.4642**	**7.51**	**8.342**	**5.9**	**12.3**	
PPBS	**Controlled**	147.26	16.713	139.21	155.32	114	170	<0.001
	Uncontrolled	283.48	78.583	254.66	312.31	165	485	
	Total	**231.72**	**91.348**	**205.76**	**257.68**	**114**	**485**	

There is a significant difference between relationship of diabetes outcome with serum magnesium level, FBS, glycosylated hemoglobin and PPBS. The mean value for magnesium in controlled patient was 1.568 and uncontrolled was 1.41. The mean value for fasting blood sugar level in controlled patient was 108.05 and uncontrolled was 238.19. The mean value for glycosylated hemoglobin in controlled patient was 6.447 and uncontrolled was 8.832. The mean value for postprandial sugar in controlled patient was 147.26 and uncontrolled was 283.48.

DATA SUMMARY			'P' value
GENDER			
Male	59%		
Female	41%		
MEAN AGE			
Male	59+/-13		>0.05
Female	55+/-12		
Overall	58+/-12		
AGE	**Cases**	**Controls**	
<40	2%	5%	
41-50	12%	15%	
51-60	16%	9%	>0.05
61-70	14%	7%	
>70	6%	14%	
GENDER			
Male	23%	36%	<0.05
Female	27%	14%	
MAGNESIUM			
<1-1	1%	0%	
1.1-1.5-2	30%	8%	>0.05
1.6-2.0-3	19%	40%	
2.1-4	0%	2%	
TREATMENT			
INSULIN	42%		
OHA	58%		
RETINOPATHY			
Present	38%		
Absent	62%		
Controlled	38%		
Uncontrolled	62%		

CAUSES			
UTI	8%	7%	
URTI	0%	4%	
LRTI	5%	5%	
FOL UP	14%	0%	
MYALGIA	0%	9%	<0.05
V FEVER	1%	9%	
GERD	0%	5%	
OA KNEE	4%	1%	
AGE	4%	1%	
APD	0%	3%	
PUO	3%	0%	
MIG	3%	0%	
GASTRITIS	2%	0%	
CELLULITIS	1%	1%	
PNEURO	2%	0%	
SINUSITIS	0%	2%	
OTHERS	3%	3%	
GROUP			
Cases	1.47	0.20	
Controls	1.71	0.20	<0.01
TREATMENT			
INSULIN	1.44	0.2	>0.05
OHA	1.49	0.2	
Present	1.45	0.19	>0.05
Absent	1.48	0.21	
Controlled	1.57	0.19	<0.01
Uncontrolled	1.41	0.19	
AGE			

Cases	57.16	11.5	>0.05
Controls	57.96	13.3	
CREATININE			
Cases	0.828	0.3	
Controls	0.778	0.2	>0.05
FBS			
Cases	188.74	92.9	
Controls	102.32	7.5	<0.05
PPBS			
Cases	231.72	91.3	<0.05
Controls	123.66	11.0	

STATISTICAL ANALYSIS:
The data are reported as the mean +/- SD or the median, depending on their distribution.
The differences in quantitative variables between groups were assessed by means of the
unpaired t test. Comparsion between groups was made by the Non parameteric Mann - whitney test
ANOVA was used to assess the quantative variables.
The chi square test was used assess differences in categoric variables between groups.
Multivariate analysisis was performed.
A p value of <0.05 using a two-tailed test was taken as being
of significance for all statistical tests. All data were analysed with a statistical software

DISCUSSION

The magnesium deficiency always been associated with underlying chronic diseases, amongst them, diabetes mellitus is the most common[51] . There are epidemiological studies which have shown that low levels of magnesium intake in the general population is aways associated between the ingestion of food rich in magnesium and the reduction of diabetes its complications. Hypomagnesemia is nowadays frequently present in diabetic patients, however there is not an exact mechanism for reason for magnesium deficiency in diabetes mellitus[52].

The present study included 50 type 2 diabetic patients and 50 control subjects. Serum magnesium levels were determined in all these subjects.

Table 23a C.S. Yajnik et al

Age Characteristics	Non diabetics (controls)	Insulin treated Diabetics	Non insulin treated diabetics	All diabetics
C.S.Yajnik et al	46.5(n=30)	45.9(n=32)	59.7(n=55)	54.7(n=87)
Present study	57.96(n=50)	53.57(n=21)	59.75(n=29)	57.16(n=50)

The present study had diabetic patients ranging from 27-82 years. The average age of controls in the present study was 57.96 years while in the study of C.S.Yajnik et al was 46.5 years. The mean age of diabetics in the present study was 57.16 years as against 54.7 in study of C.S.Yajnik et al., The mean age of patients on insulin was 53.75 years and 45.9 years in the present and the study conducted by C.S.Yajnik et al respectively and the mean age of non insulin treated diabetics was 59.75 years and 59.7 years respectively in the present study and the study of C.S.Yajnik et al.

Table 23b C.S. Yajnik et al

Men (%)	Non diabetics (controls)	Insulin treated diabetics	Non insulin treated diabetics	All diabetics
C.S.Yajnik et al	56%	59%	76%	70%
Present study	72%	43%	52%	46%

The percentage of patients in the insulin treated diabetic group who were men was 43% in the present study and the study done by C.S. Yajnik et al was 59%. The percentage of men in the non insulin treated diabetic group was 52% and 76% in the present study and the study conducted by C.S. Yajnik et al respectively.

