SERUM URIC ACID LEVEL IN TYPE 2 DIABETES MELLITUS

Dissertation submitted

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CHENNAI – TAMILNADU

CERTIFICATE

This is to certify that this dissertation titled "**SERUM URIC ACID LEVEL IN TYPE 2 DIABETES MELLITUS**" submitted by **DR.S.SENTHUR RAJA PANDIAN** to the Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfilment of the requirement for the award of M.D. Degree Branch I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

DR. D.D. VENKATRAMAN, M.D.,
Additional Professor,
Department of Medicine,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

DR. NALINI GANESH. M.D.,
Professor and Head,
Department of Medicine,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

Madurai
29.12.06

DECLARATION

I **DR. S. SENTHUR RAJA PANDIAN** declare that I carried out this work on "**SERUM URIC ACID LEVEL IN TYPE 2 DIABETES MELLITUS**" at Department of General Medicine, Government Rajaji Hospital during the period of January 2005 – February 2006. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M.D. Degree examination in General Medicine.

Govt. Rajaji Hospiptal, **DR.S.SENTHUR RAJA PANDIAN**

Madurai.

29.12.06

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CONTENTS

ABBREVIATIONS

IDDM	-	Insulin Dependent Diabetes Mellitus
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
CAD	-	Coronary Artery Disease
JNC	-	Joint National Committee
IHD	-	Ischemic Heart Disease
G.D.M	-	Gestational Diabetes Mellitus
SUA	-	Serum Uric Acid
HT	-	Hypertension
BMI	-	Body Mass Index
WHR	-	Waist Hip Ratio
DOD	-	Duration of Diabetes
B.S	-	Blood sugar
P.G	-	Plasma Glucose
MI	-	Myocardial Infarction
I	-	Ischemia
S.D	-	Standard Deviation
IFG	-	Impaired Fasting Glucose
IGT	-	Impaired Glucose Tolerance
CVD	-	Cardio Vascular Disease

INTRODUCTION

Cardiovascular disease is an epidemic of modern society. Type 2 diabetes mellitus is an epidemic in India for the past few decades. Diabetes mellitus is the most important risk factor associated with two to four fold increased incidence of coronary artery disease.

Nearly 120 years have elapsed since uric acid was first described as a potential risk factor in the development of cardiovascular disease[1].

Hyperuricemia is one of the component of syndrome – X^2. Serum uric acid is a potential cardiovascular disease risk factor has ballooned in the last several years with numerous abstracts and research papers, multiple editorials, and review articles.

The four major risk factors for CAD viz., hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking which were present in Framingham's cohort are difficult to explain among Indians with CAD. CAD in Indians is present even with low cholesterol level. Obesity, systemic hypertension, hypercholesterolemia is associated with NIDDM, as a result of insulin resistance state.

Much but not all epidemiological research identifies hyperuricemia is a independent risk factor for the development of cardiovascular disease and renal disease, particularly patients with hypertension or congestive heart failure and in women[3].

Some have found a significant and specific independent association between uric acid level and cardiovascular mortality and morbidity, while others have come to an opposite conclusion. Thus despite abundant epidemiological evidence, the role of increased serum uric acid and cardiovascular risk is controversial.

Here an attempt has been made to study the level of serum uric acid in type 2 diabetes mellitus and the correlation between elevated serum uric acid level and the component of metabolic syndrome like obesity, hypertension, dyslipidemia.

AIMS AND OBJECTIVES

1. To identify the level of uric acid in patients with type 2 diabetes mellitus.

2. To identify whether any association exist between age, sex, anthropometric measurements (BMI, WHR), hypertension, dyslipidemia and coronary artery disease with serum uric acid level.

REVIEW OF LITERATURE

Diabetes mellitus – Type 2

The previously used terminology is non insulin dependent diabetes mellitus (NIDDM). Type 2 diabetes mellitus begins in the middle age or after 40 years. It is not uncommon to come across the development of diabetes in third decade itself in our country.

Diagnosis

The national diabetes data group (1979) and World Health Organization (1985) have issued diagnostic criteria for diabetes mellitus[4].

1. Symptoms of diabetes and random blood sugar concentration ≥ 200mg/dl.
2. Fasting plasma glucose ≥126mg/dl.
3. 2 hr plasma glucose (postprandial) ≥200mg/dl during an oral glucose tolerance test.
4. IGT - Impaired Glucose Tolerance is present when fasting level is ≤126 and 2. hr value in the range of 140-200mg/dl.
5. IFG – Impaired Fasting Glucose when the fasting level is >110 and ≤126 and 2 hr value is ≤140mg/dL.

Table 1: Diagnostic Criteria for diabetes mellitus

Category	Fasting p.g	2 hr p.g.
Normal	<110mg/dl	<140mg/dl
Diabetes	≥126mg/dl	≥200mg/dl
IFG	110-125mg/dl	-
IGT	-	140-199mg/dl

Importance of IFG and IGT

There is no clear consensus (with current evidence) on whether IFG and IGT should be classified as disease, but they clearly represent risk factors and risk markers for diabetes and CVD, respectively. Both IGT and IFG are similarly associated with increased risk of diabetes, but IGT is more strongly associated with CVD outcomes. Risks are higher when IFG and IGT coexists. Lifestyle interventions are highly effective in delaying or presenting the onset of diabetes in people with IGT and may reduce CVD and total mortality.

Epidemiology

The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades. Although the prevalence of both type 1 diabetes mellitus, and type 2 diabetes mellitus is expected to rise more rapidly in the feature because of increasing obesity and reduced activity levels. In 2000 the

prevalence of diabetes mellitus was estimated to be 0.19% in people <20 years old, 8.6% in people >20 years old. In individuals >65 years the prevalence of diabetes mellitus was 20.1%. The prevalence is similar in men and women throughout most age ranges but is slightly greater is men >60 years. The prevalence of type 2 diabetes mellitus and its harbinger IGT, is highest in Pacific island, intermediate in our country and United States and relatively low in Russia and China. This variability is likely due to genetic, behavioural, and environmental factors.

On analysis of the trend in the epidemiology of diabetes, Mccarty and Zimmet (1994) have estimated, by projection, the change of prevalence of diabetes around the globe by 2010 (Table 2).

Table 2: Estimated of number of Diabetic patients in millions*

	Type of Diabetes	1994	2000	2010
GLOBAL	IDDM	11.50	18.10	23.70
	NIDDM	98.90	157.30	215.60
	Total	110.40	175.40	239.30
INDIA	IDDM	1.80	3.31	4.70
	NIDDM	15.70	28.99	42.20
	Total	17.30	32.30	46.90
CHINA	IDDM	0.57	1.40	2.26
	NIDDM	7.20	18.40	29.59
	Total	7.77	19.80	31.85
USA	IDDM	1.48	1.67	1.86
	NIDDM	12.30	13.90	15.57
	Total	13.78	15.57	17.43
JAPAN	IDDM	0.39	0.40	0.41
	NIDDM	5.18	5.30	5.40
	Total	5.57	5.70	5.81

*Ref: Maccarty and Zimmet (1994)

This table showing High prevalence of Diabetes in India and contributes 5.08% of Diabetes world wide. Japan has relatively Low incidence of Diabetes.

Pathogenesis of type 2 diabetes mellitus

Insulin resistance and insulin secretion are central to the development of type 2 diabetes mellitus.

1. Beta cell dysfunction

Beta cell dysfunction is the major genetic component contributing to the development of type 2 diabetes mellitus[5]. The beta cell mass is mildly reduced especially when obesity is taken in to account. Type 2 diabetes mellitus is a genetically programmed failure of the beta cell to compensate for insulin resistance[6].

2. Insulin resistance

The variability is insulin response was first documented by Himsworth. Who subsequently used glucose insulin sensitivity test to assess individual sensitivity to insulin[7]. Over three decades later, Reaven and coworkers (1966) introduced a new method for estimation of insulin mediated glucose uptake by peripheral tissues. Further Reaven aroused widespread interest on insulin resistance and disorders associated with it through his banting oration of 1987.

3. Genetic factors

Charack, and Susrutha, the ancient Indian physicians who first described Madhu Meha (diabetes) had stipulated that the disorder was genetically determined and hence incurable.

Results from cross sectional and longitudinal studies of families mono and dizygotic twins, offspring of diabetic parents both or either sibs and other first degree relatives of diabetic probands strongly indicate the genetic basis of diabetes[8].

4. Acquired factors

Although both impaired beta cell secretion and insulin resistance are basically inherited, acquired factors play an important role in the unmasking of type 2 diabetes mellitus. They are

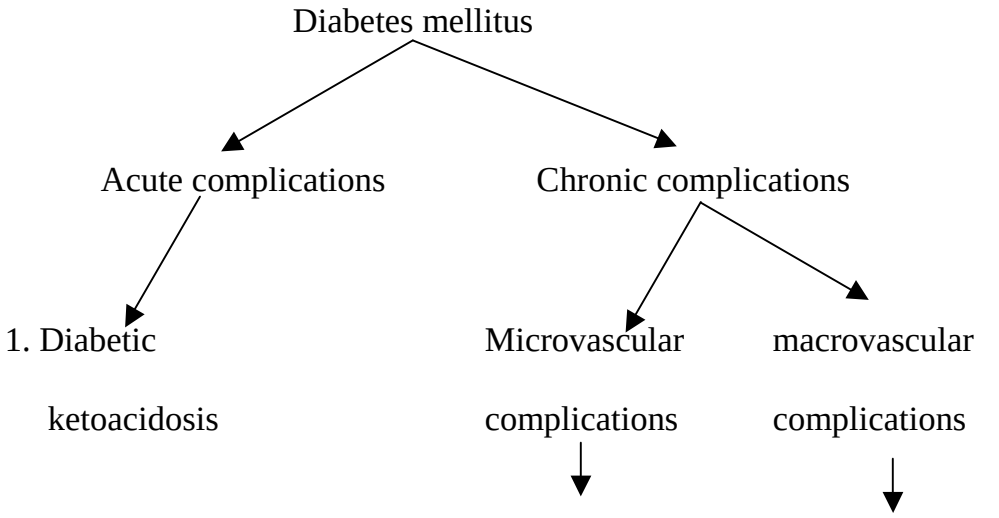
- Beta cell cytotoxic chemical or viruses
- Autoimmunity
- Ageing, obesity
- TNF α, leptin
- Physical inactivity
- Diet

Risk factors for type 2 diabetes mellitus (ADA, 2004)[9]:

- Family history of diabetes
- Obesity BMI >25kg/m^2
- Physical inactivity
- Previously identified IFG and IGT
- History of GDM
- Systemic hypertension (Bp: ≥140/90mmHg)
- HDL level ≤35mg/dl, TG level ≥250mg/dl
- Poly cystic ovarian disease or acanthosis nigricans
- History of vascular disease

(Source: Adopted form American Diabetes Association (ADA) : 2004)

Complications of diabetes mellitus



Others

1. Gastrointestinal –gastroparesis, diarrhea
2. Genitourinary – uropathy / sexual dysfunction
3. Dermatological – acanthosis nigricans.
4. Infections
5. Cataract
6. Glaucoma

INSULIN RESISTANCE

Other names

- Metabolic syndrome
- Syndrome X
- Reaven syndrome

History

In 1973, patients with anginapectoris with angiographically normal coronary arteries were recognized receiving the label of syndrome X and patients with this syndrome were also reported to have hyperinsulinemia.

In 1988, Reaven postulated the link between insulin resistance, obesity, systemic hypertension and dyslipidemia (high TG, Low HDL) and cardiovascular disease.

Again in 1993, Reaven gave an expanded definition of syndrome X.

In 1989 Kaplan also discussed deadly quartet associated with insulin resistance – central obesity, hypertension, impaired glucose tolerance, and hypertriglyceridemia.

In 1991, Defronzo and Ferraninni discussed the multifaceted nature of insulin resistance syndrome. Subsequent addition to the syndrome were small dense LDL, increased proinsulin, microalbuminuria and hyperuricemia[10].

In 1995, Godsland and Steavenson raised the question: Is insulin resistance a syndrome or a tendency?[11].

