"STUDY OF ASSOCIATION OF URIC ACID LEVELS IN PATIENTS WITH DIABETES AND ITS CHRONIC MICROVASCULAR COMPLICATIONS"

By

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In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

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Under the Guidance of

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I hereby declare that this dissertation/thesis entitled ***"STUDY OF ASSOCIATION OF URIC ACID LEVELS IN PATIENTS WITH DIABETES AND ITS CHRONIC MICROVASCULAR COMPLICATIONS"*** is a bonafide and genuine research work carried out by me under the guidance of **Dr.V.LAKSHMAIAH.** MD (Med),DCH Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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Dr. APARNA.G

ABSTRACT

STUDY OF ASSOCIATION OF URIC ACID LEVELS IN PATIENTS WITH DIABETES AND ITS CHRONIC MICROVASCULAR COMPLICATIONS

Objectives: To study the association of uric acid levels in subjects of prediabetes, diabetes and its chronic microvascular complications.

Materials and Methods: : This is a case control study of 160 subjects in R.L. Jalappa Hospital both in patients & out patients of which included are diabetics with microvascular complications, diabetics without complications, Prediabetics and normal subjects. Serum uric acid levels, diabetic control, glomerular filtration rate and lipid profile were measured in both control and patients groups.

Results: Serum glucose concentration was high in Type 2 DM group as compared with patients with prediabetics and control group. Serum uric acid concentration was lower in diabetic group without microvascular complications as compared with control group and was significant. Serum uric acid concentration was higher in prediabetic group when compared with control group and was significant.

Conclusion: Mean HbA1c was higher among diabetics with complications like neuropathy, retinopathy than nephropathy. Mean eGFR was higher among controls than in prediabetics, diabetics without complications and diabetics with neuropathy and retinopathy. Also as known eGFR is lower among diabetics with nephropathy. Nephropathy patients had lower uric acid than in retinopathy and neuropathy.

Finally Uric acid is initially increased in prediabetic state and reduced in diabetes without complications. Routine estimation of uric acid among diabetics and healthy individuals will help the clinician to find out the changing trends of uric acid levels which is likely to be influenced by control of blood sugar and progression of diabetes. Increasing levels of uric acid are found in diabetics with microvascular complications. Such cases should be carefully monitored for other microvascular complications.

Key words:

Diabetes mellitus, prediabetes , microvascular complications , uric acid.

LIST OF ABBREVIATIONS

AC	:	After Christ
ADA	:	American diabetes association
ADH	:	Anti diuretic hormone
AGE	:	Advanced glycation end-product
AMP	:	Adenosine monophosphate
ATP	:	Adenosine triphosphate
BC	:	Before Christ
BMI	:	Body mass index
BUN	:	Blood urea nitrogen
DM	:	Diabetes Mellitus
DNA	:	Deoxyribo nucleic acid
ESRD	:	End stage renal disease
Eg	:	Example
eGFR	:	Estimated glomerular filtration rate
FBS	:	Fasting blood sugar
HbA_{1C}	:	Glycosylated hemoglobin A
HDL	:	High Density lipoprotein
HGPRT	:	Hypoxanthine guanine phosphoribosyl transferace
HLA	:	Human leucocyte antigen
HNF	:	Hepatocyte nuclear transcription factor
IDDM	:	Insulin dependent diabetes mellitus

IGT	:	Impaired glucose tolerance
Kg	:	Kilogram
LDL	:	Low density lipoprotein
MDRD	:	Modification of diet in renal disease
MODY	:	Maturity onset diabetes of the young
Mg	:	Milligram
mg/dl	:	Milligram per deciliter
NIDDM	:	Non Insulin dependent diabetes mellitus
NSAIDS	:	Non steroidal anti inflammatory drugs
OGTT	:	Oral glucose tolerance test
OPD	:	Out patient department
PPBS	:	Post prandial blood sugar
PRPP	:	Phosphoribosyl pyrophosphate
RBS	:	Random blood sugar
RNA	:	Ribonucleic acid
SD	:	Standard deviation
SDUMC	:	Sri devaraj urs medical college
SUA	:	Serum uric acid
TC	:	Total cholesterol
TGL	:	Triglyceride
UA	:	Uric acid
UKPDS	:	United Kingdom Prospective Diabetes Study
WHO	:	World health organization

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INTRODUCTION

Uric acid (UA) is the end product of the purine metabolism in humans. Its concentration is determined by collaboration of genetic and environmental factors. UA levels is positively associated with serum glucose levels in healthy subjects[1]. Studies have established that UA levels are higher in subjects with prediabetes and early Type 2 diabetes then in healthy controls[2,3].

Increased serum UA level was found to increase chances for developing Type 2 diabetes in individuals with impaired glucose tolerance[4].

Recently, it has been found that there is a definitive relation between hyperglycemia and uric acid levels. Hyperuricemia is added to the set of metabolic abnormalities associated with insulin resistance in metabolic syndrome[5,6], An elevated UA levels, as reported, often precedes the development of obesity[7], hyperinsulinemia[8], and diabetes[9] .

Controversial data exist about UA levels in Type 2 diabetes, as low levels were found in diabetic patients, while elevated serum UA is a feature of hyperinsulinemia and impaired glucose tolerance[10]. Although several studies have showed the role of UA in progression of prediabetes to diabetes, studies related to UA levels in diabetes development are controversial and deserve further analysis.

Therefore, with the above background this study was done to examine serum level of UA in diabetics, diabetics with different microvascular complications, prediabetics and controls.

OBJECTIVE OF THE STUDY

To study the association of uric acid levels in subjects of prediabetes, diabetes and its chronic microvascular complications.

REVIEW OF LITERATURE

Definition:

Diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

History:

Diabetes was first recognized around 1500 b.c. by the ancient Egyptians, who considered it a rare condition in which a person urinated excessively and lost weight. The term diabetes mellitus, reflecting the fact that the urine of those affected had a sweet taste, was first used by the Greek physician Aretaeus, who lived from about 80 to 138 a.c It was not until 1776, however, that Matthew Dobson actually measured the concentration of glucose in the urine of such patients and found it to be increased[11].

Diabetes was recognized as a clinical entity in 1812 by the New England Journal of Medicine and Surgery.

Its prevalence at that time was not documented. No effective treatment was available and it was uniformly fatal after its diagnosis owing to insulin deficiency. In the intervening 200 years, major fundamental advances have been made in understanding of the underlying causes of diabetes and the approach to its prevention and treatment.

Although diabetes is still associated with a reduced life expectancy, the outlook for patients with this disease has improved. Patients usually lead active and

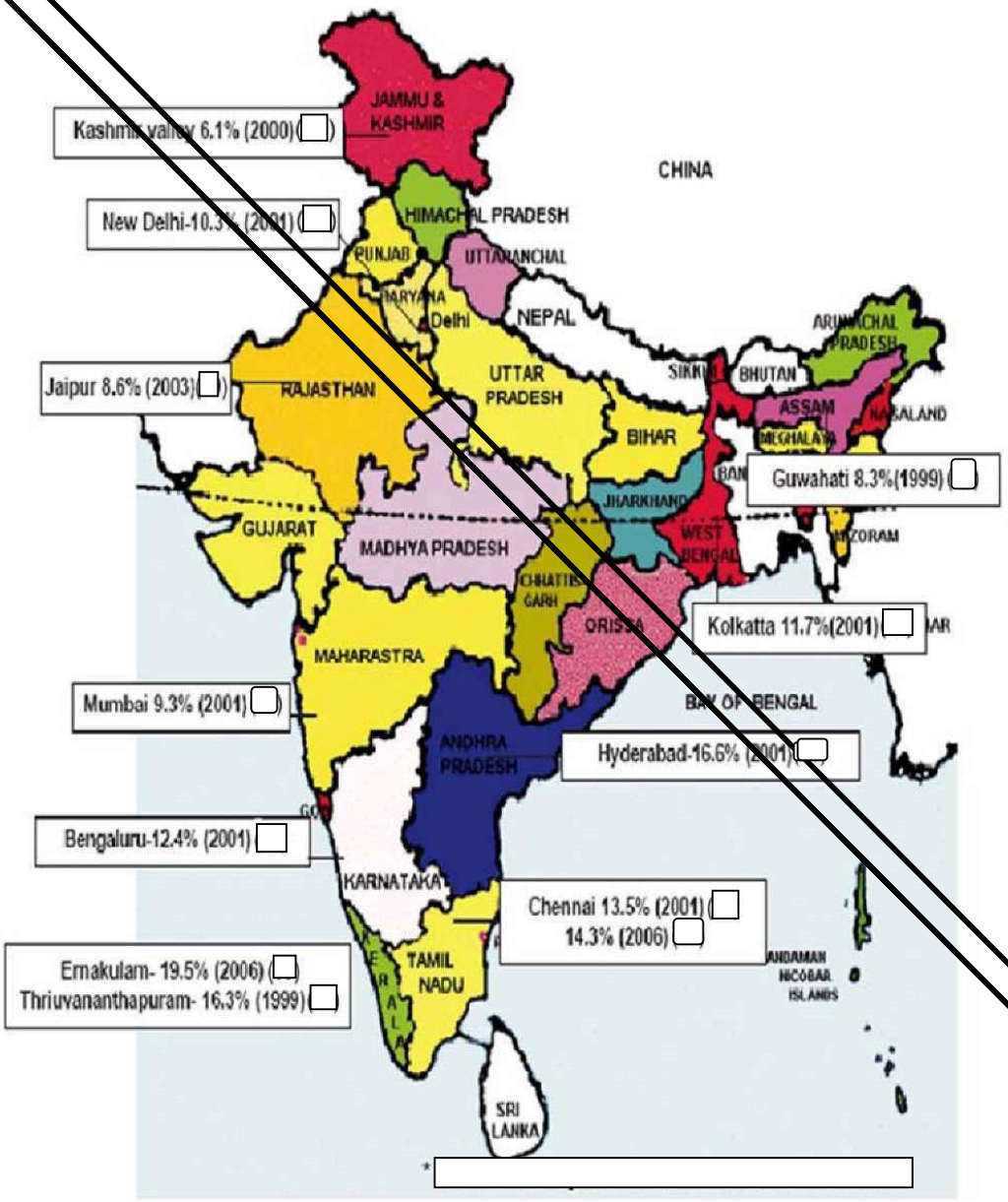
productive lives for many decades after the diagnosis has been made. Many effective therapies are available for treating hyperglycemia and its complications.

The study of diabetes and related aspects of glucose metabolism has been such fertile ground for scientific inquiry and scientists have received the Nobel Prize for diabetes related investigations since 1923.

Table 1: Nobel Prizes for Diabetes-Related Research.

Year	Category	Recipient	Contribution
1923	Medicine	F.G.Banting and J.J.R. Macleod	Discovery of insulin
1947	Medicine	C.F. Cori and G.T.Cori	Discovery of the course of catalytic conversion of glycogen.
1947	Medicine	B.A. Houssay	Discovery of the role of hormones released by the anterior pituitary lobe in the metabolism of sugar
1958	Chemistry	F. Sanger	Work on the structure of proteins, especially insulin
1971	Medicine	E.W. Sutherland	Discoveries concerning the mechanisms of action of hormones
1977	Medicine	R. Yalow	Development of radioimmunoassays for peptide hormones
1992	Medicine	E.H. Fischer and E.G. Krebs	Discoveries concerning reversible protein phosphorylation as a biologic regulatory mechanism

Figure 1 : MAP OF INDIA SHOWING THE INCIDENCE OF TYPE 2 DM IN DIFFERENT REGIONS OF INDIA


JAMMU & KASHMIR
Kashmir valley 6.1% (2000)
CHINA
New Delhi-10.3% (2001)
HIMACHAL PRADESH
PUNJAB
UTTARANCHAL
HARYANA
Delhi
NEPAL
ARUNACHAL PRADESH
Jaipur 8.6% (2003)
RAJASTHAN
UTTAR PRADESH
SIKKIM
BHUTAN
ASSAM
NAGALAND
MEGHALAYA
BIHAR
Guwahati 8.3%(1999)
JHARKHAND
GUJARAT
MADHYA PRADESH
WEST BENGAL
MIZORAM
CHHATTISGARH
ORISSA
Kolkatta 11.7%(2001)
MAHARASTRA
Mumbai 9.3% (2001)
BAY OF BENGAL
ANDHRA PRADESH
Hyderabad-16.6% (2001)
Bengaluru-12.4% (2001)
KARNATAKA
Chennai 13.5% (2001)
14.3% (2006)
Ernakulam- 19.5% (2006)
Thiruvananthapuram- 16.3% (1999)
TAMIL NADU
ANDAMAN NICOBAR ISLANDS
SRI LANKA

Classification

The most widely used classification of Diabetes mellitus was devised initially by the National Diabetes. Later World Health Organization (WHO) classification, came into vogue and was first adopted in 1980 and later modified in 1985[12].