A.P.Jain, N.N.Gupta and Abhay Kumar (1976)

Table 24a -Serum magnesium in controls and diabetics

	Controls	Diabetics
A.P.Jain, N.N.Gupta and Abhay Kumar	2.07 ± 0.25	1.67 ± 0.37
Present study	1.71 ± 0.20	1.47 ± 0.20

A.P.Jain, N.N.Gupta and Abhay Kumar (1976) selected 85 cases, which included 20 comparable healthy adults and 65 diabetics of whom 50 diabetics were without apparent renal involvement. They have studied simultaneously the intracellular (erythrocytic), extracellular (serum) and urinary magnesium levels in controls and diabetics. An attempt to compare the findings in these groups and in controlled and uncontrolled diabetics: those getting insulin with the group not getting insulin was made In the diabetic group low serum, normal erythrocyte and high urinary magnesium levels were recorded in comparison to controls (1.71 ± 0.20 v/s 2.07±0.25 in controls and 1.47 ± 0.20 v/s 1.67 ± 0.37 in diabetics).

Table 24b

Serum magnesium in controlled and uncontrolled diabetics

	Controlled	Uncontrolled
A.P.Jain, N.N.Gupta and Abhay Kumar	1.85±0.08	1.68±0.12
Present study	1.57 ± 0.19	1.41 ± 0.19

On establishing the relationship between magnesium levels and the state of control of diabetes, it was observed that in poorly controlled diabetes patient's serum and urinary magnesium levels were respectively lower and higher than that of poorly controlled (1.57 ± 0.19 v/s 1.85 ± 0.08 in fairly controlled and 1.41 ± 0.19 v/s 1.68 ± 0.12 in poorly controlled) with no significant difference in erythrocytic magnesium levels.

Table 25a

Serum magnesium in insulin treated and OHA treated diabetics

	Insulin	OHA'S
A.P.Jain, N.N.Gupta and Abhay Kumar	1.59 ± 0.13	1.90 ± 0.18
Present study	1.44 ± 0.20	1.49 ± 0.20

The diabetics getting insulin therapy had lower serum and higher urinary magnesium levels than those getting OHA'S (1.44 ± 0.20 v/s 1.59±0.13 in the insulin treated and 1.49 ± 0.20 v/s 1.90 ± 0.18 in the OHA treated subjects). The present study compared similar parameters that was done by A.P.Jain, N.N.Gupta and Abhay Kumar and found variations similar to that study.

Nadler JL (1992)

Table 25b - Serum magnesium in diabetics and controls

	Controls	**Diabetics**
Nadler JL	2.31 ± 0.12	1.94 ± 0.05
Present study	1.71 ± 0.20	1.47 ± 0.20

Nadler JL, Malayan S, Luong H, Shaw S, Natrajan RD and Rude RK (1992) evaluated intracellular (erythrocytic) Mg^{2+} concentration in 20 type 2 diabetics. In addition, effects of intravenous 3-h drip or 8 weeks of oral magnesium supplementation on intracellular Mg^{2+} concentration levels and platelet reactivity was studied.

The results showed intracellular Mg^{2+} concentration of diabetic patients was significantly reduced compared with values in non diabetic control subjects. Serum magnesium levels were also reduced in the diabetic patients compared control subjects (1.71 ± 0.20 v/s 2.31 ± 0.12 in controls and 1.47 ± 0.20 v/s 1.94 ± 0.05 in diabetics). Oral magnesium supplementation for 8 weeks (400mg/day) restored RBC magnesium 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 analog, U46619.

The present study correlated with the study done by Nadler JL, Malayan S, Luong H, Shaw S, Natrajan RD and Rude RK with respect to the comparison of serum magnesium in diabetics and controls. However the present study did not include evaluating the effects of oral or IV magnesium supplementation

Nagase N (1996)

Table 26 :

Serum magnesium in diabetics and controls

	Controls	**Diabetics**
Nagase N	2.30 ± 0.32	1.90 ± 0.37
Present study	1.71 ± 0.20	1.47 ± 0.20

Nagase N (1996) studied the interrelationships between hypertension, ischemic heart disease and diabetes mellitus and diabetes mellitus in the diabetic subjects without ischemic heart disease or with ischemic heart disease and subjects with ischemic heart disease which were not complicated with diabetes mellitus.

Their results showed serum magnesium levels of diabetes mellitus (1.90±0.37) was significantly lower than that of normal controls (2.30±0.32). 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 causes of insulin resistance. The present study did not evaluate the interrelations between hypertension, ischemic heart disease.

However the magnesium levels of diabetics as compared to controls and the Comparison of serum magnesium levels between well controlled and poorly controlled diabetics had a positive correlation with the present study.

Garland H O in his study speculated on a potential link between magnesium deficit of diabetes and several diabetic complications including cardiovascular problems and retinopathy.

Rude R K suggested 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 improve the course of diabetic condition.

LIMITATIONS OF THE STUDY

However in the present study, the complications of diabetes in relation to hypomagnesemia were not studied. Also magnesium 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 states with respect to improvement or worsening of diabetic state in the long run was not studied.

This study focuses on estimating magnesium levels in type 2 diabetics at a given point (during admission) but not on therapeutically correcting hypomagnesemia or otherwise (not correcting) in the future course of the disease and its outcome.