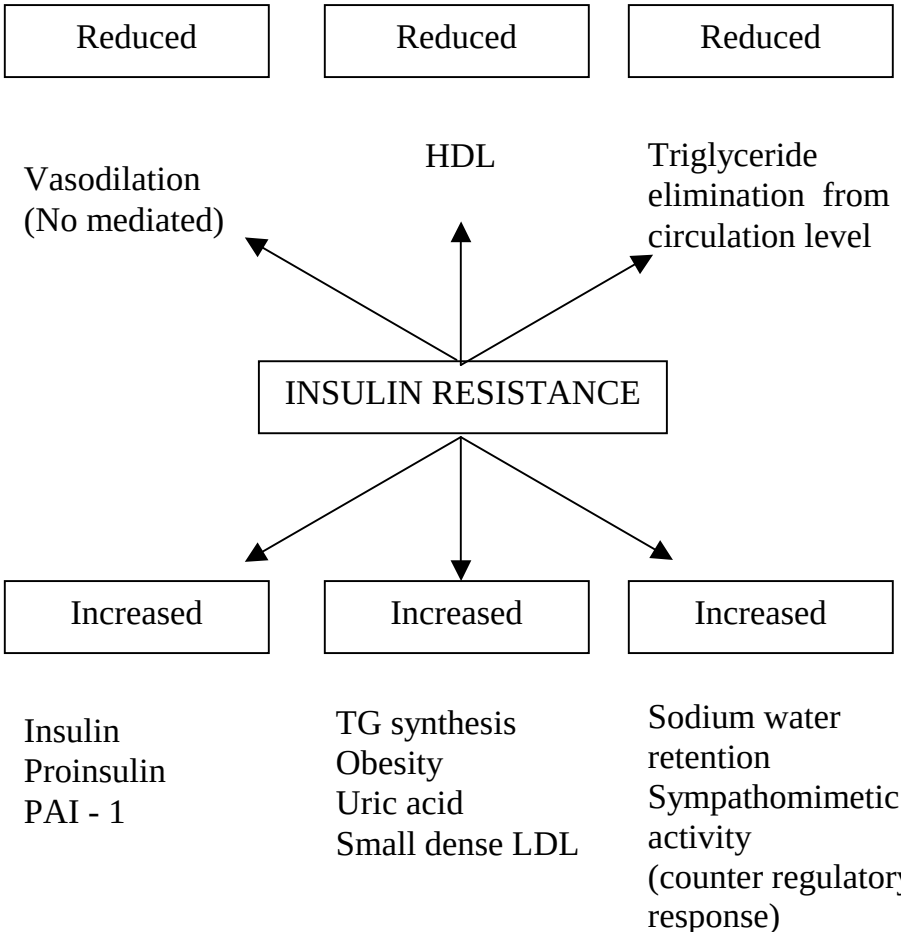
In 1995, Yudkin collaborated with Barker's group to study the relationship between low birth weight and glucose and insulin metabolism in 4 year old urban Indian children, and they told importance to be given to events in later life too for the genesis of insulin resistance syndrome. The development of cardiovascular risk is an ongoing process and prevention is possible through life style modification[12].

In 1996, Steinberg established that obesity / insulin resistance is associated with endothelial dysfunction[13].

In 1997, Marita showed insulin receptor defect in the erythrocytes of obese Asian Indian women with acanthosis nigricans and exhibiting impaired glucose tolerance[14].

In 1998, Misra has discussed the current perspective of insulin resistance syndrome and its relevance to Indians[15].

Table 3: Effects Of Insulin Resistance*



*Ref. Godsland IF, Stevenson JC [1995]

Criteria

According to ATP III guidelines metabolic syndrome is defined by the presence of three of the following:

Table 4: Criteria for metabolic syndrome[4]:

No	Risk factors	Defining level
1	Abdominal obesity: waist circumference	>102cm in men >88 cm in women
2	Triglyceride	≥150mg/dL
3	HDL cholesterol	<40mg/dL in men <50mg/dL in women
4	Blood pressure	≥130/85mmHg
5	Fasting plasma glucose	≥110mg/dL

In addition, following components are also included or expanded in metabolic syndrome:

- Raised apo B
- **HYPERURICEMIA**
- Increased small dense LDL particles
- Microalbuminuria
- Increased plasminogen activator inhibitor (PAI – 1)
- Poly cystic ovarian syndrome
- Increased fibrinogen

Types

Two different types of insulin resistance have been described in adults.

1. **Type A:** which affects young women and it is characterised by severe hyperinsulinemia, obesity, and features of hyperandrogenism. It is due to genetic defect in insulin receptor number and function[16].
2. **Type B:** which affects middle aged women and it is characterised by severe hyperinsulinemia, features of hyperandrogenism, and autoimmune disorders. It is due to antibodies against insulin receptors[17].

OBESITY

Obesity is an increasing problem in the developed and developing countries. Obesity is a state of excess adipose tissue mass. The distribution of adipose tissue in different anatomic depots also has substantial implications for morbidity specifically intra abdominal and abdominal subcutaneous fat have more significance than subcutaneous fat present in the buttocks and lower extremities. This distinction is most easily made by determining the waist hip ratio, with a ratio >0.9 in women and >1.0 in men being abnormal.

Table 5: Classification of Obesity

No.	Waist hip ratio	Type of obesity	Prognosis
1	0.8 or less	Pear shaped obesity	Good
2	0.9 or greater	Apple shaped obesity	Bad

Measures to assess obesity

- Body mass index (BMI)
- Skin fold thickness
- Densitometry
- CT or MRI
- Electrical impedance

The most widely used method to assess obesity is body mass index, it calculated by using formula.

BMI = weight (kg)/height^2 (m)

Table 6: Classification of Body Status on BMI

Classification	BMI	Risk of co morbidity
Underweight	<18.50	Low
Normal	18.50-24.99	Average
Overweight	>25.00	
Preobese	25.00-29.99	Increased
Obese class I	30.00-34.99	Moderate
Obese class II	35.00-39.99	Severe
Obese class III	>40.00	Very severe

Body mass index for the midpoint of all heights and frames among both men and women range from 19 to 26 kg/m^2, at a similar body mass index, women have more body fat than men. Based on unequivocal data of substantial morbidity, a body mass index of 30 is most commonly used as a threshold for obesity in both men and women. Large scale epidemiological studies suggest, that all cause, metabolic, cancer, and cardiovascular morbidity begin to rise when body mass index are ≥25, suggesting that the cut off for obesity should be lowered. A body mass index between 25 to 30 should be viewed as medically significant and worthy of therapeutic intervention, especially in the presence of other risk factors such as hypertension, glucose intolerance.

Table 7: Relative risk of health problems associated with obesity

Greatly Increased risk	**Moderately increased risk**	**Low risk**
Insulin resistance	CAD	Ca breast, colon endometrium
Type 2 diabetes mellitus	Hypertension	Polycystic ovarian syndrome
Gall stones dyslipidemia	Osteoarthritis (knee)	Impaired fertility
Breathlessness	Hyperuricemia (gout)	Low back ache
Sleep apnea		Faetal defects with maternal obesity

Overall cardiovascular risk

The degree of risk from diabetes can be categorized with reasonable accuracy by taking into account.

1. The level of blood sugar and the presence of insulin resistance.
2. The presence of micro and macrovascular complications of diabetes.
3. The coexistence of other cardiovascular risk factors

The major cardiovascular risk factors indicated in JNC – 7 report are[18]:

- Hypertension
- Smoking
- Obesity
- Physical inactivity
- Diabetes mellitus
- Dyslipidemia

→ **Metabolic syndrome (or) Insulin Resistance**.

- Microalbuminuria or estimated GFR <60ml/mt
- Age>55 for men >65 for women
- Family history of premature cardiovascular disease <55 for men, <65 for women

URIC ACID

Uric acid is the final breakdown product of the PURINE degradation in humans. Mammals other than primates oxidize uric acid further to allantoin. It is a weak acid with Pka of 5.75 and 10.3.

Purines

Nucleic acids (DNA, RNA) which are required for the storage and expression of genetic information is made of polynucleotide chain. Nucleotides are the building blocks of nucleic acid. These nucleotides are composed of purine or a pyramidine base, a pentose monosaccharide and one, two or three phosphate groups.

Purines are heterocytic nitrogen contain bases whose ring contain both carbon and other elements (heteroatoms). The various purine bases are: Adenine, Gaunine, Hypoxanthine and Xanthine.

Addition of a pentose sugar to a purine base produces a nucleoside. The sugar may be ribose or 2-dioxy ribose. Nucleotides are mono, di or tri phosphate esters of nucleotides.

Synthesis of purines

Humans can synthesize purines from amphibolic intermediates. Purines are not dietarily essential. The purines are contributed by 3 sources:

- Denovo synthesis
- Dietary nucleic acids
- Cellular nucleic acid

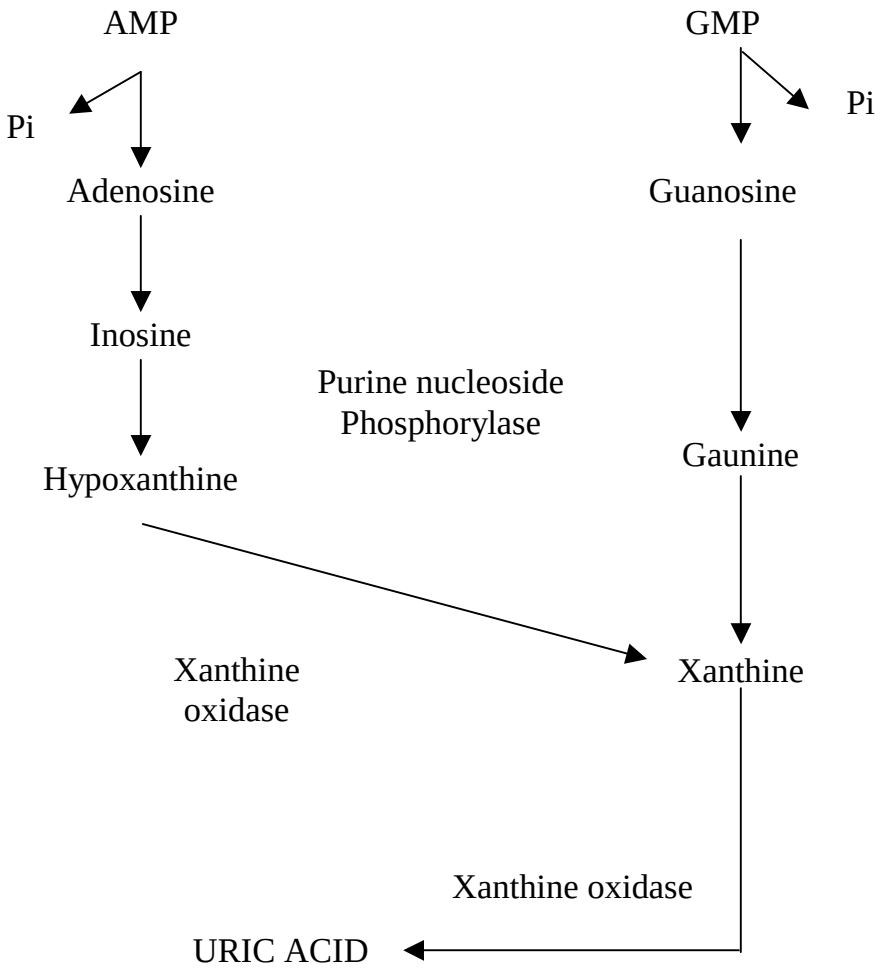
Denovo purine synthesis

The atoms of purine ring are contributed by compounds including amino acids (aspartic acid, glycine and glutamine), Co_2 and derivatives of tetrahydrofolate. The purine ring is constructed by 11 step process that results in the formation of inosine mono phosphate (IMP). IMP can be converted to either adenosine monophosphae (AMP) or guanine mono phosphate (GMP). The first step involves synthesis of phosphoribosyl pyrophosphate (PRPP). Next step involves synthesis of phosphoribosyl amine from PRPP and glutamine and is catalysed by the enzyme amido phosphoribosyl transferase. This is the rate limiting step in purine synthesis.

Degradation of purines – production of uric acid

The end product of purine catabolism in humans is uric acid. In mammals other than higher primates uricase enzyme converts uric acid to a water soluble product, allantoin. Humans lack this enzyme.

URIC ACID SYNTHESIS FROM PURINES



Uric acid is produced only in liver and small intestine because only these two tissues contain the enzyme Xanthine oxidase.

Salvage pathway for purines

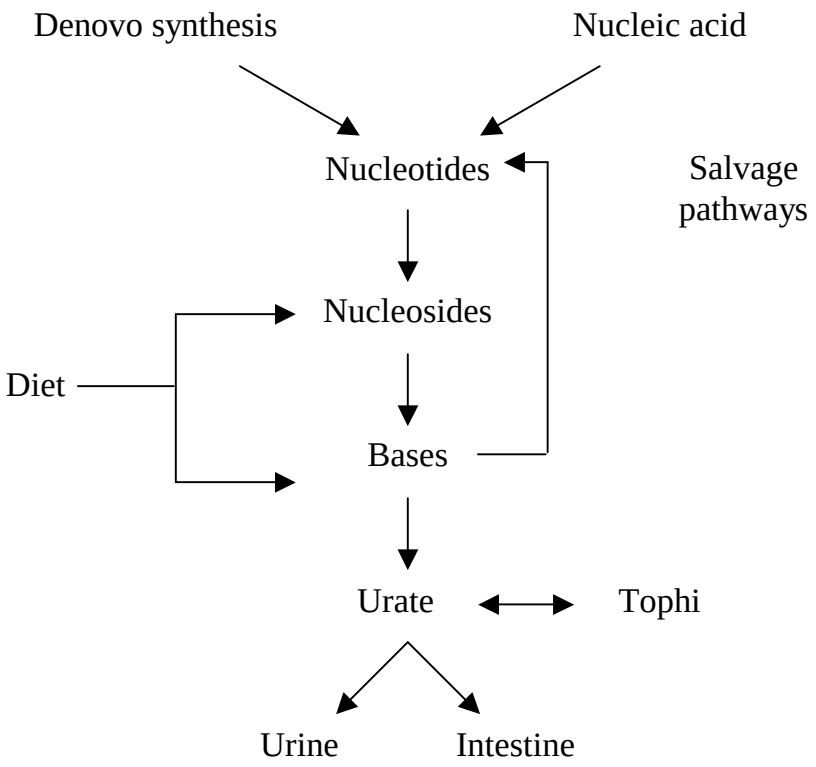
All the purines are not degraded to uric acid. Purines that result from normal turn over of cellular nucleic acids can be reconverted to nucleotides and used by the body. Two enzymes Adenine phosphoribosyl transferase (APRT) and Hypoxanthine gaunine phosphoribosyl transferase (HGPRT) are involved. Deficiency of HGPRT causes Lesch – Nyhan syndrome.