The WHO classification was based mainly on the clinical features and etiology. Based on the clinical presentation and the type of treatment used, it was variously called as Insulin dependent diabetes mellitus (IDDM), Non- insulin dependent diabetes mellitus (NIDDM) and others. This classification was discouraged because the basis of classification was the therapy used mainly and not the etiology. During that point of time, the complete knowledge on etiopathogenesis was not available. Over the years, lot of research was done and much information has gathered. This necessitated a revision of the WHO classification.

Under the sponsorship of the American Diabetes Association (ADA) [13], an expert committee was formed in 1995, to go through the various improvements since 1979 and suggest changes in the WHO classification.

WHO CLASSIFICATION

A) Clinical causes

1. Diabetes mellitus

- Insulin — Dependent Diabetes Mellitus
- Non Insulin Dependent Diabetes Mellitus
    - **Obese**

- **Non-obese**

- Malnutrition-related diabetes mellitus
- Other types associated with
  - Pancreatic disease
  - Drug / chemical induced
  - Abnormalities of insulin and its receptors
  - Certain genetic syndromes
  - Miscellaneous

2. Impaired glucose tolerance

- Obese
- Non-obese
- Associated with certain conditions and syndromes

3) Gestational Diabetes Mellitus

B) Statistical Risk Classes: (Normal glucose tolerance but substantially increased risk of developing diabetes)

1. Previous abnormality of glucose tolerance.
2. Potential abnormality of glucose tolerance.

NEWER CLASSIFICATION[14]

Type 1 (autoimmune):

- Immune-mediated
- Idiopathic

Type 2 (Non-autoimmune)

Other types

Genetic defects of beta-cell function

Eg: Maturity onset diabetes in the young

MODY 1 (HNF — 4 alfa mutation)

MODY 2 (glucokinase mutation)

MODY 3 (HNF — 1 alfa mutation)

MODY 4 (insulin promoter Factor mutation)

MODY 5 (HNF – 1 beta mutation)

Mitochondrial DNA

Subunits of ATP – sensitive potassium channel

Proinsulin or insulin

Genetic defects of insulin secretion

Type A insulin resistance

Leprechaunism

Lipoatrophic diabetes

Rabson — Mendenhall syndrome

b) Secondary

- To pancreatic disease eg: pancreatitis ,fibrocalculous pancreatopathy
- To hormonal abnormalities like Cushing's syndrome, Pheochromocytoma, hyperthyroidism and acromegaly.
- To insulin receptor antibodies
- To drugs and chemical induced

E.g: Glucocorticoids, thyroid hormones, diazoxide, beta-agonists, phenytoin, and interferons (alpa and beta)

- Associated with genetic syndromes

E.g: Down's syndrome

Klinefelter's syndrome

Turner's syndrome

Wolfram's syndrome

Friedrich's ataxia

Laurence-Moon-Biedl syndrome

Myotonic dystrophy

Lipodystrophy

Ataxia telangiectasia

- Gestational diabetes mellitus

Type 1 Diabetes-Immune mediated:

Presents with classical symptoms of polyuria, polyphagia, polydipsia and weight loss and are associated with readily detectable concentrations of glucose and ketone bodies in blood and urine. Insulin is used to treat hyperglycemia as well as prevent ketosis and death.

Type 2 Diabetes:

Patients are often asymptomatic. May present with classical hyperglycemic symptoms of polydipsia, polyuria and weight loss. Differs from type 1 diabetics in that in spite of hyperglycemia, ketone bodies are present in low concentrations in blood and urine. Coma in these patients, if present is due to hyperosmolar nonketotic coma. Lactic acidosis occurs in infections due to an acute increase in the insulin requirement. But, spontaneous ketosis does not occur.

The Role of the Pancreas and the Discovery of Insulin

In 1889, Joseph von Mering and Oskar Minkowski found that removing the pancreas from dogs resulted in fatal diabetes, providing the first clue that the pancreas plays a key role in regulating glucose concentrations[15, 16].

In 1910, Edward Albert Sharpey-Schafer hypothesized that diabetes was due to the deficiency of a single chemical produced by the pancreas, he called this chemical insulin, from the Latin word *insula*, meaning island and referring to the pancreatic islet cells of Langerhans.

In 1921, Frederick Banting and Charles Best actually discovered insulin when they reversed diabetes that had been induced in dogs with an extract from the pancreatic islet cells of healthy dogs[17].

Together with James Collip and John Macleod, they purified the hormone insulin from bovine pancreases and were the first to use it to treat a patient with diabetes. The production of insulin and its therapeutic use quickly spread around the world. Once insulin injections became available, young people with insulin deficiency who had previously faced almost certain, painful death within weeks to months were able to survive for prolonged periods of time.

INSULIN GENE:

It is located on the short arm of chromosome 11 between insulin-like growth factor-2 gene and the Harvey ras oncogene. Donald Steiner's demonstrated in 1967 that the two polypeptide insulin molecule is derived from a single-chain precursor proinsulin[18].

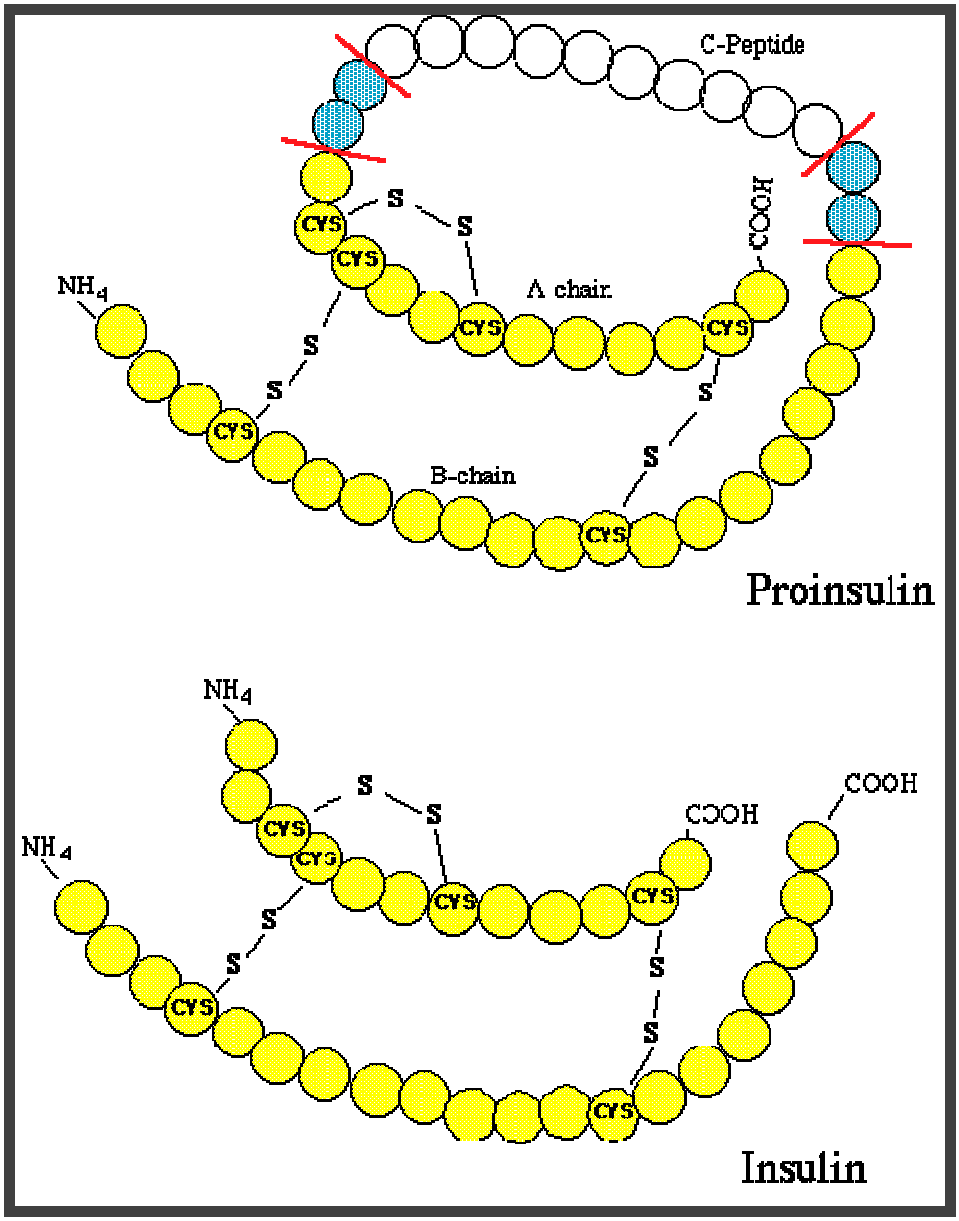


Figure 2: Structure of proinsulin and insulin

The Insulin Receptor gene[19]

It is located on chromosome no19.3 receptor mutations have been designated so far, associated with diabetes mellitus and type A insulin resistance.

DIAGNOSIS OF DIABETES MELLITUS

American Diabetes Association Recommendations[13]

1. Symptoms of diabetes with random blood glucose concentration ≥200mg/dl. Random, means any time of the day without relation to time since the last meal.
2. Fasting blood sugar> 126mg/dl. Fasting means no caloric intake for atleast past 8 hours.
3. Two hour plasma glucose >200mg/dl during an oral glucose tolerance test, as described by WHO, which is performed with a glucose load containing equivalent of 75gm of anhydrous glucose dissolved in water.

If any of the 3 are positive, it has to be confirmed with any one of the three tests on a subsequent day.

Microvascular Complications of Diabetes

The injurious effects of hyperglycemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and cerebrovascular disease) and microvascular complications (diabetic retinopathy, nephropathy, neuropathy). It is important to understand the relationship between diabetes and vascular disease because the prevalence of diabetes continues to increase.

Diabetic retinopathy

Diabetic retinopathy is the most common microvascular complication of diabetes[20]. Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in

the United Kingdom Prospective Diabetes Study (UKPDS) [21], and most patients with type 1diabetes develop evidence of retinopathy within 20 years of diagnosis[22]. Retinopathy may begin to develop as early as 7 years in patients with type 2 diabetes[20].

Aldose reductase is the initial enzyme in the intracellular polyol pathway Aldose reductase may participate in the development of diabetes complications. This pathway involves the conversion of glucose into glucose alcohol (sorbitol). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, mainly diabetic retinopathy.

Diabetic retinopathy is generally classified as either background or proliferative. Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as "dots" and therefore are frequently referred to as "dot hemorrhages." Hard exudates are caused by lipid deposition that typically occurs at the margins of hemorrhages. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy. They clinically appear as red dots during retinal examination. Retinal edema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. The appearance is one of grayish retinal areas. Retinal edema may require intervention because it is sometimes associated with visual deterioration[23].

Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. White areas on the retina ("cotton wool spots") can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous

hemorrhage and traction retinal detachment. With no intervention, visual loss may occur. Laser photocoagulation can often prevent proliferative retinopathy from progressing to blindness; therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial[23].

Diabetic nephropathy

Defined by proteinuria > 500 mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as albumin excretion of 30–299 mg/24 hours.

Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. This progression occurs in both type 1 and type 2 diabetes.

