A STUDY ON SERUM MAGNESIUM LEVELS AND ITS CORRELATION WITH HbA1C LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

By

Dr. KOTHA SUGUNAKAR REDDY MBBS

Dissertation submitted to BLDE Deemed to be University, Vijayapura

In partial fulfillment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

GENERAL MEDICINE

Under the guidance of

Dr. SANJEEVKUMAR N. BENTOOR M.D

PROFESSOR

DEPARTMENT OF MEDICINE

BLDE DEEMED TO BE UNIVERSITY'S, SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA, KARNATAKA

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2020

B.L.D.E DEEMED TO BE UNIVERSITY'S

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled **"A STUDY ON SERUM MAGNESIUM LEVELS AND ITS CORRELATION WITH HbA1C LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. SANJEEVKUMAR N. BENTOOR M.D** (MEDICINE) Professor, Department of Medicine, Shri B.M. Patil Medical College, Vijayapura, Karnataka.

Date: 25-09-2020

Place: Vijayapura

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Date: 25-09-2020

Place: Vijayapura **Dr. K SUGUNAKAR REDDY**

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Dr. KOTHA SUGUNAKAR REDDY

LIST OF ABBREVIATIONS USED

Mg - Magnesium

mg/dl - milligram/dl

T2DM - type 2 diabetes mellitus

N - Number

SD - Standard Deviation

NIN - National Institute Nutrition

1, 25$(OH)_2$ D - 1,25 Dihydroxy Vitamin D

ICMR - Indian Council of Medical Research

HbA1c - Glycosylated hemoglobin

GRF - Glomerular Filtration Rate

DKA - Diabetic Ketoacidosis

NO - Nitric oxide

RIA - Radio Immuno Assay

ECF - Extra Cellular Fluid

Dl - Deciliter

IDF- International Diabetes Federation

LADA- Latent Autoimmune Diabetes in Adults

MODY- Maturity Onset Diabetes in Young

BMI- Body Mass Index

GLP-1 -	Glucagon like peptide -1
DPP-4	Dipeptidyl peptidase – 4
PPAR-	Peroxisome proliferator activated receptor gamma
SGLT-	Sodium-glucose co-transporter
AGE -	Advanced glycation end products
GAD-	Glutamic Acid Decarboxylase
PTH	Parathormone
Na^+	Sodium
TLR-	Toll like Receptors

ABSTRACT

BACKGROUND: From times immemorial DIABETES is known to mankind with increasing prevalence of diabetes globally, it is estimated that around 6.9 crore Indians are diabetic next only to China, and with estimated 7.7 crore Indians have prediabetes. Trace elements and their homeostasis are essential for various cellular metabolic reactions, and in diabetes it is observed that trace elements are disrupted. Magnesium is an essential cofactor of more than 300 enzymes and is a vital cofactor in enzymes involved in the glucose metabolism. Magnesium has a role in production and action of insulin, and can also activate insulin receptor tyrosine activity. It is reported that magnesium is deficient in diabetes mellitus patients.

AIM: To study the levels of serum magnesium in patients with type 2 diabetes mellitus, and to correlate serum magnesium levels with HbA1c levels.

MATERIALS AND METHODS: The data for the study is collected from patients admitted to BLDEU'S Shri B.M Patil Medical college Hospital and Research center, Vijayapura from November 2018 to June 2020. Information is collected through prepared proforma from each patient. Qualified 150 patients based on inclusion and exclusion criteria, has undergone detailed history, clinical examination and laboratory investigations, and data obtained is statistically analyzed for levels of serum magnesium and their correlation to HbA1c levels.

RESULTS: In the study sample of 150, 88.7% cases over the age of 40 years with male to female ratio are 1.9:1.0. Majority of cases, with 58.7% patients in the study are with poor control level of HbA1c. In this study, 16.7% cases of T2DM are with hypomagnesaemia and 74% cases are with normomagnesaemia. Mean age with SD in hypomagnesaemia cases is found to 55.92 ± 14.51, in normomagnesaemia cases it is 57.84 ± 13.15, and in hypermagnesaemia cases it is found to be 56.43 ± 10.87. The mean HbA1c levels with SD in

hypomagnesaemia patients was found to be 9.92 ± 3.8, in normomagnesaemic cases it is 9.4 ± 3.03, and in patients with hypomagnesaemia the mean HbA1c value was found to be 8.81 ± 2.68. The Pearson correlation between serum magnesium and HbA1c, the r value is – 0.073.

CONCLUSION: In type 2 diabetes mellitus patients with lower serum magnesium levels, the mean HbA1c levels were found to be high when compared to patients with normal or higher serum magnesium levels. There is a negative correlation between serum magnesium levels and HbA1c levels, though the correlation is statistically not significant.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES

INTRODUCTION

INTRODUCTION

From times immemorial DIABETES is known to mankind with first documented evidence dating back to 1552 BC(1). But in recent times diabetes has become a global epidemic with estimated prevalence of 343 million. Obesity and type 2 diabetes have become major public health problem affecting not only western population but also Asian population in alarming numbers. “According to findings of the ICMR sponsored INDIAB study, published in diabetologia 2011, India is faced with a galloping diabetes epidemic which is progressing at speed, with estimated 62 million patients with diabetes in India and this number is projected to explode beyond 85 million by the year 2030 and more than 3 million patients die from the disease on annual basis with some Indian urban societies one out of every five adults has diabetes”(2).

With increasing prevalence of diabetes globally, it is estimated that around 6.9 crore Indians are diabetic next only to China, and with estimated 7.7 crore Indians have prediabetes. And it is estimated that 41.5 crore people diabetic globally(3).

Type 2 Diabetes Mellitus accounts for 90% of cases of total diabetes cases globally. From 2000 to 2025 it is projected that there will be 150% increase in type 2 Diabetes in South Asia. “International Diabetes Federation (IDF) projects that global prevalence will increase from an estimated 150 million in 2000 and 415 millions in 2015 to nearly 600 million by 2035”(4).

In study published in Pharmacoeconomics in 2000, stressed that a patient with diabetes suffering from one microvascular complication the financial burden of treatment increases by 1.5 times, and with one macrovascular complication the financial burden

increases by 2 times and with microvascular and macrovascular complication one each the treatment costs increases by 3.5 times(5).

Diabetes Mellitus is broadly classified into type 1 diabetes Mellitus and type 2 diabetes mellitus with other specific types secondary to causes of genetic defects, of beta cell function or insulin action, pancreatic disorders, as a part of endocrinopathies, drug induced, autoimmune disorders and certain viral infections(6).

Type 2 diabetes mellitus is heterogenous metabolic disorder with basically interplay between insulin sensitivity and its secretory dysfunction(7). The pathogenesis of type 2 diabetes mellitus is a complex interaction between various genetic factors with various environmental factors like diet, “excessive caloric intake leading to obesity and a sedentary lifestyle, epigenetic, medications, inflammation, circadian rhythm disruptions, and the microbiome”(8).

Trace elements and their homeostasis is essential for various cellular metabolic reactions, and in diabetes it is observed that trace elements are disrupted and it is reported that there is decreased serum magnesium in diabetes patients(9). Magnesium is an essential cofactor of more than 300 enzymes and is a vital cofactor in enzymes involved in the glucose metabolism(10). Magnesium has a role in production and action of insulin, and can inhibit insulin secretion and activate insulin receptor tyrosine activity(11). Hypomagnesaemia is associated with increased intracellular calcium levels which could lead to insulin resistances(12).

There are studies with contradictory conclusions with some publishing serum Magnesium being negatively correlated and some publishing no correlation with HbA1c. With low cost of magnesium supplementation and serum magnesium estimation, establishing

serum magnesium correlation with HbA1c attracts the interest to study further, which could improve and may prove cost effective in management of type 2 diabetes mellitus.

In the present study serum magnesium levels and HbA1c levels were assessed in type 2 diabetic patients and correlation between the two were analyzed and studied.

OBJECTIVES

AIM OF THE STUDY

1. To study the levels of serum magnesium in patients with type 2 diabetes mellitus.

2. To correlate the serum magnesium levels with HbA1C levels.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

MAGNESIUM

INTRODUCTION:

FIGURE 1 – MAGNESIUM ELEMENT(13)

Magnesium is the ninth most abundant element in universe, eighth most abundant in earth's crust, and is fourth most abundant cation in the body after sodium, potassium and calcium. In intracellular fluid, it is second most abundant after potassium(14).

An average adult contains about 25g of magnesium, about 70% of which is present in skeleton. The remaining 30% occurs in soft tissues (mainly liver and muscles) & body fluids. Only about 1% of body magnesium is in the blood and extra cellular fluids(14).

STRUCTURE:

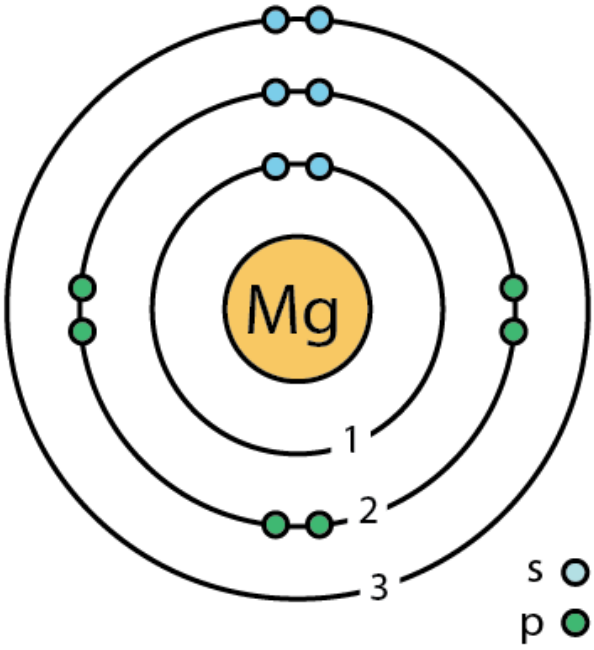


FIGURE 2 – CHEMICAL STRUCTURE OF MAGNESIUM (15)

HISTORY:

The name “magnesium” originates from the Greek word for locations related to the tribe of the Magnetes, either a district in Thessaly called Magnesia or Magnesia ad Sipylum, now in Turkey(16).

Sir Humphry Davy in England in 1808 has first isolated the metal, and first suggested name as magnium and used electrolysis on a mixture of magnesia and mercuric oxide. Antoine Bussy prepared it in coherent form in 1831(17).

METABOLISM:

Homeostasis of magnesium involves intestines, the bones and kidneys, but magnesium levels are mainly regulated by kidneys. Majority of ingested magnesium is passively absorbed by paracellular mechanism in the ileum and distal parts of the jejunum, while a small amount is absorbed by colon by active transport(18). About 50% of ingested magnesium is absorbed from the ingested food in an average diet and extent of absorption decreases with increase in dietary content of magnesium and with increase in level of serum magnesium in body(14).

Kidney are the principal organs responsible for maintaining plasma magnesium concentration within normal limits and around 98% of glomerular filtered magnesium is reabsorbed by thick ascending limb of loop of Henle and to lesser extent by distal tubules and reabsorption varies with respect to body magnesium levels(14,18).

The figure below depicts the renal regulation of serum magnesium levels. PTH, glucagon, vitamin D3 are the hormones which rises the serum magnesium levels and aldosterone, vasopressin, calcitonin, thyroxin decreases the serum magnesium levels(19).

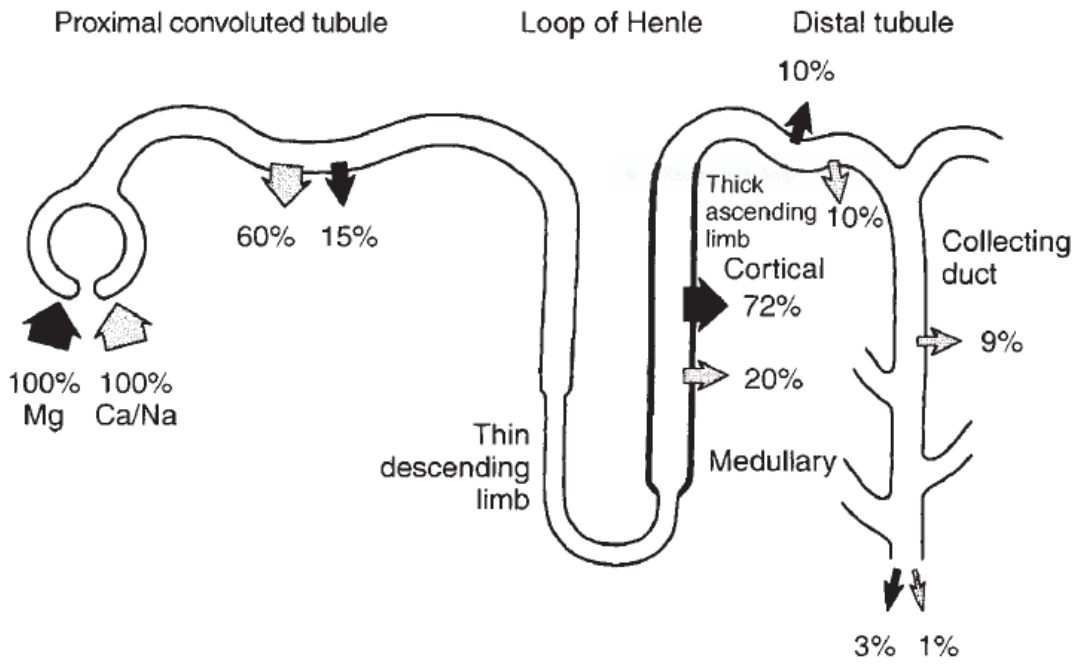


FIGURE 3: REPRESENTATION OF KIDNEYS ROLE IN HOMEOSTASIS OF MAGNESIUM.

Vitamin D (cholecalciferol), estrogen, and parathormone are the three important hormones which play a vital role in homeostasis of magnesium. Serum magnesium in higher amounts activate calcium sensing receptors present on the chief cells of parathyroid glands there by leading to suppressing parathormone secretion and reduces parathormone sensitivity. PTH enhances the reabsorption of magnesium in distal convoluted tubule and the gut and release of magnesium in bone(18).

Through electrochemical gradient of sodium ions (Na^{+}) across cation channels, magnesium enters into the cell via magnesium ($Mg^{2+)}$ anion co transport. There are eight cation channels are identified which are “transient receptor potential melastatin cation channels (TRPM 6 & 7), SLC41A1, SLC1A2 channels, ancient conserved domain protein 2 (ACDP2), magnesium transporter 1 (Magt1), the human solute carrier family 41, paracellin-

1". Mg^{2+} efflux exchanges with sodium, calcium, manganese antiporter, and cl^{-}/Mg^{2+} co transporter(20)

TRPM7 is essential for regulating intracellular magnesium level, cell function and is most selective for magnesium and is found in heart, blood vessels, lungs, liver, brain, intestine, and spleen(21).

TRPM6 is found in kidney and intestines, and has role in regulation of total body magnesium store levels(21).

Mrs2p, SLC41A1, SLC41A2 regulate Mg^{2+} in neurological, cardiovascular, and metabolic functions through magnesium transportation in mitochondria(22).

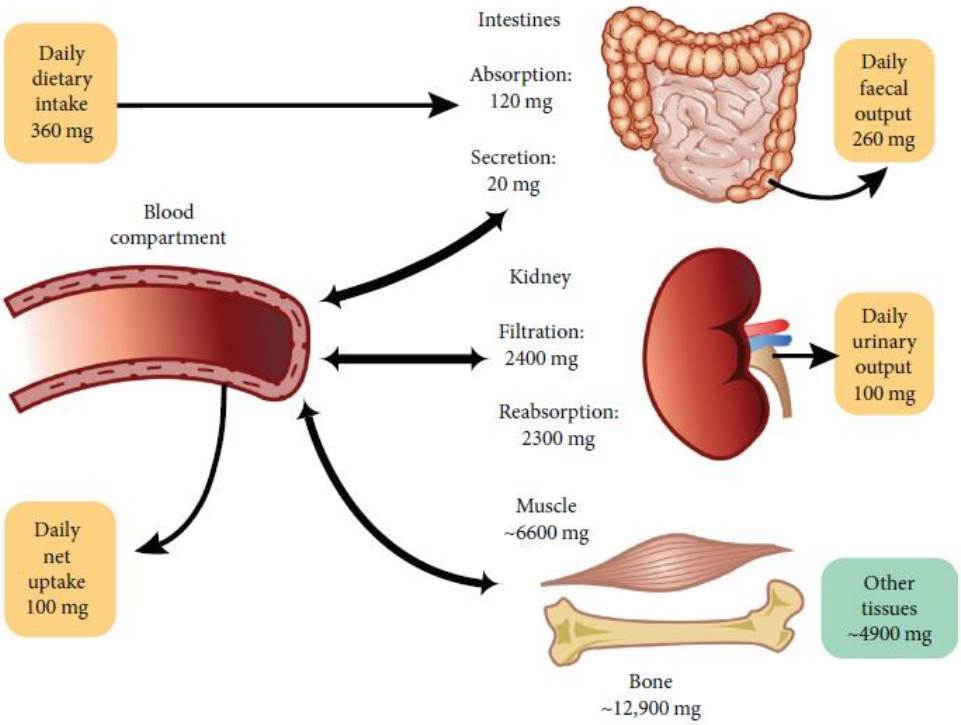


FIGURE 4 – MAGNESIUM REGULATON IN HUMAN BODY(18)

A defective absorption of magnesium from food secondary to vitamin D deficiency, malabsorption syndromes and infantile hypomagnesaemia, vomiting, diarrhea, and intestinal fistulas causing increased loss from intestine, impaired reabsorption in kidneys, and various genetic wasting syndromes, renal diseases, drugs like diuretics, alcohol, cisplatin, cyclosporine, aminoglysides, amphotericin B and various metabolic causes and cancers could lead to reduced serum magnesium levels(23).

Hypomagnesaemia is observed in alcoholism, and magnesium levels are decreased in high fat diet consumption, and magnesium has ability to predict the pancreatic exocrine insufficiency (24).

ABNORMALITIES IN SERUM MAGNESIUM:

A serum magnesium level of more than 2.3 mg/dl is considered as hypermagnesaemia. Most often hypermagnesaemia are iatrogenic, and is seen in chronic kidney disease, tumor lysis syndrome and diabetic ketoacidosis (DKA). Hypermagnesaemia clinically generally cause hyporeflexia, lethargy, weakness, drowsiness and paralysis, hypotension, bradycardia, cardiac arrest with ECG changes showing bradycardia, prolonged PR interval, QRS and QT intervals with magnesium levels of 5 to 10 mEq/l(25).

A serum magnesium level of less than 1.7 mg/dl is considered as hypomagnesaemia. Hypomagnesaemia generally results from decreased absorption or increased excretion and influence of certain drugs that impair tubular magnesium transport. Hypomagnesaemia had neurological manifestations of “lethargy, confusion, tremor, fasciculation, ataxia, nystagmus, tetany, and seizures, atrial and ventricular arrhythmias in patients with digoxin”(26).

Magnesium movement between bone and intracellular pools is reportedly slow, and in that view normal serum levels of magnesium would not exclude total body magnesium.

Hypocalcaemia and hypokalemia are seen in hypomagnesaemia because of hypomagnesaemia induced disturbance in homeostasis of minerals(26).

Genetic variations in magnesium regulating genes “lTRPM6, CLDN19, SLC41A2, CNNM2, FXYD2” through affect on serum magnesium levels can significantly impact the risk of diabetes(27).

FUNCTIONS:

Magnesium (Mg^{2+}) is an integral part in cellular function and plays a very vital role in human physiology. Mg2+ plays a major role in numerous metabolic reactions involving hundreds of enzymes in human physiological system and has multiple roles in structural and physiological functions of mitochondria, transmembrane transport, nucleic acids and proteins(18).

In cardiovascular system, Mg2+ plays a role as calcium channel blocker or as sodium antagonist, there by detecting ion exchange across cell membrane through different channels. As a cofactors of Na-K-ATP pump, Mg2+ maintains membrane potential in cardiac myocytes(28).

It is advocated that Mg2+ has anti-inflammatory properties, and it is demonstrated that dietary deficiency of magnesium up regulated two proto-oncogenes, c-fos and c-jun. Even with short term hypomagnesaemia it is seen that more than 150% increases in sphingomyelinase activity and proto-oncogene expression in both the left and right ventricular muscle, artial muscles, abdominal aortic smooth muscle(28).

Mg2+ deficiency acts as a stressor effect making body susceptible to physiological stress, activating sympathetic nervous system leading to raised oxidative stress and elevation of NFkB promoting apoptosis. It is demonstrated that “free intracellular magnesium induces

defective expression of natural killer activating receptor NKG2D in NK and CD8+T cells". Mg2+ plays a role in antiviral and anti-tumor immunity(28).

Mg2+ plays a role in sympathetic nervous system activity.(11) Neuromuscular excitability is decreased by the Mg2+ (14).

Mg2+ is an enzyme activator, it activates a number of enzymes, particularly those in which ATP-Mg^{2+} (a complex of ATP & Magnesium) is a substrate. The enzymes needing Mg2+ are involved in intermediary metabolism, the transcellular ion transport, muscle contraction, and oxidative phosphorylation, which are mostly kinases, synthatase and cyclases (14).

Mg2+ levels play a role in musculo-skeletal system. By influencing the free radical production, endothelial function, and altering PTH and vitamin D3 levels, Mg2+ affects bones through disturbances in bone turnover(29).