CONCLUSION

1. Serum magnesium levels were lower in type 2 diabetic patients when compared to controls.

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

3. Hypomagnesemia is a factor in type 2 diabetes mellitus patients leading to various complications. Hence it is worthwhile estimating magnesium levels in type 2 diabetes mellitus patients and probably correlates their relationship with various complications.

BIBLIOGRAPHY

1. Ahmad J, Masoodi MA, Ashraf M, Ahmad R, Ahmad A, Dawood S. Prevalence of Diabetes Mellitus and Its Associated Risk Factors in Age Group of 20 Years and Above in Kashmir , India. 2011;4:38-44.

2. Guerrero-Romero F, Rodríguez-Morán M. [Oral magnesium supplementation: an adjuvant alternative to facing the worldwide challenge of type 2 diabetes?]. *Cir. Cir.* 82(3):282-9.

3. Gales C, Zamfir C, Radulescu D, Stoica B, Nechifor M. Protective effect of magnesium and metformin on endometrium and ovary in experimental diabetes mellitus. *Magnes. Res.* 2014;27(2):69-76. doi:10.1684/mrh.2014.0363.

4. 11. Magnesium 11.1. 30-40.

5. Floege J. Magnesium in CKD: more than a calcification inhibitor? *J. Nephrol.* 2014. doi:10.1007/s40620-014-0140-6.

6. Razmandeh R, Nasli-Esfahani E, Heydarpour R, et al. Association of Zinc, Copper and Magnesium with bone mineral density in Iranian postmenopausal women - a case control study. *J. Diabetes Metab. Disord.* 2014;13(1):43. doi:10.1186/2251-6581-13-43.

7. Navarrete-Cortes A, Ble-Castillo JL, Guerrero-Romero F, et al. No effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia. *Magnes. Res.* 2014;27(2):48-56. doi:10.1684/mrh.2014.0361.

8. Azad KM, Sutradhar SR, Khan NA, et al. Serum magnesium in hospital admitted diabetic patients. *Mymensingh Med. J.* 2014;23(1):28-34.

9. Hirano K, Saito T, Mizuno S, et al. Total cholesterol level for assessing pancreatic insufficiency due to chronic pancreatitis. *Gut Liver* 2014;8(5):563-8. doi:10.5009/gnl13366.

10. Mudryj AN, Yu N, Aukema HM. Nutritional and health benefits of pulses. *Appl. Physiol. Nutr. Metab.* 2014:1-8. doi:10.1139/apnm-2013-0557.

11. Rahati S, Shahraki M, Arjomand G, Shahraki T. Food pattern, lifestyle and diabetes mellitus. *Int. J. high risk Behav. Addict.* 2014;3(1):e8725. doi:10.5812/ijhrba.8725.

12. Romani AMP. Magnesium in health and disease. *Met. Ions Life Sci.* 2013;13:49-79. doi:10.1007/978-94-007-7500-8_3.

13. Chiu THT, Huang H-Y, Chiu Y-F, et al. Taiwanese vegetarians and omnivores: dietary composition, prevalence of diabetes and IFG. *PLoS One* 2014;9(2):e88547. doi:10.1371/journal.pone.0088547.

14. Biernat P, Musiał W, Gosławska D, Pluta J. The impact of selected preparations of trace elements - magnesium, potassium, calcium, and zinc on the release of diclofenac sodium from enteric coated tablets and from sustained release capsules. *Adv. Clin. Exp. Med.* 23(2):205-13.

15. Solaimani H, Soltani N, MaleKzadeh K, et al. Modulation of GLUT4 expression by oral administration of Mg(2+) to control sugar levels in STZ-induced diabetic rats. *Can. J. Physiol. Pharmacol.* 2014;92(6):438-44. doi:10.1139/cjpp-2013-0403.

16. Araújo Sampaio F, Monte Feitosa M, Hermes Sales C, et al. INFLUENCE OF MAGNESIUM ON BIOCHEMICAL PARAMETERS OF IRON AND OXIDATIVE STRESS IN PATIENTS WITH TYPE 2 DIABETES. *Nutr. Hosp.* 2014;30(n03):570-576. doi:10.3305/nh.2014.30.3.7333.

17. An G, Du Z, Meng X, et al. Association between low serum magnesium level and major adverse cardiac events in patients treated with drug-eluting stents for acute myocardial infarction. *PLoS One* 2014;9(6):e98971. doi:10.1371/journal.pone.0098971.

18. Hyassat D, Al Sitri E, Batieha A, El-Khateeb M, Ajlouni K. Prevalence of Hypomagnesaemia among Obese Type 2 Diabetic Patients Attending the National Center

for Diabetes, Endocrinology and Genetics (NCDEG). *Int. J. Endocrinol. Metab.* 2014;12(3):e17796. doi:10.5812/ijem.17796.

19. Van der Wijst J, Bindels RJM, Hoenderop JGJ. Mg2+ homeostasis: the balancing act of TRPM6. *Curr. Opin. Nephrol. Hypertens.* 2014;23(4):361-9. doi:10.1097/01.mnh.0000447023.59346.ab.

20. Niranjan G, Anitha D, Srinivasan AR, et al. Association of inflammatory sialoproteins, lipid peroxides and serum magnesium levels with cardiometabolic risk factors in obese children of South Indian population. *Int. J. Biomed. Sci.* 2014;10(2):118-23.