As many as 7% of patients with type 2 diabetes may already have microalbuminuria at the time they are diagnosed with diabetes[24]. In the European Diabetes Prospective Complications Study, the cumulative incidence of microalbuminuria in patients with type 1 diabetes was 12% during a period of 7 years[24, 25]. In the UKPDS, the incidence of microalbuminuria was 2% per year in patients with type 2 diabetes, and the 10-year prevalence after diagnosis was 25%[24].

The pathological changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelsteil-Wilson bodies).

The beneficial effects of angiotensin-receptor blockade, angiotensin-converting–enzyme inhibition, and protein restriction in preventing diabetic nephropathy have been shown[26].

Data shows that in almost all diabetics with End Stage Renal Disease (ESRD) who are admitted into dialysis or transplant programmes, there is clinical evidence of diabetic retinopathy on routine fundoscopic examination[27].

Diabetic neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes"[28].

Risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia.

The precise nature of injury to the peripheral nerves from hyperglycemia is not known but likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies.

Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes. Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death.

Compared with those without neuropathy, individuals with neuropathy were nearly four times more likely to have retinopathy and two times more likely to have albuminuria[29].

Uric Acid

It is the final breakdown product of purine metabolism and it is a weak acid.

History

In 1776, the Swedish Chemist Scheele isolated uric acid from a stone of urinary tract and in 1797[30].British chemist WoIlaston isolated the substance from a tophus which he found from his own ear[31]. Fifty years later, these observations led the British Physician, Alred Barry Garrod to show by chemical isolation, the presence of high concentrations of uric acid in the blood of gouty patients. In 1913, Folin F. Denin established a reliable method of chemical determination of uric acid which led to refusal of Garrod's concept[32, 33].

Structure and Chemistry:

The chemical nature of uric acid was presented by Fisher to be 2, 6, 8, trioxypurine13. It is the most highly oxidized member of the purine class and compounds. Oxidation of uric acid in neutral alkaline solution causes disruption of the purine ring with the exclusion of carbon-6 as carbon dioxide and the formation of allantoin and other products.

When uric acid is reacted in an acidic solution, alloxan is the product, and when ammonia is added to uric acid, ammonium purpurate, a purplish red substance, accountable for the murexide test is formed.

In the murexide test, uric acid moistured with nitric acid, is subjected to heating; and then few drops of ammonium hydroxide are added. The colorimetric procedures for determination of uric acid depends on its reducing properties.

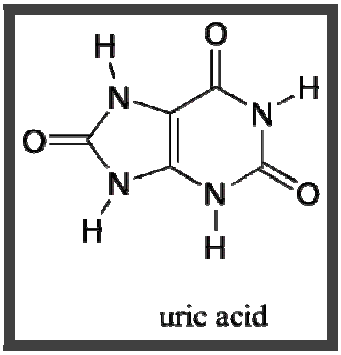


Figure 3: Structure

Pathway of Urate Production

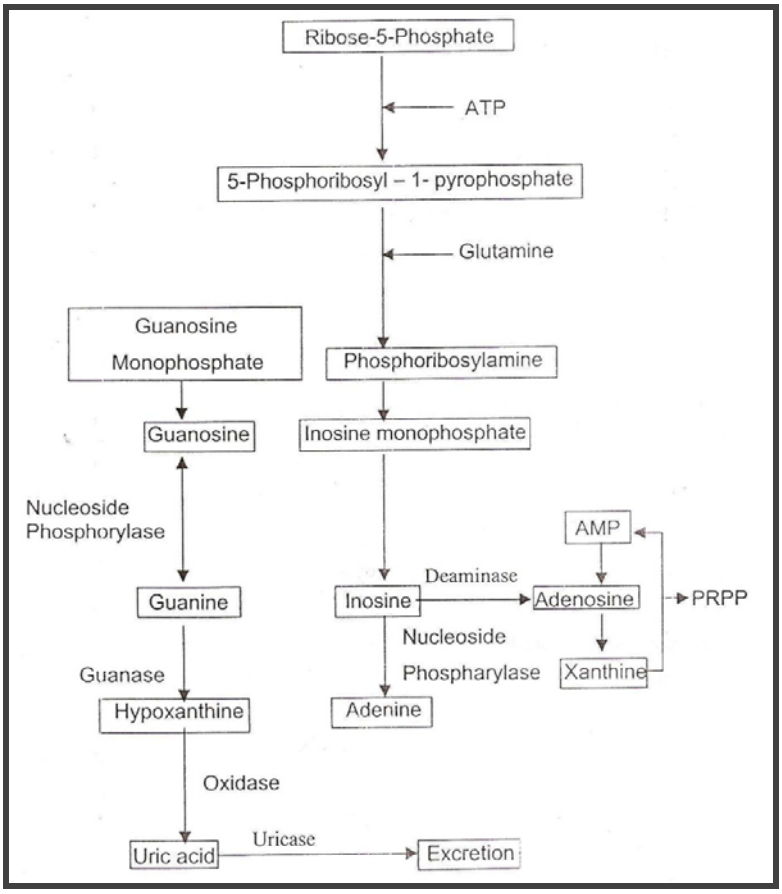


Figure 4 : Uric Acid Pathway

Dietary Intake

Exogenous source of purines is provided by diet. Dietary intake of purines / nucleic acids give to the serum urate level and the daily excretion of uric acid, this

influence being proportional to the intake. Serum urate levels decrease by only 1 mg/dl or less when an individual alters from a normal to purine free diet. On the other hand, diets more high in purines (liver, meat sweet breads, kidney and anchovy) have the potential to raise the plasma uric acid concentration.

Normal Values

The urate pool size in a adult male - 1200mg, and 700mg urate is produced daily[34]. The production is balanced by the excretion of 500mg of urate into the urine and 200mg into the small intestine. Any imbalance in the two, results in hyperuricemia or hypouricemia.

The normal serum values fluctuate with age and sex. Children have serum urate concentrations of 3 to 4 mg/dl. Levels start increasing during puberty in males, but remain low in females till menopause.

Mean serum urate values of adult men and premenopausal women is 5.3 and 4.7 mg/dl correspondingly. After menopause, values for women increase to approximate those at men. Among adults, levels fluctuate with height, body weight, blood pressure and renal status as well as alcohol intake.

Excretion of Uric Acid

Of the 700-1000mg of uric acid formed in normal man on a regular diet, about $2/3^{rd}$ to $3/4^{th}$ is excreted by the kidney. The remainder is eliminated via small intestine. The amount secreted into the intestinal lumen is probably related to the plasma concentration, so that a higher portion of daily uric acid production may be excreted via the gastrointestinal tract in hyperuricemic individuals than in normals. It is now thought that intestinal removal of uric acid represents an important controller

of the plasma urate concentration. On the other hand, renal excretion is the major regulator of plasma urate; decreases or increases in renal clearance are rapidly reflected by inverse changes in the plasma concentration.

Normally, uric acid is totally filtered in the renal glomeruli before filtered load is completely reabsorbed in the proximal tubules. Around 5-10% is later secreted to the distal tubules and excreted in the urine. The filtered urate undergoes extensive absorption and atleast 98% of the filtered load reabsorbed. Recent evidences suggest that much of the secreted urate undergoes extensive reabsorption[35]. Expansion of extracellular fluid volume increases the urate clearance by inhibiting its tubular reabsorption[36]. Conversely, contraction of extracellular fluid volume, decreases the urate clearance, enhancing its tubular reabsorption, thereby leading to hyperuricemia.

The tubular secretory component is directly related to plasma urate concentration. Secretion may be decreased, if the transport pathway is competitively blocked by other organic acids. To summarize normally kidneys excrete an amount equivalent to 5-10% of the filtered load of uric acid.

Hyperuricemia

Defined as a serum concentration more than 7mg/dl[37.] Caused due to increased production or decreased excretion of uric acid or from a mixture of the 2 processes. When measured, in unselected individuals, 95% have serum urate concentration less than 7mg/dl. Hyperuricemia is reported in 2-13.2% of ambulatory adults.

Causes: [38-41]

1 Urate overproduction

- Primary idiopathic
- HGPRT deficiency
- PRPP synthetase overactivity
- Psoriasis
- Paget's disease
- Rhabdomyolysis
- Hemolytic processes
- Lymphoproliferative diseases
- Myeloproliferative diseases
- Polycythemia vera
- Exercise
- Alcohol
- Obesity
- Purine-rich diet

- Glycogen storage diseases (types V, VII)

2 Urate underexcretion

- Primary idiopathic
- Renal insufficiency
- Polycystic kidney disease
- Diabetes insipidus
- Hypertension
- Acidosis-lactic acidosis, ketoacidosis
- Berylliosis

- Hypothyroidism
- Hyperparathyroidism
- Toxemia of pregnancy
- Lead intoxication
- Bartter's syndrome
- Down's syndrome

- Drugs
    - Salicylates (>2 g/d)
    - Diuretics
    - Alcohol
    - Levodopa
    - Ethambutol
    - Pyrazinamide
    - Nicotinamide

- Cyclosporine

3 Combined mechanism

- Glucose-6-phosphate Dehydrogenase deficiency
- Fructose-1-phosphate aldolase deficiency.
- Alcohol
- Shock
- Physical exercise
- Status epilepticus
- Myocardial infarction

- Acute respiratory failure

Hypouricemla:

Defined as a serum urate concentration less than 3mg/dl. It can occur due to decreased formation of urate or increased renal clearance of urate[42-44]. It can also occur when the xanthine oxide activity is reduced, either because of deficiency of the enzyme, as in xanthinuria, or when there is pharmacologic inhibition of xantine oxidase by allopurinol.

In a study done in UK, the occurrence of hypouricemia in hospital population was reported to be 6.5% among the males and 4.8% among the females and a large group of patients (14%) who manifested hypouricemia in that study were those with diabetes mellitus, 10% of whom were on insulin and 4% on sulphonylureas[44].

Causes of hypouricemia[45]:

- Total parenteral nutrition
- Cirrhosis
- Neoplasms
- Diabetes mellitus
- Syndrome of inappropriate secretion of ADH
- Fanconi syndrome
- Xanthine oxidase deficiency
- Drugs

• Ascorbic acid
• Dicoumarol
• Diflunisal
• Sulfinpyrazone

- NSAIDs
- Probenecid
- Estrogen
- G!ucocorticoids

Uric acid in diabetes mellitus:

Diabetes Mellitus has been reported to be one of the causes of hypouricemia[45]. The prevalence of hypouricemia in diabetes is reported to be about 14%.

Godfredsen et al showed that diabetics had a 42% increase in renal uric acid excretion rate compared with normal who had significantly lower mean serum uric acid concentrations[46].

Seventeen percent of the diabetic patients had serum concentrations below the normal mean - 2 standard deviations. In contrast, diabetics had an 83% increase in ratio of urate clearance / creatinine clearance.

In diabetics, the prevalence was reported to be 14-17%. The urate clearance was found to be significantly high in diabetics than in nondiabetics and it has been proposed that these findings could indicate the occurrence of renal tubular damage in the diabetic kidney.

Others have found a temporary increase in urate clearance during intravenous infusion of glucose and have ascribed the high urate clearance in diabetes to the increased blood glucose level. However, the mechanism of renal handling of urate in diabetes still remains unknown.

Dr. Herman and Mr. Goldbourt proposed that in hyperglycemic state, the increasing glucose reabsorption may impair the tubular reabsorption of uric acid, as both glucose as well as filtered uric acid are reabsorbed at the same site of the

proximal convoluted tubule[47]. Continued hyperexcretion of uric acid due to hyperglycemia could deplete the uric acid pool and gradually reduce serum uric acid levels.

This was supported in 1973 by Geoffrey Boner and Rieselbach who concluded that the presence of glucose in the renal tubule lumen at a site distal to that of normal glucose reabsorption inhibits the tubular reabsorption of uric acid[48].

Later in 1987, Schichiri et al emphasized that there is a possible mechanism of glomerular hyperfiltration, which brought about the increased renal clearance of urate[49].

In 2011, Pavani bandaru et al http://www.hindawi.com/23570672/established that Higher serum uric acid levels were found to be inversely associated with diabetes mellitus[50].