It is correlated that magnesium levels alter in various endocrinopathies. Magnesium has role in both insulin secretion and insulin sensitivity(28).

DISTRIBUTION IN BODY:

With total average body magnesium in adult is around 25gm, with 70% in bones and 30% in soft tissues and body fluids, only 1% of body magnesium is in blood and extracellular fluid. The skeletal and extracellular magnesium pools exchange freely with each other but not with the intracellular pool and only unbound fraction is biologically active fraction(14).

NORMAL VALUES:

Serum concentration of magnesium is 1.6-2.3 mg/dl (0.7-1.0 mmol/L), of which about 20-25% is protein bound. The intracellular magnesium concentration is much higher (about 10 mmol/L) than that in ECF, most of which is bound to organelles and in red blood cells, the concentration is about 20 mmol/L (14).

DIAGNOSTIC LABORATORY MEASUREMENT OF MAGNESIUM:

It is evident from the literature that serum magnesium constitutes only 1% of the total body magnesium. And its measurement would not assess the total body magnesium. But at the same time keeping in mind the cons of measuring serum magnesium, using serum magnesium to assess the levels is the most feasible, cheap, practical way at present if not in future. Serum magnesium can be measured by number of methods like precipitation, titration, automated absorption photometry, fluorometry, photometry, flame emission spectroscopy. At present there are number of automated machinery that use photometric method to determine the levels of serum magnesium.

Serum magnesium levels may affect by sampling errors and other confounding factors like higher phosphate levels, lipaemia, hemolysis of sample, patients with hyperbilirubinaemia and delayed processing of sample for serum separation.

SOURCES OF MAGNESIUM:

Major food sources are nuts, cereals, beans and fish. Almonds are a particularly rich source. As magnesium in the main metal content in structure of chlorophyll, all most all leafy green vegetables are a good source(14). Tender coconut water contains around 10mg% of magnesium(30).

RECOMMANDED DIETARY ALLOWANCE OF MAGNESIUM:

According to Indian Council Of Medical Research (ICMR) and National Institute of Nutrition (NIN), recommended dietary allowances for Indians are following:

TABLE 1: RECOMMANDED DIETARY ALLOWANCE(31)**:**

GROUP	AGE	RDA FOR Mg (mg/day)
MAN	ADULT	340
WOMEN	ADULT	310
INFANTS	0-6 months	30
	6-12 months	40
CHILDREN	1-3 years	50
	4-6 years	70
	7-9 years	100
BOY	10-12	120
GIRL	10-12	160
BOY	13-15	165
GIRL	13-15	210
BOY	16-17	195
GIRL	16-17	235

DIABETES MELLITUS

HISTORY(1)**:**

From time immemorial diabetes is known to mankind. German archeologist George Ebers discovered "papyrus", the first documented evidence of diabetes in humans dating back to 1552 BC. Diabetes is described as polyuric state in this ancient document.

In India, Diabetes is known as "prameha" the term literally means excess urine. Lord Shiva dictating a formulation for treating prameha is described in "Charkradatta". From 1500 BC "Charaka Samhita" describes "prameha" and 20 different types of "prameha" are described of which if not treated can develop into "Madhumeha" which is hereditary and can be diagnosed by detecting ants around urine of diabetics. In tenth century BC similar details were given in "Sushruta Samhita".

Ancient scriptures in India suggest two types of madhumeha. One specific type of madhumeha where treatment was very difficult and patient is lean, is called it "Krisha" which corresponds to insulin dependent diabetes and other type where patient is obese and suggested a treatment of controlled specific diet and physical exercise which corresponds to non insulin dependent type 2 diabetes mellitus.

Aretaeus of Cappedocia coined term "DIABETES" with a literal meaning of "siphon", which is reckoned in terms of sucking water of body through urine, and he considered diabetes as rare disease which "melts flesh and limbs into the urine"

Gale and Aretaeus reckoned that diabetes could be due to renal defect, and this view was standing its place for more than 1500 years. Chinese Chen Chhuan and Persian Avicenna gave descriptions of complications of diabetes.

Paracelsus led revival of scientific medicine in 16th century AD and evaporated urine of a diabetic patient and reckoned white precipitate as salt and professed that diabetes resulted from deposition of salt like material in kidney and bladder.

Thomas Willis first described taste of diabetic urine as sweet, and in 1772 Matthew Dobson described urine containing sugar after evaporating diabetic urine.

Scottish William Cullen described polyuria in two ways one with sweet urine and other as tasteless. In 1815 Eugene Chevreul described sugar in diabetic urine as glucose. Trommer described methods for detecting glucose in urine in 1841, which was followed by "Fehling", "Roberts" and "Benedicts".

Around 1840, Bernard discovered that glucose is present in animals in non diabetic state and identified liver as a source of glucose and glycogen as precursor.

In 1889, Minkowski and Josef von Mering discovered removal of pancreas in dogs lead to diabetes which was similar to human patient with diabete maigre (similar to type 1 diabetes mellitus).

In 1869, Paul Langerhans identified clusters of cells in pancreas that might have related to diabetes, and Gustave Laguesse named them as "islets of Langerhans", and secretions from these clusters was given name as "insuline" by Jean de Meyer in 1909.

In 1905, Eugene Gley extract from depancreatized dogs decreased glycosuria, in 1906 Georg Zuelzer along with Minkowski tried to treat glycosuria in humans with animal pancreas extracts. In 1919, Nicholai Paulescu announced that pancreatic extract cured symptoms of diabetes in depancreatized dogs.

Frederick Grant Banting along with Charles H Best did tested Banting's hypothesis in 1921, and they gave name to pancreatic extract as "isletin" and name "Insulin" was given by

Macleod. Leonard Thompson was the first patient receiving insulin on January 11th, 1922. In 1923, Banting and Macleod awarded Nobel Prize for discovery of insulin which was later shared with Best and Macleod.

In 1958, Frederick Sanger received Nobel for discovering amino acid sequence of insulin, and Dorothy Hodgkin in 1964 for deciphering 3D insulin structure, and in 1977, Rosalyn Yalow received Nobel for discovering RIA to measure insulin levels.

In 1926, Abel succeeded crystallizing insulin enabling further improvement of insulin purity. With progression in biotechnology, first human insulin was produced from Escherichia coli in 1983. First rapid acting insulin analog, insulin lispro was introduced in 1990s followed by aspart and glulisine. First long acting insulin analog, glargine in 2003 and detemir in 2006, followed by degludec are introduced.

In 1926, Frank introduced "synthalin" a first oral antidiabetic agent in 1955, Franke and Fuchs introduced "Carbutamide" into clinical practice. In 1957, phenformin was introduced followed by metformin. In 1972, HbA1c was introduced, which was widely used in clinical practice by 1980s. In 1978, first continous subcutaneous insulin infusion pump introduced by John Pickup. In 1990s, glinides, alpha glucosidase inhibitors and thiazolodinediones were introduced and marketed followed by GLP-1 analogs and DPP-4 inhibitors.

Though the history of diabetes is exciting and eventful in past 50 years in terms of treatment modalities, but journey is still far from complete and cure for diabetes is nowhere near in sight.

DIABETES MELLITUS refers to a chronic disorder characterized by phenotypic expression of hyperglycemia, by abnormal metabolic regulation and potential to cause vascular and neuropathic complications(32,33).

With the pattern of increasing statistics of prevalence and incidence of diabetes, in near future it is evident that diabetes mellitus could be the leading cause of morbidity and mortality surpassing communicable diseases in both developing and developed worlds. Globally prevalence of diabetes mellitus (DM) has risen from 3 crore to 41.5 crore in past twenty years.

International Diabetes Federation estimated that in 2014 prevalence of diabetes would be 387million, in 2035 will rise up to 592 million, and in 2040 will further rise to 642 million(34,35). Both type 1 and 2 diabetes mellitus prevalence increasing, but the trend of increasing prevalence in type 2 diabetes mellitus is much faster presumably because of increasing industrialization and globalization affecting the life style and food habits. Type 2 diabetes mellitus prevalence increases with increasing age and it is estimated that 50% of individuals with diabetes may be undiagnosed. There is considerable variation in prevalence of type 2 diabetes mellitus based on races, sex, age and geographical location. In India it is estimated that diabetes mellitus prevalence in northern India is 11% where as in southern India it is going up to 17%(34). “IDF estimates that there are 72.9 million people with diabetes in India in 2017, which is projected to rise to 134.3 million by the year 2045”. The prevalence of diabetes in urban India, especially in large metropolitan cities has increased from 2% to over 20% in 30 years and the rural areas are now competing with urban(36).

IDF estimated the enormous financial burden of managing diabetes patients globally. It is estimated that in 2015 globally 637 billion dollars i.e.., a 12% of health care expenditure is spent on diabetes, where 75% of global diabetic patients burden is borne by low and middle income countries(32). China stands first with 109.6 millions of Chinese population suffering from diabetes, followed by India, USA, Brazil, and Russia.

Several types of diabetes mellitus are due to complex interplay between environmental and genetic factors. In DM, increased blood sugars levels are due to disrupted harmony between insulin secretion, glucose utilization, and production of glucose.

CLASSIFICATION OF DIABETES MELLITUS:

Diabetes has been broadly classified into two types:

TYPE 1: Due to near total or complete lack of insulin.

TYPE 2: Due to insulin resistance, reduced insulin secretion & increased production of glucose

TABLE 2: DIABETES MELLITUS CLASSIFICATION(3)

Type of DM	SUBTYPES	NOTE
Type 1 DM	Type 1A – autoimmune Type 1B – non autoimmune LADA – latent autoimmune diabetes of adults	Due to beta cell failure, leading to poor insulin production, occurring in young
Type 2 DM		Most common due to insulin resistance with decreased insulin secretion
Gestational Diabetes		Transient form occurring due to diabetogenic effect of hormonal interplay during pregnancy
Other specific types	MODY – there are 14 types of maturity onset diabetes in young	Secondary to calculous, pancreatitis, drug related & genetic forms

TABLE 3: CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS(4)**:**

TEST	NORMOGLYCEMIA	IMPAIRED FASTING GLUCOSE	IMPAIRED GLUCOSE TOLERANCE	HIGH RISK	DIABETES MELLITUS
(PG)FASTING PLASMA GLUCOSE (mg/dl)	<100	100-125			>126
2nd hour PG	<140		140-199		>200
HbA1c	<5.7			5.7 -6.4	> 6.5
Random PG					>200 + classical symptoms of diabetes and hyperglycemic crisis

To summarize the tabulations on criteria for diagnosing diabetes mellitus:

1. Random blood glucose > 200mg/dl, plus symptoms of diabetes or

2. Fasting plasma glucose > 126mg/dl or

3. HbA1C > 6.5% or

4. Two hour plasma glucose during an oral glucose tolerance test more than 200mg/dl

PATHOGENESIS AND PATHOPHYSIOLOGY OF TYPE 1 DIABETES MELLITUS:

In type 1 diabetes mellitus insulin deficiency and immune mediated loss of beta cells of ilets of langerhans result from complex interaction between immunological factors with environmental and genetic factors. This autoimmune destruction of beta cells in ilets of langerhans can be initiated by impact of environmental factor and various infections. During infections and while attaining puberty there is an increased requirement of the insulin which may lead to manifestation of diabetes, which was previously compensated glucose intolerance with the declining beta cell mass. As the disease progresses the residual beta cell mass will be destroyed and complete absence of endogenous insulin production ensues leading to a state of complete insulin deficit state(32). These patients are prone for other autoimmune disorders like grave's disease, hashimoto's thyroiditis, Addison's disease, vitiligo and autoimmune anemia(37).

Majority of the type 1 diabetes mellitus patients are found to have auto antibodies against insulin hormone, glutamic acid decarboxylase enzyme (GAD 65 & 67), secretory granule protein islet cells antigen 512 (IA-2). Beta cell destruction is mediated by cytokines or by direct T lymphocytes causing apoptosis, destroying islets. Certain immunosuppressive drugs acting on T cell receptors are reported to delay onset of type 1 diabetes mellitus suggestive of main role of T cells in disease pathology(38).

GENETIC CONSIDERATION:

Multiple genes are reported to be involved in development of type 1 diabetes mellitus. "The susceptibility gene is located in the HLA region in chromosome 6. Polymorphism in HLA complex accounts for 40-50% of genetic risk of developing type 1 diabetes mellitus. Most individual with type 1 diabetes mellitus have HLA DR3 and (or) HLA DR4 haplotypes. The

haplotypes DQA1*0301, DQB1*0302, and DQB1*0201 are strongly associated with type 1 DM"(32).

Insulin gene on chromosome 11 and some loci related to autoimmune conditions suggest the pathways predisposing to loss of self tolerance and on chromosome 2 IFIHI gene encodes for proteins involved in innate immunity and play a role in recognition of RNA genomes of certain viruses. Viruses like mumps, rubella, coxsackie virus may contain structural molecules mimicking beta cell protein and viral infection and could start an autoimmune process leading to destruction of islets(38).

The presence of haplotype DQA1*0102, DQB1*0602 provides protection against the development of Type 1 DM, and is reported that it is very rarity to find it in type 1 diabetes mellitus patients. DR 15 DQ6 haplotype is highly protective for type 1 diabetes mellitus(38).

Metabolic disturbances of Type 1 diabetes(32)

Carbohydrate metabolism:

Decreased insulin leads to increased hepatic gluconeogenesis and peripheral under utilization of glucose by tissues which results in hyperglycemia.

.**Fat metabolism**:

In case of insulin deficiency hormone sensitive lipase enzyme which is inhibited by insulin, shows increased activity leading to lipolysis leading increased free fatty acids which in turn leads to ketosis.

Protein metabolism:

In the absence of anabolic effect of insulin, protein breakdown increases through proteosome mediated pathway and generates alanine and glutamine which are precursors of gluconeogenesis which leads to hyperglycemia and muscle wasting.

TYPE 2 DIABETES MELLITUS:

Majority of diabetes mellitus will come in the bracket of type 2 diabetes mellitus, is a heterogeneous disorder and a pan metabolic disorder characterized by chronic hyperglycemia with not totally clear highly complex pathogenicity involving genetic factors and environmental factors, but pathogenesis can be summarized mainly to abnormal insulin secretion with respect to blood sugar levels and impaired insulin sensitivity(7).

GENETICS IN TYPE 2 DIABETES MELLITUS:

It has been established beyond doubt from multiple large trials that strong genetic factors play a role in type 2 diabetes mellitus pathogenesis. Type 2 diabetes mellitus contains both monogenic and polygenic forms.

Monogenic forms are sufficient enough to cause diabetes mellitus and environment does not have any role in causation of disease. And monogenic forms of type 2 diabetes mellitus cases are detected in younger patients in 2^{nd} and 3^{rd} decades of their life. Monogenic forms are mainly two forms one associated with insulin resistance and the other associated with insulin secretion.

Monogenic forms of type 2 diabetes mellitus resulting from mutations in the insulin receptors are “type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome”. Different mechanisms are observed in impairment of insulin receptor function such as decreasing the

rate of receptor synthesis, accelerating receptor degradation, inhibiting transport and function of receptor itself. Mutations in PPAR- activated receptor Gama, lipoatrophic diabetes, neonatal diabetes are other forms of monogenic forms of diabetes with insulin resistance. Neonatal relapsing transient diabetes is uniparentral disomy 6 chromosome abnormality (UPD 6) which is resultant of methylation defect. Mutations in KCNJ11, ABCC8, insulin gene mutations could cause permanent neonatal diabetes(7).

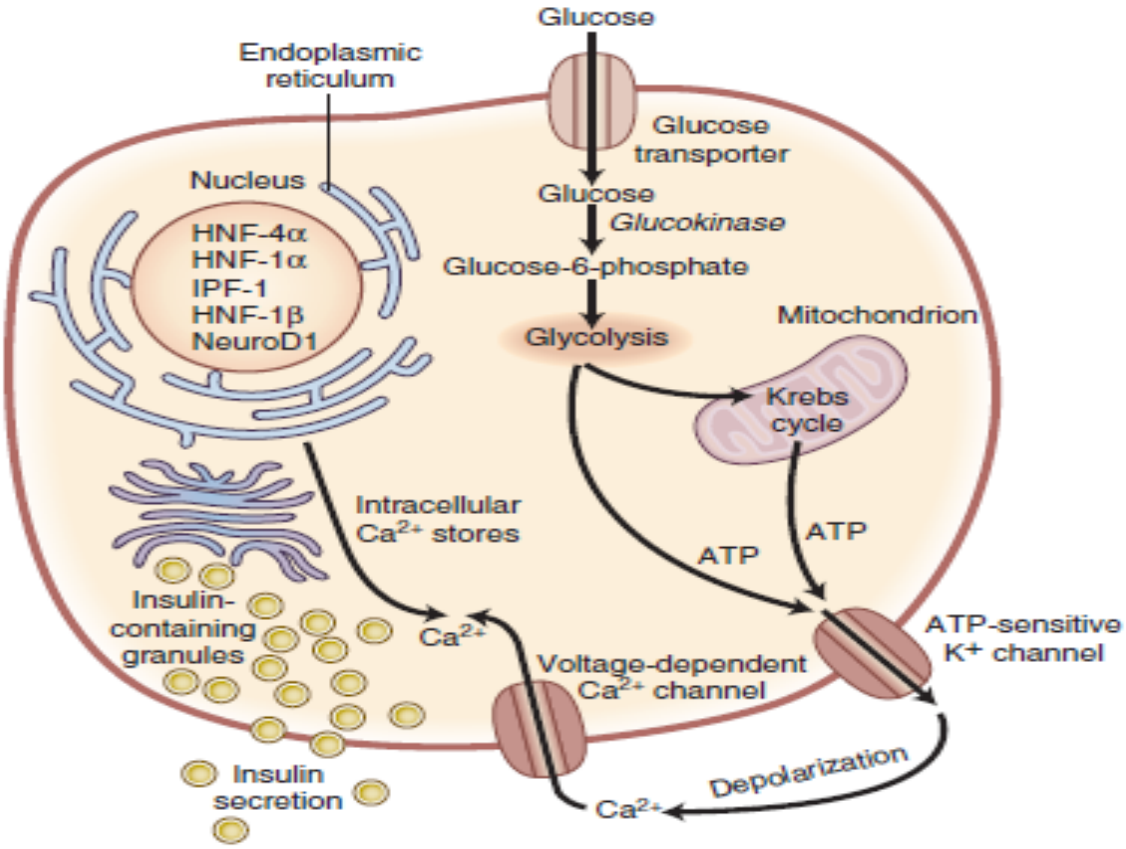


FIGURE 5: PANCREATIC BETA CELL AND THE PROTEINS IMPLICATED IN MODY(39)

Monogenic forms of diabetes with defects in insulin secretion are mutant insulin syndromes, mitochondrial diabetes, MODY (maturity onset diabetes in young). 6 different genes namely GCK (encodes the glycolytics enzyme glucokinase), HNF4A (hepatocyte nuclear factor-4alpa), HNF1A, PDX1, IPF1, HNF1B, NEUROD1 are culprits for 14 types of MODY(39).

In polygenic forms of type 2 diabetes mellitus, Calpain-10 gene, Kir6.2 gene, PPAR-Gama gene, HNF4A(hepatocyte nuclear factor 4alpha) gene, TCF7L2 (transcription factor 7 like 2) gene are implicated(39).

In genome wide association studies about 90 genetic loci are found have associated risk of T2DM (type2 diabetes mellitus).

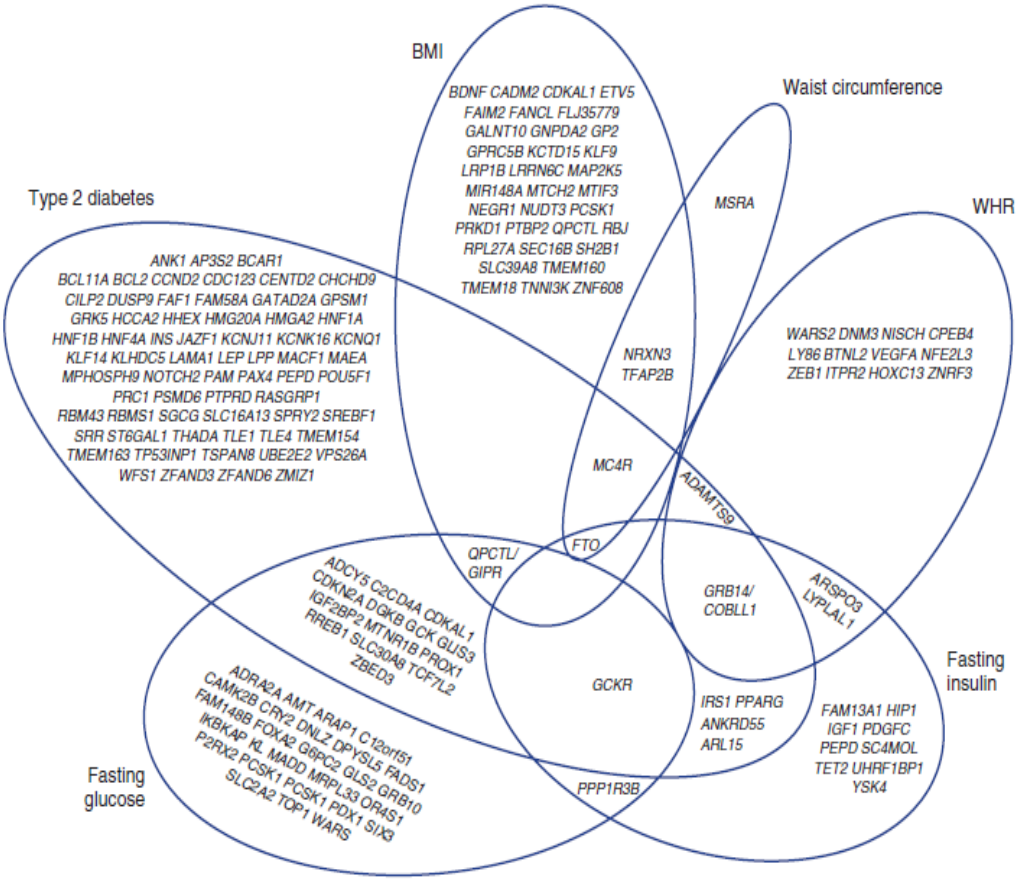


FIGURE 6: GENETIC LOCI ASSOCIATED AT GENOME WIDE SIGNIFICANCE WITH TYPE 2 DIABETES MELLITUS AND OBESITY(39)

Pathophysiology:

Type 2 diabetes is a complex interplay of insulin resistance, reduced insulin secretion, abnormal fat metabolism and increased hepatic glucose output in varying proportions with vast spectrum of variable presentation(40).