21. Akarolo-Anthony SN, Jiménez MC, Chiuve SE, Spiegelman D, Willett WC, Rexrode KM. Plasma magnesium and risk of ischemic stroke among women. *Stroke.* 2014;45(10):2881-6. doi:10.1161/STROKEAHA.114.005917.

22. Sales CH, Pedrosa LDFC. Magnesium and diabetes mellitus: their relation. *Clin. Nutr.* 2006;25(4):554-62. doi:10.1016/j.clnu.2006.03.003.

23. Parvizi MR, Parviz M, Tavangar SM, et al. Protective effect of magnesium on renal function in STZ-induced diabetic rats. *J. Diabetes Metab. Disord.* 2014;13(1):84. doi:10.1186/s40200-014-0084-3.

24. Galgon RE, Strube P, Heier J, Groth J, Wang S, Schroeder KM. Magnesium sulfate with lidocaine for preventing propofol injection pain: a randomized, double-blind, placebo-controlled trial. *J. Anesth.* 2014. doi:10.1007/s00540-014-1892-9.

25. Practice C. Magnesium and insulin-dependent diabetes mellitus. 1990;10:203-209.

26. Pushparani DS, Anandan SN, Theagarayan P. Serum zinc and magnesium concentrations in type 2 diabetes mellitus with periodontitis. *J. Indian Soc. Periodontol.* 2014;18(2):187-93. doi:10.4103/0972-124X.131322.

27. Joshi A, Bhadade R, Varthakavi PK, DeSouza R, Bhagwat NM, Chadha MD. Vitamin D deficiency is associated with increased mortality in critically ill patients especially in those

requiring ventilatory support. *Indian J. Endocrinol. Metab.* 2014;18(4):511-5. doi:10.4103/2230-8210.137504.

28. Wien M, Oda K, Sabaté J. A randomized controlled trial to evaluate the effect of incorporating peanuts into an American Diabetes Association meal plan on the nutrient profile of the total diet and cardiometabolic parameters of adults with type 2 diabetes. *Nutr. J.* 2014;13:10. doi:10.1186/1475-2891-13-10.

29. Lima de Souza E Silva M de L, Cruz T, Rodrigues LE, et al. Magnesium replacement does not improve insulin resistance in patients with metabolic syndrome: a 12-week randomized double-blind study. *J. Clin. Med. Res.* 2014;6(6):456-62. doi:10.14740/jocmr1580w.

30. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. Oral magnesium supplementation decreases C-reactive protein levels in subjects with prediabetes and hypomagnesemia: a clinical randomized double-blind placebo-controlled trial. *Arch. Med. Res.* 2014;45(4):325-30. doi:10.1016/j.arcmed.2014.04.006.

31. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes□ : Indian scenario. 2007;(March):217-230.

32. Dousdampanis P, Trigka K, Fourtounas C. Hypomagnesemia, chronic kidney disease and cardiovascular mortality: Pronounced association but unproven causation. *Hemodial. Int.* 2014. doi:10.1111/hdi.12159.

33. Joslin Diabetes Center | Joslin Diabetes Mellitus, 14th Edition.

34. Buse JB, Polonsky KS, Burant CF. *Williams Textbook of Endocrinology*. Twelfth Ed. Elsevier; 2011:1371-1435. doi:10.1016/B978-1-4377-0324-5.00031-6.

35. Human Vitamin and Mineral Requirements.

36. It WI. Diabetes Mellitus□ : Type 1.

37. Naser SA, Abdelsalam A, Thanigachalam S, Naser AS, Alcedo K. Domino effect of hypomagnesemia on the innate immunity of Crohn's disease patients. *World J. Diabetes* 2014;5(4):527-35. doi:10.4239/wjd.v5.i4.527.

38. Cryer PE. *Williams Textbook of Endocrinology*. Twelfth Ed. Elsevier; 2011:1552-1577. doi:10.1016/B978-1-4377-0324-5.00034-1.

39. Seshiah V, Ganesan VS. *A Hand Book on Diabetes Mellitus*. Diabetes Education and Research Foundation; 1997:224.

40. S N, N K, S A, Dayanand CD. The association of hypomagnesaemia, high normal uricaemia and dyslipidaemia in the patients with diabetic retinopathy. *J. Clin. Diagn. Res.* 2013;7(9):1852-4. doi:10.7860/JCDR/2013/6106.3332.

41. Sohrabipour S, Kharazmi F, Soltani N, Kamalinejad M. Effect of the administration of Solanum nigrum fruit on blood glucose, lipid profiles, and sensitivity of the vascular mesenteric bed to phenylephrine in streptozotocin-induced diabetic rats. *Med. Sci. Monit. Basic Res.* 2013;19:133-40. doi:10.12659/MSMBR.883892.

42. The Royal College of Ophthalmologists Diabetic Retinopathy Guidelines. 2013;2012(July).

43. Joob B, Wiwanitkit V. Magnesium, dietary fiber, and diabetes. *J. Formos. Med. Assoc.* 2013;112(3):173. doi:10.1016/j.jfma.2013.01.001.

44. He K, Xun P, Liu K, Morris S, Reis J, Guallar E. Mercury exposure in young adulthood and incidence of diabetes later in life: the CARDIA Trace Element Study. *Diabetes Care* 2013;36(6):1584-9. doi:10.2337/dc12-1842.

45. Najafi M. Supplemental magnesium for prevention of atrial fibrillation: role of diabetes mellitus. *J. Cardiothorac. Vasc. Anesth.* 2013;27(3):e24-5. doi:10.1053/j.jvca.2012.10.004.