In 2012, Sudhindra Rao M et al found that serum uric acid level was higher in pre-diabetes than controls and lower in diabetes mellitus than pre-diabetes[51].

MATERIALS AND METHODS

Source of data: Patients, with known diabetes or newly detected diabetes or impaired glucose tolerance treated on OPD basis or in patients in R.L.Jalappa Hospital,affiliated to Sri Devaraj urs medical college ,Tamaka, Kolar. .

Inclusion Criteria

- Diabetics with microvascular complications of diabetes
- Diabetics without microvascular complications of diabetes
- Prediabetics (Impaired fasting glucose/Impaired postprandial glucose)
- Normal subjects
- Age above 18 years

Exclusion Criteria

- Patients having diagnosed with gout
- Patients having malignancies
- Diagnosed conditions where uric acid levels are elevated

Method of collecting data

After taking informed consent from the subjects baseline data of all patients were collected including:

- Demographics
- Duration of diabetes
- Family history of diabetes
- Co morbidities

All patients underwent a detailed clinical examination including measurement of BMI, Ophthalmologic examination for evidence of diabetic retinopathy, Ankle reflex, Vibration test, sensations in lower limbs.

- eGFR was calculated for all patients by MDRD formula.
- Ultrasound abdomen was done for selected patients for kidney size and echo texture.

Sample Size :

160 subjects attending to R.L Jalappa Hospital, affiliated to SDUMC, Tamaka, Kolar, both in patients & out patients of whom

- N=40, Diabetics with microvascular complications of diabetes
- N=40, Diabetics without microvascular complications of diabetes
- N=40, Prediabetics
- N=40, Normal subjects

ESTIMATION OF BLOOD GLUCOSE - Glucose oxidase and peroxidase meathod(GOD-POD)

Test Principle: Dry chemistry analyzer – reflectance photometry

In presence of oxygen, glucose oxidase acts on glucose to give gluconic acid and hydrogen peroxide. Peroxidase breaks hydrogen peroxide to water and oxygen. Oxygen liberated is accepted by the chromogen system that gives a quinoneimine red colour compound. The red coloured complex so developed is proportional to glucose concentration and is measured at 505 nm wavelength (500-540 nm) photometrically or with green filter.

$$\text{Glucose} + O_2 + H_2O \xrightarrow[\text{Oxidase}]{\text{Glucose}} \text{Gluconate} + H_2O_2$$

$$H_2O_2 + \text{Phenol} + \text{4-Aminoantipyrine} \xrightarrow[\text{Peroxidase}]{} \text{Chrome complex} + 4H_2O$$

Specimen

Unhemolysed , fresh serum of plasma with potassium oxalate and fluoride. Deproteinised whole blood can also be used. Samples with fluoride may be left at room temperature for about 3-4 hrs with no appreciable change in glucose concentration.

Interfering substances:

Glucose estimation by this method is free of interference from lipids, bilirubin, uricacid, ascorbic acid and antidiabetic drugs

Standard OGTT

World Health Organization and other organizations interested in diabetes agreed on a standard dose and duration for OGTT since the 1970s.

Preparation

Usually OGTT is done in the morning as glucose tolerance can exhibit rhythm a diurnally with a significant low values in the afternoon. The patient fasts for 8-12 hours before to the tests. Water can be taken. The patient is told not to restrict carbohydrate intake in the days or weeks before the test. The test should not be performed during an illness, as results may not reflect the patient's glucose metabolism when healthy. Person weighing less than 43 kg should not be given full adult dose. It can produce false positive result due to exaggerated glucose.

Procedure

1. A zero time (baseline) blood sample is drawn.
2. The patient is then given a measured dose of glucose solution to drink within a 5 inute time frame.
3. Blood is drawn at intervals for measurement of glucose (blood sugar), and

sometimes insulin levels. The intervals and number of samples vary according to the purpose of the test. For simple diabetes screening, the most important sample is the 2 hour sample and the 0 and 2 hour samples may be the only ones collected .

Interpretation of OGTT results

Fasting plasma glucose (measured before the OGTT begins) should be below 110 mg/dl. Fasting levels between 110 and 125 mg/dl are borderline ("impaired fasting glycaemia"), and fasting levels repeatedly at or above 126 mg/dl are diagnostic of diabetes.

The **2 hour OGTT** glucose level should be below 140 mg/dl. Levels between 141 and 199 mg/dl indicate **"impaired glucose tolerance**". Glucose levels above 200 mg/dl at 2 hours confirms a diagnosis of diabetes.

Glucose levels	**NORMAL**		**impaired glucose tolerance (IGT)**		**Diabetes Mellitus (DM)**	
Venous Plasma	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mg/dl)	<100	<140	101-125	141-199	>126	>200

Table 2: Interpretation Of OGTT

DETERMINATION OF URIC ACID IN SERUM

Uric acid by phosphotungstic acid method- method of caraway[52]

Test Principle: Dry chemistry analyzer – reflectance photometry

The procedure is based on oxidation of uric acid by phosphotungstic acid reagent in alkaline medium. Phosphotungstic acid itself gets reduced to tungsten blue. Sodium bicarbonate is used as alkali. The amount of tungsten blue formed is estimated at wavelength from 690-710nm. λ_{max} = 660nm.

Figure 5:Dry chemistry analyser.

RESULTS

The total number of subjects included in this study was 160. Out of these 160 subjects, 40 were of type 2 DM patients with out microvascular complications,40 were of type 2 DM patients with microvascular complications,40 were prediabetics, and 40 were healthy controls.

Table-3 Details of subjects in the study

Parameter	Type 2 DM without microvascular complications	Type 2 DM with microvascular complications	Prediabetics	Controls
Total No	**40**	**40**	**40**	**40**
Age	29-96	36-85	26-82	28-84
Mean Age	54.88 ± 12.77	60.33 ±12.33	55.73 ±13.67	52.35 ±14.69
Sex	m=18 f=22	m=20 f=20	m=23 f=17	m = 26 f=14
B.M.I	26.78 ±5.57	28.41 ±6.11	26.50 ±6.30	26.18 ±6.48
FBS	212.40 ±87.44	198.58 ±99.33	110.50 ±18.40	86.25 ±13.15
PPBS	306.03 ±85.46	298.68	166.85	110.25

		±102.35	±17.41	±14.58
RBS	269.08 ±143.29	247.23 ±144.98	122.68 ±43.58	106.93 ±38.18
GLYCATED HEAMOBLOBIN	10.60 ±2.77	14.30 ±19.58	7.33 ±1.28	5.77 ±0.80
SERUM URIC ACID	3.86 ±1.28	5.56±2.39 (nephropathy-6.3;other-4.95)	4.77 ±1.48	3.89 ±1.37
eGFR	95.66 ±29.04	59.90 ±34.71 (nephropathy-28.9;other-93.7)	105.30 ±0.00	81.80 ±33.77

Analysis with respect to age:

The age of the subjects with Type 2 DM without complications ranged from 29 to 96 years. The age of the subjects with Type 2 DM with complications ranged from 36 to 85. The age of the subjects with prediabetes ranged from 26 to 82. The age of controls ranged from 28 to 84. The mean age is 54.88 ±12.77, 60.33 ±12.33, 55.73 ±13.67, 55.73 ±13.67 respectively. Difference among the cases and the controls with reference to the age was not statistically significant. The distribution in relation to age is provided in table 3 given below.

Table 4: Age distribution of patients studied

Age in years	Pre diabetics	DM without complications	DM with complications	Normal	Total
<30	1(2.5%)	1(2.5%)	0(0%)	1(2.5%)	3(1.9%)
30-40	6(15%)	4(10%)	3(7.5%)	10(25%)	23(14.4%)
41-50	7(17.5%)	9(22.5%)	7(17.5%)	7(17.5%)	30(18.8%)
51-60	12(30%)	17(42.5%)	10(25%)	10(25%)	49(30.6%)
61-70	8(20%)	6(15%)	12(30%)	8(20%)	34(21.3%)
71-80	5(12.5%)	2(5%)	7(17.5%)	3(7.5%)	17(10.6%)
>80	1(2.5%)	1(2.5%)	1(2.5%)	1(2.5%)	4(2.5%)
Total	40(100%)	40(100%)	40(100%)	40(100%)	160(100%)
Mean ± SD	55.83±13.55	54.88±12.77	60.03±12.33	52.35±14.69	55.77±13.53

P=0.081

Analysis with respect to gender:

Out of 160 cases studied, there were 87 males and 73 females. . Difference among the cases and the controls with reference to the gender was not statistically significant.

Table 5: Gender distribution of patients studied

Gender	Pre diabetics	DM without complications	DM with complications	Normal	Total
Female	17(42.5%)	22(55%)	20(50%)	14(35%)	73(45.6%)
Male	23(57.5%)	18(45%)	20(50%)	26(65%)	87(54.4%)
Total	40(100%)	40(100%)	40(100%)	40(100%)	160(100%)

P=0.295

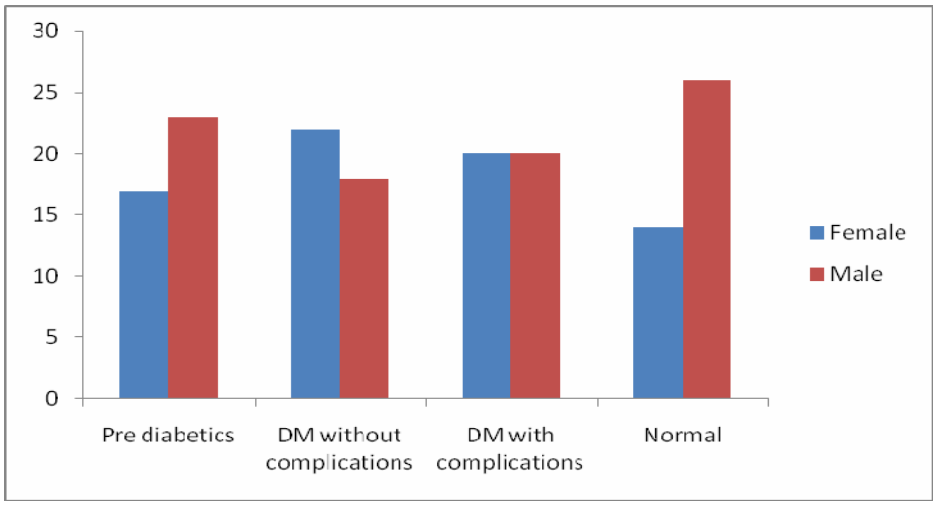


Figure 6: Bar diagram showing Gender distribution

Analysis with respect to duration of diabetes in months

Table 6: Duration of diabetes among diabetes patients

	DM without complications	DM with complications	P value
Duration of diabetes in months	40.05±52.68	84.57±84.57	0.025**

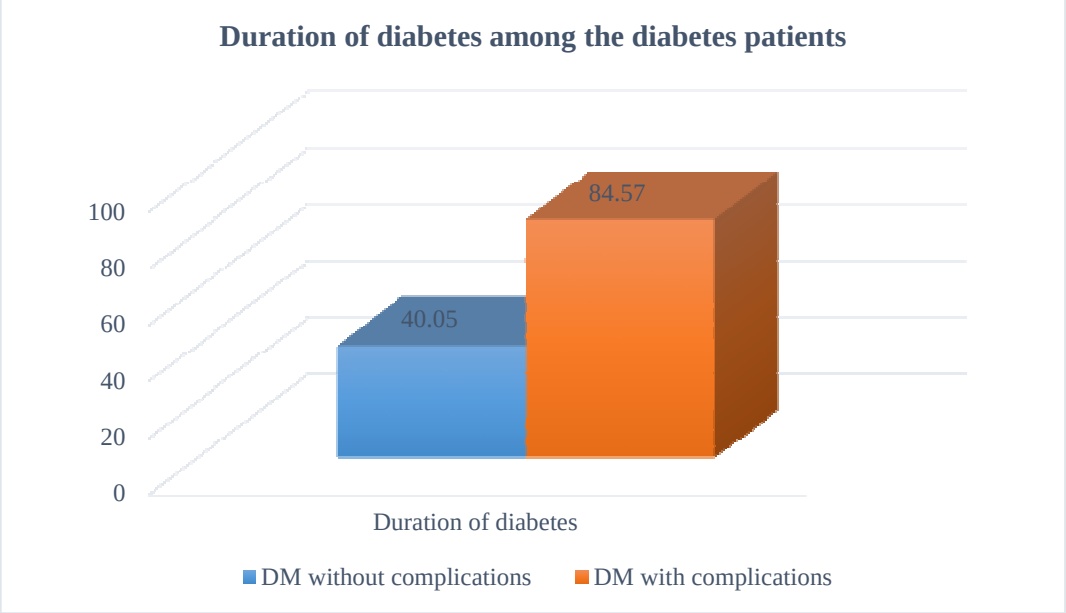


Figure 7: Bar diagram showing duration of diabetes

Duration of diabetes was higher among those who had complications. There was significant difference with respect of duration of diabetes among the patients who had complications and without complications.