Uric acid metabolism

The amount of urate in the body is the net result of the amount produced and amount excreted. The sources for uric acid are denovo synthesis of purines, purines from cellular nucleic acid, and purines from dietary nucleic acid.

The total dynamic urate metabolic pool in the body is about 1200mg expressed as uric acid of which denovo synthesis contributes about 300-600mg and dietary purines contributes about 600-700mg. Each day about 2/3 of the uric acid are excreted in the urine and 1/3 is destroyed by bacterial uricolysis in the gut.

THE TOTAL BODY URATE POOL



Urate anion is freely filtered at the renal glomerulus and kidney handles urate by following

1. Glomerular filtration of 100% of the filtered load
2. Proximal tubular absorption – of 99% of filtered load.
3. Tubular secretion of about 50% of filtered load.
4. Post secretary reabsorption of about 40% of filtered load.

The net clearance of uric acid is around 10% of the filtered load and is in the range of 6 to 11 ml / min / 1.73m^2.

Plasma urate levels

As mentioned urates, the ionized forms of uric acid, predominate in plasma extracellular fluid and synovial fluid with approximately 98% existing as monosodium urate at pH 7.4. Mono sodium urate is easily dialysed from plasma. Binding of urate to plasma proteins has little physiological significance.

Plasma is saturated with monosodium urate at a concentration of 415 μmol/L (6.8 mg/dl) at 37°C. At higher concentrations, plasma is therefore supersaturated, creating the potential for urate crystal precipitation. However, precipitation sometimes does not occur even at concentrations as high as 4800 μmol/L (80mg/dl), perhaps because of the presence of solubilizing substances in plasma.

Plasma urate levels rises at puberty with female values being lower than in men until menopause after when it gradually rises to male value. It decreases during pregnancy. Hyperuricemia is a characteristic and often an early feature of pre-eclampsia.

Extrinsic factors, particularly diet, plumbism, the prevalence of high ethanol intake in the community and diseases like malaria, thalassemia can affect plasma urate distribution in different populations. Epidemiological studies show significant variations in plasma urate concentrations between different ethnic groups. For example, Polynesians have higher values than western Europeans and Americans. This illustrates the genetic, presumably

polygenic aspects in the control of serum uric acid. Other epidemiological studies emphasize the importance of environmental factors of purine, protein and alcohol intake. For example Gress and Zollner (1991) showed that the cumulated frequency of plasma urate rose from 6.2mg/dL to about 9.0mg/dL between 1962-1971 in association with improved nutritional state of Bovarian population.

The frequency distribution of plasma urate values based on asymptomatic population is only approximately Gaussian, with an excess of higher values due to inclusion of some asymptomatic hyperuricaemic subjects. Ignoring the slight asymmetry of the frequency distribution and defining normality as the mean value ±2SD above the mean, normal upper limit of 7.0mg/dL (420μmol/dL) for mean and 6.0mg/dL (360μmol/L) for women is widely adopted.

Hyperuricemia

Hyperuricemia can result from increased production or decreased excretion of uric acid or from a combination of the two processes. When sustained hyperuricemia exists, plasma and extracellular fluids are super saturated with respect to urate and total body urate is increased.

Physiochemically, hyperuricemia is the concentration of the urate in the blood that exceeds the solutions limits of monosodium urate in plasma, 415 mol/l (6.8mg/dl). In epidemiological studies, hyperuricemia is defined as the

mean plus 2 standard deviations of values determined from a randomly selected healthy population. Hyperuricemia is present between 2.0 and 13.2% of ambulatory adults and some what more frequently in hospitalized.

Classification of hyperuricemia

Reduced renal excretion

1. An inherited defect in renal handling of urate.
2. Renal glomerular disease
3. Renal tubular dysfunction
    a. Tubulo interstitial nephritis
    b. Competition for tubute excreting mechanism (Lactic acidosis and keto acidosis)
    c. Drugs (Diuretics, Pyrazinamide, Ethambutol etc)
4. Other conditions in which renal tubular dysfunction has been proposed

    a. Hypertension
    b. Sickle cell anemia
    c. Myxedema
    d. Lead nephropathy

Increased uric acid production

1. Dietary sources
2. Hypoxanthine phosphoribosyl transferase deficiency
3. Increased phosphoribosyl pyrophosphate activity
4. Glycogen storage disorders
5. Hereditary fructose intolerance

6. Myeloproliferative diseases
7. Chronic hemolytic anaemias
8. Extensive psoriasis
9. Gauchers disease

The following abnormalities are commonly associated with but not casually related to Hyperuricemia:

i. Obesity
ii. Dyslipidemia (usually type 4 with increased VLDL and normal cholesterol)
iii. Hypertension
iv. **Insulin resistance**
v. Ischemic heart disease

These patients may display features of metabolic syndrome.

CAUSES OF HYPERURICEMIA IN TYPE 2 DIABETES MELLITUS

1. DIETARY HABITS:

An increase is serum urate level may occur is type 2 DM in various situations like purine rich diet such as non vegetarian diets-liver, anchovies, kidney, sardines, sweat breads and yeasts.

2. EXERCISE:

Exercise acutely increase serum urate levels by excessive degradation of skeletal muscle ATP.

3. ALCOHOL:

Alcohol increases serum urate level by accumulation of organic acids (betahydroxy butyrate, acetoacetate, lactate) that compete with the urate for tubular secretion and accelerated breakdown of ATP by liver is increased. (Beer contains high uric acid)

4. OBESITY:

Various mechanisms play role in increase in serum urate by obesity. Like anabolic effects of tissues because of insulin resistance, increase in denovo biosynthesis of purines, decreased excretion and increased breakdown.

5. DEHYDRATION:

Dehydration can impair uric acid excretion by decreased filtration and secretion and sometimes with acidosis by competition of H^+ ions for excretions. Starvation again causes accumulation of organic acids that compete for the excretion of urate for tubular secretion.

SYSTEMIC HYPERTENSION:

There are various studies regarding association of systemic hypertension with the elevated uric acid level. Probable mechanism suggested is impaired excretion of urate because of intrinsic renal defect in hypertension[19,20].

LACTIC ACIDOSIS AND DIABETIC KETO ACIDOSIS:

Dehydration and pre renal azotemia both can impair filtration and secretion of urate leading to retention and also these may casue diminished reabsortion of the uric acid. Again in the setting of acidosis H^+ ions compete with uric acid leading to enhanced reabsortion and retention.

HYPER GLYCEMIA:

Both uric acid and glucose levels are positively related to body mass index. The association of uric acid in relation to glucose reflects the biochemical interaction between serum glucose metabolism and purine metabolism.

RENAL INSUFFICIENCY:

Decreased urate filtration contributes to the hyperuricemia of renal insufficiency. But the correlation between Bun, serum Creatinine and serum uric acid concentration per unit of GFR increases progressively with renal insufficiency. The tubular secretory capacity tends to be preserved, the tubular reabsorbtive capacity is decreased and extrarenal clearance of uric acid increases as the renal damage becomes more severe.

DRUGS:

They mainly act by decreasing the uric acid excretion by competitive inhibition of uric acid excretion. Salicytates and nictotinic acid directly compete with the urate for tubular secretion.

Diuretics, L-dopa, Pyrazinamide, Ethambutol, Cyclosporine decreases the secretion of urate in the tubules.

URIC ACID AND INSULIN RESISTANCE

Nearly 120 years have elapsed since uric acid was first described as a potential factor in the development of cardiovascular disease[1].

The actual mechanism of hyperuricemia found in many diabetic patient is not known, but different theories have been presented.

Quiniones (1995) observed that hyperuricemia is a frequent finding in insulin resistant states. He found that insulin induces changes in fractional uric acid and sodium excretion co related with one another and physiological hyperinsulinemia acutely reduces urinary uric acid and sodium excretion in coupled patients. They also observed that in insulin resistant individuals compensatory hyperinsulinemia imposes a chronic antinatriuretic and anti uricosuric pressure on the kidney.

Moriwaki (1995) studied the effects of glucose infusion on the renal clearances of uric acid, xanthine and oxypurinol and found that the effect was not related to osmotic diuresis, but induced by glycosuria / and / or hyperglycemia.

Muscelli and Coworkers (1996) observed that effect of insulin or urinary excretion in normal subjects and found that hyperinsulinemia caused a significant decrease in the urinary excretion of uric acid.

Tkac I studied 91 type 2 DM patients, 57 patients with myocardial infraction were compared with control group of 34 diabetics without clinical or electrocardiographic sings of IHD. Higher mean serum uric acid level in infarction group was associated with increasing age and serum creatinine levels. It was associated with elevated TGL, BMI and hypertension.[21].

Woo study results found positive association between serum uric acid concentration and BMI, with systolic and diastolic BP, urea, creatinine, fasting

glucose 2 hour insulin, TGL, apolipoprotein B in men. Similar but fewer associations were seen in women with additional positive associations with age. The study suggests that serum uric acid may be a marker for the presence of an adverse cardiovascular risk profile[22].

Wannamethee concluded in their study that serum uric acid is not a truly independent risk factor for coronary art disease. Increased serum uric acid appears to be an integral part of the cluster of risk factors associated with the insulin resistance syndrome that include central obesity, increased TG level, and serum cholesterol level[23].

Pearl study concluded high molar equivalent serum antioxidant capacity (MESA) between diabetics and non diabetics showed uric acid as a free radical scavenger is NIDDM[24].

They are certain clinical clustering groups with increased cardiovascular risk, which have associated hyperuricemia. They are

1. African American patient group
2. Patients group with excessive alcohol consumption.
3. Hypertensive patient groups
4. Non diabetic patient groups with accelerated arteriosclerosis.
5. Congestive heart failure patients groups with ischaemic cardiomyopathy.
6. **Metabolic syndrome patients group.**
7. Renal disease patients group and

8. Patients group taking diuretics

Each of the clustering group has metabolic mechanisms that may help to explain which serum uric acid may be elevated.

MECHANISM:

Type 2 Diabetes mellitus is strongly associated with hyperuricemia.

Potential mechanism involved in the association of hyperuricemia and type 2 Diabetes mellitus include the following:

1. Altered renal sodium handling causes decreases renal blood flow and diminishes uric acid excretion
2. Decreased GFR stimulating urate absorption
3. Microvascular disease resulting is local tissue ischemia
4. Ischemia associated with increased lactate production.
5. Ischemic induces increased xanthine oxidase production.

Other factors which may contribute are alcohol abuse Lead intoxication, obesity, insulin resistance and diuretic use.

Mechanism of Hyperuricemia in Hyperinsulinemia

Hyperinsulinemia

↓

Altered renal

Sodium handling

↓

↑ Arterial pressure

↓ renal blood flow

↓ Uric acid excretion

↓

Hyperuricemia

(Adapted from ward, Lancet 1998)

Increased serum uric acid has been found to predict the development of renal insufficiency in individuals with normal function[20].

In type 2 Diabetes mellitus hyperuricemia seems to be associated with metabolic syndrome and with early onset or increased progression to overt nephropathy, whereas hyperuricemia was associated with hyper filtration and a later onset or decreased progression to overt nephropathy[25].

Hyperuricemia has been associated with increasing Body mass index (BMI). The role of leptin is possibly being a regulator of serum uric acid level in humans[26].

From the review the following conclusion was arrived:

Determining the truth in medical science is a difficult business. Serum uric acid may or may not be an independent risk factor because its linkage to other risk factors is so strong. However there is not much correlation regarding its role as a marker or risk factor that is clinically significant and relevant.

Hyperuricemia should alert the clinician to an overall increased risk of cardiovascular disease. Elevations of uric acid > 4 mg/dl should be considered a **"Red flag"** in those patients at risk for cardiovascular diseases and should alert the clinician to strive and utilize a global risk reduction programme to reduce the complications of atherogenic process.