46. Wang L, Pedersen P, Strong D, Tulu B, Agu E, Ignotz R. Smartphone Based Wound Assessment System for Patients with Diabetes. *IEEE Trans. Biomed. Eng.* 2014. doi:10.1109/TBME.2014.2358632.

47. Weng L-C, Lee N-J, Yeh W-T, Ho L-T, Pan W-H. Lower intake of magnesium and dietary fiber increases the incidence of type 2 diabetes in Taiwanese. *J. Formos. Med. Assoc.* 2012;111(11):651-9. doi:10.1016/j.jfma.2012.07.038.

48. Srinivasan AR, Niranjan G, Kuzhandai Velu V, Parmar P, Anish A. Status of serum magnesium in type 2 diabetes mellitus with particular reference to serum triacylglycerol levels. *Diabetes Metab. Syndr.* 6(4):187-9. doi:10.1016/j.dsx.2012.09.001.

49. Pham P-CT, Pham P-MT, Pham P-TT. Patients with diabetes mellitus type 2 and hypomagnesemia may have enhanced glomerular filtration via hypocalcemia. *Clin. Nephrol.* 2012;78(6):442-8. doi:10.5414/CN107525.

50. Kondakov A V, Kobylianskiĭ AG, Tishchenkov VG, Titov VN. [The functional tests in clinical diagnostic laboratory: the detection of magnesium deficiency in the loading test]. *Klin. Lab. Diagn.* 2012;(6):16-20.

51. Kikuchi K, Tanaka H, Gima M, et al. [Abnormalities of magnesium (Mg) metabolism and therapeutic significance of Mg administration in patients with metabolic syndrome, type 2 diabetes, heart failure and chronic hemodialysis]. *Clin. Calcium* 2012;22(8):1217-26. doi:CliCa120812171226.

52. Musso CG, Juarez R, Vilas M, Navarro M, Rivera H, Jauregui R. Renal calcium, phosphorus, magnesium and uric acid handling: comparison between stage III chronic kidney disease patients and healthy oldest old. *Int. Urol. Nephrol.* 2012;44(5):1559-62. doi:10.1007/s11255-012-0230-0.

ANNEXURES

PROFORMA

TITLE:

SERUM MAGNESIUM AS AN EFFECTIVE TOOL IN MONITORING THE CONTROL OF TYPE II DIABETES MELLITUS

PARTICULARS OF THE PATIENT:

Name: IP NO:

Age : Ward No:

Sex : Hospital: RLJH/SNRH

Religion: DOA:

Address: DOD:

Occupation: Marital Status

Education:

CHIEF COMPLAINTS:

Polyuria

Polydypsia

Blurring of vision

Weight loss

Tiredness

Polyphagia

Pruritus

Aches and pains

Skin complaints

HISTORY OF PRESENT ILLNESS:

CARDIOVASCULAR SYMPTOMS:

Angina

Exertional dyspnea

Orthopnea

Paroxysmal nocturnal dyspnea

Palpitations

Syncope

Sweating

Swelling of feet

PERIPHERAL VASCULAR SYMPTOMS

Intermittent claudication

Gangrene

Impotence

Thrombophlebitis

NEUROLOGICAL SYMPTOMS

Giddiness

Headache

Vomiting

Transient ischemic attacks

Loss of consciousness

Stroke

VISUAL SYMPTOMS

Blurring of vision

Progressive loss of vision

Sudden blindness

RENAL SYMPTOMS

Symptoms of urinary tract infection:

Dysuria

Fever with chills

Flank pains

Symptoms of nephropathy:

Puffiness of face

Nocturnal pains

Sensory ataxia

Trophic ulcers

SYMPTOMS OF NEUROLOGICAL COMPLICATIONS

Symptoms of polyneuropathy:

Tingling and numbness

Nocturnal pains

Sensory ataxia

Trophic ulcers

Charcot's joints

Symptoms of mononeuropathy:

Wrist drop

Foot drop

Symptoms of cranial nerve involvement

Diplopia

Squint

Deviation of angle of mouth

Inability to close the eyes

Symptoms of radiculopathy

Symptoms of autonomic neuropathy

Dysphagia

Vomiting

Diarrhea

Syncope

Symptoms of amyotrophy

Parasthesiae of anterior thigh

Thinning of proximal muscles

Weakness of proximal muscles

Symptoms of diabetic skin complications

DIABETES HISTORY

Diabetes diagnosed in the year

Duration of diabetes

Diabetic family history

Diabetic Ketoacidosis

Drugs used for diabetes

PAST HISTORY:

PERSONAL HISTORY:

Habits

Diet

Appetite

Bowel and bladder habits

FAMILY HISTORY:

Diabetes

Hypertension/ischemic heart disease/CVA/obesity/sudden death

OBSTETRICS AND GYNECOLOGICAL HISTORY:

Menarche Menopause

Gravida Para

Abortions

History of still births

History of delivery of large babies

GENERAL PHYSICAL EXAMINATION

Built: well/moderate/poor

Anemia/cyanosis/clubbing/koilonychias/pedal edema/lyphadenopathy/icterus

Pulse

Jugular venous pressure

Blood pressure

Peripheral pulses

Skin changes

Eyes: Normal/Xanthoma/Arcus/Cataract

Fundus

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM

Inspection

Palpation

Percussion

Auscultation

RESPIRATORY SYSTEM

Inspection

Palpation

Percussion

Auscultation

EXAMINATION OF ABDOMEN

Inspection

Palpation

Percussion

Auscultation

EXAMINATION OF CENTRAL NERVOUS SYSTEM

Higher mental functions

Cranial nerves

Motor system

Tone

Power

Reflexes

Coordination

Involuntary movements

Sensory system

Touch

Pain

Temperature

Vibration

Position

Cortical sensation

INVESTIGATIONS

Urine: Albumin

Sugar

Microscopy

Ketone bodies

Total count

Differential count

Erythrocyte sedimentation rate

Fasting blood sugar

Serum magnesium

Blood urea

Serum creatinine

Chest X-ray

ECG

USG abdomen

DIAGNOSIS

TREATMENT GIVEN

Oral hypoglycemic agents

Insulin

Oral hypoglycemic agents + Insulin

Signature of the candidate

Signature of guide

Signature of co-guide

KEY TO MASTER CHART

1. FBS- Fasting blood sugar

2. Mg- Serum magnesium

3. SC- Serum creatinine

4. RET- Retinopathy

5. C- Controlled

6. UC-Uncontrolled

7. T- Treatment

8. CFA-Cause for admission

9. NA-Not applicable

10. URTI- Upper respiratory tract infection

11. LRTI- Lower respiratory tract infection

12. MEN- Meningitis

13. MAL-Malaria

14. CVA- Cerebrovascular accident

15. IHD- Ischemic heart disease.

16. PTB- Pulmonary tuberculosis

17. APD- Acid peptic disease

18. AC- Acute cholecystitis

19. UTI-Urinary tract infection’

20. I- Insulin

21. OHA- Oral hypoglycemic agents

CASES:

S.NO	AGE	SEX	OP/IP	MAGNESIUM	CREATININE	TREATMENT	DM RETINOPATHY	CONTROLLED/ UNCON	CAUSE	FBS	HbA1C	PPBS
1	46	M	I14017670	1.1	0.72	INSULIN	NIL	UNCONTROLLED	CELLULITIS	256	8.2	362
2	82	M	I14017636	1.3	1	OHA	PRESENT	CONTROLLED	LRTI	114	6.5	165
3	65	F	I14017717	1.3	0.76	INSULIN	PRESENT	UNCONTROLLED	GASTRITIS	241	7.3	245
4	52	F	I14017807	1.7	0.69	INSULIN	NIL	UNCONTROLLED	VIRAL FEVER	214	9.2	289
5	72	F	I14017528	1.5	0.6	OHA	NIL	CONTROLLED	UTI	120	6.3	156
6	80	F	I14017907	1.7	0.52	OHA	NIL	CONTROLLED	BA	102	6.7	169
7	32	F	I14018015	1.5	0.96	INSULIN	PRESENT	UNCONTROLLED	PUO	156	8.3	365
8	72	M	I14017806	1.7	0.45	INSULIN	PRESENT	UNCONTROLLED	HEADACHE	289	11.2	358
9	52	F	O14033635	1.6	0.57	OHA	NIL	UNCONTROLLED	FOLLOW UP	165	8	254
10	45	F	O14039203	1.3	1.2	OHA	NIL	CONTROLLED	FOLLOW UP	96	6.1	160
11	56	M	O14035409	1.4	1	OHA	PRESENT	UNCONTROLLED	FOLLOW UP	198	8.5	369
12	52	M	O14030602	1.3	0.5	OHA	PRESENT	UNCONTROLLED	FOLLOW UP	69	9.1	298
13	53	M	O12064062	1.2	0.6	INSULIN	PRESENT	CONTROLLED	FOLLOW UP	115	6.8	145
14	65	M	O13056574	1.2	0.9	INSULIN	NIL	UNCONTROLLED	FOLLOW UP	359	9.1	214
15	56	M	O13082690	1.7	1.2	INSULIN	NIL	CONTROLLED	FOLLOW UP	102	6.9	170
16	45	M	O12017429	1.5	1	OHA	NIL	CONTROLLED	FOLLOW UP	110	6.5	156
17	58	F	O13056307	1.6	0.5	OHA	PRESENT	UNCONTROLLED	FOLLOW UP	485	8.6	245
18	27	M	I14018500		1	INSULIN	PRESENT	UNCONTROLLED	UTI	321	8.4	312
19	50	M	I14018567	1.3	1.1	OHA	PRESENT	UNCONTROLLED	AGE	254	8.2	389
20	65	F	I14018397	1.1	1.2	OHA	NIL	UNCONTROLLED	UTI	214	8.6	415
21	50	F	I14017656	1.5	1.1	INSULIN	NIL	UNCONTROLLED	PUO	210	7.5	225
22	50	M	I14018794	1.8	1.2	OHA	NIL	CONTROLLED	OA KNEE	110	6.6	138
23	65	M	I14018765	1.4	0.5	OHA	NIL	UNCONTROLLED	UTI	165	9.5	365
24	62	F	I14019320	1.4	0.65	OHA	PRESENT	UNCONTROLLED	LRTI	303	9.5	225
25	65	F	I14019215	1.4	0.8	OHA	NIL	CONTROLLED	UTI	120	6.1	138
26	56	F	I14019198	1.6	0.5	OHA	NIL	CONTROLLED	LRTI	102	6.2	140
27	74	M	I14018722	1.4	0.89	OHA	NIL	UNCONTROLLED	OA KNEE	105	9.2	201
28	55	F	I14019233	1.2	1.2	INSULIN	PRESENT	UNCONTROLLED	PERIPHERAL NEUROPATHY	198	9.5	298
29	52	F	I14019013	1.5	0.42	INSULIN	NIL	UNCONTROLLED	PERIPHERAL NEUROPATHY	231	8.8	319
30	70	F	I14019104	1.7	0.75	INSULIN	NIL	UNCONTROLLED	LRTI	186	7.8	347
31	56	F	I14019513	1.5	0.67	OHA	NIL	UNCONTROLLED	AGE	250	8.6	223
32	66	M	I14019423	1.5	0.93	OHA	PRESENT	UNCONTROLLED	MIGRAINE	230	9.3	316
33	51	M	I14019495	1.6	1.08	INSULIN	NIL	UNCONTROLLED	AGE	198	12.3	485
34	73	M	I14019323	1.8	1.02	OHA	NIL	CONTROLLED	BPPV	121	6.5	124
35	54	M	O14039633	1.7	0.68	OHA	PRESENT	CONTROLLED	FOLLOW UP	103	6.6	168
36	45	F	O13035362	1.3	0.84	INSULIN	NIL	UNCONTROLLED	FOLLOW UP	200	10.5	225
37	65	M	O12071843	1.6	1.2	INSULIN	NIL	CONTROLLED	FOLLOW UP	100	6.7	158
38	46	F	O14046252	1.6	0.49	OHA	NIL	UNCONTROLLED	FOLLOW UP	201	7.5	165
39	65	M	O12010803	1.6	1.07	OHA	NIL	CONTROLLED	FOLLOW UP	103	6.4	114
40	65	M	I14019879	1.8	1.2	OHA	NIL	CONTROLLED	LRTI	106	6.5	125
41	66	F	I14019764	1.8	0.54	INSULIN	PRESENT	CONTROLLED	UTI	105	5.9	160
42	49	F	I14020107	1.2	0.49	INSULIN	PRESENT	UNCONTROLLED	OA KNEE	423	9.6	225
43	69	F	I14020150	1.4	0.57	OHA	NIL	CONTROLLED	OA KNEE	114	6.1	135
44	56	F	I14019800	1	0.81	INSULIN	NIL	UNCONTROLLED	UTI	218	9.5	191
45	56	F	I14020025	1.5	0.67	OHA	NIL	UNCONTROLLED	UTI	198	8.6	221
46	41	F	I14019629	1.7	0.87	OHA	PRESENT	CONTROLLED	PUO	106	6.3	142
47	45	M	I14020484	1.2	0.92	OHA	NIL	UNCONTROLLED	AGE	353	8.5	254
48	56	F	I14021013	1.4	0.64	INSULIN	NIL	CONTROLLED	ACUTE GASTRITIS	104	6.8	135
49	42	F	I14020538	1.4	1.02	INSULIN	PRESENT	UNCONTROLLED	MIGRAINE	304	7.6	201
50	68	M	I14020690	1.4	1.2	OHA	PRESENT	UNCONTROLLED	VERTIGO	190	7.3	187

CONTROLS :

S.NO	AGE	SEX	OP/IP	MAGNESIUM	CREATININE	TREATMENT	DM RETINOPATHY	CONTROLLED/ UNCON	CAUSE	FBS	PPBS
1	48	M	I14021249	1.8	0.62	NA	NA	NA	LRTI	105	125
2	61	M	I14020996	1.7	0.6	NA	NA	NA	VIRAL FEVER	96	120
3	51	M	I14020510	1.2	0.89	NA	NA	NA	AGE	105	112
4	62	F	I14021161	1.7	0.95	NA	NA	NA	UTI	93	128
5	40	M	I14021240	2	0.61	NA	NA	NA	UTI	91	123
6	73	M	I14020252	1.5	0.42	NA	NA	NA	URTI	96	114
7	75	F	I14021443	1.6	1.01	NA	NA	NA	MYALGIA	99	125
8	49	M	I1402494	2	0.84	NA	NA	NA	GERD	102	124
9	40	F	I14021638	1.6	0.53	NA	NA	NA	APD	103	129
10	81	M	I14020584	1.8	0.48	NA	NA	NA	APD	100	112
11	52	M	I14021120	1.9	0.65	NA	NA	NA	URTI	86	91
12	40	F	I14021492	1.6	0.53	NA	NA	NA	UTI	101	115
13	56	F	I14021470	1.4	0.67	NA	NA	NA	MYALGIA	109	110
14	41	F	I14021594	2	0.75	NA	NA	NA	APD	92	115
15	63	M	I14019835	1.7	1.07	NA	NA	NA	URTI	104	116
16	41	M	I14018351	1.8	0.91	NA	NA	NA	MYALGIA	106	125
17	73	M	I14016975	1.9	0.84	NA	NA	NA	OA KNEE	104	135
18	57	M	I14019532	1.3	1.08	NA	NA	NA	VIRAL FEVER	98	124
19	40	F	I14019924	1.6	0.66	NA	NA	NA	LRTI	102	114
20	80	M	I14020067	1.5	0.55	NA	NA	NA	MYALGIA	110	138
21	58	M	O02025990	1.8	1.1	NA	NA	NA	MYALGIA	108	128
22	43	M	I14019826	1.9	0.91	NA	NA	NA	GERD	102	125
23	60	M	I14019699	1.6	1.02	NA	NA	NA	UTI	104	130
24	48	F	I14023338	1.7	1.02	NA	NA	NA	GERD	102	136
25	74	F	I14023291	1.6	0.6	NA	NA	NA	GERD	96	135
26	42	M	I14022922	1.6	0.5	NA	NA	NA	FEVER	85	126
27	82	M	I14022940	1.5	0.3	NA	NA	NA	UTI	98	137
28	72	M	I14022915	1.7	0.9	NA	NA	NA	LRTI	102	110
29	50	M	I14022936	2.1	1.2	NA	NA	NA	MYALGIA	106	105
30	63	M	I14022959	1.7	1	NA	NA	NA	MYALGIA	103	116
31	60	M	I14022939	1.9	0.8	NA	NA	NA	LRTI	115	118
32	62	M	I14022733	1.8	0.7	NA	NA	NA	MYALGIA	114	111
33	76	M	I14022874	1.8	0.9	NA	NA	NA	SINUSITIS	119	108
34	71	F	I14024570	1.3	0.8	NA	NA	NA	LRTI	110	139
35	63	M	I14024325	1.8	0.2	NA	NA	NA	ACUTE PROSTATITIS	102	132
36	76	M	I14025324	1.6	0.3	NA	NA	NA	COPD	98	130
37	57	M	I14025325	1.7	0.9	NA	NA	NA	VIRAL FEVER	98	134
38	48	M	I14025336	1.7	1.2	NA	NA	NA	LIVER ABSCESS	104	115
39	45	M	I14025338	1.5	0.6	NA	NA	NA	DENGUE	114	132
40	65	F	I14025246	1.7	1.1	NA	NA	NA	UTI	98	110
41	50	M	I14024110	1.9	1	NA	NA	NA	MYALGIA	105	125
42	73	M	I14024704	1.8	0.8	NA	NA	NA	GERD	114	136
43	44	M	I14024873	2.1	0.7	NA	NA	NA	MALARIA	102	140
44	48	F	I14025190	1.7	0.8	NA	NA	NA	VIRAL FEVER	105	125
45	47	F	I14025203	1.6	0.9	NA	NA	NA	VIRAL FEVER	110	136
46	75	M	I14023532	1.7	0.8	NA	NA	NA	URTI	104	136
47	60	M	I14025114	1.6	1.1	NA	NA	NA	ACUTE SINUSITIS	114	125
48	38	M	I14025189	1.9	0.9	NA	NA	NA	CELLULITIS	86	140
49	48	F	I14025019	2	0.7	NA	NA	NA	UTI	94	112
50	77	M	I14025125	1.7	0.5	NA	NA	NA	VIRAL FEVER	102	136

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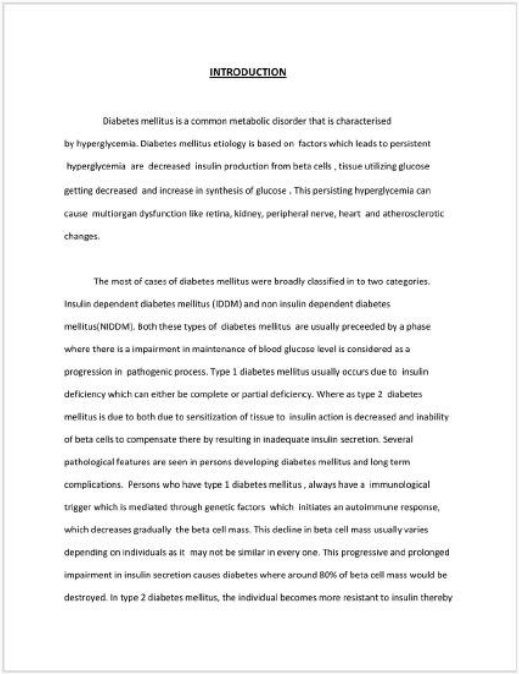

INTRODUCTION

Diabetes mellitus is a common metabolic disorder that is characterised by hyperglycemia. Diabetes mellitus etiology is based on factors which leads to persistent hyperglycemia are decreased insulin production from beta cells , tissue utilizing glucose getting decreased and increase in synthesis of glucose . This persisting hyperglycemia can cause multiorgan dysfunction like retina, kidney, peripheral nerve, heart and atherosclerotic changes.

The most of cases of diabetes mellitus were broadly classified in to two categories. Insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus(NIDDM). Both these types of diabetes mellitus are usually preceeded by a phase where there is a impairment in maintenance of blood glucose level is considered as a progression in pathogenic process. Type 1 diabetes mellitus usually occurs due to insulin deficiency which can either be complete or partial deficiency. Where as type 2 diabetes mellitus is due to both due to sensitization of tissue to insulin action is decreased and inability of beta cells to compensate there by resulting in inadequate insulin secretion. Several pathological features are seen in persons developing diabetes mellitus and long term complications. Persons who have type 1 diabetes mellitus , always have a immunological trigger which is mediated through genetic factors which initiates an autoimmune response, which decreases gradually the beta cell mass. This decline in beta cell mass usually varies depending on individuals as it may not be similar in every one. This progressive and prolonged impairment in insulin secretion causes diabetes where around 80% of beta cell mass would be destroyed. In type 2 diabetes mellitus, the individual becomes more resistant to insulin thereby

introduction

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