Analysis with respect BMI

Table 7: BMI among the subjects

	Pre diabetics	DM without complications	DM with complications	Normal	Total	P value
BMI	26.5 ± 6.3	26.77 ± 5.56	28.41 ± 6.11	26.17 ± 6.47	26.96 ± 6.12	0.370

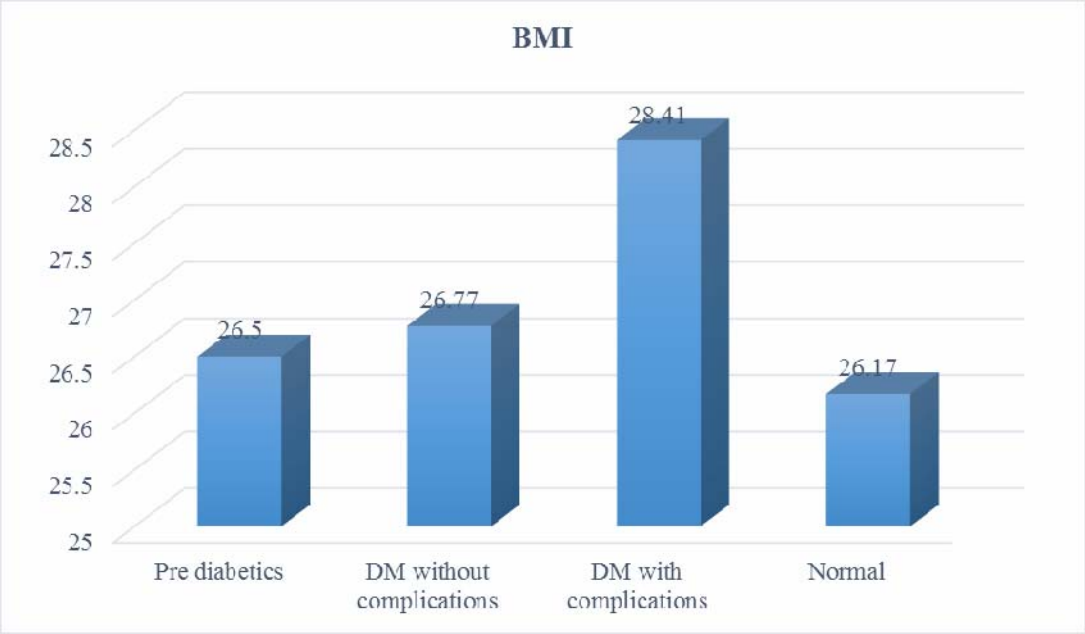


Figure 8: Mean BMI among the groups

There was no significant difference with respect to BMI.

Analysis with respect to symptoms

Table 8 : Symptoms of patients studied

Symptoms	Pre diabetics (n=40)	DM without complications (n=40)	DM with complications (n=40)	Normal (n=40)	Total (n=160)
Nil	40(100%)	39(97.5%)	28(70%)	40(100%)	147(91.9%)
Yes	0(0%)	1(2.5%)	12(30%)	0(0%)	13(8.1%)
• Blurring	0(0%)	0(0%)	3(7.5%)	0(0%)	3(1.9%)
• Dec urine	0(0%)	0(0%)	2(5%)	0(0%)	2(1.3%)
• Numbness	0(0%)	0(0%)	4(10%)	0(0%)	4(2.5%)
• Pain paras	0(0%)	0(0%)	1(2.5%)	0(0%)	1(0.6%)
• Polydipsia	0(0%)	1(2.5%)	2(5%)	0(0%)	3(1.9%)

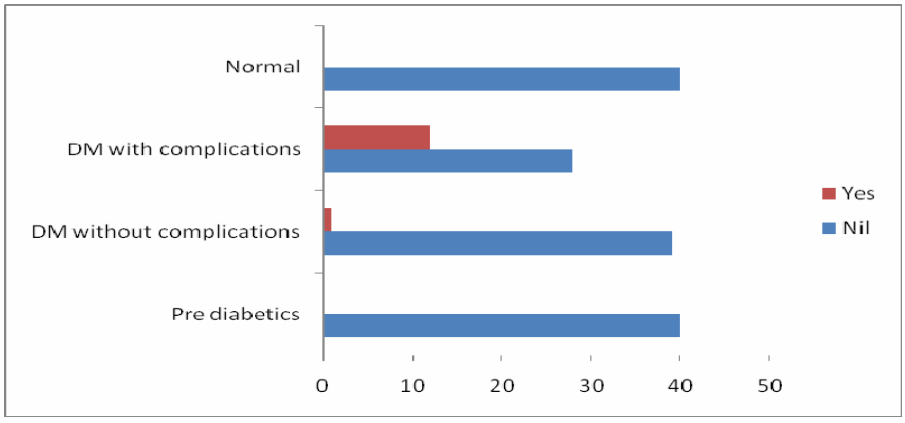


Figure 9: Symptoms of patients studied

Most patients presented without symptoms of diabetes.

Analysis with respect to family history

Table 9: Family history of patients studied

Family history	Pre diabetics	DM without complications	DM with complications	Normal	Total
Absent	40(100%)	30(75%)	30(75%)	39(97.5%)	139(86.9%)
Present	0(0%)	10(25%)	10(25%)	1(2.5%)	21(13.1%)
Total	40(100%)	40(100%)	40(100%)	40(100%)	160(100%)

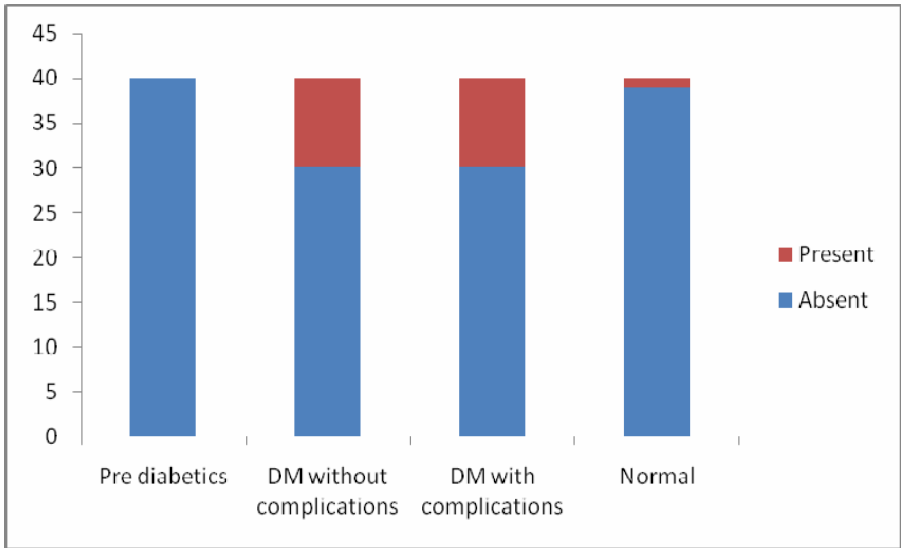


Figure 10: Bar diagram Family history of patients studied

Family history is more in diabetics than controls.

Analysis with respect to sugar values

Table 10: Comparison of RBS, FBS, PPBS of patients studied

	Pre diabetics	DM without complications	DM with complications	Normal	Total	P value
RBS	122.68±43.58	269.08±143.29	247.23±144.98	106.93±38.18	186.48±127.58	<0.001**
FBS (mg/dl)	110.50±18.40	212.40±87.44	198.58±99.33	86.25±13.15	151.93±86.05	<0.001**
PPBS (mg/dl)	166.85±17.41	306.03±85.46	298.68±102.35	110.25±14.58	220.45±107.92	<0.001**

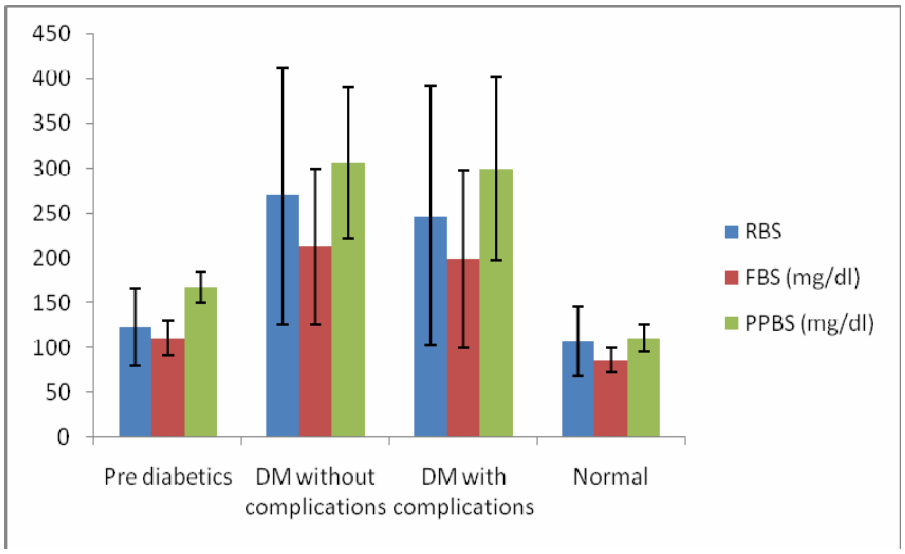


Figure 11: Bar diagram comparing of RBS, FBS, PPBS of patients studied

Sugar values are higher in diabetes with out complications than with complications.

Table 11: Comparison of RBS, FBS, PPBS between diabetes with and without complications

	DM without complications	DM with complications	P value
RBS (mg/dl)	269.08±143.29	247.23±144.98	0.4998
FBS (mg/dl)	212.40±87.44	198.58±99.33	0.5109
PPBS (mg/dl)	306.03±85.46	298.68±102.35	0.728

Sugar values in DM without complications is more than DM with complications. But this is not statistically not significant.

Analysis with respect to Lipid profile

	Pre diabetics	DM without complications	DM with complications	Normal	Total	P value
Total cholesterol(mg/dl)	158.98±37.23	161.80±32.71	159.45±51.85	154.78±43.59	158.75±41.65	0.900
TGL(mg/dl)	181.43±106.12	228.80±125.91	209.45±125.58	153.38±97.36	193.26±116.89	0.022*
HDL(mg/dl)	37.83±11.08	32.95±8.08	30.35±9.68	37.13±13.42	34.56±11.08	0.006**
LDL(mg/dl)	85.10±36.66	73.30±37.66	79.40±41.37	79.73±34.29	79.38±37.46	0.579

Table 12: Comparison of lipid parameters

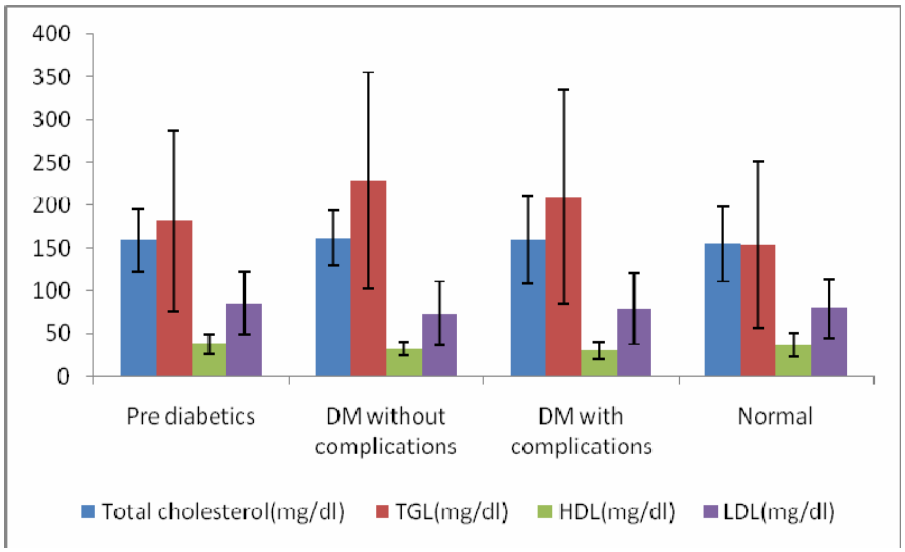


Figure 12: Bar diagram comparing of lipid parameters of patients studied

Triglycerides are significantly increased in diabetics than in controls and prediabetics. HDL cholesterol is significantly decreased in diabetics than in controls and prediabetics.