MATERIALS AND METHODS

Setting	:	Government Rajaji Hospital and Madurai Medical College, Madurai
Collaborative Department	:	Department of Biochemistry, Madurai Medical College, Madurai
Study Design	:	Descriptive analytical study
Period of study	:	January 2005 to February 2006
Sample size	:	70 cases
Ethical committee approval	:	The present project was approved by the Ethical committee

Inclusion criteria

1. Patients with type 2 diabetes mellitus (patients were taken irrespective of their glycemic control and their duration of diabetes)
2. Patients who were above 40 years were included
3. Both sexes were included

Exclusion criteria

1. Patients with renal failure
2. Pregnancy and lactating mothers.
3. Patients who were on long term diuretics and steroid.
4. Patients who were regularly consuming alcohol

5. Patients who were on anti metabolite and chemotherapy drugs
6. Patients who had hepatic and metabolic disorders.
7. Patients who had PVD / CVA / Pulmonary tuberculosis.
8. Renal transplant patients.

Controls

Subjects who were above 40 years and had normal blood sugar and who met the above exclusion criteria.

Consent

The study group thus identified by the above criteria (inclusion and exclusion) were first instructed about the nature of study. Willing participants were taken up after getting a written informed consent from them.

Materials

Thus a total of 70 cases who satisfied the inclusion and exclusion criteria above were taken up for subsequent study. 30 age and sex matched subjects were kept as control.

Conflict of interest

There was no conflict of interest.

Financial support

Nil

Limitations

1. Because of limited resources GTT, Hb A1c, leptin level, C peptide assay, plasma insulin assay could not be tested.
2. Xray chest was not performed in every case due to technical limitation.
3. Only serum uric acid levels were analysed, urinary excretion and urate clearance was not done.

Methods

Selected socio-demographic, clinical, laboratory data were elicited from the patients and controls and recorded in proforma.

1. Socio demographic data
    - ❖ Age
    - ❖ Sex
2. Clinical data
    - ❖ Body weight
    - ❖ Height
    - ❖ BMI, waist hip ratio (WHR)
    - ❖ Systolic diastolic blood pressure
    - ❖ Cardiovascular risk factors
    - ❖ Clinical examination

3. Laboratory data

- ❖ Blood urea estimation was done manually by using diacetyl monoxime method (DAM).
- ❖ Serum creatinine estimation was done by using COBAS auto analyzer.
- ❖ Serum uric acid was done by using semi auto analyzer.

Principle

Uric acid is converted by uricase to allantoin and hydrogen peroxide in the presence of peroxidase (POD) oxidiz`es the chromogen to a red coloured compound which is read at 500mm.

$$\text{Uric acid} + 2H_2O + O_2 \xrightarrow{\text{Uricase}} \text{Allantoin} + Co_2 + H_2O_2$$

$$2H_2O_2 + \text{4aminophyrine} + \xrightarrow{\text{DHBS POD}} \text{Red quinolone} + H_2O + Hcl$$

(DHBS 3, 5 – Dichloro – 2 hydroxy benzene sulphonic acid)

Statistical analysis

Data was entered in Microsoft excel spread sheet and analysed statistically using standard statistical software. Student ‘t’ values was applied for significance. Significance was considered, if the ‘p’ value was below 0.05.

DEFINITIONS USED IN THE PRESENT STUDY

1. Diabetes mellitus

Criteria for the diagnosis diabetes mellitus (modified form of American Diabetes Association, 2004)[4].

1. Symptoms of diabetes + (R) blood glucose ≥200mg/dL
2. Fasting plasma glucose ≥126mg/dL
3. Two hour plasma glucose (postprandial) ≥ 200mg/dL during an oral glucose tolerance test

2. Hyperuricemia

Hyperuricemia is defined as serum uric acid level ≥8mg/dL in males and ≥6mg/dL in females[4].

3. Body mass index

It is estimated by using the following formula: weight (kg)/ height^2 (m)

4. Obesity

Obesity is usually defined as body mass index >30, body mass index between 25 to 30 is known as overweight. Body mass index between 25 to 30 should be viewed as medically significant, especially in the presence of other risk factors like hypertension, diabetes. Large scale epidemiological studies suggest that cardiovascular morbidity begins to rise when body mass index ≥ 25, suggesting that the cut off for obesity should be lowered.

Waist hip ratio

The waist is measured by taking a circumference that gives the narrowest measurement between the ribcage and the iliac crest. The hip measurement is taken by measuring at a level that gives the maximal measurement of hip over the buttocks. It is a simple, and convenient measurement that is unrelated to height, correlates closely with body mass index and waist hip ratio is an approximate index of intra abdominal fat mass and total body fat.

Waist hip ratio >0.9 in women and >1.0 in men being abnormal.

Conversion of blood glucose to plasma glucose:

John Neale (1999) described the conversion of blood glucose to plasma glucose by using this formula:

Plasma glucose = whole blood glucose × 1.12

RESULTS

The total number of subjects included in this study was 100. Among those 100 subjects, 70 were cases (type 2 Diabetes mellitus) and 30 were controls (Non Diabetic).

Table 8: Introduction

	CASES	**CONTROLS**
Total No	70	30
Gender	M = 46 F = 24	M = 18 F = 12
Age (years)	41 to 75	43 to 73
Mean Age (years)	60	56
BMI	19.4-29.2	18.4-26.0
WHR	0.76-1.14	0.76-1.10
FBS (mg/dl)	128-196	84-122
PPBS (mg/dl)	154-323	136-184
SUA (mg/dl)	3.0 to 8.1	2.7 to 5.5

Analysis of cases and controls with respect to age:

The age of the subjects in the study group ranged from 41 to 75 years. The mean and standard deviation for age of the cases and controls were 60.1± 8.82 and 56.27 ± 7.84 respectively, there was no significant difference among the cases and controls with reference to the age. The distribution of cases and controls in relation to age is provided in table 9 given below:

Table 9: Cases and controls in relation to age

Age group	Cases*		Controls	
	No	%	No	%
40-50	11	15.7	8	26.7
51-60	23	32.9	12	40.0
61-70	27	38.6	9	30.0
71-80	9	12.8	1	3.3
Mean	60.01		56.27	
S.D	8.82		7.84	

*p= 0.0529 (not significant)

Analysis of cases and controls with respect to gender:

Among 70 cases studied, there were 46 males and 24 females. Among 30controls there were 18 males and 12 females. The details are given in table 10 provided below:

TABLE: 10 Cases and Controls in relation to gender

	CASES*		**CONTROLS**	
Sex	No	%	No	%
Male	46	65.7	18	60
Female	24	34.3	12	40
Total	70	100	30	100

*p = 0.7503 (not significant)

The sex composition of the study group and control group does not differ significantly.

Analysis of cases and controls with respect to B.M.I:

Among 70 cases and 30 controls screened for BMI, non were obese. The mean and standard deviation for BMI of the cases and controls were 24.1 $\pm$ 2.98 and 21.6 $\pm$ 2.3 respectively. The details are shown in table 11 given below:

Table: 11 Cases and control with respect to BMI

	CASES*		**CONTROLS**	
BMI	No	%	No	%
<25	38	52.9	26	66.7
$\geq$25	32	47.1	4	33.33
Total	70	100	30	100
Mean	24.1		21.6	
S.D	2.98		2.3	

*p = 0.0002 (significant)

The BMI of the study group was significantly higher than that of the control group.

Blood sugar distribution among cases:

The details of fasting and post prandial blood sugar distribution among the cases are shown in the table 12 given below:

Table: 12 (F) BS and (PP) BS among cases

Bl sugar	Mean	S.D
(F) BS	144.28	38.21
(pp) BS	212.01	42.13

The Mean and Standard deviation for fasting blood sugar was 144.28 $\pm$ 38.21 similarly for post prandial blood sugar was 212.01 $\pm$ 42.13 among diabetics. Thus showing that their diabetic status was under poor control.

Distribution of Cases and Controls In Relation to Selected Cardiovascular Risk Factors

Analysis of cases and controls in relation to selected cardiovascular risk factors are provided in Table 13 given below.

Table 13: Selected Cardiovascular risk factors

Risk factor	CASES		CONTROLS	
	No	**%**	**No**	**%**
Family history				
Yes*	17	24.3	5	16.7
No	53	75.7	25	83.3
*p VALUE 0.5622 (Not Significant)				
Smoking among males				
Yes**	18	40	5	27.8
No	28	60	13	72.2
**p VALUE 0.5746(Not Significant)				
Hypertension				
Yes ***	15	21.4	4	13.3
No	55	78.6	26	86.7
***p VALUE 0.5044 (Not Significant)				

There was no significant difference between cases and controls in relation to selected cardiovascular risk factors.

Distribution of cases and controls in relation to serum uric acid Level (SUA):

Serum uric acid in the study population and control varied from 3.0 to 8.1 and 2.7 to 5.5 mg/dl respectively. The mean and standard deviation of uric acid among cases was 5.08 $\pm$ 1.42 while in control it was 3.55 $\pm$ 0.62 respectively.

The details are shown in the table 14 given below:

Table 14: Serum Uric Acid level in diabetics and controls

	Cases		**Controls**	
Serum uric acid*	**Mean**	**S.D**	**Mean**	**S.D**
	5.08	1.42	3.55	0.62

*p value : 0.0001 (significant)

The serum uric acid level of diabetics was very much elevated compare with controls and it was highly significant.

Analysis of Hyperuricemia in cases and controls

Hyperuricemia is defined as SUA level ≥8mg/dL in males and ≥6mg/dL in females. 7 cases had hyperuricemia while none in controls. The results are displayed in table 15 given below:

Table 15: Hyperuricemia in cases and controls

Hyperuricemia	Cases				Controls			
	No	**%**	**Mean**	**S.D**	**No**	**%**	**Mean**	**S.D**
+*	7	10	7.54	0.5	0	-	-	-
-	63	90	4.81	1.21	30	100	3.55	0.62

*p value = 0.0001 (significant)

This table clearly shows that the prevalence of hyperuricemia more in diabetic patients when compared to controls.

Analysis of Gender distribution with serum uric acid among the cases

The mean value of serum uric acid was 4.77±1.4 in males and 5.68±1.3 in females and details are given table 16 below.

Table 16: Serum uric acid values in relation to gender among cases

Sex	No	Mean	S.D	p value
Male	46	4.77	1.4	0.0196
Female*	24	5.68	1.3	

* p value = 0.0196 (significant)

In the study group mean uric acid values were higher in females than males and the difference was statistically significant.

Serum uric acid value in relation to BMI in cases

The mean value of serum uric acid was 6.35±0.82 in those with BMI>25, it was significantly higher when compared to those having BMI<25. The mean value of serum uric acid in BMI < 25 was 4.01±0.81.

The details are shown in table 17 given below:

Table 17: Uric acid with regard to BMI among cases

BMI	No	Mean	S.D
< 25	38	4.01	0.81
> 25*	32	6.35	0.82

*p value = 0.0001 (significant)

Mean uric acid level was positively correlated with BMI

Serum uric acid value in relation to waist hip ratio (WHR)

Uric acid level increases with increasing WHR. The WHR abnormality was considered in 36 cases based on, WHR as 1.0 and above for men, 0.90 and above for women and correlated with uric acid level, it was significant. The details are shown in table 18 given below.

Table 18: Waist hip ratio and Hyperuricemia

WHR abnormality	No	Mean	S.D
Yes *	36	6.12	0.72
No	34	3.97	0.43

*p value = 0.0001 (significant)

Smoking and serum uric acid among the cases (only in males)

The mean value of serum uric acid level was slightly higher among smokers 4.80±1.12 when compared to non smokers 4.56±1.06, but the difference was not significant statistically. This is shown in table 19 given below:

Table 19: Uric acid values in relation to smoking (only in males)

Smoking	No	Mean	S.D
Yes*	18	4.80	1.12
No	28	4.56	1.06

*p value = 1.5472 (not significant)

Serum uric acid values in hypertensive patients

The mean serum uric acid level in the hypertensive group (6.15±0.92) was significant more than non hypertensive group (5.15±1.40) in the cases and the results are shown in the table 20 given below:

Table 20: Serum uric acid values in relation to hypertension

HT	No	Mean	S.D
Yes*	15	6.15	0.92
No	55	4.79	1.4

*p value = 0.0001 (significant)

Serum uric acid level in relation to lipid profile abnormality

The mean serum uric acid level in patients with lipid profile abnormality was 6.49±0.85, while it was 4.52±1.20 in patients without lipid profile abnormality, and it was highly significant. The results are shown in table 21 given below.

Table 21: Serum uric acid value in relation to lipid profile abnormality:

Lipid profile abnormality	**No**	**Mean**	**S.D**
Yes*	20	6.49	0.85
No	50	4.52	1.2

*p value = 0.001(significant)

Table 22: CAD and Hyperuricemia

Type of CAD	No of Patients	Total no of hyperuricemia	Sex	%
Ischemia	10	2	IM + IF	20 %
Infarction	5	3	0 M + 3F	60%

This table was showing number of patients with ischemia – 10

Of these only 2 had hyperuricemia with equal sex distribution (1:1)

Number of patients with infarction was 5

Of these only 3 had hyperuricemia, all are female patients (0:3)

Percentage of hyperuricemia in infarction is higher than in ischemia, and female patients were more involved in CAD than males in relation to hyperuricemia.

Serum uric acid value in relation to duration of diabetes

Mean value of serum uric acid level was higher in longer duration (8-12 years) of diabetes 6.34±0.84, when compared to shorter duration (2-4years) of diabetes 3.88±0.93.