Impaired response to either exogenous or endogenous insulin is considered as “insulin resistance”. Insulin resistance is observed with decreased insulin mediated transmembranous transport of glucose and metabolism in adipocytes, and skeletal muscles, impaired insulin suppression of lipolysis, and glucose output from liver. Strong genetic and environmental factors play a role in insulin resistance(41).

Obesity and insulin resistance are very closely associated, net amount of fat in the body has effect on insulin sensitivity, but central obesity is strongly associated with insulin resistance. The abdominal fat and glucose tolerance are associated independent of total body fat. It is proposed that abdominal fat is lipolytically active than subcutaneous fat, and is resistant to insulins’s antilipolytic effects of insulin, resulting in more fatty acid load increased conversion of cortisone to cortisol, and alter production of adipokines there by effecting glucose metabolism(41).

It is hypothesized that hyperinsulinemia could cause insulin resistance by “down regulating insulin receptors and desensitizing post receptor pathways”.

Adipocytes are storage cells and regulate uptake and release of fatty acids, leptin, hormones that signal status of energy in the body, and secrete cytokines, IL-6, IL-8, monocyte chemoattractant protein 1, and granulocyte colony stimulating factor. These may attract proinflammatory macrophages which release TNF-alpha which has local and systemic inflammatory effects(41).

Mammalian Target of Rapamycin (mTOR) is part of a multisubunit serine/threonine protein kinase complex that integrates signaling from insulin and other growth factor receptors and regulates many cell processes including growth, autophagy, apoptosis, protein synthesis and transcription. Activation of TORC1 propagates anabolic signal ultimately leading to insulin resistance(41).

Acute infections and bacterial cell wall lipids induce innate immunity through toll like receptors (TLR2 & 4). This is associated with significant resistance(41).

Disturbed circadian rhythm and sleep disruption can directly impair insulin action, alters the secretion of leptin, ghrelin with appetite stimulation, increased inflammatory cytokine production(41).

Immediate post prandial surge of glucose is managed by absorption of glucose by skeletal muscle and conversion to hepatic storage form called glycogen by action of insulin. In obesity skeletal muscle insulin resistance appears much before the defective signaling in adipose tissues and liver. With insulin resistance there is a defect in non oxidative utilization of glucose. Elevated free fatty acids in obesity predict the progression of impaired tolerance to frank diabetes mellitus. Randle hypothesis predicts increase in glucose 6 phosphate concentrations which ultimately results in insulin resistance. It is reported that “insulin stimulated glucose uptake is inversely related to amount of intramuscular triglycerides”(41).

Increased intra myocyte fat in muscles could alter mitochondrial mass which in turn results in oxidative capacity reduction ultimately causing insulin resistance and type 2 diabetes mellitus.

In T2DM hepatic glucose output is not suppressed by low or high plasma insulin levels, there by hepatic glucose output is elevated early in the course history of the disease(41).

Both in short term and long term effects of glucocorticoids on insulin resistance is by direct modulation of transcriptional events, with inhibition of insulin and growth factor signaling(41).

Hyperglycemia itself results in insulin resistance and vice versa, there by initiating a vicious cycle. In HIV infections protease inhibitors are supposed to be cause insulin resistance(41).

PATHOBIOLOGY OF TYPE 2 DIABETES MELLITUS(42)**:**

IMPAIRED INSULIN SECRETION:

It is both quantitative and qualitative factors are cause for the relative insulin deficiency which the characteristic feature of T2DM. impaired glucose sensing, loss of beta cell mass, loss of normal physiological pattern of insulin secretion with amyloid accumulation in islet cell mass are observed in T2DM. And there is progressive loss of beta cell with the progression of disease.

IMPAIRED INSULIN ACTION:

Insulin resistance is due to pre-receptor defects, abnormal insulin receptors, and post receptor defects. Impaired insulin action is compensated by hyperinsulinemia in early stages of disease which is eventually destined to fail and hyperglycemia occurs.

OMNIOUS OCTET:

There are eight pathogenic mechanisms of Type 2 Diabetes mellitus(43). Gut, liver, kidney, adipose tissue, muscle, pancreatic alpha cells and beta cells, brain are main eight pathogenic

mechanisms in pathogenesis of type 2 diabetes mellitus.

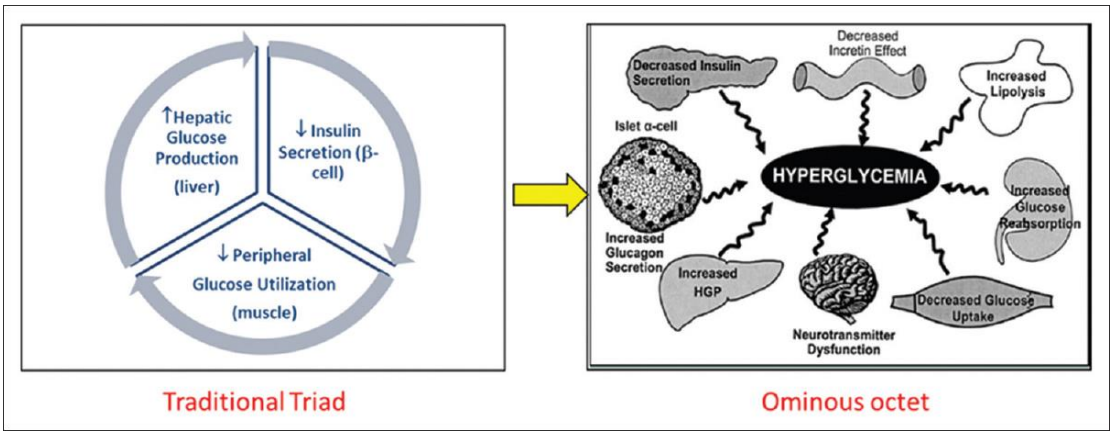


FIGURE 7: DIABETES PATHOPHYSIOLOGY: TRADITIONAL TRIAD TO OMINOUS OCTET (44)

Incretins are the hormones from intestinal epithelium, and are two namely, GLP 1(glucagon like peptide) and GIP (glucose dependent insulinotropic peptide) which inhibits glucagon, delays gastric emptying and produces satiety. In T2DM GLP1 is deficient.

Hepatic insulin resistance is caused by excessive fat deposition in liver, they by resulting in increase hepatic output of glucose into the blood. Hyperglucagonemia increases free fatty acids aggravating insulin resistance.

Increased adipocytes results in increased free fatty acids and cytokine release ultimately resulting in IR (insulin resistance). Maladaptive kidneys in filtration and reabsorption through SGLT-2 and SGLT-1 result in hyperglycemia in T2DM.

Diminished magnitude of inhibitory response in controlling appetite following ingestion from specific centers of hypothalamus in noted in T2DM.

METABOLIC SYNDROME(45)**:**

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

COMPLICATIONS OF DIABETES MELLITUS:

Acute metabolic complications are

1. Diabetic ketoacidosis (DKA)

2. Hyperglycemic hyperosmolar state (HHS)

3. Hypoglycemia.

DIABETIC KETOACIDOSIS (DKA)(46):

Diabetic ketoacidosis is more common in type 1 diabetes and may be the presenting feature in type 1 diabetes and is rare in T2DM. It is associated with relative or absolute insulin deficiency, volume depletion and acid base abnormalities. Counter regulatory hormones such as glucagon, cortisol, growth hormone and catecholamine play an important role in DKA. Glucagon excess and insulin deficiency is necessary for DKA to develop. Decrease in insulin level augments the activity of phosphoenol pyruvate carboxykinase; increase in glucagon level reduces the activity of pyruvate kinase. These changes cause pyruvate to get converted to glucose. Increases in catecholamine level causes glycogenolysis. Increased levels of

counter regulatory hormones and decreased levels of insulin causes increase in lipolysis and release of free fatty acids. The increased free fatty acids causes increase in triglyceride and very low density lipoprotein level. In DKA, increase in glucagon level alters liver metabolism in favour of ketone body formation by activating the enzyme carnitine palmitoyl transferase. At normal pH these ketone bodies exists as ketoacids and these are neutralized by bicarbonate. Once bicarbonate stores are depleted metabolic acidosis ensures.

CLINICAL FEATURES:

Thirst, polyuria, abdominal pain, nausea, vomiting and breathlessness are clinical features of DKA. DKA is precipitated by infarction, infection, inadequate dose of insulin administration .Drugs

such as cocaine can precipitate. Pregnancy itself can precipitate DKA. Physical signs include dehydration, hypotension, tachypnea, tachycardia, respiratory distress, and kussmals breathing. In case of severe acidosis lethargy, cerebral edema and coma can occur.

LAB ABNORMALITIES AND DIAGNOSIS:

Blood glucose is only mildly elevated often >250 mg/dl. Serum bicarbonate is <10 mmol/lit, the pH is in the range of 6.8 to 7.3 depending on the severity of acidosis. Hyperproteinemia, hypertriglyceridemia and leucocytosis can occur. Serum sodium, phosphorous, chloride and magnesium levels are reduced in ketoacidosis. There is mild elevation of blood urea nitrogen and serum creatinine level. Serum levels of β hydroxybutyrate level are in diagnosis.

HYPERGLYCEMIC HYPEROSMOLAR STATE(46):

It occurs as a result of decreased fluid intake and relative insulin deficiency. Insulin

deficiency causes increased glucose output from the liver and decreased glucose utilization in

skeletal muscle. Hyperglycemia causes osmotic diuresis and leads to intravascular volume loss which is further accentuated by decreased fluid intake. The absence of ketosis in hyperglycemic hyperosmolar state is not known. Studies have shown that the levels of counter regulator hormones and free fatty acids levels are low in hyperglycemic hyperosmolar state when compared to DKA. It is said that insulin/glucagon ratio doesn't favors ketogenesis.

CLINICAL FEATURES:

Patients present with weight loss, weeks history of polyuria and decreased oral intake which ultimately results in lethargy, mental confusion or coma. It is usually precipitated by sepsis, pneumonia, and concurrent illness such as stroke or myocardial infarction. Examination will reveal tachycardia, hypotension, profound dehydration, hyperosmolality, and altered mental status. Absence of nausea, vomiting, abdominal pain and kussmaul breathing favor the diagnosis of hyperglycemic hyperosmolar state.

LAB ABNORMALITIES AND DIAGNOSIS:

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

HYPOGLYCEMIA(47)**:**

Hypoglycemia is one of the most important complications of diabetes. It occurs due to excess administration of insulin or oral hypoglycemic agent particularly in the setting of organ failure or sepsis.

Hypoglycemia is documented by whipple′s triad.

1. Reduced plasma blood sugar.

2. Symptoms of hypoglycemia.

3. Relief of symptoms after giving glucose.

Symptoms of hypoglycemia and blood sugar value less than 55mg/dl and improvement of symptoms after giving glucose documents hypoglycemia.

As the blood sugar falls below the physiological range counter regulatory hormones comes into action. First defense is reduced insulin secretion. Second defense is the glucagon, which causes hepatic glycogenolysis. Third is the epinephrine which stimulates hepatic glycogenolysis and gluconeogenesis. When hypoglycemia is for more than 4 hours cortisol and growth hormone comes into action and promotes glucose production.

CLINICAL MANIFESTATION:

Symptoms in hypoglycemia are classified in to two broad categories namely neurogenic and neuroglycopenic symptoms. Neuroglycopenic symptoms are due to reduced sugar level in the brain. In neurogenic symptoms like sweating, hungry, tingling are cholinergic Symptoms and tremors, palpitations, and nervous anxiousness are adrenergic symptoms.

Signs of hypoglycemia are pallor and diaphoresis. Blood pressure and heart rate are increased, but may not be increased in patients with recurrent episodes of hypoglycemia secondary to hypoglycemia associated autonomic failure due to impaired hypoglycemic awareness.

TABLE 4: SYMPTOMS OF HYPOGLYCEMIA(47)

NEUROGENIC SYMPTOMS	**NEUROGLYCOPENIC SYMPTOMS**
Sweating	Warm, weak
Hungry	Difficulty in thinking, confused
Tingling	Tiredness and drowsiness
Tremors	Fainting, dizzy
Palpitations	Difficulty in speaking
Nervousness and anxiety	Blurred vision

CHRONIC COMPLICATIONS OF DIABETES:

Chronic complications can be classified into microvascular and macrovascular.

TABLE 5: CHRONIC COMPLICATIONS OF DIABETES MELLITUS(48)

MICROVASCULAR COMPLICATIONS	MACROVASCULAR COMPLICATIONS
Retinopathy	Stroke – cerebrovascular disease
Nephropathy	Peripheral arterial disease
neuropathy	Coronary artery disease

CORONARY ARTERY DISEASE:

Diabetes mellitus patients have dyslipidemia. Increased triglyceride level and the small dense lipoprotein particles found in diabetics have more atherogenic potential and they are more

easily glycated and susceptible to oxidation(49). Risk factors for coronary artery disease in diabetic patients are smoking, reduced physical activity, obesity, dyslipidemia and hypertension. Patients with essential hypertension have elevated levels of insulin level in the fasting and postprandial state when compared to the normotensive people regardless of BMI. This implies that hypertension is an insulin resistance state(50). Other risk factors associated with diabetes are macroalbuminuria, microalbuminuria, abnormal platelet function and increased serum creatinine level. Patients with diabetes and insulin resistance have elevated levels of fibrinogen and plasminogen activator inhibitors there by augments the coagulation process and impairs fibrinolysis(51). Thus leading patients have impaired vascular smooth muscle and endothelial dysfunction, these also contributes to thrombus formation, thus increasing the cardiovascular morbidity and mortality. Diabetic patients have fourfold (in women) and two fold (in men) increase in mortality due to cardiovascular events.

CEREBRO VASCULAR DISEASE:

Type 1 and Type 2 diabetic patients are more prone for stroke. Diabetes increases carotid atherosclerosis and mortality due to stroke is about threefold high(52).

DIABETIC NEUROPATHY:

Prevalence of diabetic peripheral neuropathy is from 5% to 100%.The most common form of diabetic neuropathy is predominantly sensory or sensory motor distal polyneuropathy. Classification is based on clinical presentation.

Modified classification of diabetic neuropathy by Thomas is as below(53):

1. SYMMETRIC NEUROPATHY:
2. FOCAL AND MULTIFOCAL NEUROPATHY

OCULAR COMPLICATIONS OF DIABETES:

Diabetic retinopathy important complications of diabetes and is one of the preventable cause of blindness. Other complications include, mononeuropathies involving the 3rd, 4th and 6th nerve, decreased sensitivity and recurrent erosion in the cornea, neovascularisation of iris and neovascular glaucoma, refractive fluctuations, premature cataract and diabetic cataract. Causes of blindness include clinically significant macular edema and diabetic retinopathy. Retinopathy can be classified into proliferative and non-proliferative retinopathy. Non proliferative diabetic retinopathy occurs after 10 to 20 years of diabetes and is characterized by vascular microaneurysm, cotton wool spots and blot hemorrhages. More extensive disease is characterized by microaneurysm formation and hemorrhages, intraretinal microvascular abnormalities and change in venous vessel caliber(54).

The best predictors for the development of the diabetic retinopathy are duration of diabetes and degree of glycemic control. Macular edema usually occurs only when there is non proliferative retinopathy.

DIABETIC NEPHROPATHY:

Among diabetic patients only 30% develop diabetic nephropathy. Familial predisposition to raised blood pressure is an important determinant of susceptibility to renal disease in patients with diabetes. The risk of nephropathy is 3 times higher in type 1 diabetic patients who have history of hypertension in at least one parent(55).

HYPERGLYCEMIA:

Poor glycemic control is associated with diabetic nephropathy. High blood sugar levels induce hypertrophy of mesangial cells and protein secretion of extracellular matrix components such as collagen, laminin and fibronectin. Hyperglycemia reduces the activity of metalloproteases, which is an enzyme responsible for degradation of extracellular matrix. The four hypothesis by which hyperglycemia induces renal damage are,

1. Formation of advanced glycated end products (AGE)

2. Increased polyol pathway flux

3. Activation of protein kinase

4. Increased hexosaminase pathway flux.

A physiological reaction, non enzymatic glycation of proteins is increased with hyperglycemia. The glycated proteins undergo progressive dehydration, cyclization, oxidation and rearrangement to form AGE products (56). AGEs accumulate in the glomeruli and tubules and leads to albuminuria, mesangial expansion and thickening of glomerular basement membrane. Interaction of AGE modified proteins with its receptors degrades AGE proteins but also stimulates the synthesis and release of cytokines such as platelet derived growth factor, transforming growth factor β and insulin like growth factor, these results in increased production of fibronectin, collagen and laminin (57,58).

In hyperglycemia, the excess glucose is converted to sorbitol by the enzyme aldose reductase, excess sorbitol is oxidized to fructose by the enzyme fructose dehydrogenase (59). Fructose is a reactive sugar that leads to the formation of AGE products. The increased ratio of

NADH/NAD and oxidation of sorbitol to fructose results in the formation of reactive oxygen species (60).

In diabetic nephropathy, with hyperglycemia there is over expression of glutamine fructose 6 phosphate aminotransferase leading to increased formation of TGF β and fibronectin(61). There is a significant correlation between the blood pressure levels and rate of decline in glomerular filtration rate(62). Hyperglycemia causes vasodilatation and in diabetic patients there is a marked reduction in the afferent and lesser reduction in the efferent arteriolar resistance. This leads to elevated glomerular pressure (63). The mechanism by which increased glomerular capillary pressure leads to kidney damage is due to the unique elastic properties of the glomerular structure and the response of the mesangial cells to mechanical stretch. Cyclical stretch stimulates the synthesis of deposition of matrix components such as fibronectin, laminin and collagen in proportion to the intensity of the stretch (64).

MAGNESIUM AND DIABETES

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

Aetiology of hypomagnesaemia in diabetes(66)**:**

Diet low in magnesium, reduced intestinal absorption of magnesium, increased renal magnesium loss due to glycosuria dieresis, Insulin effect causes redistribution of magnesium from plasma to red blood cells, insulin insensitivity affects magnesium transport and glucose metabolism, loop and thiazide diuretic use promotes magnesium loss.

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

Role of Magnesium in Glucose homeostasis and insulin sensitivity:

In patients with diabetes magnesium deficiency have shown a negative impact on glucose homeostasis and insulin sensitivity(67). In diabetics uptake of magnesium in erythrocytes in response to insulin is reduced. This change was associated with an increase in erythrocyte membrane microviscosity(68). Changes in the physical state of plasma membrane and insulin resistance were responsible for the lower erythrocyte magnesium level .Plasma membrane changes impair the interaction of insulin with its receptors and reduce glucose tolerance. The reduced insulin sensitivity is due to defective tyrosine kinase activity of the insulin receptor. Several enzymes are involved in glucose metabolism, which requires high energy phosphate

bonds. Magnesium acts as a cofactor in these enzymatic reactions. Intracellular magnesium deficiency leads to worsening of insulin action and insulin resistance. Thus low magnesium level contributes to insulin resistance, which in turn reduces magnesium uptake in insulin sensitive tissues.

Magnesium and diabetic nephropathy:

Magnesium acts as cofactor in Na/K- ATPase plays an important role in the development of diabetic nephropathy. Na/K- ATPase is involved in the maintenance of gradients of Na and K and in glucose transport. Magnesium deficiency affects the activity of Na/K- ATPase. Magnesium deficiency augments intracellular inositol depletion(69), which results in reduced activity of regulatory proteins and leads to diabetic nephropathy.

Magnesium deficiency and other complications of diabetes:

Magnesium deficiency has also been implicated in some of the other complications of diabetes. Studies have shown that low serum magnesium was associated with severe background and proliferative diabetic retinopathy. Diabetic neuropathy and peripheral vascular disease contributes to the development of foot ulcers. Studies have shown that there is a strong association between low serum magnesium level and development of foot ulcers in diabetes (70).

Magnesium and Dyslipidemia:

Dyslipidemia is strongly associated with magnesium deficiency. Magnesium modulates HMG-CoA reductase which is the rate limiting enzyme involved in cholesterol metabolism.

Deficiency of magnesium is associated with decrease in HDL, inhibition of the enzyme lipoprotein lipase and elevation of triglyceride level.