Table 13: Comparison of HbA1c and Various renal parameters with different groups

	Pre diabetics	DM without complications	DM with complications other than nephropathy	DM with nephropathy	Normal	Total (n=120)	P value
HbA1c	7.32 ± 1.27	10.59± 2.77	17.25 ± 26.14	10.68±3.08	5.77 ± 0.80	9.48 ± 10.33	<0.0001**
eGFR	101.27 ±32.3	102.35±33.9	93.77±22.79	28.94±15.44	120.42 ±38.8	97.16 ± 40.97	<0.0001**
Serum creatinine	0.83±0.21	0.78±0.21	0.83±0.21	3.06±2.55	0.722± 0.20	1.04±1.12	<0.0001**
Blood urea	29.18± 10.2	28.7±12.2	30.50±10.6	98.78± 74.15	23.08± 11.4	35.56± 34.85	<0.0001**
BUN	8.13±1.71	10.19±4.37	10.0±2.87	40.67±30.51	6.61±1.81	11.7± 13.3	<0.0001**
Uric acid	4.76±1.48	3.85±1.27	6.61±1.81	6.3±2.66	3.89±1.36	4.51± 1.81	<0.0001**

Table 14: Analysis with respect to Glycated heamoglobin

	Pre diabetics	DM without complications	DM with complications other than nephropathy	DM with nephropathy	Normal	Total (n=120)	P value
HbA1c	7.32 ± 1.27	10.59± 2.77	17.25± 26.14	10.68±3.08	5.77± 0.80	9.48 ± 10.33	<0.0001**

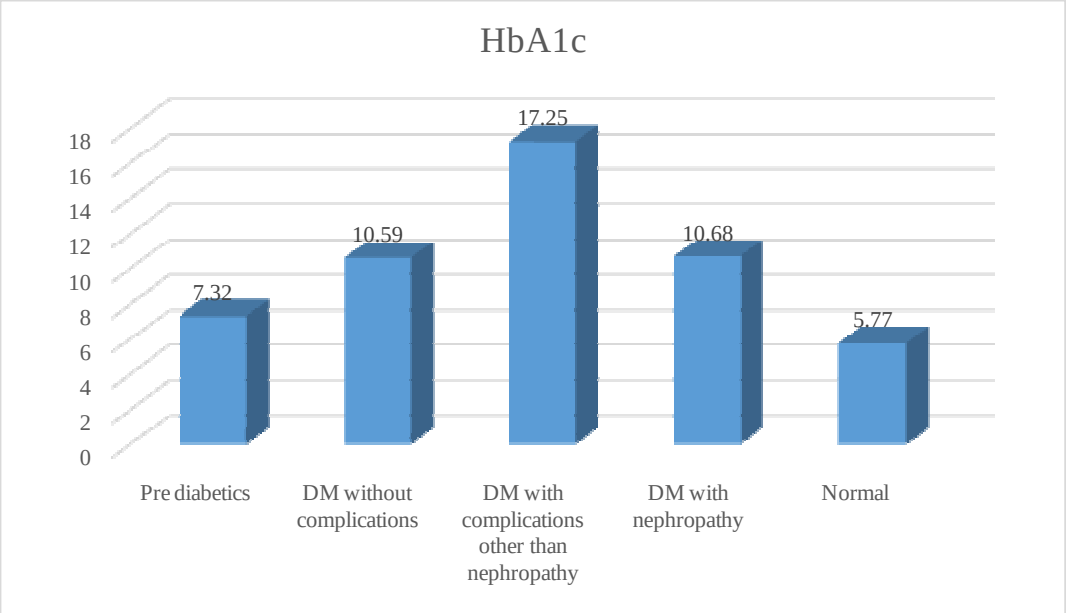


Figure 13: Bar diagram showing mean HbA1c among different groups

Mean HbA1c was highest among diabetics with complications like neuropathy, retinopathy than nephropathy. This difference was statistically significant.

Table 15 :Analysis with respect to eGFR

	Pre diabetics	DM without complications	DM with complications other than nephropathy	DM with nephropathy	Normal	Total (n=120)	P value
eGFR	101.27 ±32.3	102.35±33.9	93.77±22.79	28.94±15.44	120.42 ±38.8	97.16 ± 40.97	<0.0001**

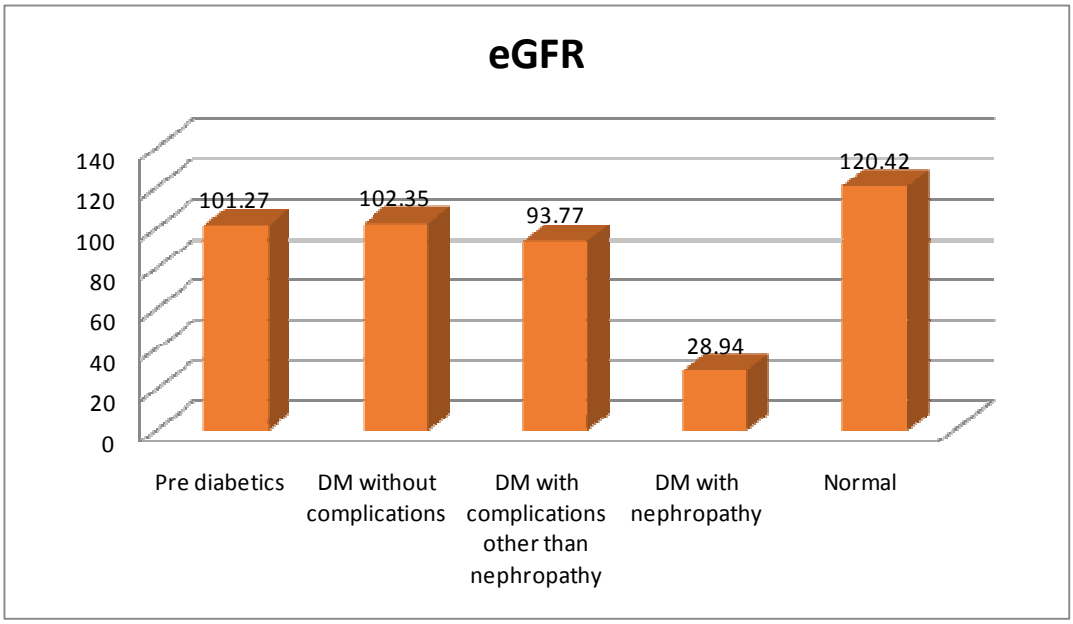


Figure14 : Bar diagram showing mean eGFR among different groups

Mean eGFR was highest among controls than in prediabetics, diabetics with out complications and diabetics with neuropathy and retinopathy. This difference was statistically significant. Also as known eGFR is lowest among diabetics with nephropathy.

Table 16: Analysis with respect to Uric acid levels

	Pre diabetics	DM without complications	DM with complications other than nephropathy	DM with nephropathy	Normal	Total (n=120)	P value
Uric acid	4.76± 1.48	3.85±1.27	6.61±1.81	6.3±2.66	3.89±1.36	4.51± 1.81	<0.0001 **

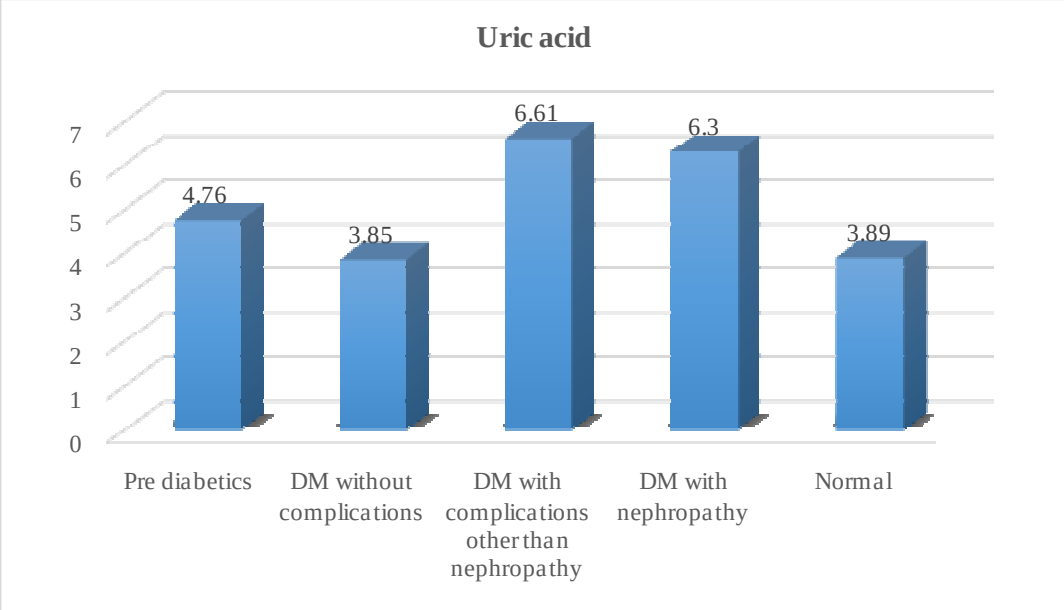


Figure 15 : Bar diagram showing Mean uric acid levels among different groups

Mean Uric acid was highest among Diabetic with complications. Nephropathy patients had lower uric acid than in retinopathy and neuropathy. On average Uric acid is initially increased in prediabetic state and reduced in diabetes without complications. This difference was statistically significant.

Table17: Association between Uric acid and Sex

		Sex		Total
		Female	Male	
Uric acid	<3 Hypouricemia	13	17	30
	3 to 7	56	62	118
	> 7 Hyperuricemia	4	8	12
Total		73	87	160

P value = 0.621

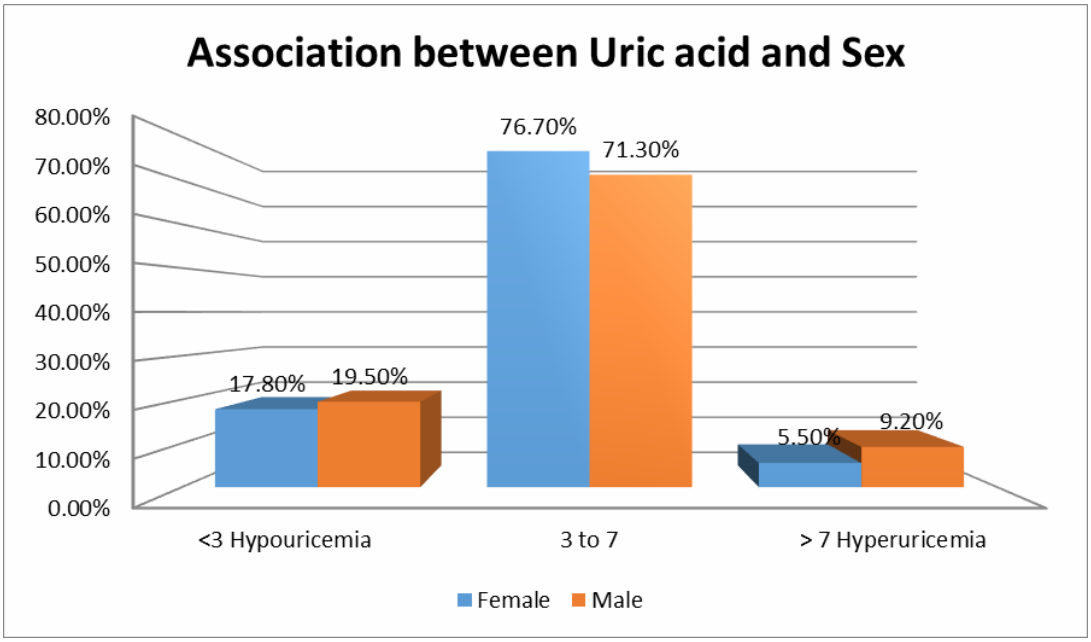


Figure 16: Bar diagram showing association between uric acid and sex

There was no significant difference between uric acid levels and Sex.