This is shown in table 23 given below:

Table 23: Duration of Diabetes and Hyperuricemia

DOD	No	Mean	S.D
2-4 yrs	13	3.88	0.93
4-8 years	34	4.69	1.27
8-12 years*	23	6.34	0.84

*p value = 0.001 Significant

Uric acid level increases with increasing duration of diabetes and it was statistically significant.

DISCUSSION

Diabetes is the most common risk factor for cardiovascular disease, and it is present in nearly 25% adults and increases in prevalence with age.

Hyperuricemia is one of the component of metabolic syndrome[2]. “In the absence of gout the presence of hyperuricemia in patients with type 2 diabetes mellitus is an important marker as well as an added risk factor for atherosclerosis”.

In this study the relation between serum uric acid level and diabetes was examined. Uric acid is a marker for CAD in combination with other risk factors among diabetics.

Though uric acid level and age was independent, it is possible that duration of the illness may have an impact on uric acid levels.

In the present study females have higher uric acid level when compared to males. The mean uric acid value in males 4.71±1.4 while in females it was 5.68±1.3, and the difference was statistically significant in this study. The possible reasons for such difference may be attributable to increased BMI and increased WHR among women.

In the present study serum uric acid correlated well with body mass index (BMI). The mean uric acid in those subjects with BMI>25 were higher than those with BMI < 25 (6.35±0.82 Vs 4.01±0.81) and the difference was statistically significant[27,28].

Rathman (1997) assessed the various components of insulin resistance syndrome in young black and white adults. They concluded body mass index showed strongest positive correlation with the uric acid among insulin resistance components[29].

Waist hip ratio is an important measure of obesity, especially central obesity. Intra abdominal fat has significant implication for morbidity than subcutaneous fat present in buttocks and extremities.

Abdominal obesity is a component of metabolic syndrome[2]. Abdominal obesity >102cm in men and >88cm in women is abnormal. In this study patient with higher waist hip ratio has higher uric acid level when compared with low waist hip ratio.

The mean uric acid value in patients with waist hip ratio abnormality and patients without waist hip ratio abnormality was 6.12±0.72 and 3.97±0.43 respectively and the difference was statistically significant.

Strong epidemiologic data have linked serum uric acid to hypertension in humans[19] and experimental animal data suggests hyperuricemia causes hypertension[30,31]. The Olivetti heart study had shown a independent positive association between serum uric acid and development of hypertension[32].

When the level of serum uric acid in hypertensive patients was compared with non hypertensive patients in cases, the difference was significantly higher

in the present study. The present observation on uric acid among diabetic hypertensives is in consistent with other studies.

Elevated triglycerides which is the most important risk factor in acceleration of atherosclerosis[21]. There is a significant relationship between serum uric acid and dyslipidemia[33]. In the present study dyslipidemia was noticed as a risk factor in those with CAD, Who had significantly elevated serum uric acid levels.

"Uric acid stabilizes the platelet aggregation and enhances thrombotic tendency", thus suggested hyperuricemia as a strong predictor of myocardial infarction and stroke and all causes of mortality.

Patients with poor metabolic control and longer duration of diabetes were more susceptible to develop various complications including hyperuricemia as observed in the present study. Our study also shows that higher level of serum uric acid was seen in patients with longer duration of diabetes when compared with shorter duration of diabetes. This difference was statistically significant.

Uric acid >4mg/dL should be considered as a **"Red flag"** in those patients at risk for cardiovascular disease. In this study 74.3% of diabetic patients have serum uric acid level >4mg/dL, while only 23.3% of the control have serum uric acid >4mg/dL. In these patients the clinician should strive to utilize global risk reduction Programme to reduce the complications of

atherogenic process. The details in relation to this study is shown in the table 25 given below:

Table 24: Cases and controls in relation to uric acid

Serum Uric Acid	Cases		Controls	
	No.	**Percentage**	**No.**	**Percentage**
<4mg	18	25.7	23	76.7
>4mg	52	74.3	7	23.3
p value = 0.0001 significant				

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century[1]. However, it role as a cardiovascular risk factor remains controversial. The Framingham heart study concluded that uric acid does not have a causal role in the development of coronary artery disease and death from cardiovascular disease. In an epidemiologic follow up study an association between serum uric acid and cardiovascular disease was shown. The recent PIUMA study also concluded that raised serum uric acid is a powerful risk marker for subsequent cardiovascular disease and all cause mortality[34].

Of the 70 cases of type 2 diabetes mellitus serum uric acid was elevated in 7 patients which accounts for 10% of cases. Canon showed a prevalence of hyperuricemia in 25% of longstanding uncontrolled diabetes. But in this study many of the cases were on treatment which might have affected the results.

A large Body of evidence links uric acid with metabolic syndrome of insulin resistance, obesity, hypertension, and dyslipidemia. In this study relationship between obesity, hypertension, dyslipidemia and hyperuricemia was statistically significant.

CONCLUSION

- Uric acid was significantly elevated in diabetic population.
- The serum uric acid level was independent of age and smoking status in males.
- Significant correlation was noticed between serum uric acid and BMI as well as WHR.
- Significant elevation of uric acid level was observed more among females.
- Elevated uric acid levels were significantly noticed among those with hypertension, dyslipidemia, coronary artery disease and chronicity of the diabetes.
- Uric acid level above 4mg/dl in diabetic population (considered as a **"Red flag"** sign) was a marker or risk factor for CAD, which was present in 70% of study population.

RECOMMENDATIONS / SUGGESTIONS

Routine annual estimation of uric acid among diabetics from the identification of diabetes will help the clinician to find out the changing trends of uric acid level which is likely to be influenced by control of blood sugar and development of hypertension, such cases should be carefully monitored for CAD as well as other vascular episodes.

Since uric acid is a confounding factor and multiple factors are involved for elevated uric acid. A meticulous control of blood sugar, hypertension, dyslipidemia among diabetics will bring down elevated uric acid level in diabetics.

Let us have a moto of

"**A**sses diabetics for risk factors,
Assist to control them and
Arrest the development of complications"

With the pharmacological and non pharmacological means.

SUMMARY

Diabetes mellitus is strongly associated with hyperuricemia. The role of uric acid is a independent risk factor for cardiovascular disease is a matter of controversy. The present study was proposed to asses the uric acid status in patients with diabetes mellitus and to find out its association with age, gender, BMI, WHR, smoking and CAD. With rigid criteria, patients were selected carefully and evaluated on social, clinical, and laboratory aspects after getting institutional, ethical clearance and informed consent. 30 healthy age, sex matched individuals were kept as control. There were 46 males and 24 Females in the study group and 18 males and 12 females in the control group. The mean and standard deviation of age among the patient group was 60.01± 8.82 and 56.27 ± 7.84 in control group. There was no significant difference among cases and controls in relation to age.

In study group, BMI below 25 seen in 32 cases (45.7%) BMI above 25 seen in 38 cases (54.3%) which was significantly more than controls. BMI had significantly correlated with hyperuricemia. Similarly WHR was greater among women than men in diabetics, which also correlated with elevated serum uric acid significantly.

Elevated serum uric acid level was noticed more among those who had hypertension (21.4%), dyslipidemia (28.6%), Coronary artery disease (21.4%)

and they were significant. Patients with longer duration of diabetes also had elevated uric acid level.

The factors contribute to hyperuricemia in diabetes are

1. Hyperinsulinemia acutely reduces urinary uric acid and sodium excretion.
2. Hyperinsulinemia imposes a chronic antinatriuretic and antiuricosuric pressure on the kidney.
3. Microvascular disease in diabetes mellitus causes local tissue ischemia, and decreased renal blood flow. Ischemia with associated lactate production that blocks urate secretion in proximal tubules. Increased uric acid synthesis due to increased purine metabolism, ischemia induced increased xanthine oxidase production, **insulin resistance**, and diuretic use.

Meticulous control of blood sugar, hypertension, dyslipidemia, body weight and abdominal girth, form an essential component of diabetes which will bring down uric acid level, a less discussed issue among diabetic population.

In view that it is worth to explore uric acid levels atleast in patients with family history of diabetes and in obese diabetic patients to detect early cardiovascular complications.

BIBLIOGRAPHY

1. Gerteler MM, GAM S.M. Lerine SA: Serum Uric Acid in relation to age and physique in health and CAD. An intern med 1951; 34: 1421-1431.
2. Reaven GM. Role of insulin resistance in human disease diabetes 1993; 37:1595-1607.
3. Alderman MH, Cohen H, Madhasen S, Kirilinghn S: Serum uric acid and cardiovascular events in successfully treated hypertensive patients, Hypertension 1999; 34: 144-150.
4. Harrison's principles of internal medicine 16th edition: 2005; Vol 2; 2152-2153:A-6.
5. Gerich JE. Addressing the insulin secretion defect. A logical first line approach metabolism 2000; 49 (Suppl 2) : 12-16.
6. Pulansky Ks, Sturis J. BellGI. Non insulin dependent diabetes mellitus: a genetically programmed failure of the beta cell to compensate for insulin resistance N. Engl. J. Med. 1996: 334-771-783.
7. Himmsworth H. Diabetes mellitus – a differentiation into insulin sensitive and insulin insensitive types lancet 1936; I:127-130.
8. Ramachandran A et al, Decreased insulin sensitivity in off springs whose both parents have NIDDM. Diabetes med 1990; 7: 331-334.

9. American Diabetes Association: Clinical practice recommendations 2002: Diabetes case: 27:51, 2004.
10. Defronzo KA, Hendler R, Simonson D. Insulin resistance is a prominent feature of insulin dependent diabetes 1982; 31: 795-801.
11. Godsland IF et al, insulin resistance syndrome or tendency? Lancet 1995; 346: 100-103.
12. Yudkin JS. Coronary artery disease in diabetes mellitus three new risk factors and a unifying hypothesis. J Int Med 1995; 238; 21-30.
13. Steinberg HO et al, Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J clin invest 1996; 97: 2601-2610.
14. Marita RA et al, Insulin receptor defects in the RBC of obese Indian women with acanthosis nigricans. Clin Chim Acta 1997; 265: 139-142.
15. Misra A: Insulin resistant syndrome current prospecture and its relevance in Indians. Indian neat J 1998: 50: 385-395.
16. Grunberger et al, Tyrosine kinase activity of the insulin receptor of patients with type A extreme insulin resistance studied with circulating mononuclear cells and cultured lymphocytes. J clin Endo metabolism 1984; 59: 1152-1158.

17. Taylor SI et al, Insulin resistance associated with androgen excess in women with auto antibodies to insulin receptors. Ann int Med 1982, 97: 851-855.
18. JNC 7: The seventh report of the Joint National committee on prevention, Detection, Evaluation and treatment of High Blood Pressure U.S. NIH Publication No. 03-5233, May 2003.
19. Cannon PS, Stason WB, Demartini FE, Laragh JH Hyperuricemia in primary and renal hypertension. N. Engl. J.Med. 1966, 275: 457-464.
20. Johnson RJ. Kang DH, Mazzali M: IS there a pathogenic role for uric acid in hypertension and cardiovascular disease, renal disease, hypertension, 2003: 41(6): 1183-1190.
21. Tkac I Bombay J, Cvanigo A: Uric acid a risk factor or atherosclerosis marker in type 2 diabetes? Vnitr Lek 1990 Aug; 36(8) 763 – 768
22. Woo J et al, Association between serum uric acid and some cardiovascular risk factors in Chinese population. Post grad J need 1994 Jul.70(825): 486-491.
23. Wannamethe SG, et al, Serum urate and risk of major coronary events, H cart 1997 Aug: 78(2) 1479-53.
24. Pearl A et al, Serum urate as a free radical scavenger in diabetics. J med syst 1993 Aug: 17(3-4): 233-237.

25. Bos Cavallo-Perin P, Gentile L, Reoetti E, Pagano G: Hypouricemia and hyperuricemia in type 2 diabetes, two different pnenotypes. Eur J Clin Invest 2001; 31(4): 319-321.
26. Bedir A, Tophhas,. A lvur M, Arik N.: Leptin might be a regulator of serum uric acid concentration in humans. JPN Heart J. 2003; 44(4): 527-536.
27. Shoba Ketker, Mukund Ketker, S.Bose and K.S. Sharma, Ponderal index and serum uric acid levels in healthy medical students. Jr. Association. Phys. Ind. Vol.27: June 1979.
28. Healey L.A, Caner J.E.Z., Bassett DR and Deeker J.L : Serum uric acid and obesity in Hawaiians: 1 A.M. of 196; 364: 1966.
29. Rathmann W et al, Relations of hyperuricemia with various components of insulin resistance syndrome in young black and white adults the CARDIA study, Ann epidemiol 1998 May; 8(94) 250-261.
30. Mazzali M, Hughes J, Kim Yu, Jefferson JA, Kang DH- Elevated Uric acid increases blood pressure in the rat by a novel crystal independent mechanism. Hypertension. 2001;38: 11001-1106.
31. Sanchiz – Lozada LG: Tapia E, Francom, Johnson RJ, Nakagawa J; Mild hyper ureicemia induces glomerular hypertension in normal rats. Am J physiol renal physiol. 2002; 283: F 1105-1110.

32. Jossa. F., Farinaro F., Panico S, Krogh V, Celentano E, Galarso R, Serum uric acid in hypertension. The Olivetti heart study J Hum Hypertens 1994; 8: 677-681.
33. Bouvenot G et al, Serum uric acid and serum lipids statistical correlations. Report of 1000 cases sem hop 1980 Feb 8-15; 56 (5-6): 263-264.
34. Paolo – Verdecchia, Giveseppe, Gian Paolo, Rebodi, Fausto et al, Retation between serum Uric acid and risk of cardio vascular disease in essential hypertension. The PIUMA study hypertension 2000 ; 36: 1072-1078.

SERUM URIC ACID LEVEL IN TYPE 2

DIABETES MELLITUS

Name:

Age: Sex: M/F

Ip No: Ward:

Duration of Diabetes: BMI: WHR:

Symptoms:

Polyuria, Polydypsia, Polyphagia ☐

Chest pain, Pedal edema ☐

Breathlessness Headache Vomiting

Fever Numbness, Paraesthesia

Personal / Family history:

Smoking Family history

Alcohol Chronic drug intake

Clinically:

Hypertension : Bp: / mmHg

Obesity : BMI

Retinopathy :

Neuropathy :

IHD :

Stroke/ TIA :

PVD :

Investigations:

Urine alb : Sug: Dep:

Usg abd :

ECG :

ECHO :

Lipid profile abnormality :

Renal parameters (urea, creatinine):

Bl. Sugar (F) :

Bl. Sugar (PP) :

Sr. Uric acid :

SERUM URIC ACID LEVEL IN TYPE 2

DIABETES MELLITUS

Dissertation submitted

in partial fulfillment for the Degree of

DOCTOR OF MEDICINE

BRANCH I - M.D., (General Medicine)

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DEPARTMENT OF MEDICINE

MADURAI MEDICAL COLLEGE

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

Introduction

Aims and Objectives

Review of Literature

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Conclusion

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Proforma

Master Chart

CONTROLS MASTER CHART

S.No	Age	Sex	DOD	BMI	WHR	Smoking	Family History of Diabetes	Systemic Hyper Tension	IHD	BS(F)	BS (PP)	Renal Parameters	USG Abd	ECHO/ECG	IHD	Lipid Profile abnormality	Retino pathy	Neuro pathy	Sr.Uric acid
1	54	M	6	20.6	0.83	N	Y	N	N	N	N	92	116	N	N	N	N	N	2.7
2	46	M	3	19.4	0.8	N	N	N	N	N	N	78	126	N	N	N	N	N	4.2
3	62	M	8	20.3	0.81	N	Y	N	N	N	N	106	148	N	N	N	N	N	2.9
4	64	M	10	25.4	0.84	N	N	Y	N	N	N	126	147	N	N	N	N	N	3
5	43	F	2	18.6	0.78	N	N	N	N	N	N	110	167	N	N	N	N	N	3.6
6	59	F	7	21.4	0.82	N	N	N	N	N	N	120	172	N	N	N	N	N	4.5
7	67	M	8	22.4	1.1	N	N	Y	N	N	N	130	161	N	N	N	N	N	5.5
8	52	M	3	20.6	0.81	N	N	N	N	N	N	121	147	N	N	N	N	N	3.2
9	63	M	8	24.7	0.88	N	N	N	N	N	N	120	162	N	N	N	N	N	3.7
10	60	F	4	23.8	0.87	N	N	N	N	N	N	110	128	N	N	N	N	N	3.8
11	55	F	3	21.7	0.8	N	N	N	N	N	N	144	168	N	N	N	N	N	4.2
12	49	F	3	19.6	0.78	N	N	N	N	N	N	133	167	N	N	N	N	N	4
13	44	M	3	18.4	0.82	N	N	N	N	N	N	128	149	N	N	N	N	N	2.8
14	55	M	6	20.4	0.83	N	N	N	N	N	N	112	160	N	N	N	N	N	3.2
15	57	M	7	21.2	0.84	Y	N	N	N	N	N	113	163	N	N	N	N	N	3.9
16	62	M	5	26	1.02	N	Y	N	N	N	N	140	172	N	N	N	N	N	4.3
17	67	F	7	24.3	0.9	N	N	Y	N	N	N	106	128	N	N	N	N	N	2.9
18	49	F	2	20.6	0.84	N	N	N	N	N	N	112	142	N	N	N	N	N	3
19	51	F	3	21.4	0.86	N	N	N	N	N	N	119	167	N	N	N	N	N	3.7
20	55	M	3	20.8	0.8	N	N	N	N	N	N	106	143	N	N	N	N	N	3.8
21	66	F	10	25.8	0.87	N	N	N	N	N	N	111	132	N	N	N	N	N	3.4
22	62	M	9	23.2	0.83	N	N	N	N	N	N	107	167	N	N	N	N	N	4
23	64	M	8	23.6	0.82	Y	Y	N	N	N	N	121	148	N	N	N	N	N	3.8
24	47	M	2	20	0.84	N	Y	N	N	N	N	110	151	N	N	N	N	N	2.7
25	53	F	6	19.6	0.76	N	N	N	N	N	N	122	170	N	N	N	N	N	3.3
26	57	F	5	20.3	0.8	N	N	N	N	N	N	96	130	N	N	N	N	N	3.1
27	48	M	2	20.4	0.81	Y	N	N	N	N	N	98	127	N	N	N	N	N	3.2
28	45	M	2	19.6	0.8	N	N	N	N	N	N	102	118	N	N	N	N	N	3.7
29	59	F	7	18.4	0.8	N	N	N	N	N	N	100	128	N	N	N	N	N	3.1
30	73	M	8	25.6	1.08	Y	N	Y	N	N	N	126	170	N	N	N	N	N	3.4

CASES MASTER CHART																		
S.No	Age	sex	DOD	BMI	WHR	Smoking	Family History of Diabetes	Systemic Hyper Tension	IHD	BS (F)	BS (PP)	Renal Parameters	USG Abd	ECHO /ECG	Lipid Profile abnormality	Retino pathy	Neuro pathy	Sr.Uric acid
1	52	M	6	20.6	0.86	N	N	N	N	192	222	N	N	N	N	N	N	4.2
2	69	M	10	25.8	1.08	Y	Y	Y	Y	143	213	N	N	I	Y	Y	N	5.9
3	41	M	2	19.7	0.76	N	N	N	N	130	196	N	N	N	N	N	N	3.1
4	55	M	5	20.2	0.8	N	N	N	N	113	173	N	N	N	N	N	N	3.8
5	62	M	8	28.8	1.12	Y	N	N	N	196	243	N	N	N	Y	N	N	8.0
6	51	M	3	21.9	0.86	N	N	N	N	115	173	N	N	N	N	N	N	4.6
7	61	M	7	23.2	0.8	Y	N	N	N	126	200	N	N	N	N	4.8	3.7	3.5
8	47	M	3	20.4	0.78	N	Y	N	N	108	187	N	N	N	N	N	N	3.7
9	62	M	6	23.7	0.84	N	N	N	N	192	273	N	N	N	N	Y	N	4.8
10	44	M	4	23.3	0.83	N	N	N	N	184	192	N	N	N	N	N	N	4
11	71	F	12	25.7	0.91	N	N	Y	Y	192	212	N	N	I	Y	Y	Y	5.9
12	59	F	9	25.3	0.89	N	Y	N	N	113	170	N	N	N	N	N	N	5.3
13	75	F	14	27.4	0.93	N	N	Y	N	215	233	N	N	N	Y	Y	N	5.9
14	53	M	4	21.4	0.8	Y	N	N	Y	214	222	N	N	N	N	N	N	3
15	67	M	4	22.6	0.83	N	N	N	N	223	245	N	N	N	N	N	N	3.7
16	77	M	10	25.8	0.97	Y	N	Y	Y	147	192	N	N	I	Y	Y	N	6.4
17	60	F	8	26.9	0.94	N	N	N	YES	248	291	N	N	MI	N	N	N	7.9
18	47	M	5	20.2	0.8	N	N	N	N	143	175	N	N	N	N	N	N	3.8
19	55	F	7	24.8	0.84	N	Y	N	N	132	165	N	N	N	N	N	N	4
20	66	F	10	26.3	0.92	N	N	N	N	130	145	N	N	N	Y	Y	N	5.8
21	42	M	2	19.4	0.76	N	N	N	N	148	192	N	N	N	N	N	N	3.8
22	67	M	7	20.4	0.8	Y	N	N	N	157	211	N	N	N	N	N	N	4.6
23	63	M	9	25.4	0.82	Y	N	N	N	215	253	N	N	N	N	N	N	5.8
24	73	F	12	27.2	0.92	N	N	Y	N	205	261	N	N	N	Y	Y	N	5.9
25	59	M	10	27.4	1.14	Y	Y	Y	Y	196	243	N	N	I	Y	N	N	8.1
26	57	F	6	23.2	0.81	N	N	N	N	163	174	N	N	N	N	N	N	4.6
27	62	F	6	24.5	0.92	N	N	N	N	105	126	N	N	N	N	N	N	4
28	63	M	7	25.2	1.02	Y	N	Y	Y	175	233	N	N	MI	N	N	N	6.5
29	60	F	10	27.4	1.12	N	Y	N	N	196	221	N	N	N	N	Y	N	5.8
30	58	F	9	27.2	1.1	N	N	N	N	144	216	N	N	N	Y	N	N	5.7
31	61	M	7	20.4	0.8	Y	N	N	N	224	247	N	N	N	N	N	N	3.2
32	63	M	8	22.3	0.84	N	N	N	N	143	196	N	N	N	N	N	N	4.6

33	69	M	10	25.4	1.02	N	Y	Y	Y	132	176	N	N	I	Y	Y	N	6.7
34	65	M	6	24.7	0.99	Y	N	N	N	149	191	N	N	N	N	N	N	5.6
35	53	M	3	22.3	0.84	N	N	N	N	283	263	N	N	N	N	N	N	5
36	54	M	6	23	0.86	N	N	N	N	240	271	N	N	N	N	N	N	4.8
37	67	F	12	28.6	1.08	N	Y	YES	YES	211	243	N	N	MI	YES	YES	N	6.7
38	63	M	7	25.9	1.02	N	N	N	N	187	211	N	N	N	N	N	N	6.8
39	66	F	6	25.8	1	N	Y	N	N	143	209	N	N	N	N	N	N	5.4
40	61	M	6	23.8	0.88	N	N	N	N	173	231	N	N	N	N	N	N	3
41	62	M	6	20.8	0.8	Y	N	N	N	143	199	N	N	N	N	N	N	3.1
42	72	M	10	25.8	0.92	N	Y	Y	Y	145	211	N	N	I	Y	Y	Y	6.7
43	57	M	7	20.2	0.8	N	N	N	N	127	192	N	N	N	N	N	N	3.2
44	44	M	4	20	0.8	N	N	N	N	108	142	N	N	N	N	N	N	3
45	76	F	14	29.2	1.08	N	N	N	Y	227	265	N	N	I	Y	N	Y	7.7
46	54	M	7	25.4	0.92	N	Y	N	N	191	211	N	N	N	N	N	N	5.2
47	63	M	7	25.8	0.88	N	N	N	N	219	248	N	N	N	Y	N	N	5.8
48	57	M	6	20.1	0.8	N	N	N	N	119	187	N	N	N	N	N	N	3.6
49	67	M	10	26.7	0.96	Y	N	N	Y	129	147	N	N	MI	N	N	N	6.6
50	69	M	12	27.8	1	N	N	Y	N	136	191	N	N	N	Y	Y	N	6.8
51	59	M	9	21.3	0.78	N	N	N	N	286	323	N	N	N	N	N	N	4.6
52	73	M	10	25.6	0.92	N	Y	Y	N	215	223	N	N	N	Y	N	Y	6.6
53	48	M	3	23.2	0.82	Y	N	N	N	207	219	N	N	N	N	N	N	4.2
54	57	F	7	26.8	0.88	N	N	N	N	126	200	N	N	N	Y	N	N	4.8
55	69	F	10	27.8	0.96	N	Y	N	YES	247	261	N	N	MI	YES	YES	N	7.9
56	52	F	5	25	0.9	N	N	N	N	145	203	N	N	N	N	N	N	4.2
57	48	F	6	21.2	0.8	N	N	Y	N	192	196	N	N	N	N	N	N	3.3
58	47	M	5	20.6	0.78	Y	N	N	N	183	180	N	N	N	N	N	N	3.1
59	62	M	7	25.4	1.07	N	N	N	Y	273	322	N	N	I	N	N	N	6.3
60	55	M	3	23.2	0.92	Y	N	N	N	250	271	N	N	N	N	N	N	4.7
61	65	M	8	25.8	1.02	N	Y	N	N	160	178	N	N	N	N	Y	N	6
62	63	F	7	20.4	0.8	N	N	N	N	185	213	N	N	N	N	N	N	4.2
63	76	F	14	29.2	1.09	N	Y	Y	Y	192	261	N	N	I	Y	Y	Y	5.9
64	51	F	3	23.1	0.84	N	N	N	N	193	199	N	N	N	N	N	N	5.8
65	50	F	6	21.4	0.87	N	N	N	N	143	173	N	N	N	N	N	Y	5.5
66	57	M	3	19.6	0.78	Y	N	N	N	113	161	N	N	N	N	N	N	2.8
67	49	M	3	20.1	0.81	Y	N	N	N	105	122	N	N	N	N	N	N	3
68	73	F	12	28.4	1.09	N	Y	N	Y	241	283	N	N	N	Y	Y	Y	8.1
69	59	M	7	24.7	1.06	N	N	N	N	139	171	N	N	N	N	N	N	4.9
70	67	F	12	29.3	1.08	N	Y	Y	Y	149	199	N	N	I	N	Y	N	5.9