Osteoporosis and Magnesium:

Deficiency of magnesium increases the risk of osteoporosis. Diabetics have reduced bone mass which is due to decreased parathormone. In diabetics reduced serum magnesium level and increase in serum ionized calcium level inhibits parathormone secretion(71).

Hypertension and Magnesium:

Magnesium is an activator of Na K- ATPase and it also acts as a calcium antagonist(72). Deficiency of magnesium causes increase in intracellular concentration of calcium and potassium which causes vasoconstriction and increase in peripheral vascular resistance. Studies have shown that there is an inverse correlation between blood pressure and serum magnesium level.

Magnesium and coronary artery disease:

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

Magnesium and acute myocardial infarction:

Reduced magnesium is often found in acute myocardial infarction. In acute myocardial infarction, when there is mild hypomagnesaemia the risk of ventricular arrhythmia in the first 24 hours is high. Studies have also shown that ventricular arrhythmias occurring in the second or third week after acute myocardial infarction is associated with low serum magnesium level(73).

SERUM MAGNESIUM AND ORAL HYPOGLYCEMIC AGENTS

In 2013, G. Niranjan et al. in a prospective study of three months duration reported that with pioglitazone treatment for T2DM, is associated with improved status of serum magnesium levels and improved glycemic control(74).

In 2016, Richard E gilbert et al. from post hoc analysis of 4 placebo controlled studies on "canagliflozin" in T2DM patients, reported that "canagliflozin is associated with normalization of serum magnesium in hypomagnesaemia with improved cardio metabolic outcomes"(75).

In 2017, Anna Wahlen et al. from Sweden, reported that "to fully benefit from metformin, routine testing of vitamin B_{12} and serum magnesium levels in metformin treated morbidly obese patients should be performed, with consideration of substitution to avoid low levels"(76).

HbA1C – GLYCOSYLATED HEMOGLOBIN (77)

Nonenzymatic glycosylation of hemoglobin results in formation of glycosylated hemoglobin, where N terminal valine residue of each beta chain gets glycated and it reflects the exposure of hemoglobin A molecule to glucose concentration in its lifespan of RBCs of 120 days.

HbA1c was introduced and used clinically for assessing glycemic control in diabetics from 1980s, with recent ADA guidelines HbA1c is now used for diagnosing patients with diabetes and prediabetes in increased certainity.

As it is a nonenzymatic reaction resulting HbA1c, it has a predictable but a non linear relationship with the mean plasma glucose levels during 4 preceding months, but preceding 1 month relatively contributes more to the glycosylation. HbA1c has its limitations as some collateral conditions will have some influence the glycosylation there by decreasing the confidence of usage of this entity in clinical scenario.

In such a situation measuring fructosamine and glycated albumin could be used to assess and they reflect more accurate and recent glucose levels of preceding 3 weeks.

TABLE 6: CONDITIONS AFFECTING INTERPRETION OF HbA1c (77)

REDUCED RBC LIFE SPAN	Hemolytic anemia, Acute blood loss, Hyperspleenism
INCREASED RBC LIFE SPAN	Iron deficiency anemia
ASSAY INTERFERENCE	Hemoglobin S, G, D, C, E, F
MISCELLANEOUS	CLD, CKD, red cell transfusion

MATERIAL AND METHODS

METHODOLOGY

1. SOURCE OF DATA:

The information for the study will be collected from patients admitted to BLDEDU'S Shri B.M Patil Medical college Hospital and Research center, Vijayapura from November 2018 to June 2020.

2. METHOD OF COLLECTION OF DATA:

Information will be collected through prepared proforma from each patient. Qualifying patients will be undergoing detailed history, clinical examination and laboratory investigations and analyzed.

- **Inclusion Criteria:**

  1. Patients with newly detected or untreated type 2 Diabetes Mellitus.
  2. The patients on treatment for type 2 Diabetes Mellitus not on multivitamin and trace elements supplements.
  3. Patients whose age is above 25 years are included.
  4. Both sexes are included.

- **Exclusion Criteria:**

  1. Patients already on multivitamin and trace elements supplements
  2. Patients on loop and thiazide diuretics
  3. Patients with renal disease
  4. Pregnant females
  5. Patients on long term use of proton-pump inhibitors

6. Patients taking antibiotics like aminoglycosides, amphotericin, petamidine, gentamicin, tobramycin, and viomycin

7. Patients with Acute Diarrhoeal disease, steatorrhoea, chrons, Ulcerative colitis, Whipple's disease and celiac sprue

8. Patients on drugs; Digitalis, Adrenergics, Cisplatin, Cyclosporine, Mycophenolate mofetil

9. Patients of Acute myocardial infarction, Malabsorption, Acute pancreatitis, Massive blood transfusion

3. BLOOD SAMPLE COLLECTION AND ANALYSIS:

2ml of blood samples were drawn in EDTA sampling tubes and were analyzed in Bio rad d10 automated analyzer for HbA1c levels measurement. 2ml of blood samples were drawn in plain sampling tubes in 8 hrs of fasting state and samples were allowed to clot followed by centrifugation and were analyzed in Vitros 5,1 FS chemistry analyzer for serum magnesium levels. Hypomagnesaemia is defined as serum magnesium levels below 1.7mg/dl that is levels less than or equal to 1.6mg/dl, and data grouped and analyzed accordingly(78).

TABLE 7: GROUPING RANGE FOR HbA1c LEVELS IN ANALYSIS

HbA1c level – Group	Reference range
Normal	4 – 6%
Good control	6.1 – 7%
Fair control	7.1 – 8%
Poor control	>8%

4. TYPE OF STUDY: Cross Sectional study

5. SAMPLE SIZE:

With 95% confidence level and margin of error of ±7.5%, a sample size of 146 subjects will allow the study to determine the levels of serum magnesium and its correlation with HbA1c in patients of type 2 Diabeties Mellitus with finite population correction (79,80).

By using the formula:

$$n = \frac{z^2 p(1-p)}{d^2}$$

Where

Z= z statistic at 5% level of significance

d is margin of error

p is anticipated prevalence rate (50%)

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value. C= (number of rows-1)* (number of columns-1)

The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance.

ANOVA

Source	d.f.	SS	MS	F
Treatment	$a-1$	SS_{treat}	$\frac{SS_{treat}}{a-1}$	$\frac{MS_{treat}}{MS_{error(a)}}$
Error (a)	$N-a$	$SS_{error(a)}$	$\frac{SS_{error(a)}}{N-a}$	
Time	$t-1$	SS_{time}	$\frac{SS_{time}}{t-1}$	$\frac{MS_{time}}{MS_{error(b)}}$
Treat x Time	$(a-1)(t-1)$	$SS_{treat\ x\ time}$	$\frac{SS_{treat\ x\ time}}{(a-1)(t-1)}$	$\frac{MS_{treat\ x\ time}}{MS_{error(b)}}$
Error (b)	$(N-a)(t-1)$	$SS_{error(b)}$	$\frac{SS_{error(b)}}{(N-a)(t-1)}$	
Total	$Nt-1$	SS_{total}		

The sources of the variation include treatment; Error (a); the effect of Time; the interaction between time and treatment; and Error (b). Error (a) is the effect of subjects within treatments and Error (b) is the individual error in the model. All these add up to the total.

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23 (IBM Statistics, Chicago, USA) and Microsoft office 2007.

RESULTS

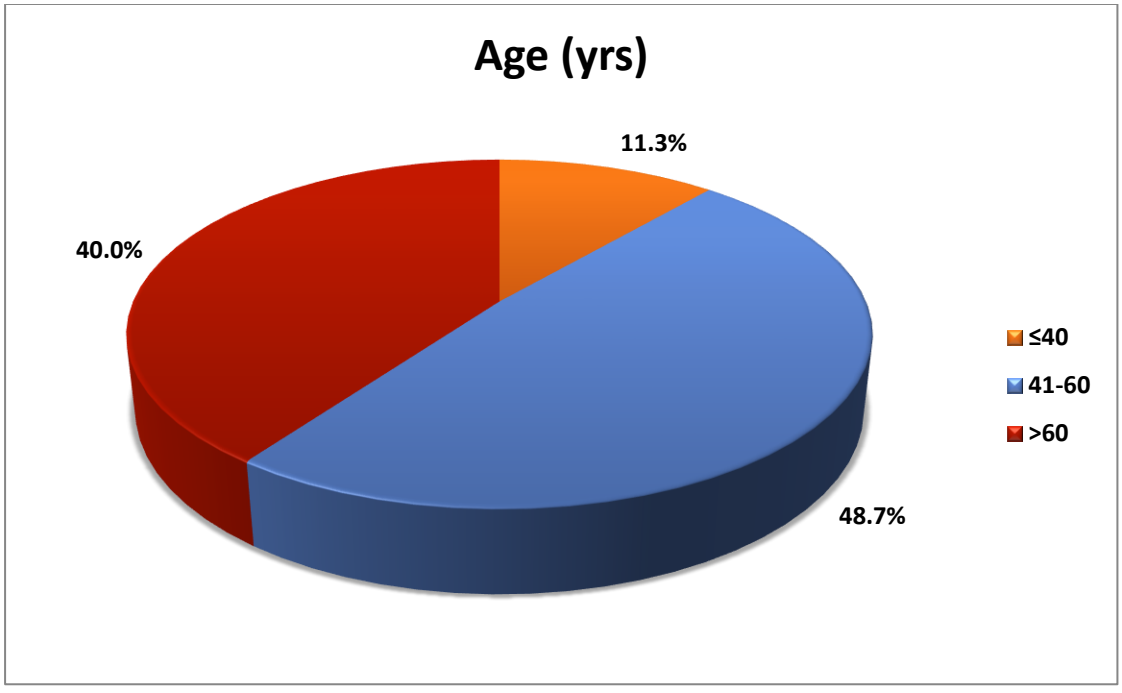
RESULTS

This study on serum magnesium and HbA1c levels is done on total of 150 patients, who were grouped into 3 age groups and following results were obtained, with 88.7% patients over the age of 40 years.

TABLE 8: DISTRIBUTION OF CASES BY AGE

AGE (YEARS)	N	Percent %
≤40	17	11.3
41-60	73	48.7
>60	60	40
Total	150	100

FIGURE 8: DISTRIBUTION OF CASES BY AGE



DISTRUBUTION OF CASES BY GENDER:

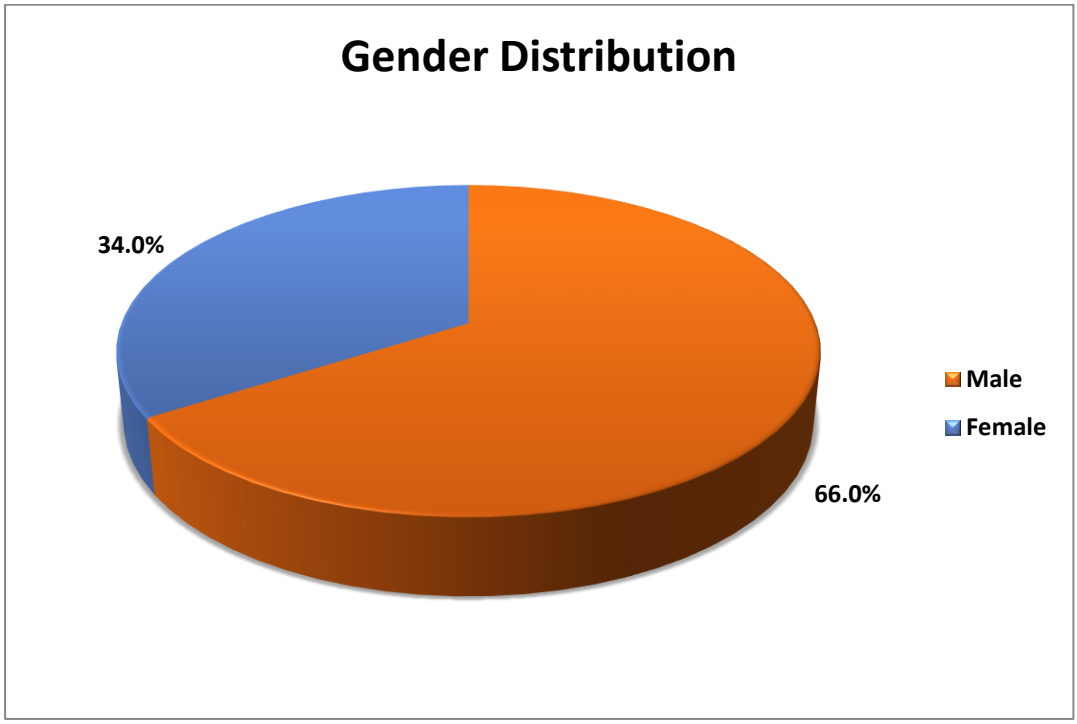
In this study, the number of male and female case distribution in total 150 cases is found to be 66% males and 34% were females, with male to female ratio 1.9:1.0

TABLE 9: DISTRIBUTION OF CASES BY GENDER

Sex	N	Percent
Male	99	66
Female	51	34
Total	150	100

Male to Female Ratio = 1.9:1.0

FIGURE 9: DISTRIBUTION OF CASES BY GENDER

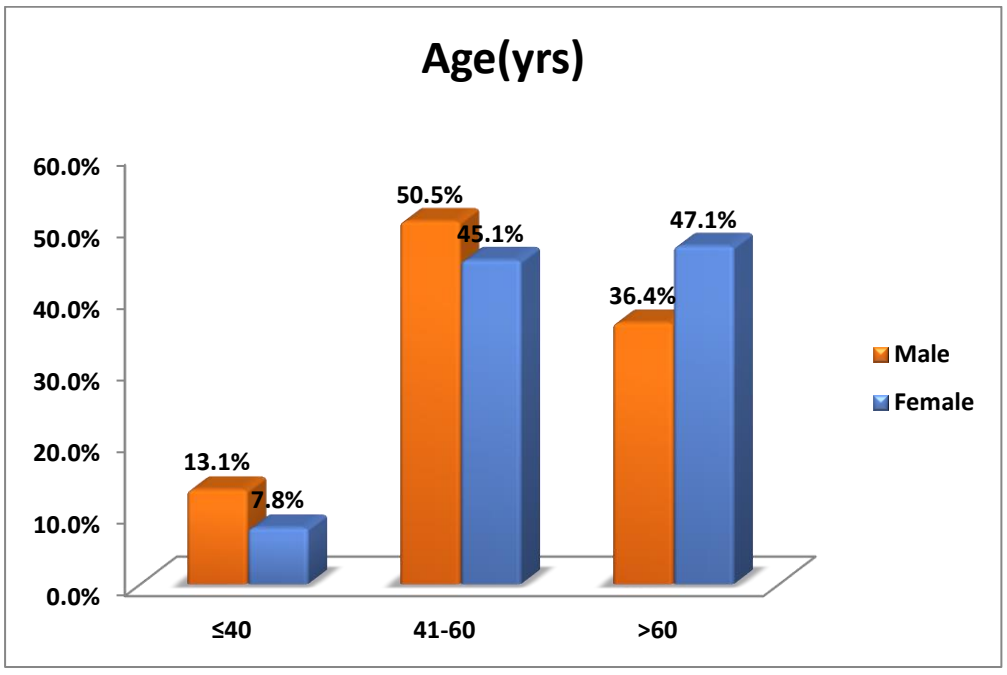


ASSOCIATION OF AGE AND GENDER:

TABLE 10: ASSOCIATION OF AGE AND GENDER

AGE (years)	MALE		FEMALE		p value
	N	%	N	%	
≤40	13	13.1%	4	7.8%	0.369
41-60	50	50.5%	23	45.1%	
>60	36	36.4%	24	47.1%	
Total	99	100.0%	51	100.0%	

FIGURE 10: ASSOCIATION OF AGE AND GENDER



In middle age group from 41 – 60 years, males were 50.5% and females were 45.1%.

In geriatric age group with >60 years females were 47.1%, and males were 36.4%.

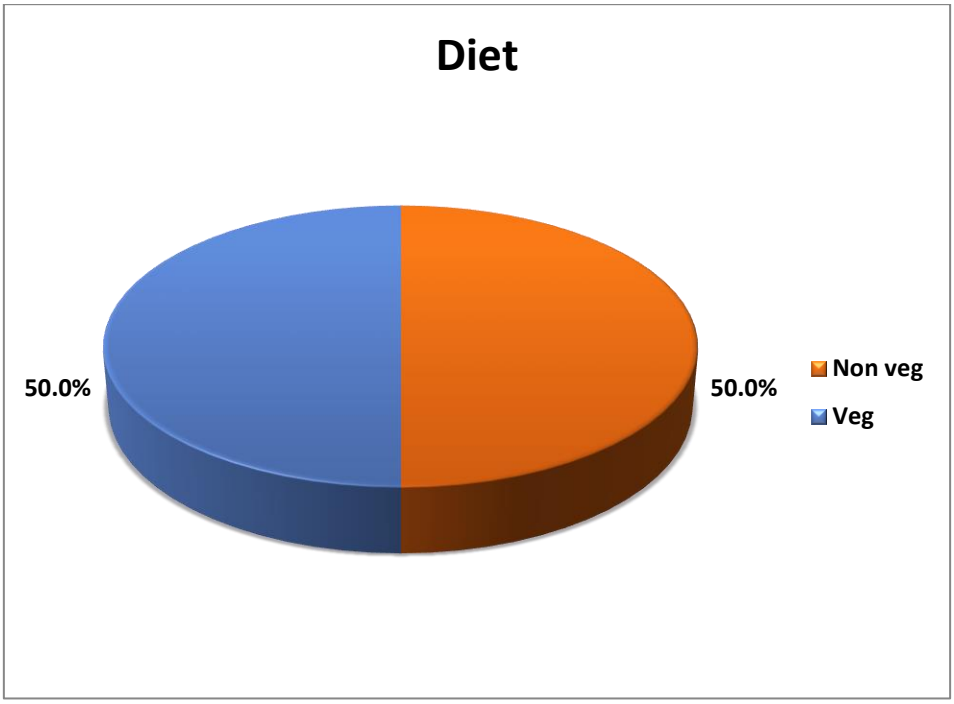
DISTRIBUTION OF CASES ACCORDING DIET:

In this study 50% cases were vegetarians and 50% cases were non vegetarians.

TABLE 11: DISTRIBUTION OF CASES ACCORDING TO DIET

Diet	N	Percent
Non vegetarian	75	50
Vegetarian	75	50
Total	150	100

FIGURE 11: DISTRIBUTION OF CASES ACCORDING TO DIET

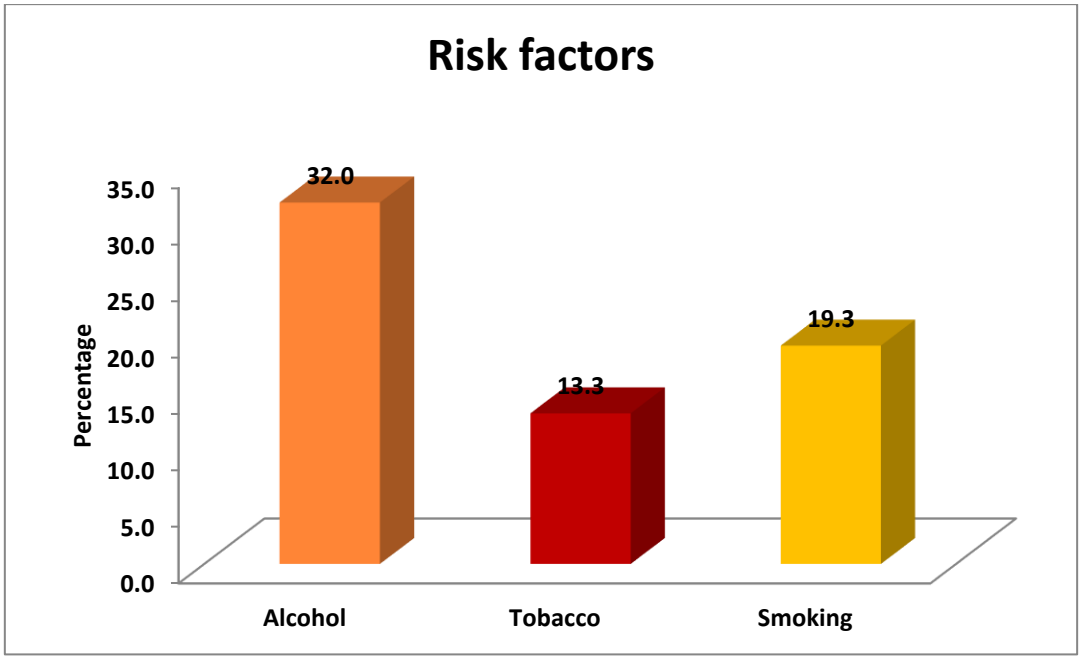


DISTRIBUTION OF CASES ACCORDING TO HABITS OF ALCOHOL, TOBACCO, AND SMOKING:

TABLE 12: DISTRIBUTION OF CASES ACCORDING TO HABITS

Risk factors	N	Percent
Alcohol	48	32.0
Tobacco	20	13.3
Smoking	29	19.3
Nil	89	59.3

FIGURE 12: DISTRIBUTION OF CASE ACCCORDING TO HABITS



In this study 59.3% study sample were not having any habits of smoking alcoholism and tobacco consumption. And majority had habit of consuming alcohol with 32%, 13.3% consumed tobacco, 19.3% has habit of smoking.

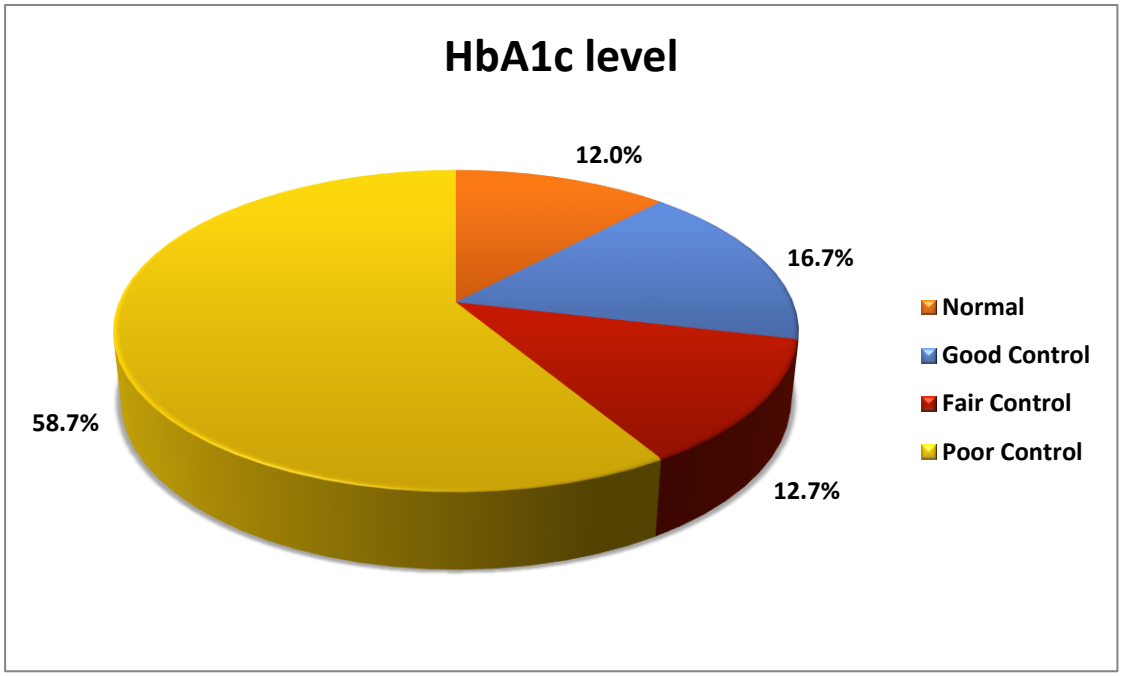
DISTRIBUTION OF CASES WHEN GROUPED ACCORDING TO HbA1c LEVELS:

In this study majority of cases, with 58.7% cases are in the bracket of poor control of glycemic levels.

TABLE 13: DISTRIBUTION OF CASES ACCORDING TO HbA1c LEVELS

HbA1c level	N	Percent
Normal	18	12
Good Control	25	16.7
Fair Control	19	12.7
Poor Control	88	58.7
Total	150	100

FIGURE 13: DISTRIBUTION OF CASES ACCORDING TO HbA1c LEVELS



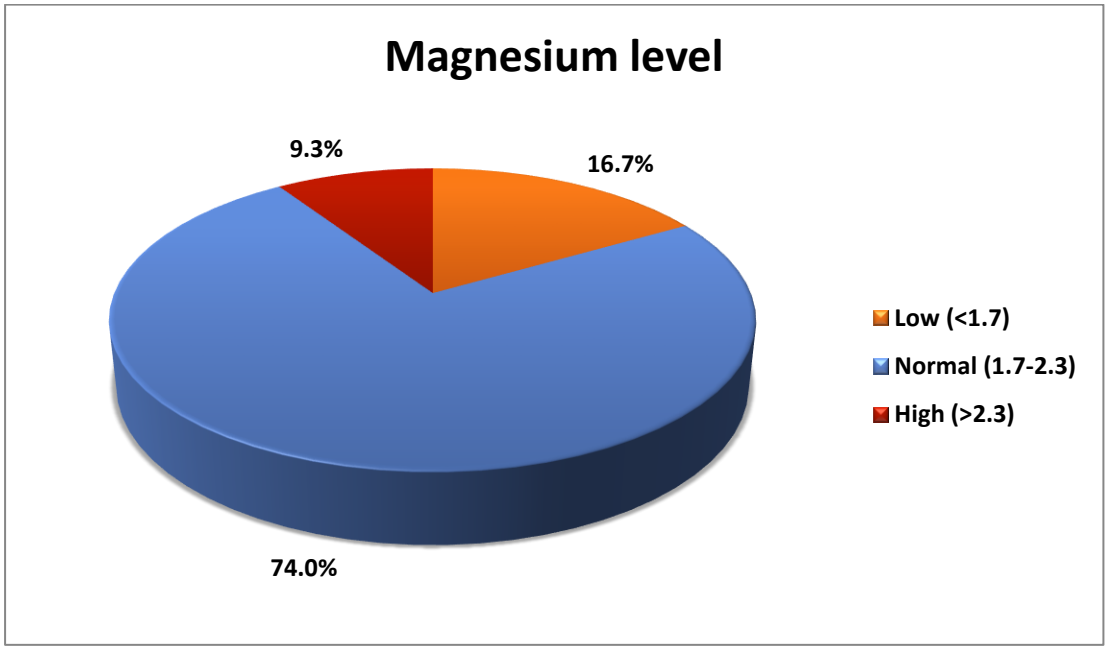
DISTRIBUTION OF CASES ACCORDING TO MAGNESIUM LEVELS:

In the present study serum magnesium levels were normal in 74% cases and 16.7 % patients were having hypomagnesaemia.

TABLE 14: DISTRIBUTION OF CASES ACCORDING TO SERUM MAGNESIUM LEVELS

MAGNESIUM LEVELS	N	Percent %
Low (<1.7)	25	16.7
Normal (1.7-2.3)	111	74
High (>2.3)	14	9.3
Total	150	100

FIGURE 14: DISTRIBUTION OF CASES ACCORDING TO SERUM MAGNESIUM LEVELS



ASSOCIATION OF HbA1c ACCORDING TO SERUM MAGNESIUM LEVELS:

In this study, lower serum magnesium levels were found in 31.6% cases in fair control bracket and in 15.9% cases of poor control bracket. Serum magnesium was within normal limits in majority of cases in patients with HbA1c levels in normal and good control levels.

TABLE 15: ASSOCIATION OF HbA1c ACCORDING TO SERUM MAGNESIUM LEVELS

HbA1c	Low (<1.7) Mg level		Normal (1.7-2.3) Mg level		High (>2.3) Mg level		Total		p value
	N	%	N	%	N	%	N	%	
Normal	1	5.6%	16	88.9%	1	5.6%	18	12.0%	0.465
Good Control	4	16.0%	18	72.0%	3	12.0%	25	16.7%	
Fair Control	6	31.6%	11	57.9%	2	10.5%	19	12.7%	
Poor Control	14	15.9%	66	75.0%	8	9.1%	88	58.7%	
Total	25	16.7%	111	74.0%	14	9.3%	150	100.0	

FIGURE15: ASSOCIATION OF HbA1c ACCORDING TO MAGNESIUM LEVELS

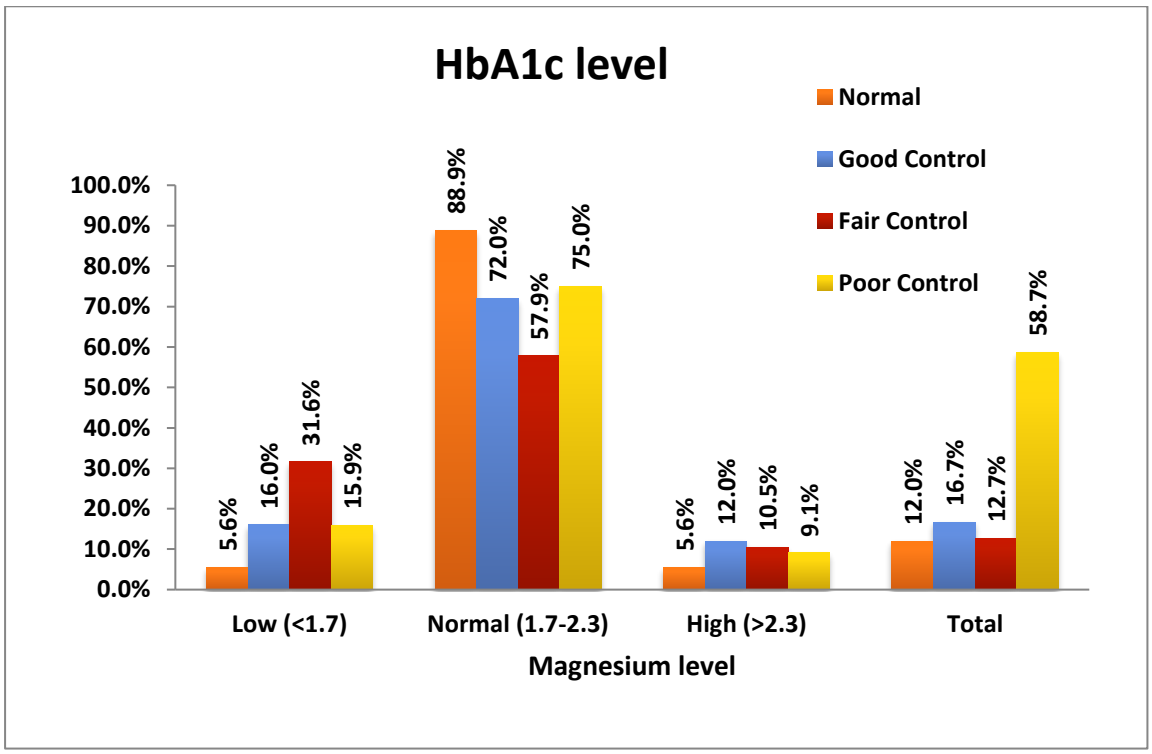
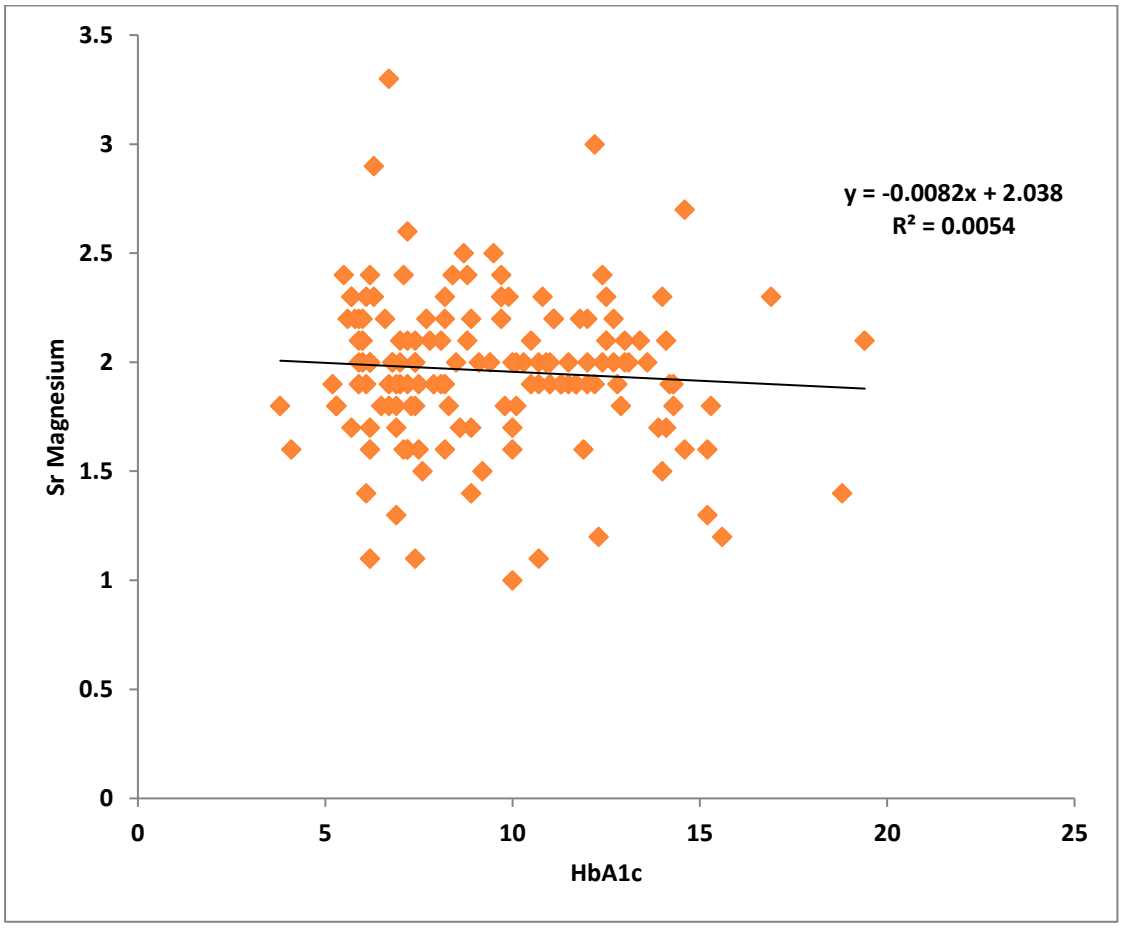


TABLE 16: CORRELATION BETWEEN SERUM MAGNESIUM AND HbA1c

	r value	p value
Pearson Correlation between Sr Magnesium & HbA1c	-0.073	0.373

FIGURE 16: CORRELATION BETWEEN SERUM MAGNESIUM AND HbA1c



MEAN HbA1c ACCORDING TO SERUM MAGNESIUM LEVELS

In the cases with serum magnesium levels below 1.7mg/dl, the mean HbA1c value was found to 9.92, in patient with normal serum magnesium levels the mean HbA1c levels were found to be 9.4 and patients with higher serum magnesium levels had mean HbA1c levels were 8.81.

TABLE 17: MEAN HbA1c ACCORDING TO SERUM MAGNESIUM LEVELS

Parameters	Magnesium level			p value
	Low (<1.7)	Normal (1.7-2.3)	High (>2.3)	
HbA1c	9.92±3.8	9.4±3.03	8.81±2.68	0.556

FIGURE 17: MEAN HbA1c ACCORDING TO SERUM MAGNESIUM LEVELS

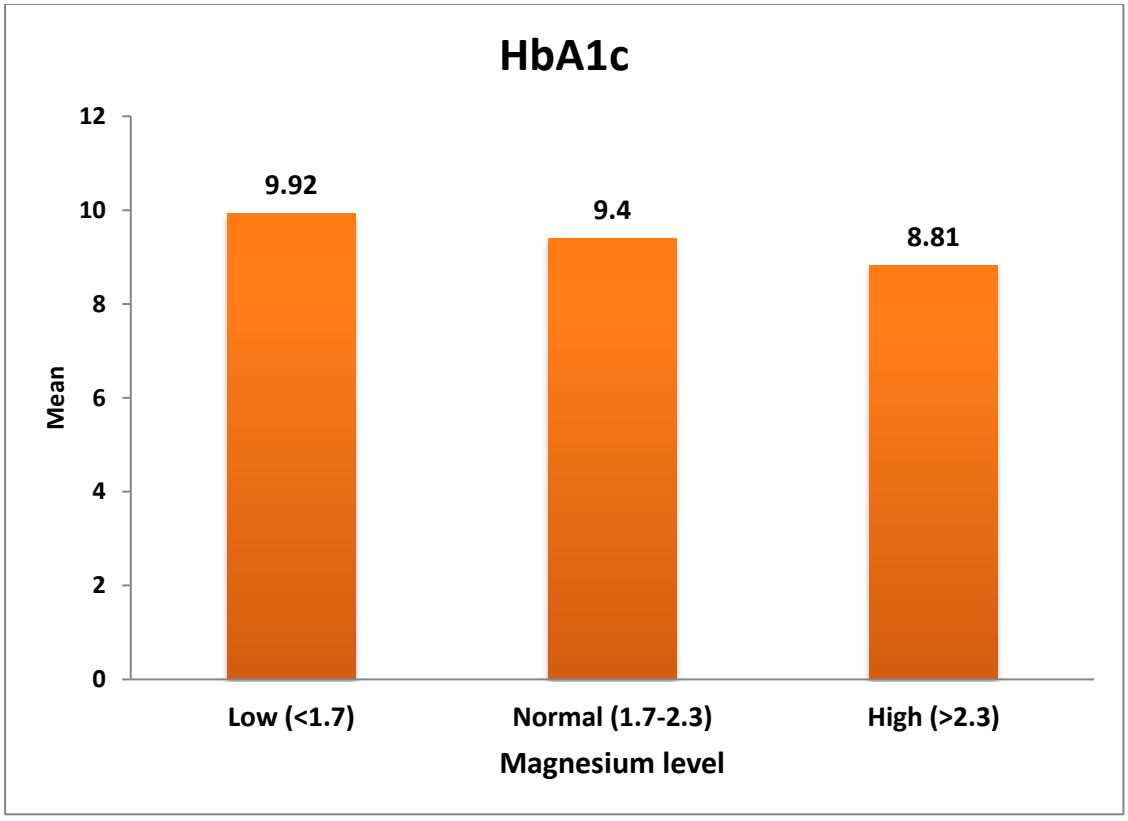


TABLE 18: ASSOCIATION OF AGE ACCORDING TO MAGNESIUM LEVEL

Age (yrs)	Magnesium level						p value
	Low (<1.7)		Normal (1.7-2.3)		High (>2.3)		
	N	%	N	%	N	%	
≤40	3	12.0%	13	11.7%	1	7.1%	0.897
41-60	14	56.0%	52	46.8%	7	50.0%	
>60	8	32.0%	46	41.4%	6	42.9%	
Total	25	100.0%	111	100.0%	14	100.0%	

FIGURE 18: ASSOCIATION OF AGE ACCORDING TO MAGNESIUM LEVEL

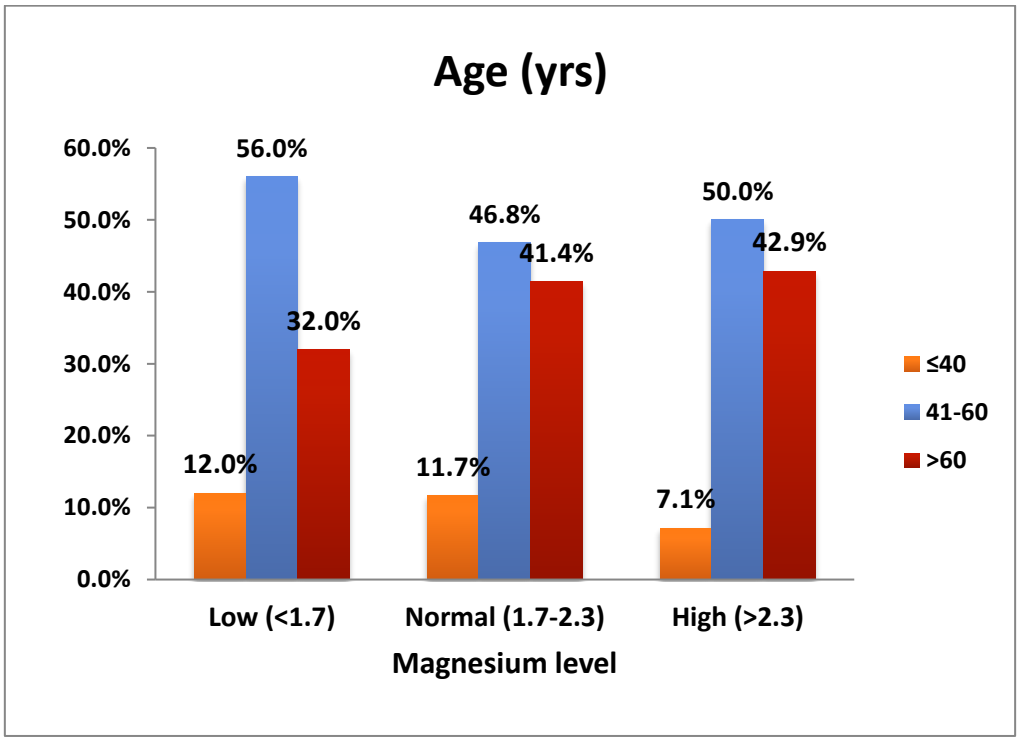
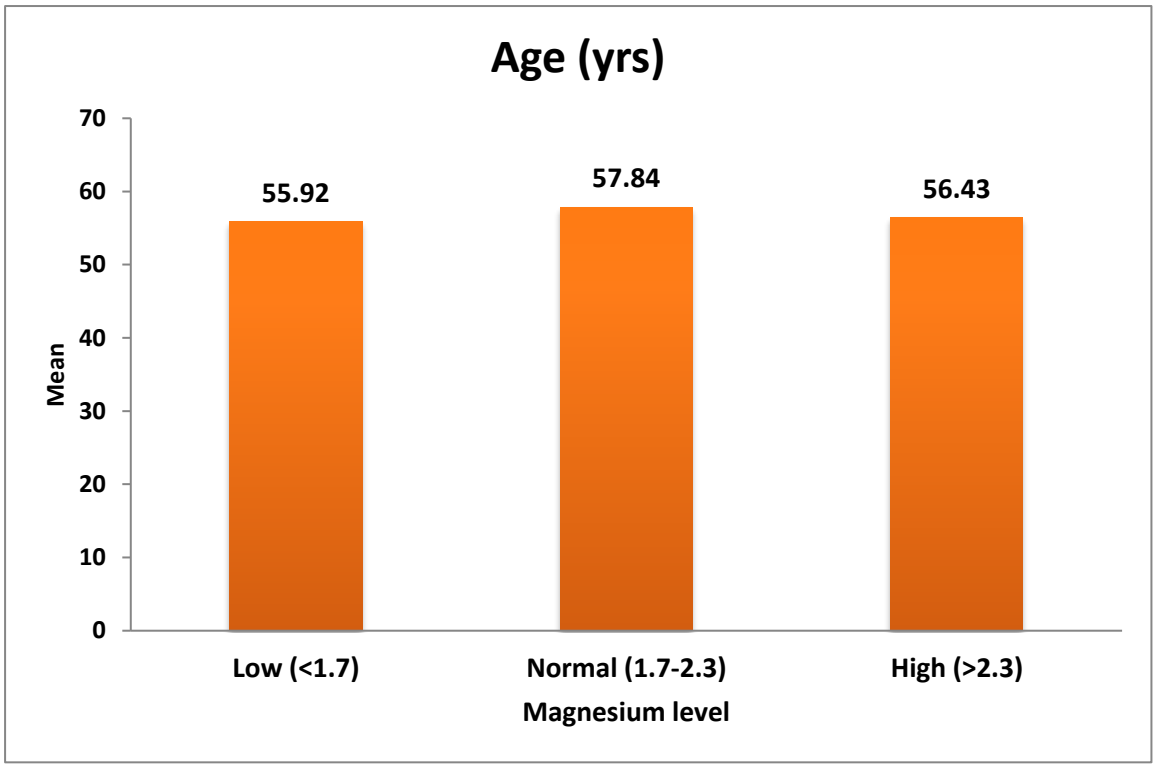