Table 18: Association between Uric acid and Duration of Diabetes Mellitus

		Duration of DM			Total
		<5 yrs	5 to 10 yrs	>10 yrs	
Uric acid	<3 Hypouricemia	12	3	2	17
	3 to 7	37	10	8	55
	> 7 Hyperuricemia	3	1	4	8
Total		52	14	14	80

P value = 0.158

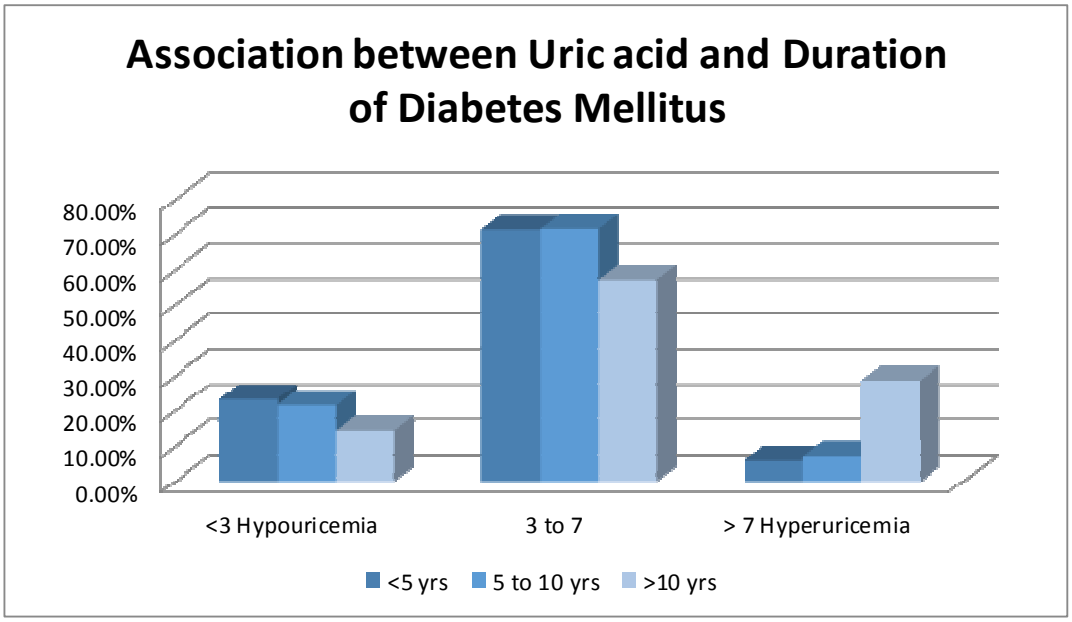


Figure 17: Bar diagram showing Association between Uric acid and Duration of Diabetes Mellitus

There was no significant difference between uric acid levels and duration of diabetes..

Table 19:Association between Uric acid and BMI

		BMI			Total
		18.5 to 24.99	**>25**	**<18.5**	
Uric acid	**<3 Hypouricemia**	9	18	3	30
	3 to 7	38	72	8	118
	> 7 Hyperuricemia	3	9	0	12
Total		50	99	11	160

P value = 0.769

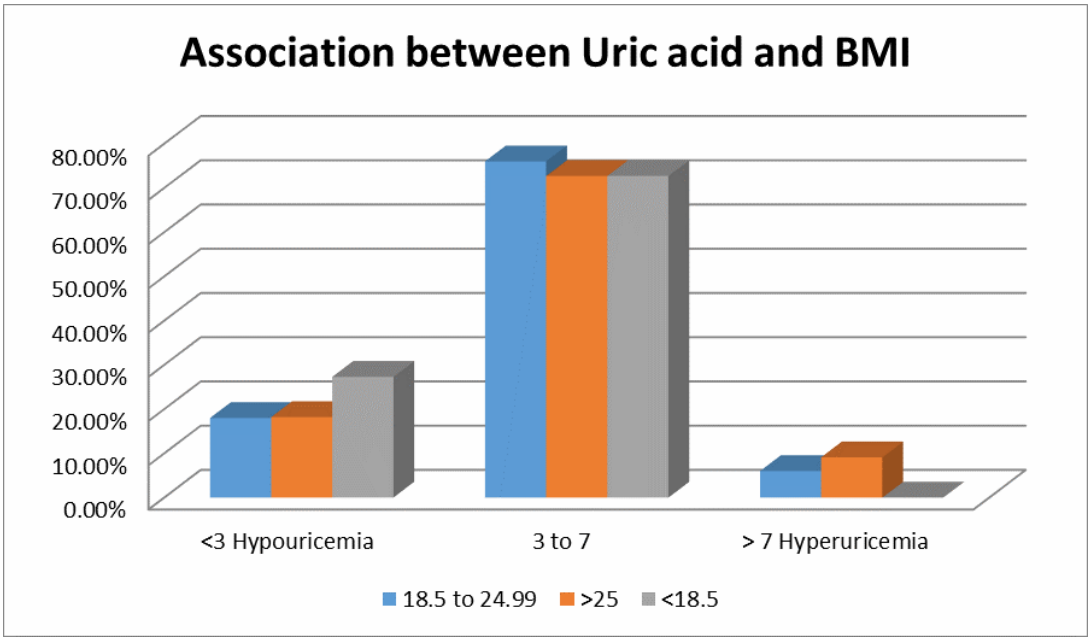


Figure 18 : Bar diagram showing association between uric acid and BMI

There was no significant association between uric acid and BMI.

Table 20: Mean uric acid levels with respect to HbA1c among different groups

		Uric acid levels				
		DM without complications	**DM with Complications other than nephropathy**	**Prediabetics**	**Normal**	**DM with Nephropathy**
HbA1c	**<8**	4.61 ± 0.79	3.2	4.73 ± 1.51	3.89 ± 1.36	5.36 ± 2.47
	>8	3.72 ± 1.31	5.1 ± 2.01	4.84 ± 1.46	-	6.66 ± 2.73
p value		0.389	0.366	0.836	-	0.924

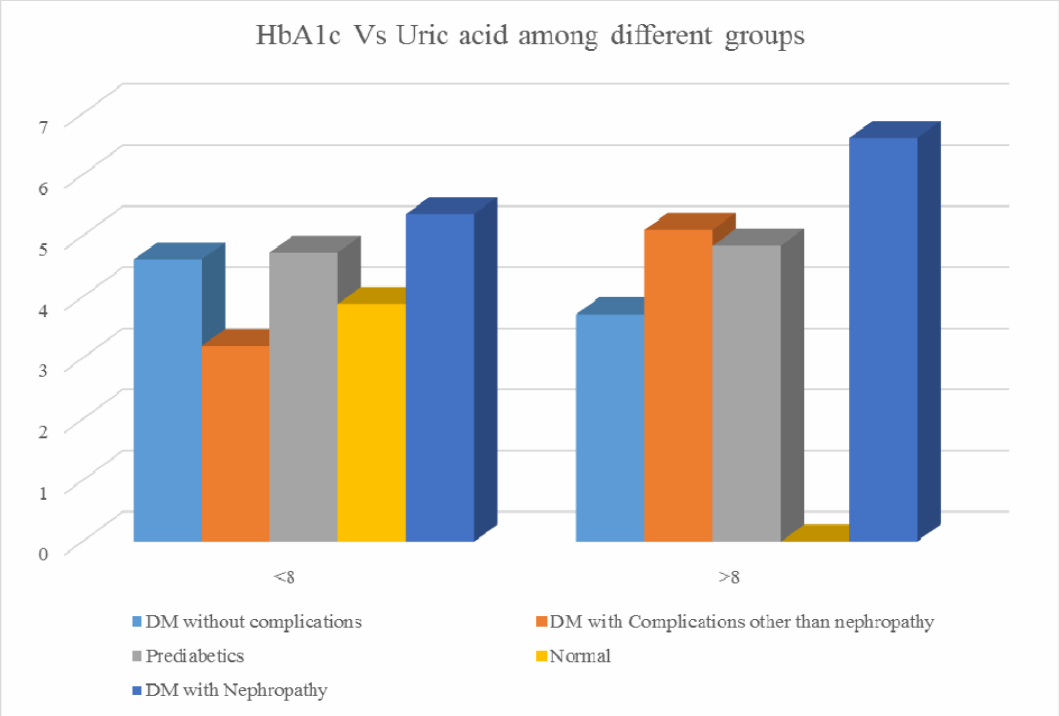


Figure 19: Bar diagram showing association between and Uric acid and HbA1c

It was observed that values in relation to uric acid was not statistically significant.

Table 21: Association between Urine albumin and Uric acid

		Uric acid		Total
		<5	>5	
Urine Albumin	1	14 (12.4%)	13(27.7%)	27
	2	3(2.7%)	6(12.8%)	9
	3	2(1.8%)	2(4.3%)	4
	Nil	83(73.5%)	22(46.8%)	105
	traces	11(9.7%)	4(8.5%)	15
Total		113	47	160

p = 0.0005**

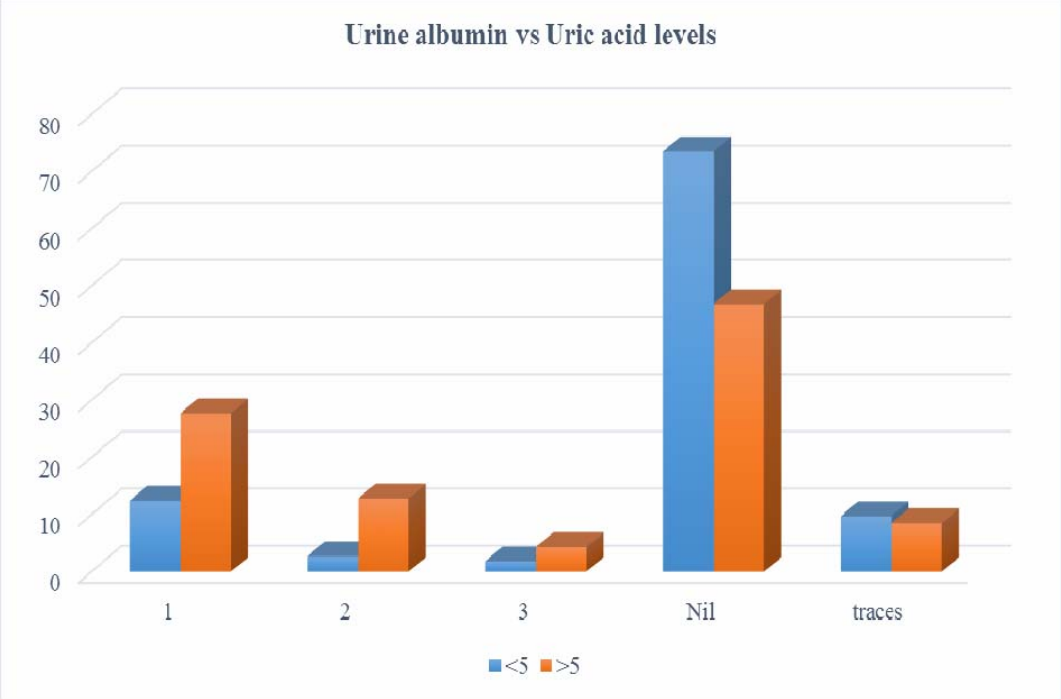


Figure 20: Bar diagram showing Urine albumin and Uric acid association

It was observed that >50% of subjects with urine albumin had uric acid levels >5. This observation was statistically significant.