DOD - Duration of Diabetes
N - Normal
Y - Yes
I - Ischemia
MI - Myocardial infarction

FIG: 1
AGE DISTRIBUTION

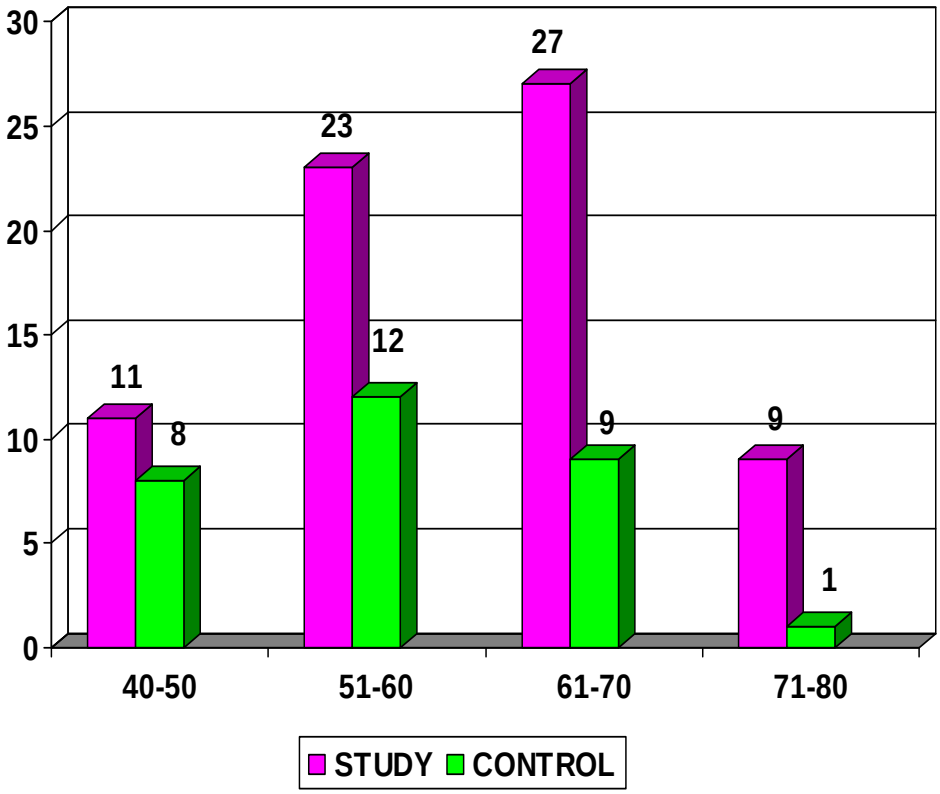


FIG:2
SEX DISTRIBUTION

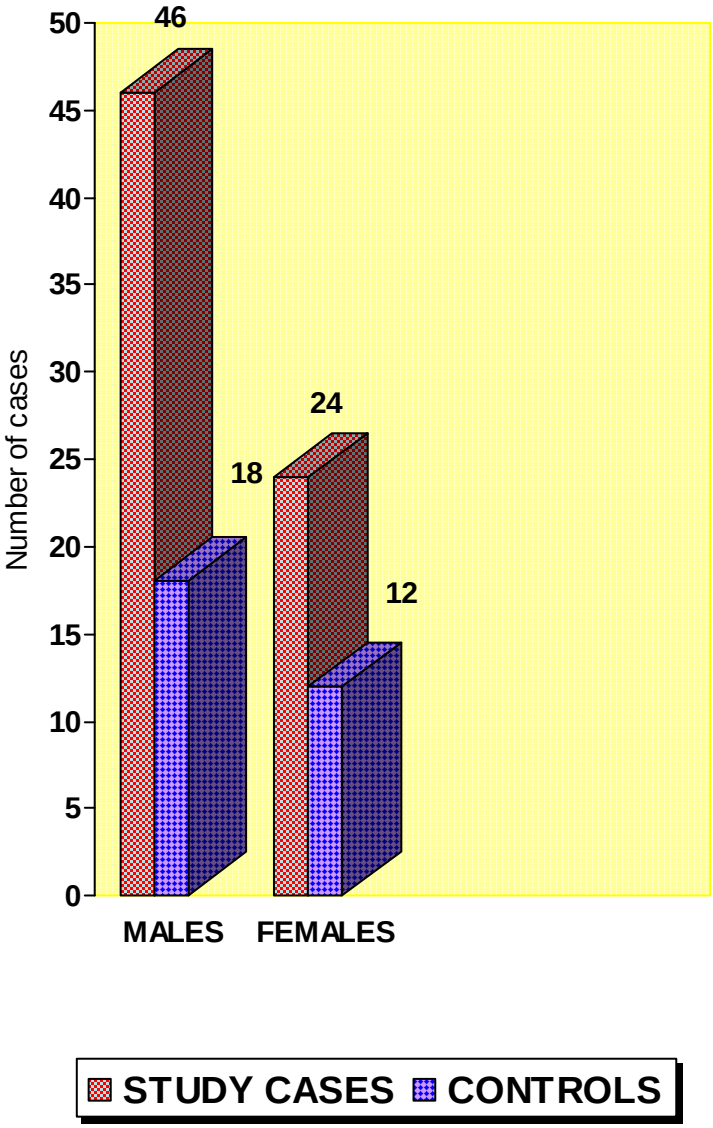


FIG :1
MEAN SERUM URIC ACID LEVEL IN CASES AND CONTROLS

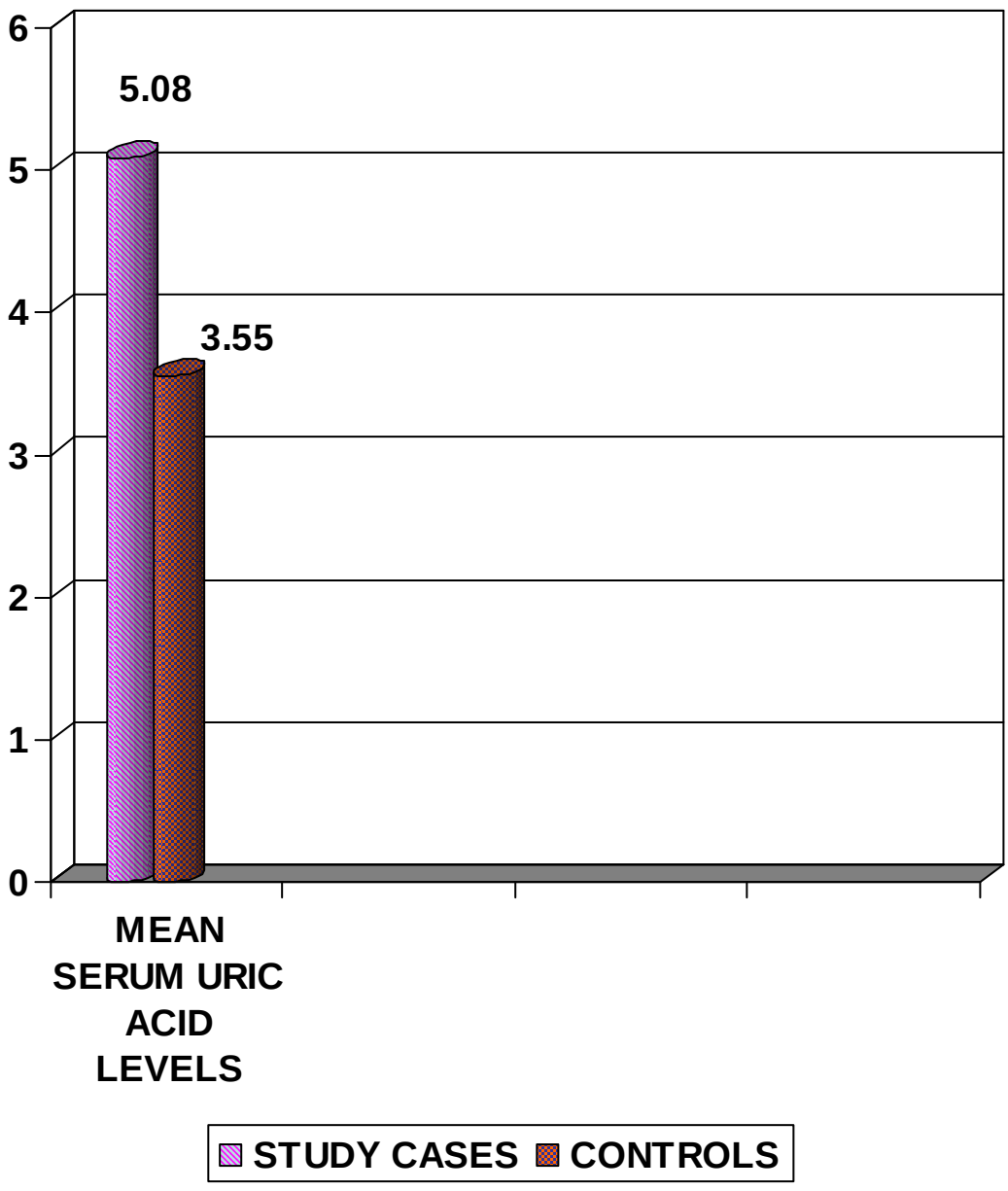


FIG:2
HYPERURICEMIA IN CASES & CONTROLS

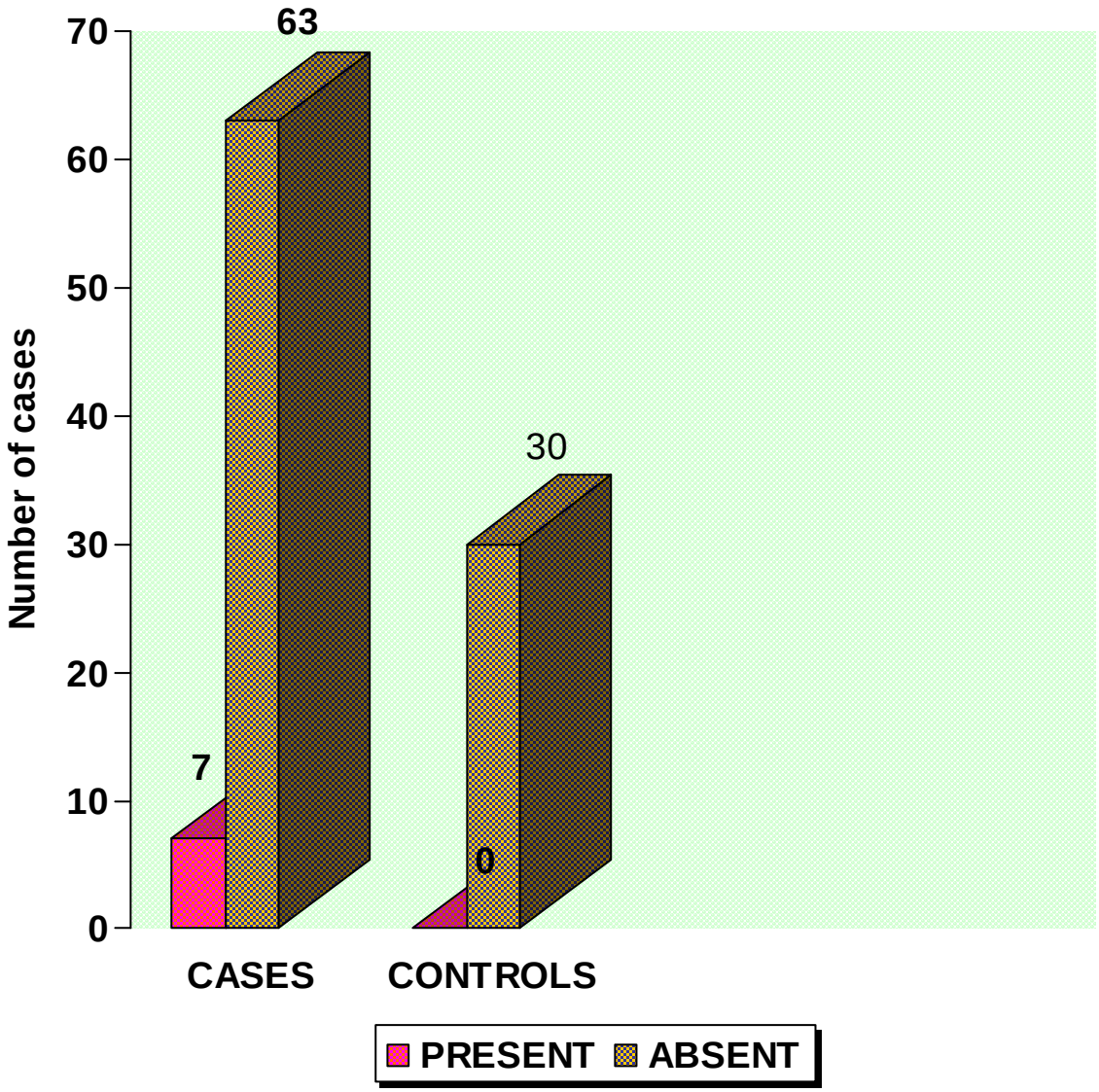


FIG:3
SERUM URIC ACID LEVEL AND BMI

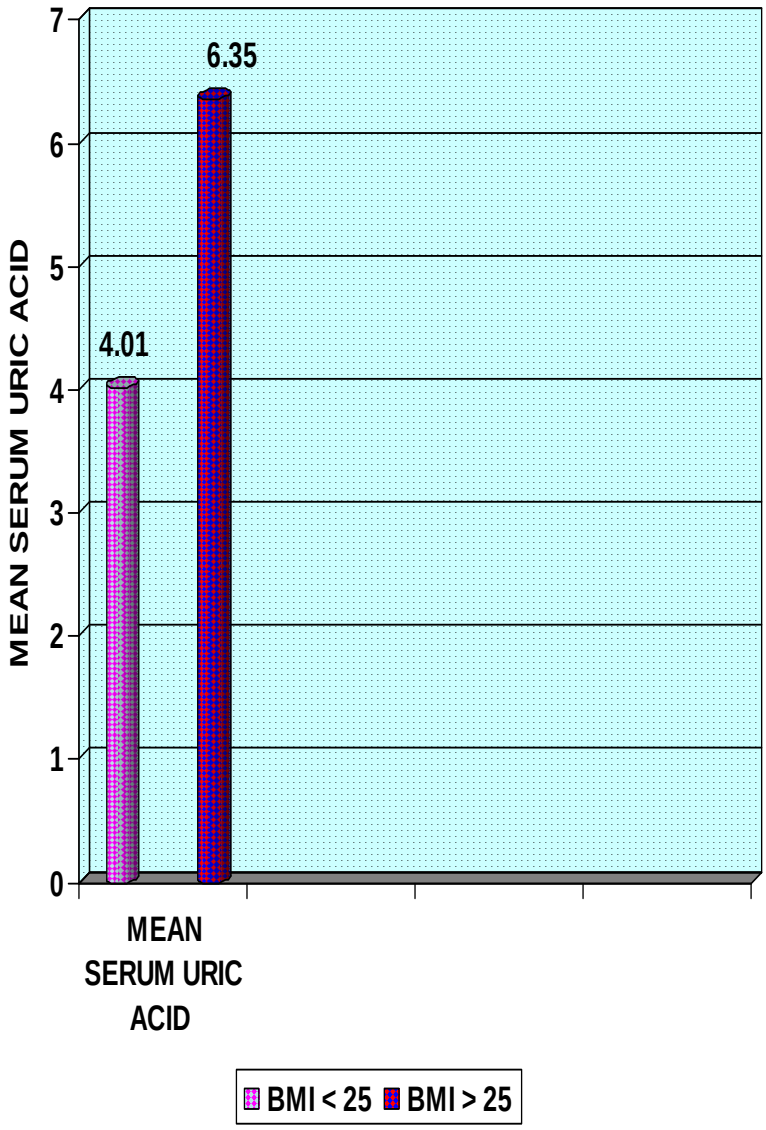
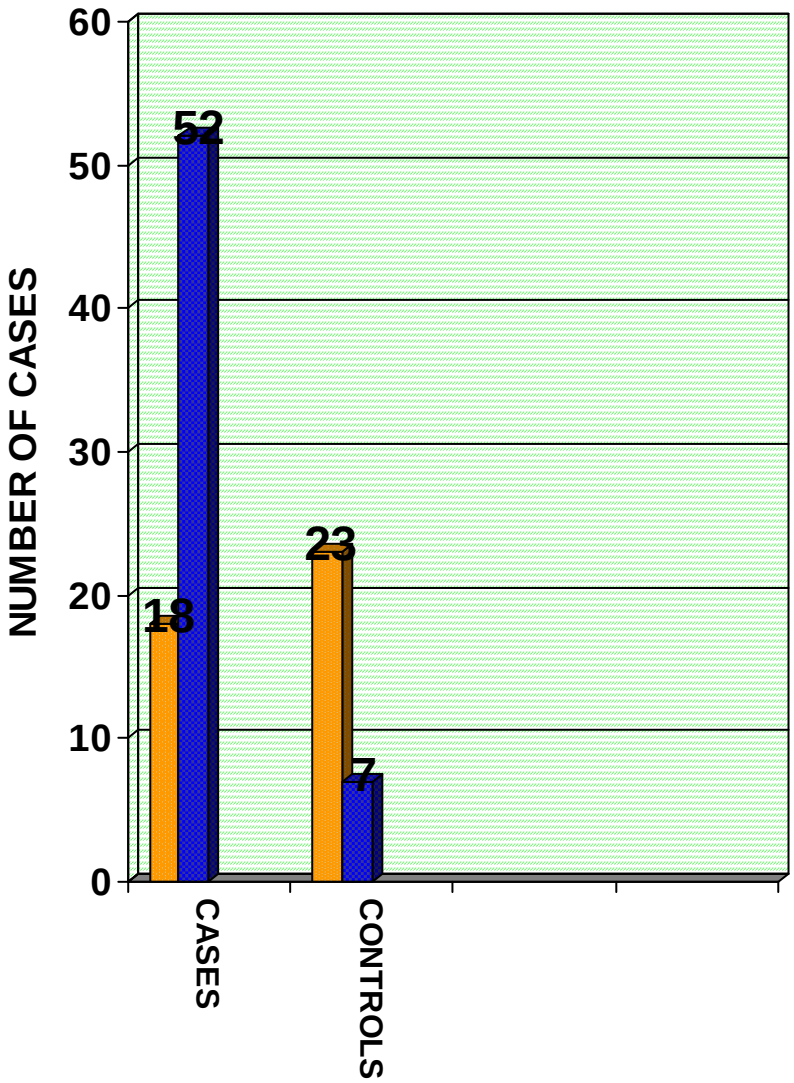


FIG: 6
DISTRIBUTION OF CASES AND CONTROLS ACCORDING TO SERUM URIC ACID LEVELS



CAD AND HYPERURICEMIA

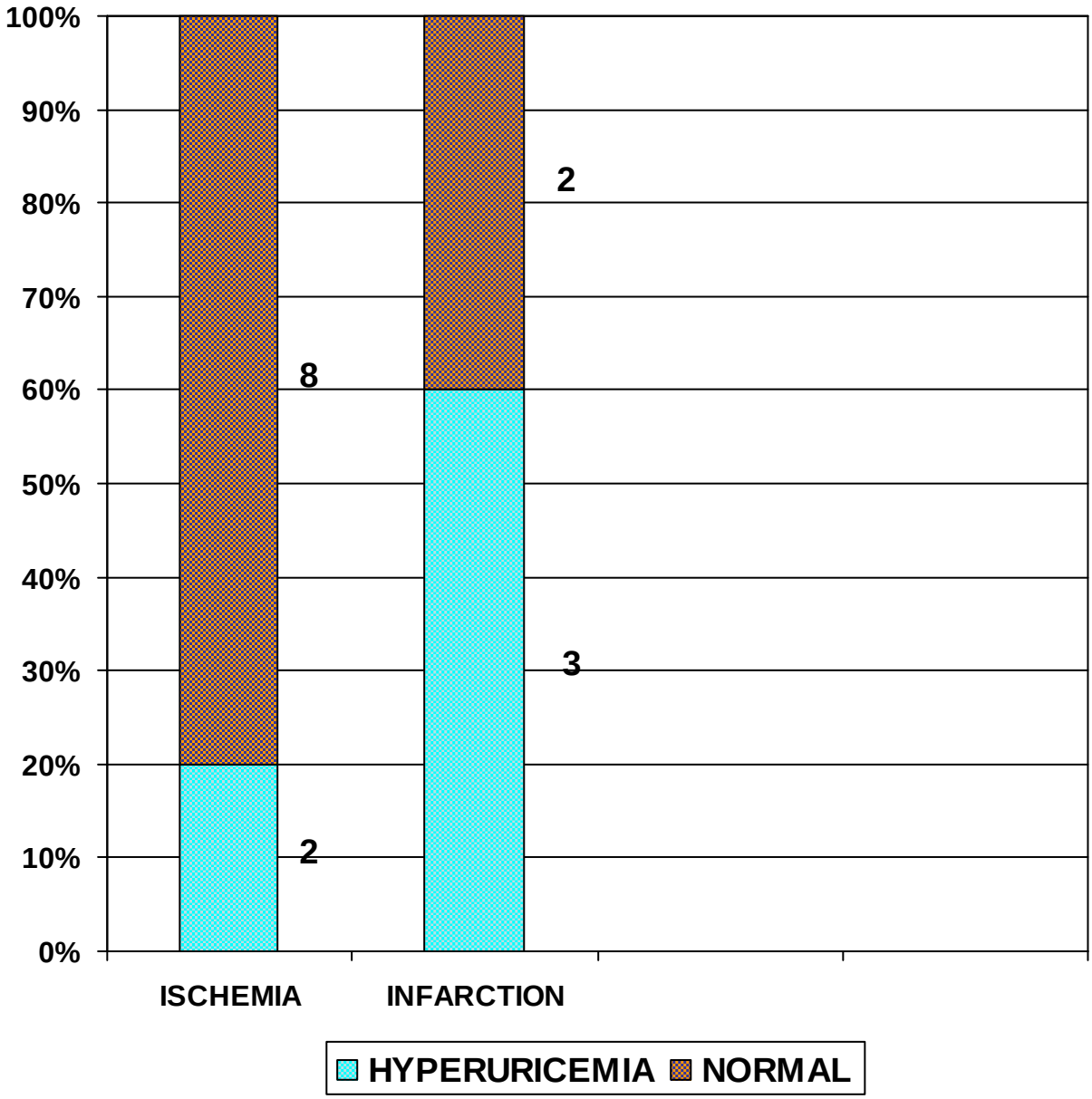


FIG:4
DURATION OF DIABETES AND HYPERURICEMIA

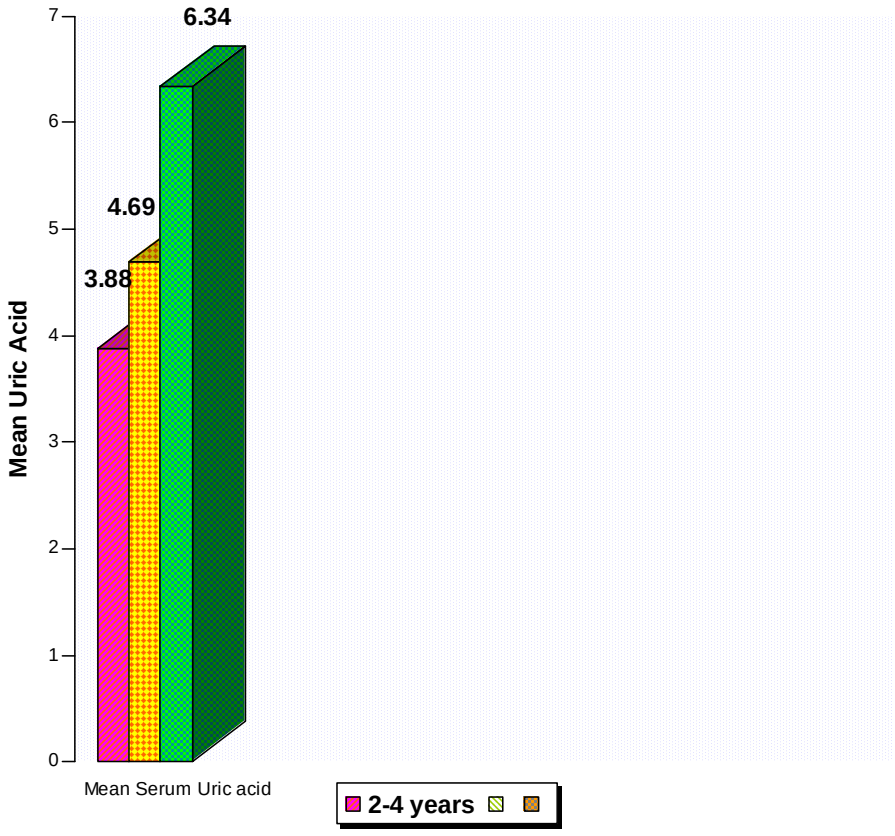


FIG :5
WAIST HIP RATIO AND HYPERURICEMIA