TABLE 19: MEAN AGE ACCORDING TO MAGNESIUM

Parameters	Magnesium level			p value
	Low (<1.7)	Normal (1.7-2.3)	High (>2.3)	
Age (yrs)	55.92±14.51	57.84±13.15	56.43±10.87	0.774

FIGURE 19: MEAN AGE ACCORDING TO MAGNESIUM

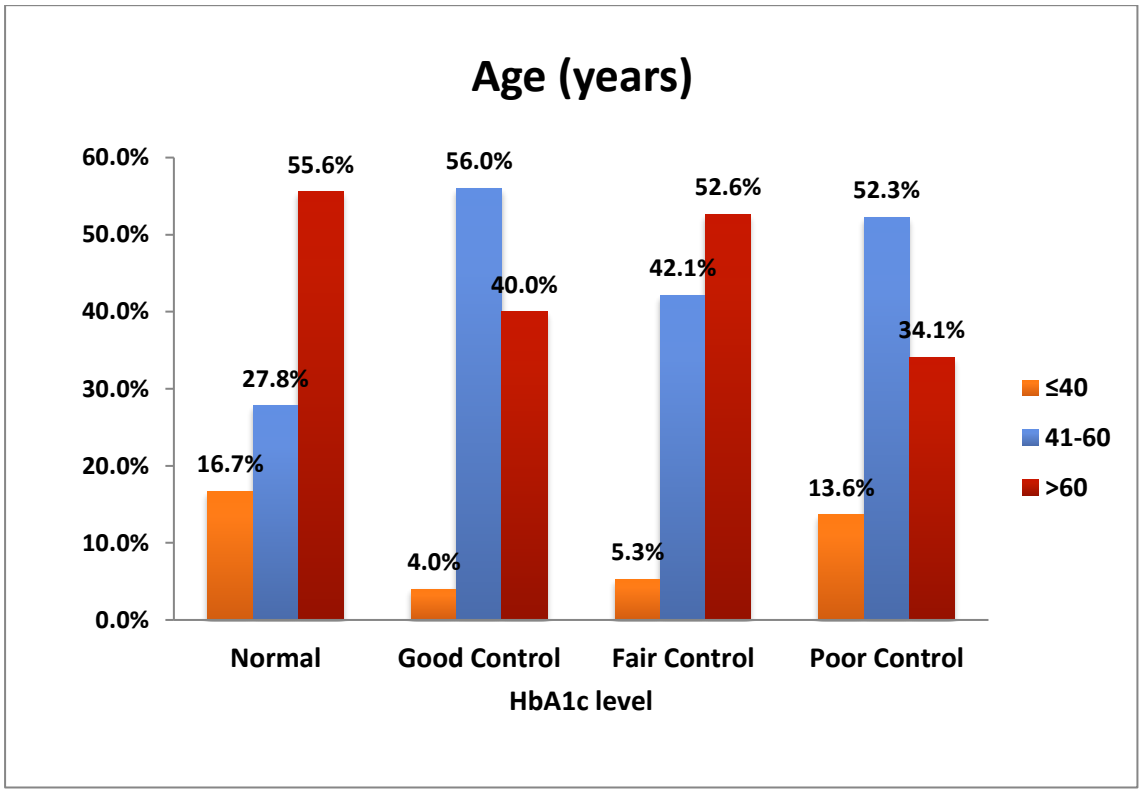


ASSOCIATION OF AGE ACCORDING TO HbA1c LEVEL

TABLE 20 : ASSOCIATION OF AGE ACCORDING TO HbA1c LEVEL

Age (yrs)	HbA1c level								p value
	Normal		Good Control		Fair Control		Poor Control		
	N	%	N	%	N	%	N	%	
≤40	3	16.7%	1	4.0%	1	5.3%	12	13.6%	0.271
41-60	5	27.8%	14	56.0%	8	42.1%	46	52.3%	
>60	10	55.6%	10	40.0%	10	52.6%	30	34.1%	
Total	18	100.0%	25	100.0%	19	100.0%	88	100.0%	

FIGURE 20: ASSOCIATION OF AGE ACCORDING TO HbA1c LEVEL

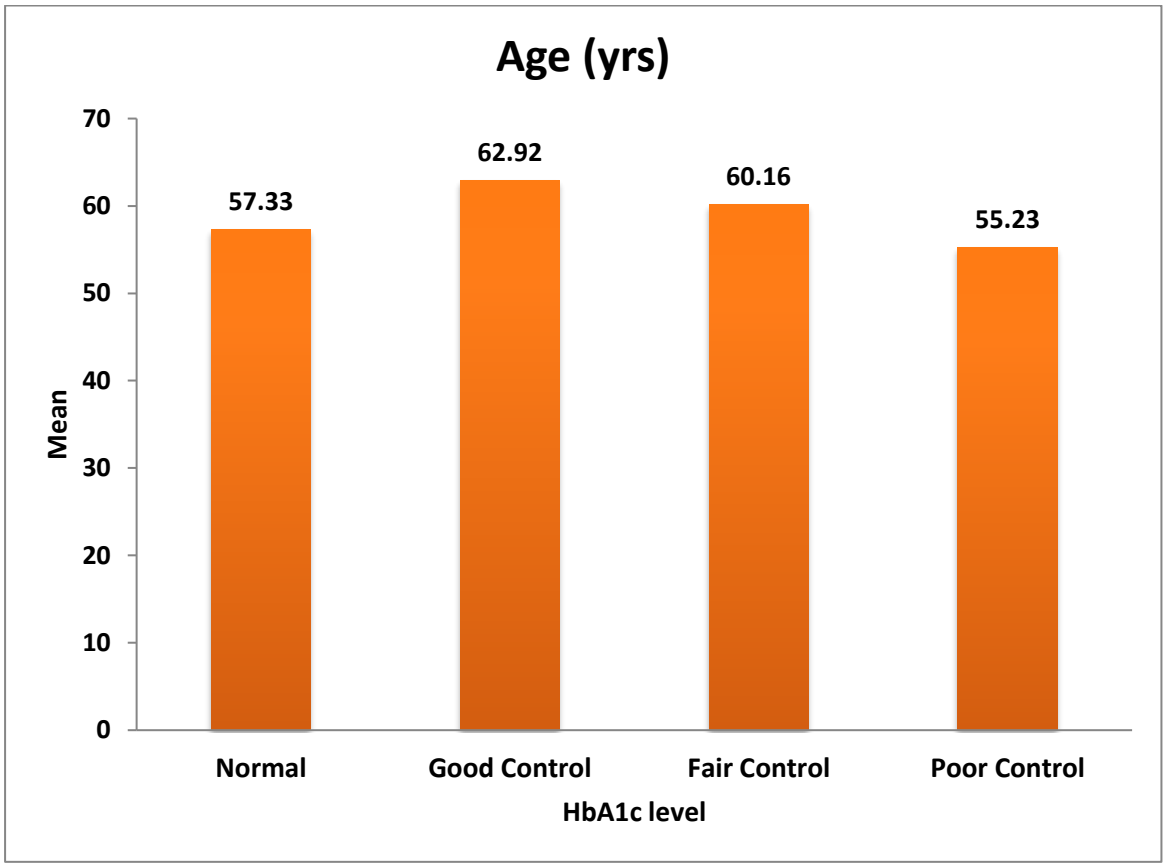


MEAN AGE ACCORDING TO hBA1c LEVEL

TABLE 21: MEAN AGE ACCORDING TO HbA1c LEVEL

Parameters	HbA1c level				p value
	Normal	Good Control	Fair Control	Poor Control	
Age (yrs)	57.33±16	62.92±12.7	60.16±12.39	55.23±12.41	0.052

FIGURE 21: MEAN AGE ACCORDING TO HbA1c LEVEL



ASSOCIATION OF DIET ACCORDING TO SERUM MAGNESIUM LEVELS

In this study population, vegetarians were found to be 50% and non vegetarians were 50%, in patients with low serum magnesium levels were 52% were vegetarians and 48% were non vegetarians. Band in patients with higher serum magnesium levels vegetarians were 64.3% and non vegetarians were 35.7%.

TABLE 22: ASSOCIATION OF DIET ACCORDING TO MAGNESIUM LEVEL

Diet	Magnesium level						p value
	Low (<1.7)		Normal (1.7-2.3)		High (>2.3)		
	N	%	N	%	N	%	
Non vegetarian	12	48.0%	58	52.3%	5	35.7%	0.495
Vegetarian	13	52.0%	53	47.7%	9	64.3%	
Total	25	100.0%	111	100.0%	14	100.0%	

FIGURE 22: ASSOCIATION OF DIET ACCORDING TO MAGNESIUM LEVEL

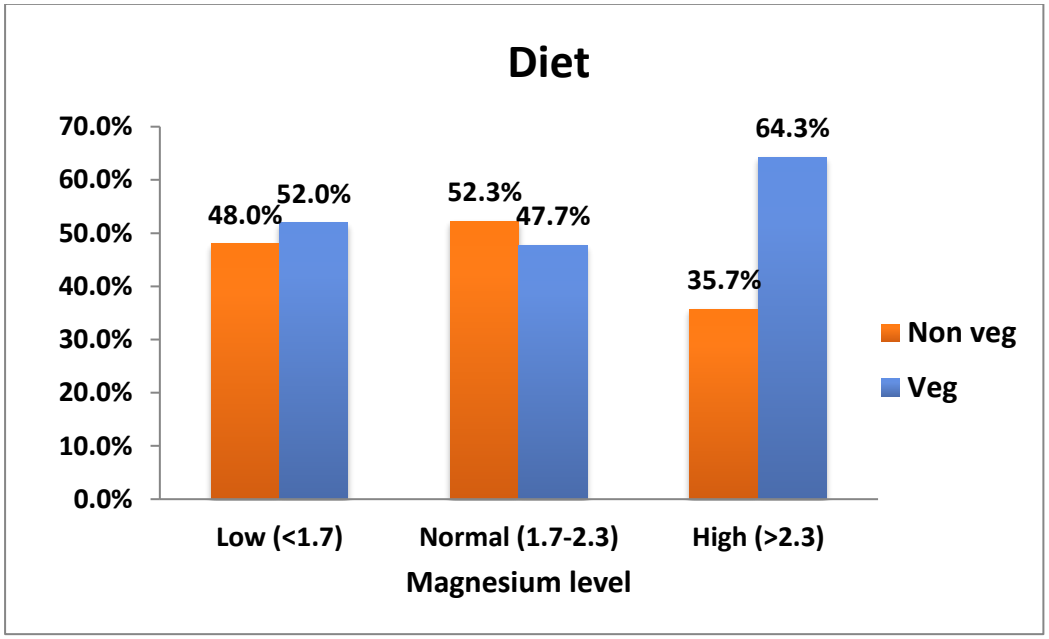
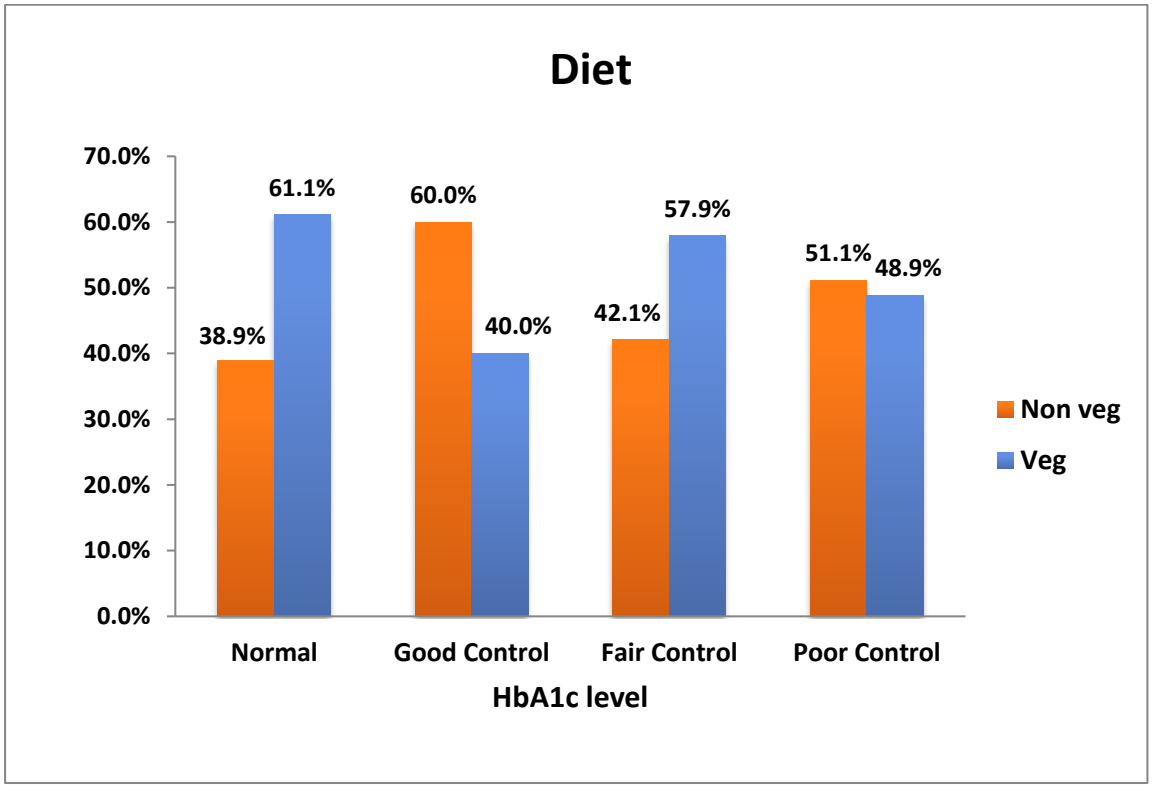


TABLE 23: ASSOCIATION OF DIET ACCORDING TO HbA1c LEVEL

Diet	HbA1c level								p value
	Normal		Good Control		Fair Control		Poor Control		
	N	%	N	%	N	%	N	%	
Non veg	7	38.9%	15	60.0%	8	42.1%	45	51.1%	0.492
Vegetarian	11	61.1%	10	40.0%	11	57.9%	43	48.9%	
Total	18	100 %	25	100.0%	19	100.0%	88	100.0%	

FIGURE 23: ASSOCIATION OF DIET ACCORDING TO HbA1c LEVEL



ASSOCIATION OF RISK FACTORS ACCORDING TO MAGNESIUM LEVELS

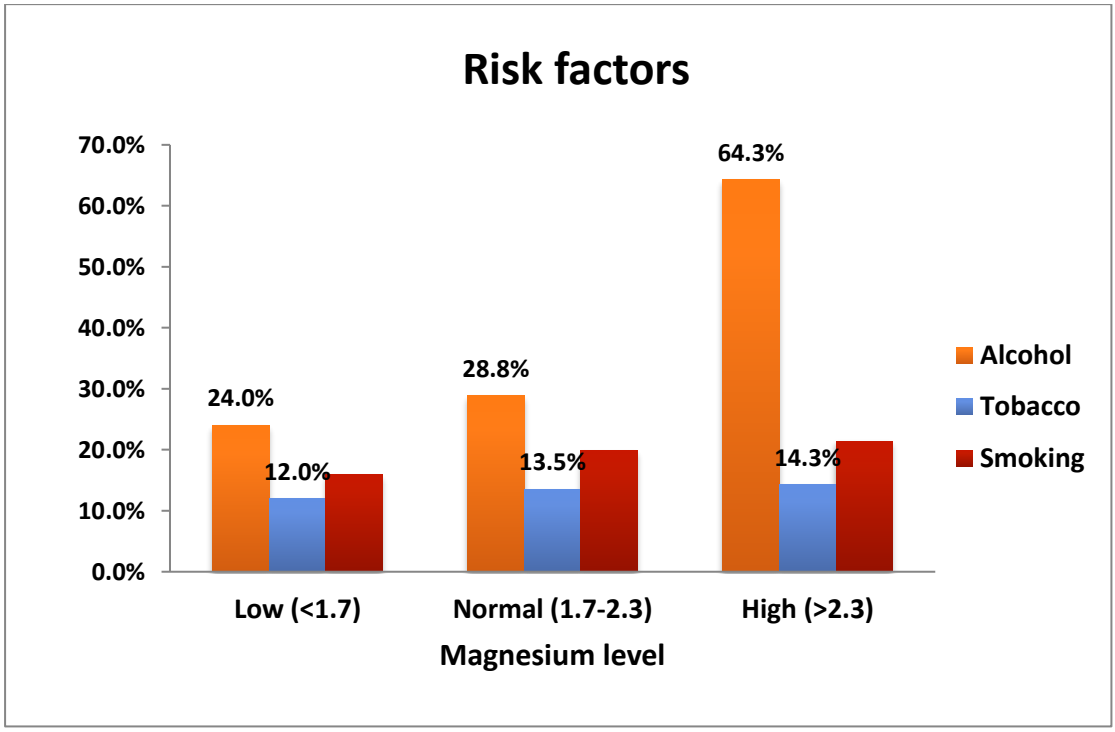
In patients with habit of consuming alcohol and tobacco majority were having normal serum magnesium levels.

TABLE 24: ASSOCIATION OF HABIT RISK FACTORS ACCORDING TO MAGNESIUM LEVEL

Risk factors	Magnesium level						p value
	Low (<1.7)		Normal (1.7-2.3)		High (>2.3)		
	N	%	N	%	N	%	
Alcohol	6	24.0%	32	28.8%	9	64.3%	0.018*
Tobacco	3	12.0%	15	13.5%	2	14.3%	0.974
Smoking	4	16.0%	22	19.8%	3	21.4%	0.889

Note: * significant at 5% level of significance (p<0.05)

FIGURE 24: ASSOCIATION OF HABIT RISK FACTOR ACCORDING TO MAGNESIUM LEVEL



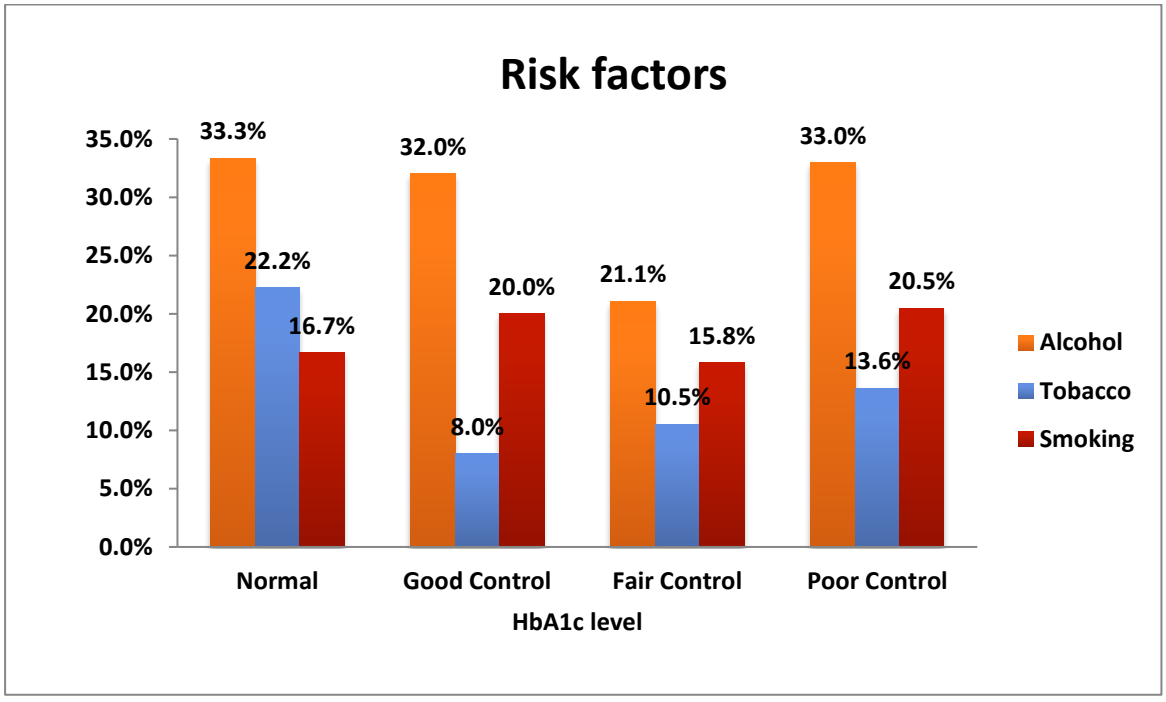
ASSOCIATION OF RISK FACTORS AND HbA1c LEVELS

In patients having habit of consuming alcohol, tobacco and smoking, HbA1c levels were observed with majority in poor control group.

TABLE 25: ASSOCIATION OF HABIT RISK FACTOR ACCORDING TO HbA1c LEVEL

Risk factors	HbA1c level								p value
	Normal		Good Control		Fair Control		Poor Control		
	N	%	N	%	N	%	N	%	
Alcohol	6	33.3%	8	32.0%	4	21.1%	29	33.0%	0.782
Tobacco	4	22.2%	2	8.0%	2	10.5%	12	13.6%	0.576
Smoking	3	16.7%	5	20.0%	3	15.8%	18	20.5%	0.958

FIGURE 25: ASSOCIATION OF HABIT RISK FACTOR ACCORDING TO HbA1c LEVEL



ASSOCIATION OF DRUGS ACCORDING TO SERUM MAGNESIUM LEVELS

TABLE 26: ASSOCIATION OF DRUGS ACCORDING TO MAGNESIUM LEVEL

Drugs	Magnesium level						p value
	Low (<1.7)		Normal (1.7-2.3)		High (>2.3)		
	N	%	N	%	N	%	
Insulin	2	8.0%	7	6.3%	0	0.0%	0.580
OHA	16	64.0%	73	65.8%	10	71.4%	0.891
ARB	5	20.0%	12	10.8%	2	14.3%	0.451
ACEI	2	8.0%	1	0.9%	0	0.0%	0.062
CCB	3	12.0%	11	9.9%	0	0.0%	0.429
Others	2	8.0%	9	8.1%	0	0.0%	0.543

FIGURE 26: ASSOCIATION OF DRUGS ACCORDING TO MAGNESIUM LEVEL

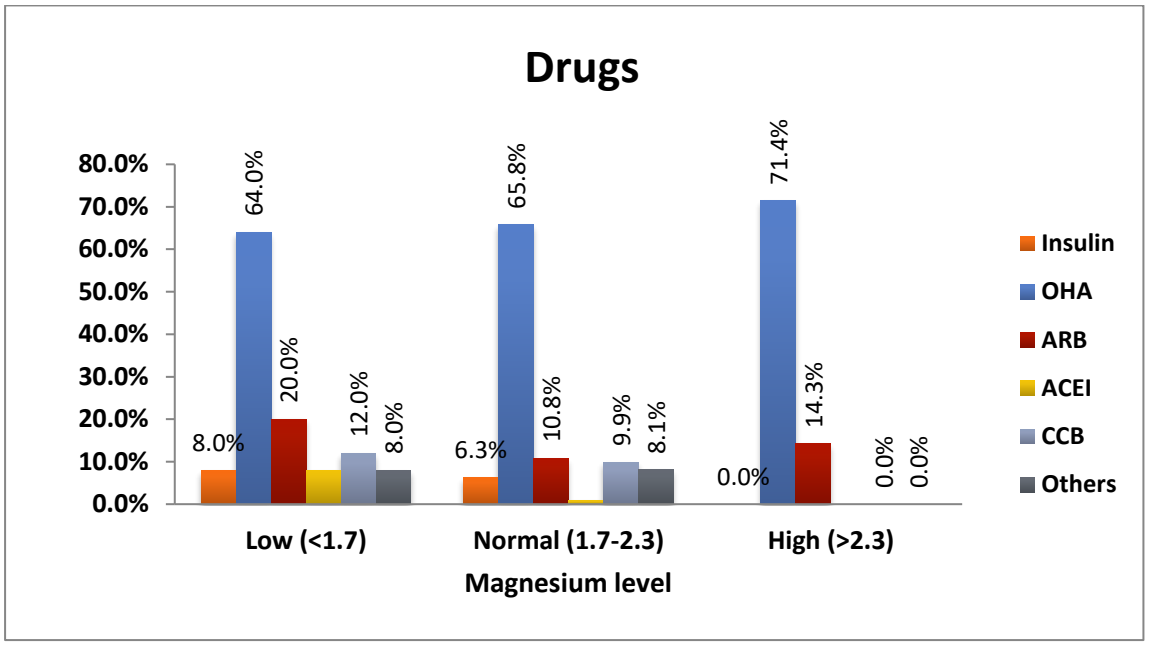
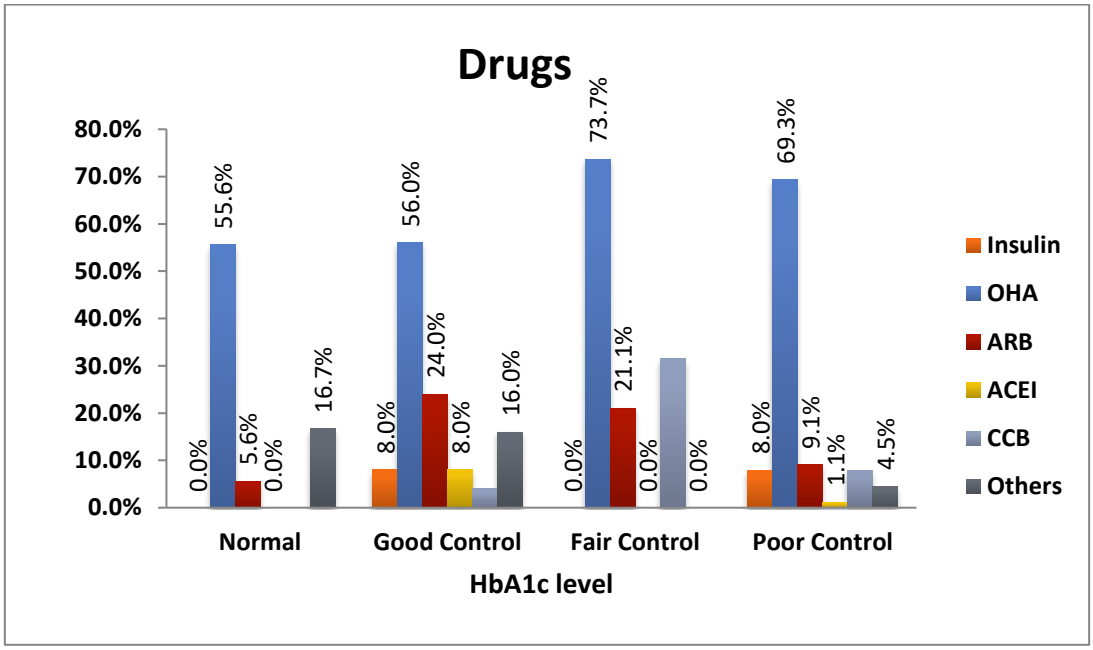


TABLE 27: ASSOCIATION OF DRUGS ACCORDING TO HbA1c LEVEL

Drugs	HbA1c level								p value
	Normal		Good Control		Fair Control		Poor Control		
	N	%	N	%	N	%	N	%	
Insulin	0	0.0%	2	8.0%	0	0.0%	7	8.0%	0.371
OHA	10	55.6%	14	56.0%	14	73.7%	61	69.3%	0.404
ARB	1	5.6%	6	24.0%	4	21.1%	8	9.1%	0.114
ACEI	0	0.0%	2	8.0%	0	0.0%	1	1.1%	0.128
CCB	0	0.0%	1	4.0%	6	31.6%	7	8.0%	0.003*
Others	3	16.7%	4	16.0%	0	0.0%	4	4.5%	0.056

Note: * significant at 5% level of significance (p<0.05)

FIGURE 27: ASSOCIATION OF DRUGS ACCORDING TO HbA1c LEVEL



DISCUSSION

DISCUSSION

As diabetes mellitus has reached the prevalence of global epidemic in recent times not only in developed world but also in developing countries, with rising health care costs and economic burden of treatment of diabetes itself and over burdened by diabetes related complications, it is the need of the hour to put efforts into development of cheap, sustainable, feasible, and affordable monitoring investigations and interventions in management of T2DM patients.

This present cross sectional study was conducted in BLDE's (Deemed to be University) Shri B M Patil Medical College and Research Centre over a period of 2 years, on 150 T2DM patients. In 150 patients, HbA1c levels and serum magnesium levels were obtained after proper blood sampling and laboratory processes. Obtained parameters are tabulated and by statistical analysis an association of serum magnesium and HbA1c is drawn.

In this present study on T2DM patients, it is found that 11.3% of study sample were below 40years of age, and 48.7% are between 41 to 60 years and 40% are above 60 years of age. And it is understandable that type 2 diabetes mellitus is disease most often seen in elderly, T2DM prevalence in the elderly in this study is in accordance with the literature. In this study, in males 86.9% are over 40 years age, and in females 92.2% are over 40years age. In this study group 66% of patients were males and 34% were females, with male to female ratio 1.9:1.0

In this study, majority of patients were having HbA1c levels of more than 8%, 58.7% cases were with poor control glycemic levels (HbA1c >8), and 12.7% were having fair control (HbA1c 7.1 – 8), 16.7% patients had good control (HbA1c 6.1 – 7). The

majority of patients being with uncontrolled HbA1c levels is in accordance with a study conducted in Azadi Teaching Hospital, Iraq in 2018 by Hajar Saeed et al(81).

In this study on 150 patients, the prevalence of hypomagnesaemia is found to be 16.7%. The prevalence of hypomagnesaemia in a observational study conducted in Zagazig University, Egypt in type 1 diabetes patients is 28.2%(82). In a study on hypomagnesaemia in T2DM in Gauhati Medical College in 2010, prevalence of hypomagnesaemia is found to be 11.33%(83), and in a study from New Delhi, India hypomagnesaemia prevalence is found to be 44% in T2DM patients and diabetic retinopathy(84). In a case control study from Nigeria, serum magnesium levels were lower in 23.2% in T2DM patients(85). Hypomagnesaemia is found in 18.5% cases in a study conducted in Erciyes University, Turkey, and directly associated with poor metabolic control(86). In a study from fauji foundation hospital from Pakistan, it is reported that hypomagnesaemia is 33.89% prevalent in T2DM patients and increases with the duration of the diabetes(87). Based on the available studies prevalence of hypomagnesaemia is in the range of 11.33% to 33.89% in diabetes patients, and is increased to 44% in case of T2DM patients with complications. In my study the prevalence at 16.7% is well within the range of prevalence in the earlier studies. In this study, on statistical analysis for association of HbA1c levels with serum magnesium levels, it is found that there is a negative correlation with r value of -0.073, which is not significant statistically (p value >0.05).

Hongmei Zhang, chonghuai Yan et al., in an epidemiological study on trace elements in T2DM, found that a statistically significant negative association was found between diabetes and serum magnesium(9). In a study by Assimina GALLI-TSINOPOULOU, loanna MAGGANA et al., concluded that serum magnesium levels are lower in patients with poor glycemic control with negative correlation with HbA1c value(88).

Arpaci D, Tocoglu AG et al. reported a weak negative correlation between serum magnesium and HbA1c levels (ARPACI D). Salini Scaria Joy, Teena P. George, Khalid Siddiqui in a study on low magnesium level as an indicator of poor glycemic control in T2DM with complications, reported that serum magnesium levels were significantly lower among patients with poor glycemic control and complications(89). Hatice Ozcaliskan lLkay et al. reported significant correlation between serum magnesium levels with postprandial plasma glucose levels, HbA1c values and fasting plasma glucose levels(86). Though in this study results and serum magnesium levels are in negative correlation with HbA1c values, but the correlation is not significant statistically.

Albert Lecube et al. in a cross sectional study found that serum magnesium levels were negatively correlated with HOMA-IR (insulin resistance) but statistically not significant(90). Dana Hyassat et al., reported hypomagnesaemia in obese T2DM patients but reported no significant association was noticed between hypomagnesaemia and diabetes complications(91). In a research study on vitamin intake and mineral supplements in association with HbA1c by Sigrid Schwab et al. found that magnesium intake is not associated and no correlation was found with changes in HbA1c values(92). Shamima Akter et al. concluded serum magnesium and HbA1c are though inversely associated but not statistically not significant when diabetic patient were excluded(93). In a study conducted by Nadia Zghoul et al. following supplementation of magnesium though serum levels were increased but statistical clinical improvement in HbA1c levels were not observed(94).

Though negative correlation between serum magnesium levels and HbA1c values which are in accordance with the above mention studies, in this study we did not find any statistically any significant correlation, which could be due to not taking duration of diabetes into consideration which was the case in the earlier studies and due to smaller sample size.

Following grouping T2DM patients into 3 groups with hypomagnesaemia, normomagnesaemia and hypermagenesaemia, mean HbA1c values were obtained and are found to be 9.92, 9.4 and 8.81 respectively. With increase in levels of serum magnesium, mean HbA1c values are decreasing with negative correlation, which are statistically not significant (p value > 0.05).

In this study there is no statistical correlation in serum magnesium levels when analyzed with age and sex of the study population (p value >0.05). When analyzed for any association between HbA1c levels with age and gender of this study population no significant association drawn.

Though it was found in the literature that non vegetarian diet is rich in dietary magnesium, and in this study in patients with hypomagnesaemia 48% were non vegetarians and 52% were vegetarians and no significant association found between serum magnesium and dietary habits, but lack of proper standardized dietary intake history would have influenced the results.

From reviewed literature, it is understood that alcohol consumption is negatively correlated with serum magnesium levels and HbA1c values, but in this study normal and higher levels of serum magnesium were found in patients who had habit of consuming alcohol. Not considering the amount and frequency of alcohol consumed

interpreting this positive correlation is not prudent. Smoking and oral tobacco consumption is not correlated with both HbA1c values and serum magnesium levels.

A Back ground history medications for T2DM and co morbid conditions was taken and were grouped into groups taking insulin, OHAs, ARBs, ACE I, calcium channel blockers and others. On analyzing no significant association is found between any group of drugs with serum magnesium levels and HbA1c values.

Though the negative correlation between serum magnesium levels and HbA1c values is found in this study, there was no statistically significant association, which could due to smaller sample size and ignoring the duration of T2DM, and being a cross sectional study, the acute and chronic dynamic changes in serum magnesium levels and HbA1c and their association could not be ascertained with confidence. Therefore it is advisable that larger study sample with a prospective study design aiming at studying of dynamic changes in serum magnesium levels and HbA1c values with standardized dietary intake assessment and duration of diabetes could help to ascertain relationship between serum magnesium and HbA1c which could influence the dietary interventions in management of T2DM patients.

CONCLUSION

CONCLUSION

The prevalence of hypomagnesaemia in type 2 diabetes mellitus patients is found to be 16.7%. In T2DM patients with hypomagnesaemia are found to have higher HbA1c levels indicating poor glycemic control and with increasing magnesium levels mean HbA1c levels were decreasing indicating better glycemic control.

In this study, there is a negative correlation between serum magnesium levels and HbA1c values though statistically not significant, showing lower HbA1c values with higher magnesium levels. Magnesium supplementation for improving serum magnesium levels could improve glycemic control with lower HbA1c values.

SUMMARY

Diabetes mellitus is a non communicable disease which is increasing in prevalence in global epidemic proportions putting stress on health care expenditure and it is the need of the hour put efforts in developing sustainable dietary intervention for management of diabetes. In diabetes it is observed that trace elements are disrupted and it is reported that there is decreased serum magnesium in diabetes patients. Magnesium is an essential cofactor of more than 300 enzymes and is a vital cofactor in enzymes involved in the glucose metabolism. Magnesium has a role in production and action of insulin, and can inhibit insulin secretion and activate insulin receptor tyrosine activity. To study the association between diabetes and serum magnesium, in this study serum magnesium and HbA1c levels were assessed in T2DM patients and their correlation was studied.

Data for the study was collected from patients admitted to BLDE'S (Deemed to be University) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura from November 2018 to June 2020. Patients were screened and who met inclusion criteria was included in the study. A cross sectional study was done on 150 patients, and HbA1c levels with serum magnesium levels were obtained and were analyzed for association and correlation.

In our study majority of patients with 88.7% cases are over the age of 40 years and male to female ratio are 1.9:1.0 in the study sample. Majority of cases with 58.7% patients in the study are within poor control level of HbA1c. In this study 16.7% cases of T2DM are with hypomagnesaemia and 74% cases have normomagnesaemia. Mean

age with SD in hypomagnesaemic cases is found to 55.92 ± 14.51, in normomagnesaemic case it is 57.84 ± 13.15, in hypermagnesaemia cases it is found to be 56.43 ± 10.87. The mean HbA1c levels with SD in hypomagnesaemia patients was found to be 9.92 ± 3.8, in normomagnesaemic case it is 9.4 ± 3.03, and in patients with hypermagnesaemia the mean HbA1c value was found to be 8.81 ± 2.68. The Pearson correlation between serum magnesium and HbA1c, the r value is – 0.073 and p value is 0.373. There was no association between age, gender, and vegetarian and non vegetarian diet with both serum magnesium levels and HbA1c levels.

In type 2 diabetes mellitus patients with lower serum magnesium levels, the mean HbA1c levels were found to be high when compared to patients with normal or higher serum magnesium levels. There is a negative correlation between serum magnesium and HbA1c levels.

LIMITATIONS OF THE STUDY

1. Sample size is relatively small
2. Serum magnesium does not reflect total body magnesium and it represents only a small fraction of total body magnesium but at present is the cheap and feasible parameter to measure.
3. Study design is cross sectional which could be confounding in a casual relation between serum magnesium and HbA1c.
4. This study does not evaluate dietary influences on serum magnesium levels due to lack of proper data on dietary intake.
5. Duration of diabetes is not considered in the study.

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ANNEXURE I

ETHICAL C LEARANCE CERTIFICATE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC-No-286/18
17/11/2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : A study on serum magnesium levels & its correlation with HbA1C levels in patients with type 2 diabetes mellitus.

Name of P.G. Student : Dr Kotha Sugunakar Reddy.
Department of General Medicine.

Name of Guide/Co-investigator: Dr Sanjeevkumar N.Bentoor, Professor of General Medicine.

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College, VIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

ANNEXURE II

CONSENT FORM

BLDEDU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT - A STUDY ON SERUM MAGNESIUM LEVELS AND ITS CORRELATION WITH HbA1C LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

PRINCIPAL INVESTIGATOR - Dr. KOTHA SUGUNAKAR REDDY

+91 9963576031

P.G.GUIDE NAME - Dr. SANJEEVKUMAR N. BENTOOR

PROFESSOR OF MEDICINE

08352-, Ext-2148

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS:

I understand that my participation in this study will help to patient's survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime.

Dr. KOTHA SUGUNAKAR REDDY is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. KOTHA SUGUNAKAR REDDY may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I

understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr. KOTHA SUGUNAKAR REDDY Date

(Investigator)

II) **STUDY SUBJECT CONSENT STATEMENT:**

I confirm that Dr. KOTHA SUGUNAKAR REDDY has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE – III

CASE PROFORMA

A STUDY ON SERUM MAGNESIUM LEVELS AND ITS CORRELATION WITH HbA1C LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.

Name:	CASE NO:
Age:	IP NO:
Sex:	DOA:
Religion:	DOD:
Occupation:	
Residence:	

Presenting complaints with duration:

History of present complaints:

Past History:

Family History:

Personal History:

Diet/appetite

Sleep

Bladder and bowel habits:

Addictions

Drug allergy

Treatment History:

General Physical Examination

Height:

Weight:

Body Mass Index:

Vitals

PR:
BP:
RR:
Temp:

Neck:

Upper Limbs:

Chest:

Abdomen:

Lower Limbs:

Skin:

SYSTEMIC EXAMINATION.

- Respiratory System

- Cardiovascular System

- Central Nervous System

- Per abdomen

INVESTIGATIONS

PATHOLOGY

Complete Blood Count	
Total Count	Cells/cumm
Differencial counts Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
HB	gm%
Platelets	lakhs/cumm
ESR	mm/1st hour
Urine routine	
Urine albumin	
Urine sugar	
RBC	
Epithelial cell	
Pus cell	
casts	

BIOCHEMISTRY

HbA1c	%
Serum Creatinine	mg/dl
Serum MAGNESIUM	mg/dl

ECG

FINAL DIAGNOSIS

ANNEXURE IV

MASTERCHART

S. no	IP/OP no.	NAME	AGE (YRS)	SEX	DIET	HABITS	DRUGS	HB	URINE ALBUMIN	URINE SUGAR	HbA1c	SERUM CREATININE	SERUM MAGNESIUM	SERUM SODIUM	SERUM POTASSIUM
1	3319	mandakini	77	f	VEG	NIL	none	10.6	absent	1000	11.9	1.4	1.6	129	4.5
2	2559	shivasharannappa	65	m	NON VEG	NIL	OHA/ACE	13.1	15	NIL	6.5	1.4	1.8	131	4.4
3	1266	SIDAPPA	60	M	VEG	NIL	INSULIN	11.9	15	2000	9.8	0.9	1.4	130	4.2
4	2816	SHANKERAMMA	55	F	NON VEG	NIL	OHA	10.5	30	NIL	8.3	1	1.8	135	4.7
5	43238	SANGAMESH	37	M	NON VEG	NIL	OHA	12	NIL	NIL	6.8	0.6	2.2	142	4.3
6	1149	BHIMABAHI	65	F	NON VEG	NIL	OHA	12.4	absent	2000	14.6	0.9	1.6	134	5.5
7	991	vijaylakshmi	50	f	NON VEG	NIL	OHA	14.7	15	nil	8.1	0.7	1.9	141	5
8	43524	nagamma	50	f	NON VEG	NIL	OHA	15.3	NIL	NIL	6.1	0.5	1.9	134	4.1
9	43441	SUBHAS	67	M	NON VEG	SMOKER	NONE	11.9	ABSENT	2000	9.8	1.1	1.8	130	5.7
10	43433	SANGOND	66	M	NON VEG	NIL	WARF,BD	14.2	Nil	NIL	6.4	0.8	2.1	135	2.9
11	43503	SIDAPPA	75	M	NON VEG	NIL	OHA	14.2	100	2000	14.3	1	1.8	135	6.1
12	41642	PARAPPA	61	M	VEG	NIL	OHA	12.2	NIL	2000	8.8	1	2.4	125	5
13	41912	SABEHGODA	85	M	VEG	NIL	BD	13.9	NIL	NIL	6.2	0.9	1.1	136	5.6
14	40860	DILEEP	52	M	VEG	NIL	OHA/HTN	13.6	ABSENT	2000	14	1.2	2.3	133	4.8
15	42899	KAREPPA	30	M	VEG	NIL	OHA	12.6	30	2000	7.4	0.5	1.8	134	4.2
16	42689	GOURAVVA	80	F	VEG	NIL	OHA	12.2	30	50	15.3	1	1.8	138	3.3
17	1138	sakina	62	f	NON VEG	NIL	none	12.9	NIL	2000	12.7	0.6	2	142	5.1
18	4878	IRANNA	36	M	NON VEG	ALCHOLIC	NONE	13.4	NIL	1000	8.2	0.8	2.2	139	4.1
19	4175	SRIDEVI	50	F	VEG	NIL	OHA	12.7	NIL	2000	13.6	0.6	2	135	4.1
20	5656	SHIVALIGAVVA	60	F	VEG	NIL	OHA	11.1	NIL	NIL	7.4	1.5	2	141	4.6

21	598	LAKAWWA	65	F	VEG	NIL	NONE	10.9	NIL	NIL	6.3	0.7	1.8	140	3.9
22	6376	SUNIL	46	M	VEG	TOBACCO	NONE	17.1	NIL	300	12.4	0.8	2	134	4.6
23	6411	NEELAMMA	60	F	VEG	NIL	OHA	10.4	TRACE	ABSENT	6.7	0.7	1.9	125	4.4
24	6041	CHENNAYYA	55	M	VEG	ALC/SMOKE	OHA	11	100	NIL	6.9	1.1	2.2	141	4.9
25	6153	SHAHEDA	56	F	NON VEG	NIL	NONE	11.9	ABSENT	2000	14.2	0.6	1.9	136	3.7
26	5054	PATHU	60	M	VEG	ALC/SMK	OHA	13.6	30	1000	10.3	0.9	2	137	3.7
27	6148	RAVI	45	M	NON VEG	SMK	OHA	14.4	15	1000	12	0.7	2.2	135	3.7
28	40643	BASAPPA	60	M	VEG	NIL	OHA	14.7	ABSENT	2000	11.5	0.8	2	140	3.9
29	40449	DASTAGIRI	29	M	NON VEG	NIL	OHA	10.6	NIL	NIL	6.3	0.8	2.1	138	4.3
30	40841	RASHIDA	44	F	NON VEG	NIL	NONE	11.2	NIL	2000	12.5	0.5	2.3	135	3
31	40890	MAHADEVAPPA	70	M	VEG	SMK,TOBACCO	BD	11	NIL	NIL	5.9	0.6	2		
32	40118	SHAKARAPPA	58	M	VEG	NIL	OHA	11.5	100	1000	9.2	1.2	1.5	131	4.6
33	40843	NAGAPPA	70	M	VEG	NIL	OHA	12.6	NIL	NIL	6.7	1	2.3	131	4.6
34	41625	SHRISHAIL	38	M	NON VEG	NIL	OHA	13.1	NIL	NIL	14.3	0.5	1.9	121	4.2
35	5975	BHUVANESHWARIU	21	F	NON VEG	NIL	NONE	10.7	15	1000	11.1	0.5	2.2	140	2.9
36	7320	CHANDBASHA	55	M	NON VEG	ALC/SMK	INS/ARB	10.6	30	2000	6.7	0.9	1.8	136	4.7
37	7257	SHIVAPPA	43	M	NON VEG	TOBACCO	OHA	12.4	TRACES	1500	10.1	1.1	2	135	4.2
38	7246	GURUPADDAPPA	49	M	VEG	ALC	OHA	13	30	300	6.3	0.6	2.9	131	3
39	84115	SHRISHAIL	69	M	VEG	NIL	OHA/ARB	15.5	15	1000	8.2	0.9	2.3	139	3.1
40	7248	DANAPPA	49	M	NON VEG	ALC/TOBC	OHA/ARB	13.8	NIL	1000	12.2	1	1.9	137	4.1
41	83624	RAMANGOUDA	62	M	VEG	NIL	OHA	14.5	NIL	NIL	5.7	0.7	2.3	140	4.2
42	5957	JANARDHAN	52	M	NON VEG	NIL	NONE	12.8	30	300	10.8	0.7	2.3	135	3.7
43	6558	HANAMATH	60	M	NON VEG	NIL	OHA	12.6	NIL	NIL	5.9	1.1	1.9	138	4.1
44	6338	PRAKASH	65	M	VEG	SMK/ALC	OHA,CCB	10.7	NIL	2000	11.5	0.8	1.9	140	4.1
45	6561	SHARANAMM	55	F	NON VEG	NIL	NONE	10.3	100	2000	10.7	0.9	1.9	137	2.8
46	6547	BHUVANESHWARIU	38	F	NON VEG	NIL	OHA/CCB	10.5	30	NIL	12.7	0.6	2.2	135	4.6
47	6424	BASAPPA	72	M	VEG	SMOKER	OHA/CCB	12.1	15	NIL	7.8	1	2.1	132	4.7

48	8719	BASAVARAJ	35	M	NON VEG	ALCOHOL	OHA	11.2	NIL	NIL	6.7	1.5	3.3	137	3.6
49	9225	SIDAPPA	60	M	VEG	NIL	OHA	16	100	2000	8.9	1.4	1.4	130	4.7
50	9431	MALLANNAGOUDA	25	M	VEG	ALC/TOBACCO	NONE	15.2	NIL	2000	6.2	1.4	1.9	144	3.7
51	9038	PREMA	56	F	NON VEG	NIL	OHA	10.7	NIL	100	7	0.6	1.9	141	4.5
52	9168	NEELAMMA	19	F	NON VEG	NIL	NONE	13.2	15	2000	6.1	0.5	1.6	153	4.1
53	7447	MUSTAQ	60	M	NON VEG	NIL	ATT	13.6	NIL	NIL	6.2	0.7	1.7	145	3.9
54	8988	RAMARAO	65	M	NON VEG	NIL	OHA/ARB	15.2	30	NIL	7.2	1.2	1.6		3.4
55	8859	YELAPPA	63	M	VEG	ALC/SMK/TOB	ARB	18	15	300	11.3	0.7	1.9	130	4.2
56	8899	PREMA	58	F	VEG	NIL	ARB/INSULIN	13.9	15	2000	14.1	0.5	2.1	137	4.5
57	9151	IRAWWA	60	M	VEG	NIL	OHA	10.7	30	NIL	6.2	1.1	2	133	2.7
58	8924	MALLAMMA	60	F	VEG	NIL	NONE	12.6	NIL	2000	12.2	0.9	3	127	6.6
59	8802	ANNAPPA	48	M	VEG	SMK/ALC	OHA	11.8	NIL	2000	14.6	1.5	2.7		
60	8866	IRAYYA	25	M	VEG	NIL	INSULIN	10.4	30	1000	13.4	1.2	2.1	130	3.9
61	8083	SHIVAYYA	71	M	NON VEG	NIL	INSULI/OHA	10	15	1000	11.7	1.1	1.9	141	5
62	8065	SATTAWWA	65	F	VEG	NIL	OHA/CCB	11.1	NIL	2000	10	0.8	2	140	4.5
63	8111	SAYAWWA	65	F	NON VEG	TOBACO	NONE	10.2	15	NIL	8.5	1.2	2	140	3.9
64	8074	GIDAPPA	60	F	NON VEG	SMK/ALC	ATT/OHA	10.8	100	NIL	6.7	0.7	1.7	139	4.3
65	8069	PARASHURAM	64	M	NON VEG	NIL	OHA/ARB	13.5	15	NIL	5.9	0.4	2.1	138	5.8
66	8072	BHEMANGOUDA	50	M	NON VEG	NIL	NONE	10	NIL	NIL	7.2	0.7	2.6	135	4.5
67	9749	SHAKARAYYA	60	M	NON VEG	ALC	OHA/CCB	11.5	15	ABSENT	10.5	1.2	1.9	139	4.7
68	9853	DADU	42	M	VEG	TOB/ALC	OHA	10	30	ABSENT	7.4	0.8	1.1	135	2.9
69	10096	LESU	60	M	NON VEG	SMOKER/ALC	OHA/ARB	12.7	30	ABSENT	6.9	1	1.8	139	4.3
70	113403	SAHADEVI	50	F	NON VEG	NIL	OHA	14.2	NIL	100	6.6	0.6	2.2	140	5.1
71	9899	DASTAGIRI	53	M	NON VEG	NIL	INSULIN/ARB	16.2	NIL	2000	6.9	0.7	1.9	141	4.6
72	9760	GOLALLAPPA	72	M	VEG	ALC/SMK	CCB/OHA	13.4	100	100	11.1	0.4	2.2	134	3.6
73	9842	BADUMA	68	F	NON	NIL	NONE	12	NIL	nil	7.4	0.7	2.1	140	4.3

					VEG										
74	9816	mahadevi	48	m	VEG	NIL	none	10	nil	nil	6.3	1	2.2	135	4.3
75	9911	bowravva	75	f	VEG	NIL	OHA/ARB	11.5	15	ABSENT	7.5	1	1.9	146	4.1
76	110519	nisarbhi	62	f	NON VEG	NIL	none	12.4	30	nil	10.7	0.6	2	139	3.9
77	9484	goudappa	62	m	VEG	ALCOHOL	ARB/OHA	14.6	NIL	2000	8.7	0.6	2.5	148	4
78	9499	SURESHBABU	55	M	VEG	ALCOHOLIC	ARB/OHA	14.1	30	2000	13	0.6	2	138	3.7
79	9660	CROSSWIN	50	M	NON VEG	ALC/SMK	OHA	13.7	15	500	8.1	0.9	2.1	135	4.6
80	9289	SAMMAWAA	70	F	NON VEG	TOBACO	NONE	11.2	15	2000	13.9	1	1.7	133	3.9
81	10335	BALAPPA	60	M	VEG	ALC/TOBACO	OHA	10.2	NIL	NIL	7	1.2	2.1	138	4.1
82	10320	BHIMASHANKAR	22	M	NON VEG	NIL	INSULIN	12.3	NIL	NIL	13	0.9	2.1	140	4.3
83	9625	SHANKEREMMA	75	F	VEG	NIL	BD	13.2	NIL	NIL	6.3	0.6	2.3	137	4.1
84	10672	SHARANAPPA	74	m	VEG	ALC/TOBACO	none	14.6	nil	nil	5.3	0.9	1.8	134	3.9
85	10695	SHIVANAND	40	M	NON VEG	ALC/TOBACO	OHA	13.6	100	NIL	8.8	0.6	2.1	141	3.3
86	11459	NIJAWWA	92	F	VEG	NONE	NONE	13	300	NIL	6.1	1.3	2.3	137	3.9
87	11205	TARASINGH	72	M	NON VEG	ALC/SMOKING	NONE	15.1	NIL	2000	9.7	0.6	2.2	147	4.2
88	11287	MALLAPPA	49	M	VEG	NONE	OHA	14.4	NIL	2000	12.3	0.7	1.2	139	4.1
89	11260	SUMITRA	63	F	NON VEG	NONE	OHA	12.8	NIL	2000	12.8	0.5	1.9	139	4.4
90	9222	MAHADEVI	55	F	NON VEG	NONE	OHA	11.2	30	NIL	8.4	0.7	2.4	142	3.8
91	10655	JANAKIBAI	50	F	VEG	NONE	OHA	10.7	NIL	100	9.5	0.6	2.5	133	3.5
92	11849	NINGAWWA	40	F	VEG	NONE	OHA	11.1	30	300	11	0.7	1.9	140	3.7
93	11298	VENKATESH	76	M	NONVEG	NONE	OHA	12.2	100	2000	9.7	1.3	2.3	136	3.9
94	8054	NINGANAGOUDA	60	M	VEG	NONE	OHA	10.1	15	NIL	7.2	1.3	1.9	135	4
95	9898	ISHAWARAPPA	70	M	NONVEG	NONE	OHA	10	300	1000	7.9	0.7	1.9	135	3.9
96	12265	KALAPPA	68	M	VEG	ALC	OHA	13.6	NIL	2000	12.4	0.9	2.4	134	5.3
97	12183	BASUVANTH	60	M	VEG	ALC,TOBACO	OHA	17	300	2000	9.1	1.3	2	139	4.5
98	12433	VEERUPUKASHI	43	M	VEG	ALC,TOBACO	OHA	12.8	100	2000	12.5	0.7	2.1	140	4.4
99	13003	SHARANAPPA	38	M	VEG	NONE	OHA/INSULIN	14.5	NIL	1000	9.4	1	2	135	4.3
100	13061	INDUMATI	75	F	VEG	NONE	OHA/CCB	13.2	100	300	7.4	0.8	2	140	3.8
101	14927	SHIVUBHAI	65	F	VEG	NONE	OHA/CCB	13.3	100	NIL	7.5	0.7	1.6	137	4
102	14948	RAMANGOUDA	55	M	VEG	NONE	OHA/ACE	9.8	2000	2000	14	1.1	1.5	143	3.9
103	15036	PARASHURAM	70	M	VEG	EX-ALC,TOBACO	NONE	11.6	NIL	NIL	6.5	1.4	2.4	149	2.7

104	13433	KANTILAL	63	M	NONVEG	ALC/SMOKER	NONE	11.4	30	NIL	6.2	0.5	2.4	142	3.2
105	14912	SANGAMMA	58	F	VEG	NONE	NONE	10.4	NIL	1000	12	0.7	2	142	3.3
106	15678	CHIDANAND	44	M	NONVEG	ALC/SMOKER	NONE	15.3	NIL	1000	7.2	1	2.1	140	3.4
107	15672	SHANTABHAI	68	F	VEG	NONE	OHA/ARB	10.3	30	NIL	12	0.9	1.9	142	3.7
108	16787	SHAKUNTHALA	72	F	VEG	NONE	OHA	10.3	NIL	NIL	5.6	1.3	2.2	130	5.7
109	21902	DHARMANNA	74	F	VEG	EX-ALC,TOBACO	OHA/ARB	12.9	NIL	NIL	7.1	0.7	2.4	137	4.3
110	22560	SHIVANAND	53	M	VEG	ALC	OHA	10.8	NIL	NIL	5.8	1	1.8	139	3.9
111	25070	MUNIRA KASHIM	48	F	NONVEG	NONE	OHA	11.8	NIL	2000	10.7	0.5	1.1	142	4
112	24728	BASAVARAJ	43	M	VEG	TOBACO	OHA	14.4	NIL	2000	15.6	0.4	1.2	132	3
113	25932	SUGALABHAI	65	F	VEG	NONE	OHA	13.2	NIL	NIL	6	0.6	2	138	3.1
114	26426	SHARANU	44	M	VEG	ALC	NONE	14.3	15	2000	9.9	0.7	2.3	135	4.4
115	27146	MUTTAWWA	60	F	VEG	NONE	OHA/CCB/BB	11.7	15	NIL	8.2	0.6	1.6	142	3.8
116	26898	SURESH	78	M	NONVEG	TOBACO	NONE	13.2	NIL	1000	10.9	0.9	2	134	3.8
117	26623	GOVIND	67	M	NONVEG	NONE	BRON-DILATOR	14.1	NIL	1000	10.5	1.4	2.1	133	4.9
118	26606	DILIP	58	M	VEG	NONE	OHA/CCB	12.7	NIL	100	7.7	1.2	2.2	132	5
119	27691	KALLAPPA	55	M	NONVEG	ALC/SMOKER	NONE	15.8	30	NIL	7.2	1	1.6	131	4.3
120	28449	MADEVA HADAPAD	77	M	VEG	NONE	OHA	11.7	30	100	6.8	0.8	2	138	4.1
121	29854	HANAMANTH	66	M	VEG	TOBACO	NONE	13.9	NIL	300	7	1	2	140	4.2
122	28987	ISHWARAPPA	80	M	VEG	NONE	OHA	13.7	NIL	NIL	6.2	0.9	2	134	3.6
123	29835	SAIBANNA	63	M	NONVEG	ALC/SMOKER	ASPIRIN	11.5	30	NIL	11.8	1.3	2.2	132	3.8
124	30062	BASAVARAJ	60	M	NONVEG	ALC/SMOKER	ARB	10	30	NIL	6.1	0.9	1.4	146	5
125	5920	ARJUN	55	M	NONVEG	ALC	ARB/OHA	16.7	NIL	NIL	10	0.8	1.6	141	4.4
126	5403	LAXMANNA	60	M	NONVEG	ALC/SMOKER	ACEI	14.4	NIL	NIL	6.9	1.1	1.3	134	4.3
127	6351	SHIVASHARANNAPPA	77	M	NONVEG	NONE	ARB	16.5	300	NIL	6.2	1.5	1.6	137	4.7
128	6442	RAIBAI	65	F	VEG	NONE	CCB	12.2	30	2000	7.3	0.7	1.8	134	3.6
129	6353	DANESHWARI	49	F	VEG	NONE	OHA	12.3	NIL	0.5	11	0.7	2	138	3.8
130	6897	MAHADEVI	47	F	VEG	NONE	OHA/BB	13.6	30	2000	12.9	0.6	1.8	145	5
131	7535	BABU USTAD	55	M	NONVEG	NONE	OHA/BB	14.1	TRACES	NIL	6.9	0.7	1.7	134	4.7
132	7525	RUDRAGOUIDA	67	M	NONVEG	ALC/SMOKER	OHA	15.3	TRACES	NIL	8.9	0.8	2.2	129	3.8
133	7585	SANYAWWA	65	F	NONVEG	ALC/TOBACO	INSULIN	10.8	30	1000	10	1.3	1	131	3.9
134	7156	SATISH	46	M	NONVEG	NONE	OHA	10.1	30	100	8.9	1.4	1.7	138	4.5
135	9381	SEETRAM	70	M	VEG	ALC/SMOKER	OHA	13.3	30	1000	9.7	0.9	2.3	139	3.4
136	9459	TIPANNA	50	M	VEG	ALC/SMOKER	OHA	14.5	NIL	200	8.6	0.8	1.7	148	4.7
137	9634	LAXMIBHAI	50	F	VEG	NONE	NONE	11.9	NIL	2000	15.2	0.5	1.6	141	5
138	9347	IMAMSAB	70	M	NONVEG	NONE	OHA/ARB/CCB	13.6	30	100	6.8	0.8	2	140	3.8
139	9260	MADIWALAPPA	60	M	NONVEG	SMOKER	OHA	12.3	30	1000	11.7	0.6	1.9	134	3.5
140	9812	SHIVAYYA	45	M	NONVEG	NONE	NONE	12.6	30	50	6	0.8	2.2	141	3.7
141	9572	VIJAYA PATIL	30	M	VEG	SMOKER	OHA/INSULIN	13	NIL	200	15.2	0.9	1.3	133	3.2

142	10098	BHALABHIM	54	M	VEG	ALC	NONE	16	NIL	200	8.2	0.9	1.9	145	3.5
143	10318	MOULASAB	54	M	NONVEG	ALC	OHA	17.9	NIL	200	10.1	0.6	1.8	138	3.9
144	10344	SHANKAREPPA	60	M	NONVEG	ALC/SMOKER	OHA	10.1	NIL	200	10	0.5	1.7	137	3.6
145	10240	AKKUBHAI	57	F	NONVEG	NONE	OHA	11.5	NIL	200	13.1	0.6	2	134	4.4
146	10417	SUSALA	62	F	NONVEG	NONE	OHA	10.9	30	200	14.1	1	1.7	131	3.8
147	10487	KASHINATH	50	M	NONVEG	ALC	OHA	15.3	30	NIL	7.6	0.7	1.5	137	3.6
148	11026	MALLAPPA	65	M	NOVEG	SMOKER/ALC	OHA	14	300	2000	16.9	1	2.3	134	4
149	11419	LAXIBAI	40	M	NOVEG	NONE	OHA	13.8	30	200	19.4	0.9	2.1	143	3.1
150	13644	BASANNA	40	M	VEG	NONE	OHA	12.3	NIL	200	18.8	0.4	1.4	134	3.6