Table 22 : Association between Uric acid and groups

		Groups					Total
		DM without complications	DM with Complications other than nephropathy	Prediabetics	Normal	DM with Nephropathy	
Uric acid	<3 Hypouricemia	11	2	4	10	3	30
	3 to 7	28	18	33	29	10	118
	> 7 Hyperuricemia	1	2	3	1	5	12
Total		40	22	40	40	18	160

p = 0.013*

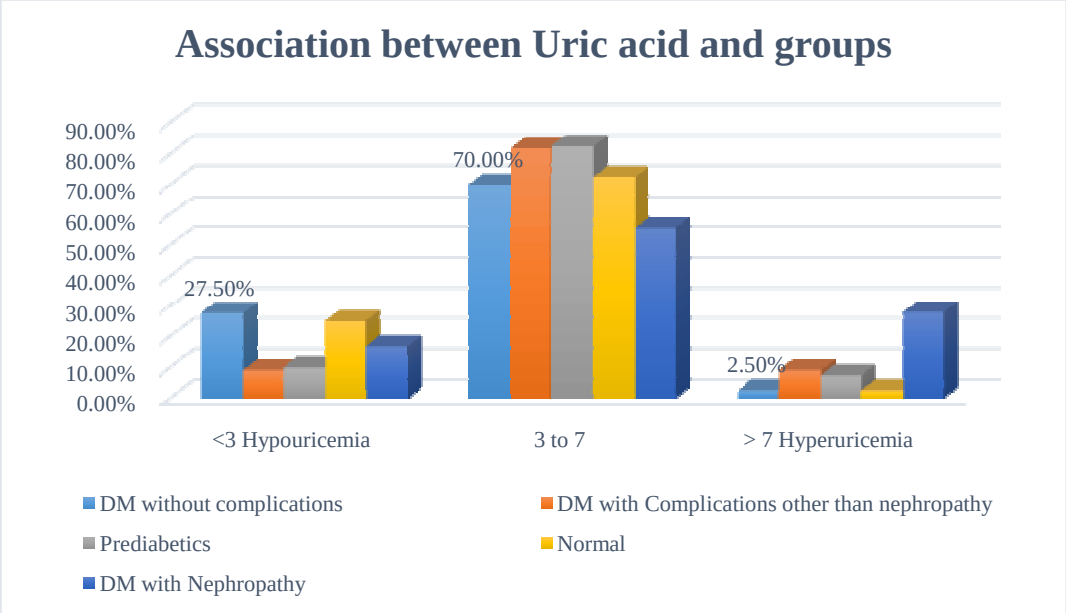


Figure 21: Bar diagram showing association between uric acid and groups

It was observed that Hypouricemia was common among DM without complications and Hyperuricemia was common among DM with nephropathy. But there was no significant association between the groups.

DISCUSSION

The present study of association of uric acid levels in patients with diabetes and its chronic microvascular complications was done in the department of General Medicine, R.LJalappa Hospital, affiliated to Sri devaraj urs medical college, Tamaka, Kolar from December 2012 to October 2014.

The patients were divided into study group (patients with type 2 DM without microvascular complications, type 2 DM with microvascular complications and prediabetics) and control group (normal patients). The objective of the study was to study the association of uric acid levels in subjects of prediabetes, diabetes and its chronic microvascular complications.

The main finding of our study was that plasma uric acid levels were raised in diabetic patients with retinopathy and neuropathy than with nephropathy. The lowest plasma uric acid levels were found in diabetic patients without microvascular complications. Plasma uric acid levels were clearly decreased in diabetic patients without microvascular complications than the control group.

Studies have shown that uric acid is significantly elevated in prediabetic stages and low in diabetes, and rises again after the development of renal insufficiency[53].

A negative association of plasma uric acid with overt diabetes was found earlier in several other studies [12,19,27,35-36,52-56]. Our results endorse this finding in spite the methodological differences and the different diagnostic criteria for diabetes mellitus used in these studies.

Hyperuricemia has been found to be linked with obesity and insulin resistance, and subsequently with type2 diabetes. Further potentially important biological effects of uric acid relate to endothelial dysfunction by bringing antiproliferative effects on

endothelium and impairing nitric oxide production and inflammation, through raised C reactive protein expression, although these issues are considered controversial. Uric acid may play a role in immune activation with consequent increased chemokine and cytokine expression[54].

In a prospective study of 10,000 Israeli men, it was found that diabetic men had lower plasma uric acid levels than "prediabetic" men, who had higher levels than nondiabetic men[57, 58].In our study plasma uric acid levels were clearly reduced in diabetics without microvascular complications patients when compared with nondiabetic patients while the levels increased after development of complications.

Derek G Cook et al, showed that there was a positive relationship between serum glucose and serum uric acid concentrations, at higher levels of glucose serum uric acid levels decreased[59]. That study concluded that serum uric acid probably reflects the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyperglycemia and glycosuria.

In our study Mean HbA1c was highest among diabetics with complications like neuropathy, retinopathy than nephropathy. Mean uric acid level differed in different groups and is not significant.

Table 23: Association between Uric acid among different groups

			Groups					Total
			DM without complications	DM with Complications other than nephropathy	Prediabetics	Normal	DM with Nephropathy	
Uric acid	<5	Count	36 (90%)	12 (54.5%)	25 (62.5%)	34 (85%)	6 (33.3%)	113
	>5	Count	4 (10%)	10 (45.5%)	15 (37.5%)	6 (15%)	12 (66.7%)	47
Total		Count	40	22	40	40	18	160

p <0.0001**

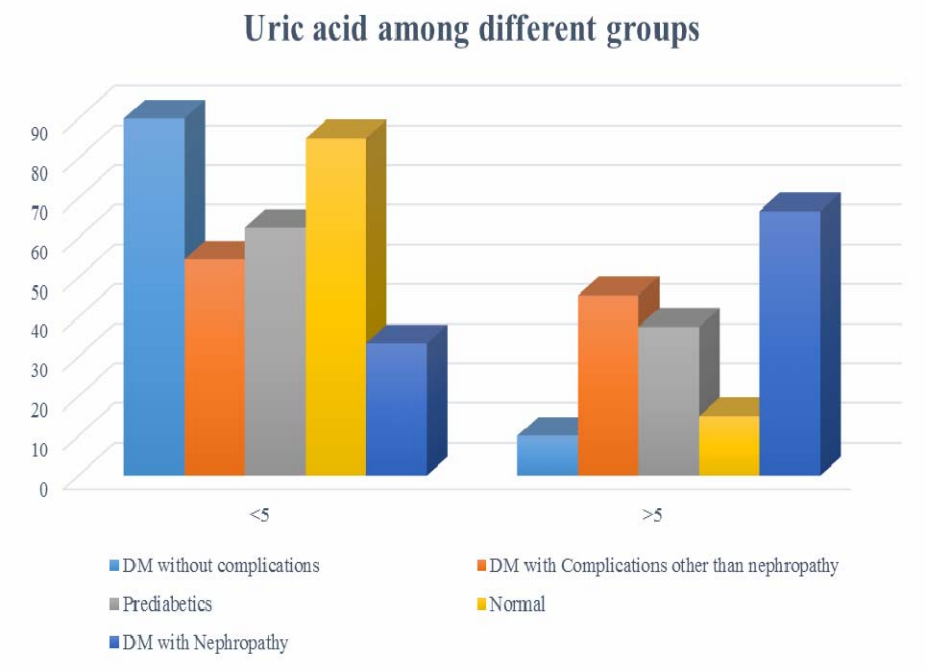


Figure 22: Bar diagram showing Uric acid among different groups

It was observed that Uric acid was >5mg/dl is found among 47 people totally. most of them are of Diabetic complications patients and prediabetics. This observation was statistically significant.

Serum uric acid >5 mg/dl should be considered as a red flag, at risk for developing Type 2 DM and these are more prone for development of complications.

In this study serum uric acid >5 mg/dl is found in 66.7% of diabetics with nephropathy , 45.5% of diabetics with retinopathy and neuropathy, 37.5% of prediabetics compared to 15% in controls and 10% in diabetics without complications.

CONCLUSION

- Plasma uric acid levels were elevated in diabetic patients with retinopathy and neuropathy than with nephropathy.
- The lowest plasma uric acid levels were found in diabetic patients without microvascular complications.
- Plasma uric acid levels were clearly decreased in diabetic patients without microvascular complications than the control group.
- Triglycerides are significantly increased in diabetics than in controls and prediabetics. HDL cholesterol is significantly decreased in diabetics than in controls and prediabetics.
- Mean eGFR was highest among controls than in prediabetics, diabetics with out complications and diabetics with neuropathy and retinopathy. This difference was significant. Also as known eGFR is lowest among diabetics with nephropathy.
- It was observed that Hypouricemia was common among DM without complications and Hyperuricemia was common among DM with nephropathy. But there was no significant association between the groups.
- Serum uric acid >5 mg/dl should be considered as a red flag, at risk for developing Type 2DM and these are more prone for complications development.

SUMMARY

Of the 160 patients presented to department of General Medicine, R.L Jalappa Hospital, affiliated to Sri devaraj urs medical college, Tamaka, Kolar , 40 patients with type 2 DM without microvascular complications ,40 patients of type 2 DM with microvascular complications, 40 prediabetics and 40 healthy control group were selected for the study.

Study was made in detail regarding age, sex, history, glycemic status, duration of diabetes and investigations.

Age distribution of the study ranged from 26-96 years. There was no significant difference among cases and controls in relation to age and sex.

There was no significant difference between uric acid levels and duration of diabetes and also uric acid and BMI.

HbA1c was highest among diabetics with complications like neuropathy, retinopathy than nephropathy.

The present study showed that there is a mild decrease in serum uric acid levels in patients with Type 2 DM without complications than controls.

The present study also showed that patients shown to have prediabetis had high serum uric acid values than healthy controls.

Routine estimation of uric acid among diabetics and healthy individuals will help the clinician to find out the changing trends of uric acid levels which is likely to be influenced by control of blood sugar and progression of diabetes. Increasing levels of uric acid are found in diabetics with microvascular complications. Such cases should be carefully monitored for microvascular complications.

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ANNEXURES

PROFORMA

STUDY OF ASSOCIATION OF URIC ACID LEVELS IN PATIENTS WITH DIABETES AND ITS CHRONIC MICROVASCULAR COMPLICATIONS

Candidate Name : Dr Aparna.G (PG MD Gen medicine)

Guide: Dr . Lakshmaiah . V

PATIENT DETAILS:

Name:

Age:

Sex: M F

IP /OP no:

Duration of diabetes:

Symptoms:

Polyuria:

Polydipsia:

Polyphagia:

Chest pain:

Swelling of extremities:

Breathlessness:

Headache:

Vomiting:

Fever:

Numbness/ Paraesthesia:

Blurring of vision:

Decreased urine output:

Personal history:

Smoking:

Alcohol:

Drug abuse:

Dietary habit:

Family history of diabetes:

Clinical examination:

Pulse:

Blood pressure:

Respiratory rate:

Temperature:

Weight :

Height :

Body mass index:

Pallor:

Cyanosis/ icterus/ clubbing:

Pedal oedema:

Cardiovascular system:

Respiratory system:

Abdomen:

Central and peripheral nervous system:

Ankle Reflex :

Vibration test :

Sensation in lower limbs :

Evidence of peripheral vascular disease:

Opthal examination including Fundus:

eGFR :

Investigations:

RBS:

FBS:

PPBS:

HbA_1c:

Serum creatinine:

Blood urea nitrogen (BUN):

Serum uric acid:

Urine albumin:

Urine sugar:

Urine deposits:

Lipid profile: Cholesterol: Triglyceride: HDL: LDL:

Complete blood count:

Chest X-ray:

ECG:

Echocardiogram:

USG abdomen: