A DISSERTATION ON

" STUDY ON ASSOCIATION OF SERUM URIC ACID LEVEL WITH

URINE ALBUMIN LEVEL IN TYPE 2 DIABETES MELLITUS"

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APRIL 2017

CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr.P.N.KARTHIGEYAN,** Post - Graduate Student (May 2014 TO April 2017) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on **"STUDY ON ASSOCIATION OF SERUM URIC ACID LEVEL WITH URINE ALBUMIN LEVEL IN TYPE 2 DIABETES MELLITUS"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2017.

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DECLARATION

I, Dr.P.N.KARTHIGEYAN declare that I carried out this work on **"STUDY ON ASSOCIATION OF SERUM URIC ACID LEVEL WITH URINE ALBUMIN LEVEL IN TYPE 2 DIABETES MELLITUS"** at the out patient department and Medical wards of Government Stanley Hospital . I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

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

DR.P.N.KARTHIGEYAN

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INTRODUCTION

Nephropathy related to type 2 diabetes is one of the leading causes of end-stage renal disease (ESRD), and is also associated with an increased risk of cardiovascular morbidity and mortality. Over the past 15 years, it has emerged as the primary reason for initiating dialysis[1] . Modifiable factors, such as arterial blood pressure, albuminuria, glycemic control and lipid control, play a role in the progression of diabetic nephropathy[2].

In the early microalbuminuria stage, intensive multifactorial therapy that includes glycemic, lipid and blood pressure control, in addition to smoking cessation, has induced remission and improved renal function[3, 4]. There is little evidence of the contribution of these factors in the prevention of the progressive loss of renal function in advanced diabetic nephropathy[5]. The evidence is limited to the effect of hypertension management and a low-protein diet[6]. Despite the use of these intensive therapies, the loss of renal function progresses, after the onset of overt nephropathy, to ESRD in the majority of cases. One study reported that various recent early biomarkers are associated with the development of diabetic nephropathy[7].

Studies have documented that elevated serum uric acid (SUA) levels are positively associated with the development of type 2 diabetes itself[8]. SUA is also associated with known risk factors for kidney disease progression[9], including hypertension[10], cardiovascular disease[11-13] and

atherosclerosis[12]. SUA has not been investigated as a risk factor for declining renal function in patients with type 2 diabetes who are at the onset of overt nephropathy, although SUA was previously reported in the early stage of diabetic nephropathy[14].

An elevated SUA level within the normal range (>380 μmol/L [6.4 mg/dL] in men, >303 μmol/L [5.1 mg/dL] in women) emerged as a strong and independent risk factor for renal function decline.

Renal condition at baseline, measured as the eGFR, is another important predictor of the decline in renal function. Generally, low eGFR is considered a risk factor for the progression of renal dysfunction. However, in patients with type 2 diabetes, glomerular hyperfiltration and the accompanying increase in eGFR, which is observed in 0–40% of patients with type 2 diabetes, contributes to loss of renal function and nephropathy.

The recommended multifactorial management of type 2 diabetic nephropathy is to stop smoking and to maintain the following: blood pressure <130/85 mmHg, HbA1c <7.0% and LDL-C < 100 mg/d. Of these, poor glycemic control, elevated LDL-C and smoking were significant risk factors for renal dysfunction . In addition to these known factors, SUA also probably increased the risk of declining renal function. Further evidence for the use of UA-lowering treatment for renoprotection is required.

REVIEW OF LITERATURE

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (15). There are mainly two types of diabetes; Type 1 diabetes is immune-mediated and requires daily administration of insulin. The other common type is type 2 diabetes and characterized by insulin resistance or relative insulin deficiency[15,16]. Type 2 diabetes is the most common form and comprises of 90% of people with diabetes around the world (15). The prevalence of type 2 diabetes rates continue to increase with increasing number of patients at risk of serious diabetes-related complications. Having type 2 diabetes increase the risk of a myocardial infarction two times and the risk of suffering a stroke two to four times. It is also a leading cause of blindness, limb amputation and kidney failure(17,18). Studies of adherence to guidelines for CVD prevention targets in patients with diabetes in general practice have shown that only 13% reach all the targets (19). Previous studies have found appropriate lifestyle intervention and/or drug treatment are effective in delaying or preventing both diabetes and its complications (20-23).

TYPES OF DIABETES MELLITUS

TYPE 1 DIABETES

Type 1 Diabetes is characterized by inappropriate hyperglycemia primarily a result of pancreatic islet Beta cell destruction and a 2 tendency to ketoacidosis. Type 1 Diabetes mellitus is a result of pancreatic islet Beta cell

destruction and a tendency to ketoacidosis. Type 1 Diabetes mellitus is a result of cellular - mediated auto immune destruction of the pancreas, causing an absolute deficiency of insulin secretion. Upper limit of 110 mg/dl on the fasting plasma glucose is designated as the upper limit of normal blood glucose. Type 1constitutes only 10% to 20% of all cases of diabetes and commonly occur in child hood and adolescence .This disease is usually initiated by an environmental factor or infection (usually a virus) in individuals with genetic predisposition and causes the immune destruction of Beta cells of pancreas and, therefore, a decrease production of insulin.

Characteristics of Type 1 diabetes include abrupt onset, insulin dependence, and ketosis tendency & genetically related. One or more of the following markers are found in 85% to 90% of individuals with fasting hyperglycemia: Islet cell auto anti bodies, insulin auto antibodies, and Glutamic acid decarboxylase auto anti bodies, and tyrosine phosphatase IA-2and IA-2B auto antibodies (Bishop *et al*., 2010). Signs and symptoms include polydipsia (excessive thirst), polyphagia (increase food intake), polyuria (excessive urine production), rapid weight loss, hyperventilation, mental confusion, and possible loss of consciousness (due to increase glucose to brain). Complications include microvascullar problems such as nephropathy, neuropathy, and retinopathy. Increased heart disease is also found in patients with diabetes (Bishop *et al*., 2010).

TYPE 2 DIABETES

Type 2 diabetes mellitus is characterized by hyperglycemia as a result of an individual's resistance to insulin with an insulin secretary 3 defect. This resistance result in relative, not an absolute insulin deficiency. Type2 constitutes the majority of the diabetes cases. Most patients in this type are obese or have an increased percentage of body fat distribution in the abnormal region. This type of diabetes often goes undiagnosed for many years and is associated with a strong genetic predisposition, with patients at increased risk with an increase in age, obesity, and lack of physical exercise. Characteristic usually include adult onset of the disease and milder symptoms than in type1, with ketoacidosis seldom occurring. However, these patients are more likely to go into a hyperosmoler coma and are at an increased risk of developing macro vascular and micro vascular complications (Bishop *et al*., 2010).

OTHER SPECIFIC TYPE OF DIABETES

Other specific type of diabetes are associated with certain conditions (secondary), including genetic defect of Beta-cell function or insulin action, pancreatic disease, disease of endocrine origin, drug or chemical induced insulin receptor abnormalities, and certain genetic syndromes. The characteristics and prognosis of this form of diabetes depend on primary disorder (Bishop *et al*., 2010).

GESTATIONAL DIABETES MELLITUS (GDM)

GDM is any degree of glucose intolerance with onset or first recognition during pregnancy. Causes of GDM include metabolic and hormonal changes. Patients with GDM frequently return to normal post partum. However, GDM is associated with increased prenatal complications and an increased risk for development of diabetes in later years. Infants born to mothers with diabetes are at increased risk for respiratory distress syndrome, hypocalcaemia, and hyperbilirubinemia.

EPIDEMIOLOGY OF TYPE 2 DIABETES

The world prevalence of diabetes in 2010 among adults aged 20-79 years is estimated to 6.4%, affecting 285 millions adults (24). Between 2010 and 2030, there is an expected 70% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (24). Each year more than 231,000 people in the United states and more than 3,96 million people worldwide die from diabetes and its complications (16). This number is expected to increase by more than 50 percent over next decade (15). It has been shown in several studies that a clustering of features, such as high plasma glucose, obesity, dyslipidemia (high triglyceride and total cholesterol levels low high density lipoprotein (HDL) cholesterol levels and hypertension, referred to as insulin resistance or the metabolic syndrome, is a marker of increased risk for the development of type 2 diabetes as well as for CVD

(27,28). Environmental and lifestyle factors are the main causes of the dramatic increase in type 2 diabetes prevalence (29-31). Genetic factors probably identify those most vulnerable to these changes. Further more, studies have shown certain ethnic groups to be more susceptible to developing diabetes than others (32,33).

AETIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes results from an imbalance between insulin sensitivity and insulin secretion. Both longitudinal and cross-sectional studies have demonstrated that the earliest detectable abnormality in type 2 diabetes is an impairment of the body's ability to respond to insulin. Impaired insulin action is observed in several tissues e.g., skeletal muscle, adipose tissue and the liver. It leads to increased insulin secretion from the pancreas to overcome impaired insulin action. Compensatory hyperinsulinemia maintains glucose level within normal range, but in individual at high risk of developing diabetes, beta cells function eventually declines and leads to the development of impaired glucose tolerance and eventually overt diabetes mellitus (34-36).

RISK FACTORS FOR TYPE 2 DIABETES

Many studies have elaborated the associations between several risk factors and the risk of type 2 diabetes. Body mass index (BMI), lipids, hypertension**,** smoking, physical inactivity, low education, dietary patterns,

family history, and recently also specific genes are the most frequently documented risk factors for type 2 diabetes.

BMI

Many longitudinal studies have reported that increased BMI is a strong risk factor for type 2 diabetes (37, 38-41). A strong positive association between obesity and type 2 diabetes is found both in men (38,41-43), and women (37,38,41,44). Obesity is associated with increased risk of developing insulin resistance and type 2 diabetes. In obese individuals adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of the beta cells, the following fall in insulin secretion results in failure to control blood glucose level leading to type 2 diabetes. Many genes interact with the environment leading to obesity and in some also to diabetes. Many genes have been shown to be involved in determining the whole range of BMI in a population, with each gene only explaining a few hundred grams difference in body weight (45). Genes responsible for obesity and insulin resistance interact with environmental factors such as increased fat/ calorie intake and decreased physical activity resulting in the development of obesity and insulin resistance followed ultimately by the development of type 2 diabetes (46,47).

LIPIDS

Unfavourable blood lipids has been reported as a risk factor for type 2 diabetes by several prospective studies (37,38,40,41,). An inverse relationship between HDL cholesterol and risk of type 2 diabetes have been documented in several of these (37,40). Some prospective studies found low HDL cholesterol to be a stronger risk factor for type 2 diabetes in women only (40,). Only one previous study measuring non-fasting triglycerides found an independent risk of type 2 diabetes connected to elevated triglyceride levels (41). High plasma triglycerides and low plasma HDL cholesterol levels are both seen in the insulin resistance syndrome, which is a prediabetic state , suggesting that nonfasting triglycerides and HDL cholesterol levels reflect the degree of insulin resistance. The mechanisms suggested are increased circulating levels of free fatty acids due to increased insulin levels and increased chylomicron-assembly and secretion in the gut, the latter process being a result of localized insulin resistance in the intestine. Cross sectional studies have shown that high BMI is associated with a higher level of total cholesterol and unfavourable lipids pattern, with low concentrations of HDL cholesterol and high triglycerides concentrations . Longitudinal studies have shown BMI change over time to be positively associated with changes in total cholesterol, triglycerides, and low density lipoprotein (LDL) cholesterol and negatively associated with HDL cholesterol change. Apart from triglycerides, all these lipids have been shown

to convey diabetes risk independently of BMI, but how they interact have been little studied.

HYPERTENSION

Previous prospective and case control studies have shown that hypertension progression is an independent predictor of type 2 diabetes (48,49). Several possible factors are likely causes of the association between type 2 diabetes and hypertension. Endothelial dysfunction could be one of the common pathophysiological pathways explaining the strong association between blood pressure and incident type 2 diabetes. Studies have shown that markers of endothelial dysfunction are associated with new-onset of diabetes (50), and endothelial dysfunction is closely related to blood pressure and hypertension . Markers of inflammation such as C-reactive protein have been consistently related to incident of type 2 diabetes , and to increasing blood pressure levels , suggesting that inflammation might be another explanatory factor for the association between blood pressure, the metabolic syndrome, and incident type 2 diabetes . Finally, insulin resistance could be another potential link between blood pressure levels and the incidence of type 2 diabetes (51). In addition evidence from cross sectional and cohort studies suggests a strong relation between blood pressure and BMI and risk of type 2 diabetes . Although studies show that blood pressure increases with increasing BMI, the risk of type 2 diabetes associated with hypertension is independent of BMI and BMI change. A causal relationship between hypertension and type 2 diabetes is

further strengthened by a recent randomized clinical trial study showing a 14% reduction of risk of diabetes in subjects with glucose intolerance by allocation to 5 year treatment with valsartan, an angiotensin II blocker with antihypertensive properties (52).

SMOKING

Several prospective studies reported that current smoking is a risk factor for developing type 2 diabetes (30). Recently, a meta- analysis including 25 prospective studies showed that current smoking was associated with a 44% increased risk of diabetes(53). The association between smoking and type 2 diabetes was stronger for heavy smokers more than 20 cigarettes/day compared with light smokers or former smokers . In addition some studies found an increased risk of type 2 diabetes the first 2-3 years after smoking cessation , with a risk in the ARIC study equalling the smokers first after 12 years. Smoking leads to insulin resistance and inadequate compensatory insulin secretion response . This could be due to a direct effect of nicotinic or other components of cigarette smoke on beta cells of the pancreas as suggested by the association of cigarette smoking with chronic pancreatitis and pancreatic cancer . Also, some studies suggest that heavy smokers with evidence of increased systemic who gain substantial in weight after quitting, are at high risk of developing type 2 diabetes. However over longer follow up, smoking cessation is associated with a reduction in risk of developing type 2 diabetes.

PHYSICAL INACTIVITY

Longitudinal studies have found physical inactivity to be a strong risk factor for type 2 diabetes (41). Prolonged television watching as a surrogate marker of sedentary lifestyle, was reported to be positively associated with diabetes risk in both men and women (54,55). Moderate and vigorous physical activity was associated with a lower risk of type 2 diabetes . Evidence from clinical trials which included physical activity as a integral part of life style interventions suggested that onset of type 2 diabetes can be prevented or delayed as a result of successful lifestyle interventions that included physical activity as a part of this interventions (20-22). Physical activity plays an important role in delaying or prevention of development of type 2 diabetes in those at risk both directly by improving insulin sensitivity and reducing insulin resistance, and indirectly by beneficial changes in body mass and body composition .

DIABETIC COMPLICATIONS

MICROVASCULAR

Natural history and epidemiology of DIABETIC NEPHROPATHY

The renal involvement in diabetes mellitus is a gradual process and rather well defined in T1D. Mogensen [56] suggested that the development of renal changes may be divided into five different stages . Stage 1 is present at diagnosis of diabetes and includes hyperfunction/ hypertrophy of the kidneys.

Urinary albumin excretion rate (UAE) may be increased, however not permanently. Most of the abnormalities seen at this stage may be reversed with improvement of metabolic control by initiation of insulin treatment. Stage 2 usually lasts at least five years from diagnosis. The glomerular filtration rate (GFR) is increased and exercise-induced microalbuminuria may be present. Blood pressure is however normal. Stage 3 is present typically after 6-15 years of diabetes and UAE is 20-200 μg/min. Overt nephropathy (stage 4) occurs usually 15-25 years from the onset of T1D. GFR declines 10 ml/min per year and if not treated, the blood pressure is high. Stage 5 represents the final outcome of diabetic kidney disease with ESRD and usually occurs 25-30 years or more after diagnosis of diabetes. GFR is now <10 ml/min and blood pressure is always high if untreated.

PATHOGENESIS

Diabetic nephropathy is thought to develop 10-15 years after the onset of diabetes in association with renal fibrosis, defined as the replacement of normal kidney (i.e., glomeruli and tubules) with connective tissue [57,58]. Fibrosis is evident first as deposition of collagen and other extracellular matrix proteins in mesangial matrix and basement membrane of glomeruli and tubules [57]. Expansion of the mesangial matrix, quantified in renal biopsy specimens, is a strong, independent predictor of a subsequent decline in glomerular filtration rate in patients with type 2 diabetes [58,59], as is tubulointerstitial fibrosis [60-62]. The cause of diabetic nephropathy is likely to be

multifactorial. Genetic determinants of diabetic nephropathy remain elusive , but modifiable and non modifiable risk factors for onset and progression of nephropathy have been identified.

RISK FACTORS FOR THE DEVELOPMENT AND PROGRESSION OF DIABETIC KIDNEY DISEASE

Modifiable risk factors	Non-Modifiable Risk Factors
Poor glycemic control Hypertension American, Asian Reninangiotensin system activation Proteinuria Smoking Elevated cholesterol	Genetic susceptibility [familial clustering]Ethnicity (higher risk in African American]

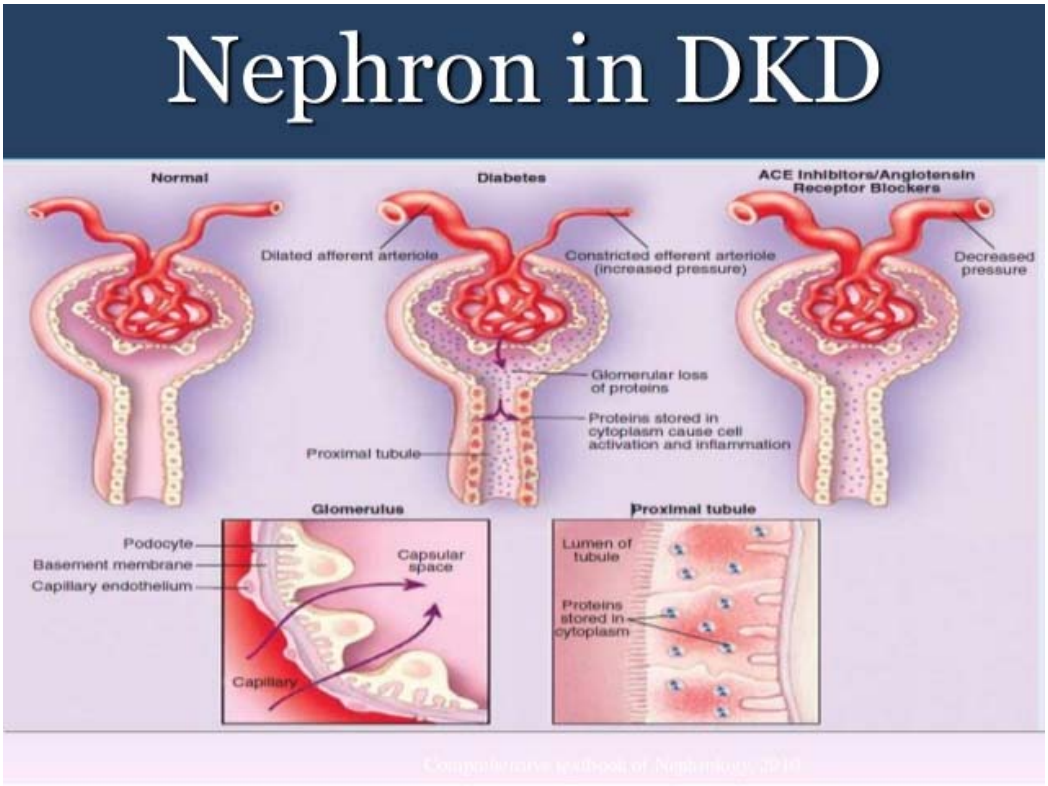
The course of kidney disease seems to be similar in T2DM [26] with some important exceptions. High blood pressure is normally present in T2DM patients even before the onset ofdiabetic nephropathy. Because T2DM can remain undiagnosed several years, microvascular complications like nephropathy may be present already at the time of diagnosis. The peak incidence of nephropathy in T1DM is 15 years from the onset of diabetes. Patients who do not develop nephropathy during the first 20-25 years of diabetes have a very low risk to develop nephropathy later on (about 1 % per year) [63]. It has been estimated that diabetic nephropathy will ultimately develop in 35 % of the patients with T1D .. The incidence of diabetic nephropathy in T1D patients is however declining as shown in several populations.

Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>300 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

The prevalence of diabetic nephropathy has previously been reported to be lower in T2DM than in T1DM patients. The prevalence of diabetic nephropathy seems to differ between different ethnic groups. Because proteinuria is a risk factor for cardiovascular disease it is possible that previous studies underestimate the prevalence of diabetic nephropathy. It seems that the risk for proteinuria at any given duration of diabetes is similar in both T1DM and T2DM. As 90% of the diabetic patients have T2DM and the diabetes prevalence is increasing, there has also been a

rise in the prevalence of diabetic nephropathy and diabetes is now the most common single cause of ESRD in Europe [64].



NATURAL HISTORY AND EPIDEMIOLOGY OF DIABETIC RETINOPATHY

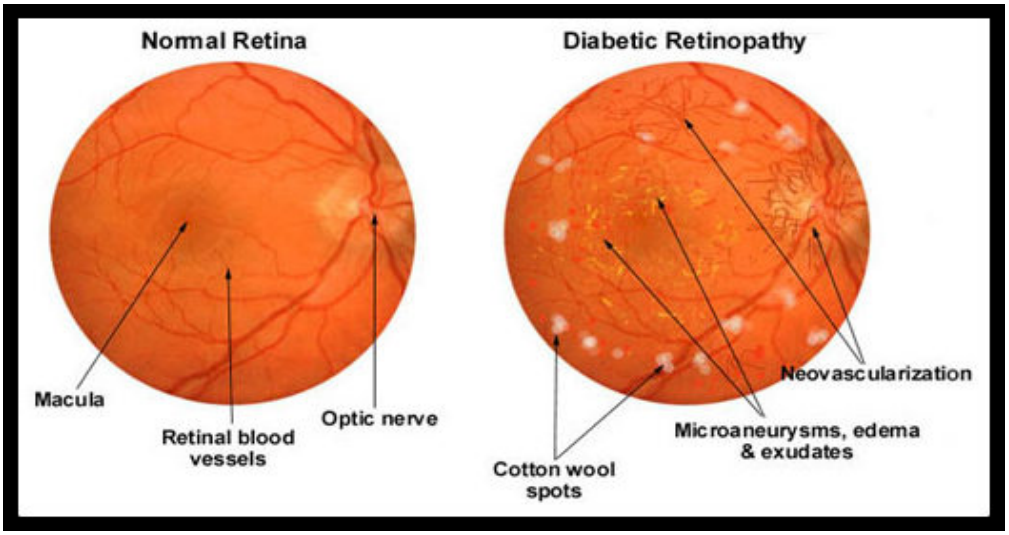
The early stage of diabetic retinopathy (DR) is characterized by loss of retinal pericytes. This is followed by development of weakness in the capillary wall that leads to formation of micro aneurysm and leakage from capillaries as their walls become more permeable. Impaired vascular function gradually develops leading to areas of ischemia and infarction. In response to these changes local growth factors are secreted that contribute to new vessel formation[65]. Macular edema (ME), and proliferative retinopathy are the two major sight threatening manifestations of diabetic retinopathy and they

represent the end manifestations of increased vascular permeability and vascular occlusion.

Macular edema (if present) is divided in three categories: 1) Mild with some retinal thickening or hard exudates in the posterior pole but distant from the center of the macula, 2) Moderate with retinal thickening or hard exudates approaching the center of the macula but Diabetic complications 15 not involving the center, and 3) Severe with retinal thickening or hard exudates involving the center of the macula .

DR is still the leading cause of blindness in older adults (45-74 years) accounting for more than one third of the cases and the fourth common cause of blindness in younger adults (15-44 years) in the Western world. The prevalence of diabetic retinopathy is correlated to diabetes duration but unlike nephropathy, retinopathy shows no decline in incidence after 15- 20 years of diabetes duration. The Wisconsin study reported a 70% overall prevalence of diabetic retinopathy in T1DM patients (onset of diabetes before 30 years) and 39% in insulin treated T2D patients (age at onset ≥30 years). Prevalence of proliferative diabetic retinopathy (PDR) was 23% and 14%, respectively, and clinically significant ME 14% and 11% in T1D and insulin treated T2D patients, respectively . The incidence of severe retinopathy seems to be declining, perhaps due to better metabolic control .

In a 14-year follow-up to the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the cumulative incidence of PDR over a period of 15 years in persons with T1D was still 37% but there appeared to be a decline in the estimated annual rates of progression to proliferative retinopathy and the incidence of ME in the last 4-year period of the study compared to earlier periods of the study. A Swedish study from Linkoping showed also that the cumulative proportion of severe retinopathy in T1DM patients diagnosed in childhood is declining.



NATURAL HISTORY AND EPIDEMIOLOGY OF DIABETIC NEUROPATHY:

Diabetic neuropathy encompasses a wide range of nerve abnormalities and is common, with prevalence rates reported between 5–100% depending on the diagnostic criteria [66,67]. Due to the variety of clinical manifestation there

is no universally accepted classification of diabetic neuropathy. Neuropathy is often divided into sensory motor and autonomic neuropathy .

CLASSIFICATION OF DIABETIC NEUROPATHY

Sensory motor neuropathy

Distal symmetric polyneuropathy

Focal neuropathy

Diabetic mononeuropathy (cranial, truncal, peripheral nerves)

Mononeuropathy multiplex

Diabetic amyotrophy

Autonomic neuropathy

Hypoglycemic unawareness

Abnormal pupillary function

Cardiovascular autonomic neuropathy

Vasomotor neuropathy

Sudomotor neuropathy (sweat glands)

Gastrointestinal autonomic neuropathy

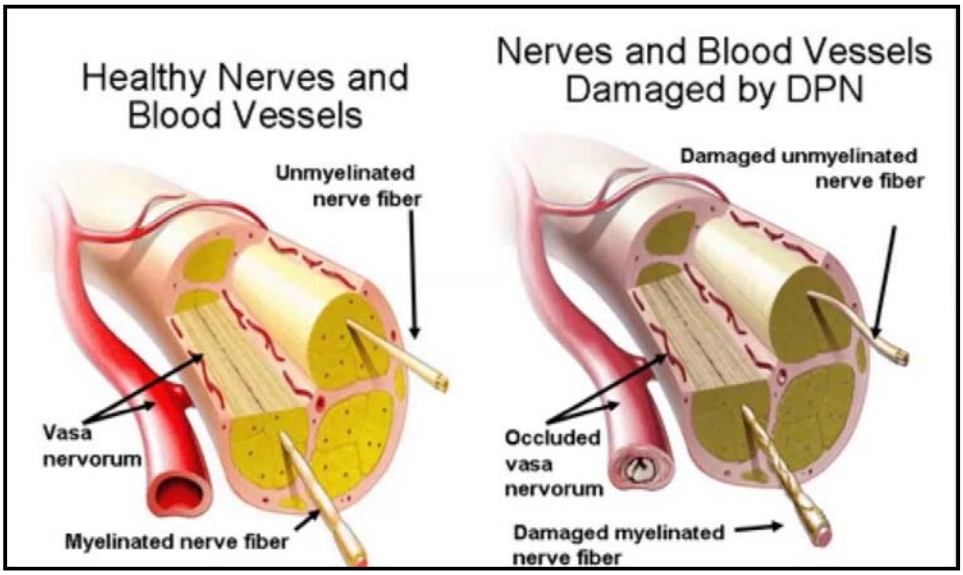
Gastric atony

Diabetic diarrhea or constipation

Genitourinary autonomic neuropathy

Bladder dysfunction

Sexual dysfunction



Macrovascular

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system (Lehto, 1996).

Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound (Laing et al 2003).

Cardiovascular disease is a major complication and the leading cause of premature death among diabetic patients(Merz et al 2002). Diabetic patients

have a 2 to 6 times higher risk for developing complications such as ischemic heart disease, cerebrovascular disease and peripheral vascular disease than the general population.

Among macrovascular diabetes complications, coronary heart disease has been associated with diabetes in numerous studies beginning with the Framingham study (Kannel et al 1979).

The major cardiovascular risk factors in the non-diabetic population (smoking, hypertension and hyperlipidemia) also operate in diabetes, but the risks are enhanced in the presence of diabetes. Overall life expectancy in diabetic patients is 7 to 10 years shorter than non-diabetic people.

Type II diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia. These other factors can also act to promote CVD. Even in this setting of multiple risk factors, type II diabetes acts as an independent risk factor for the development of ischemic disease, stroke, and death (Almdal et al 2004), Diabetes is also a strong independent predictor of risk of stroke and cerebrovascular disease, as in coronary artery disease (Lehto et al 1996).

The increased risk of CVD has lead to more aggressive treatment of these conditions to achieve primary or secondary prevention of coronary heart disease before it occurs. Studies in Type I Diabetes have shown that intensive diabetes control is associated with a lower resting heart rate and that patients

with higher degrees of hyperglycaemia tend to have a higher heart rate, which is associated with higher risk of CVD (Paterson et al 2007).

Once clinical macro-vascular disease develops in diabetic patients they have a poorer prognosis for survival than normoglycaemic patients with macrovascular disease.

In addition, the combination of hypertension and diabetes is a serious situation, posing increased predisposition to cardiovascular morbidity and mortality. There is no doubt that hypertension occurs more commonly in diabetic patients, and confer a greater prospect of development of complications; it should therefore be taken as seriously as glycaemic control when planning treatment strategies.

Hyperlipidemia can occur as a result of poorly controlled diabetes, or may occur as an independent risk factor for macrovascular disease. About 25% of patients attending a diabetes clinic will have elevated lipid levels (Jacobson, 1985).

INFECTIONS :

Diabetic patients are also in greater risk of infections than healthy individuals. The association between diabetes and increased susceptibility to infection in general is not supported by strong evidence. However, many specific infections are more common in diabetic patients and some occur

almost exclusively in them. Other infections occur with increased severity and are associated with an increased risk of complications.

Several aspects of immunity are altered in patients with diabetes. There is evidence that improving glycaemic control improves immune function. Fungal cystitis, rhino-cerebral mucormycosis and community-acquired pneumonia are among the most common infections the diabetic patients suffer from (Gu, 1998).

RECOMMENDATIONS FOR MANAGING THE COMPLICATIONS OF DIABETES MELLITUS :

- Blood pressure should be measured routinely. Goal blood pressure is < 130/80 mmHg. Patients with a blood pressure ≥ 140/90 mmHg should be treated with drug therapy in addition to diet and lifestyle modification.

- Patients with a blood pressure of 130-139/80-89 mmHg may attempt a trial of lifestyle and behavioral therapy for three months and then receive pharmacological therapy if their goal blood pressure is not achieved.

- Lipid testing should be performed in patients with diabetes at least annually. Lipid goals for adults with diabetes should be an LDL < 1000 mmol/l (or < 700mmol/l in patients with overt CVD), HDL > 500mmol/l, and fasting triglycerides < 1500mmol/l.

- All patients with diabetes should be encouraged to limit consumption of saturated fat and cholesterol.

- Patients with type I diabetes should receive a comprehensive eye examination and dilation within 3-5 years after the onset of diabetes. Patients with type II diabetes should undergo such screening at the time of diagnosis.

- Patients should strive for optimal glucose and blood pressure control to decrease the likelihood of developing diabetic retinopathy or experiencing progression of retinopathy (Paterson et al, 2007).

- All patients with diabetes should undergo screening for distal symmetric polyneuropathy at the time of diagnosis and yearly thereafter.

- Patients who experience peripheral neuropathy should begin appropriate foot self-care, including wearing special footwear to decrease their risk of ulceration.

- In addition to the above pharmacological recommendations, patients with diabetes should be encouraged to not begin smoking or to stop smoking to decrease their risk of CVD and benefit their health in other ways.

PHARMACOLOGICAL TREATMENT

Old approaches to the treatment of this chronic progressive disease include diet modification and oral hypoglycemic medications, which have proven inadequate, while insulin therapy only solves the problem temporarily. Even with the newest pharmaco-therapies, patients continue to develop macro- and microvascular complications. Diabetes is associated with increased cardiac- and stroke-related deaths, kidney failure, blindness, and 60% of non-trauma lower-limb amputations (National diabetes fact sheet,Atlanta2004).

Alternative treatments targeting different models of this disease require careful and responsible examination.

INSULIN THERAPY

Diabetes, being one of the primary causes of increased cardiovascular morbidity and mortality in India, constitutes a large burden to health care systems in terms of both direct and indirect costs. Therefore, efficient glucose control (attainment of normal HbA1C, prandial and postprandial glucose levels) is essential to the prevention of the life-threatening complications of this disease.

Insulin is a hormone that treats diabetes by controlling the amount of sugar (glucose) in the blood. When used as a medication, it is derived from

either pork (porcine), beef (no longer available in the U.S.), or is genetically made to be identical to human insulin (Buysschaert, 2000).

Patients with type I diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type II diabetes mellitus are insulin resistant, have relatively low insulin production, or both; certain patients with Type II diabetes may eventually require insulin if other medications fail to control blood glucose levels adequately.

There are many types of insulin used to treat diabetes. They are classified by how fast they start to work, when they reach their "peak" level of action (i.e. when the concentration of insulin in the blood is highest), and how long their effects last.

TYPES OF INSULIN

There are several types of insulin. These types are classified according to how quickly the insulin begins to work and how long it remains active:

Injectable insulin

- Rapid-acting (eg, insulin lispro [brand name: Humalog], insulin aspart [brand name: NovoLog], and insulin glulisine [brand name: Apidra])
- Short-acting (eg, insulin regular)

- Intermediate-acting (eg, insulin NPH, NPL [neutral protamine lispro])
- Long-acting (eg, insulin glargine [brand name: Lantus], insulin detemir [brand name: Levemir])
- Very long-acting (eg, insulin degludec [brand name Tresiba])

The various types of insulin can be used in combination to achieve around-the-clock blood sugar control.

Inhaled insulin

An inhaled form of rapid-acting insulin was available for a short time but was discontinued in 2007. In 2015, another formulation of inhaled insulin (brand name: Afrezza) became available for clinical use in the United States. Once inhaled, it begins to work quickly, similar to rapid-acting insulin, and is therefore considered a prandial (mealtime) insulin. Inhaled insulin has not been shown to lower A1C levels to the usual target level of less than 7 percent in most studies. In addition, lung function testing is required before starting it and periodically during therapy.

OTHER FACTORS AFFECTING INSULIN ACTION

Several factors can affect how injected insulin works.

Dose of insulin injected — The dose of insulin injected affects the rate at which the body absorbs it. Larger doses of insulin may be absorbed more slowly than smaller doses.

Site of injection — Clinicians usually recommend rotating injection sites to minimize tissue irritation. When changing sites, it is important to keep in mind that insulin is absorbed at different rates in different areas of the body.

Insulin is absorbed fastest from the abdominal area, slowest from the leg and buttock, and at an intermediate rate from the arm. This may vary with the amount of fat present; areas with more fat under the skin absorb insulin more slowly .

It is reasonable to use the same general area for injections given at the same time of the day. Sometimes abdominal injections, which are absorbed more quickly, are preferred before meals. Injection into the thigh or buttock may be best for the evening dose because the insulin will be absorbed more slowly during the night.

Smoking and physical activity — Any factors that alter the rate of blood flow through the skin and fat will change insulin absorption. Smoking decreases blood flow. In contrast, factors that increase blood flow (such as exercise, saunas, hot baths, and massage of the injection site) increase insulin absorption and can result in hypoglycemia. Therefore, to avoid low blood sugar, insulin injections should be given after a bath or sauna. It is best to inject insulin into the arm or abdomen and wait 30 minutes before running. A lower dose of insulin may be recommended before or after exercise; this should be discussed with a healthcare provider.

Time since opening the bottle — Most insulin remains potent and effective for up to a month after the bottle has been opened (if kept in the refrigerator between injections). However, the potency of intermediate and long acting insulin begins to decrease after 30 days. This can be a problem for people who require very small doses of insulin, for whom a bottle might last two months or more. It is advisable to start a new bottle at least every 30 days.

For very rapid acting insulin used in pen injectors, it is acceptable to keep the pen injector at room temperature (in a purse or jacket pocket) for up to 14 days, provided that the pen is not exposed to temperature extremes. However, after 14 days, a new insulin cartridge or pen should be used, even if there is insulin left in the old cartridge.

Individual differences — The same dose of the same type of insulin may have different effects in different people with diabetes. Some trial and error is usually necessary to find the ideal type(s) and dose of insulin and schedule for each person.

Insulin needs often change over a person's lifetime. Changes in weight, diet, health conditions (including pregnancy), activity level, and occupation can have an impact on the amount of insulin needed to control blood sugar levels. Patients are often able to adjust their own insulin dose, but may require assistance in some situations.

Complications of the insulin therapy

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycaemia, which when untreated can lead to long-term complications, including micro- and macrovascular complications. Tight glycaemic control with intensive insulin therapy has been suggested to reduce the risk of such complications in several diabetes populations; however, such an approach can also be associated with risks and challenges.

The major side effects of insulin taken for diabetes include low blood sugar (hypoglycemia), hypertrophy (enlargement of the area of the body that has received too many insulin injections), and rash at the site of injection or over the entire body (rare). The symptoms of the most common complication, i.e. low blood sugar, include extreme hunger, fatigue, irritability, cold sweats, trembling hands, intense anxiety and a general sense of confusion. They might be the signs of an insulin overdose, a potentially dangerous complication with diabetes, which happens to many diabetic patients (Gkaliagkousi, 2007).

Non-Insulin Diabetes Treatment

There is a relatively new class of drugs called incretinmimetics, which mimic certain substances that can be found in the stomach and intestinal tract. These substances are normally released in response to food intake and signal the release of insulin from the pancreas. Since this reaction is reduced in people with type II diabetes, incretinmimetics work to stimulate insulin release and

help lower blood sugar. These medications are taken by injection, either once or twice a day.

For people with type II diabetes, medications called DPP-4 inhibitors can be taken alone or in combination with other diabetes medications. DPP-4 inhibitors prevent the breakdown of incretin hormones. In turn, the incretins can help their body produce insulin to lower elevated blood sugar levels (Gkaliagkousi, 2007).

ORAL HYPOGLYCEMIC AGENTS (OHA)

The following five categories will be presented in brief: Sulphonylureas and similar (secretagogues), Biguanides (sensitizers), Thiazolidindiones, Alpha glucosidase inhibitors, and Incretine analogues/agonists (Boulton, 2005).

As concerns the mode of action of the secretagogues like sulphonylureas, they block the ATP-sensitive K+ channel and as a result they stimulate the insulin secretion. They are indicated to be the first choice once a patient is diagnosed with Type II Diabetes. The side effects include hypoglycaemia and disulfiram reaction, while its interaction is the competition for protein binding/metabolism/secretion.

The first-generation agents include tolbutamide, acetohexamide, tolazamide, and chlorpropamide ;

The second-generation agents include glipizide , glyburide , and gliclazid;

The third-generation agents include glimepiride.

The Meglitinides are short acting secretagogues, similar to sulphonylureas. They also block the ATP-sensitive K+ and they open the Ca2 + channels, thus stimulating insulin secretion. Their side effects include weight gain and hypoglycaemia.

As concerns the mode of action of the sensitisers such as the Biguanides, they reduce the hepatic synthesis and the output of glucose, while they increase the insulin uptake in the skeletal muscle. They are actually antihyperglycaemic and not hypoglycaemic. They are indicated for Type II Diabetes Mellitus and polycystic ovary syndrome. They help reduce LDL cholesterol and triglyceride levels and they may help with the weight loss. Their side effects include lactate acidosis, GIT discomfort, diarrhea, renal toxicity, but they do not cause hypoglycemia.

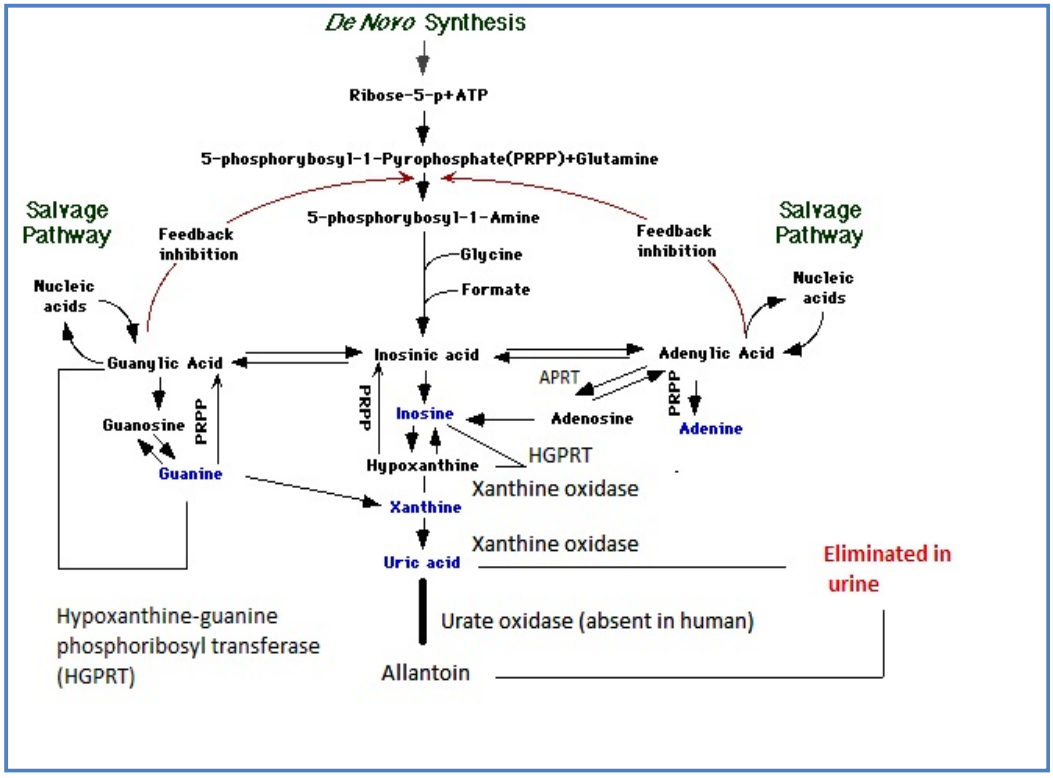
As concerns the mode of action of the glitazones such as the Thiazolidinediones, they are selective agonists of PPARγ receptors, thus activating the insulin-sensitive genes regulating the glucose and fat metabolism. As a result, they increase the insulin sensitivity in the periphereal tissue. Their side effects include hepatotoxicity (troglitazone).

As concerns the mode of action of the inhibitors of the alpha-glucosidase or the alpha amylace, they reduce the intestinal absorption of starch, dextrins, and disaccharides and as a result they reduce the postprandial plasma glucose. They are indicated both for Type I and Type II Diabetes, in combination with diet and insulin. Their side effects include malabsorption, flatulence, and diarrhea.

As concerns the mode of action of the peptide analogues such as the GLP-1 agonists, they bind to a membrane GLP-1 receptor. They are metabolized by the dipeptidyl peptidase IV enzyme (DPP-IV). Their side effects include nausea, hypoglycemia (if given together with insulin secretagogue).

URIC ACID

Uric acid is the products of catabolism of the purine nucleic acids. Although it is filtered by the glomreulus and secreted by the distal tubules into the urine, most uric acid is reabsorbed in the proximal tubules and reused. Uric acid is relatively in soluble in plasma, at high concentration, can be deposited in the joints and tissue, causing pain full inflammation. The range of plasma urate in men and women is, increasing slightly with age.



FUNCTION OF URIC ACID:

Uric acid, or more correctly (at physiological ph values), it is mono anion urate is traditionally considered to be metabolically inert end – produce of purine metabolism in man without any physiology value . However this ubiquitous compound has proven to be selective anti oxidant, capable especially of reaction with hydroxyl radical and hypochlorous acid, itself being converted to innocuous product (allantoina, allanotdate, glyoxylate, uria oxalate). There is now evidence for such processes not only in vitro and in isolated organ, but also in the human lung in vivo. Urate may also serve as an oxidase substrate for enzyme cyclooxygenase.

Physiology of uric acid

Purine, such as adenosine and guanine from the breakdown of ingested nucleic acid or from tissue destruction, are converted into uric acid, primarily in the liver. Uric acid is transported in the plasma from the liver to the kidney, where it is filtered by the glomerulus. Reabsorption of 98% to 100% of uric acid from the glomerular filtrate occurs in the proximal tubules. Small amounts of uric acid are secreted by the distal tubules into urine. Renal excretion accounts for about 70% of uric acid elimination, the remainder passes into the gastrointestinal tract and is degraded by bacterial enzymes (Bishop *et al*., 2010). Nearly all of the uric acid in plasma is present as monosodium urate. At the ph of plasma (ph 7), urate is relatively insoluble, at concentration greater than 6.8 mg/dl, the plasma is saturated. As a result, urate crystal may form and precipitate in the tissue. In acidic urine (ph <5.75), uric acid is the predominant species and uric acid crystal may form (Bishop *et al*., 2010).

CLINICAL SIGNIFICANT OF URIC ACID

HYPERURICEMIA

Hyperuricemia is a result of over production of uric acid, although Hyperuricemia may be exacerbated by purine –rich diet, drug, and alcohol. Plasma uric acid concentration in affected individual is usually greater than 6.0 mg/dl. Patients with gout are very susceptible to the development of renal calculi, although not all people with high serum urate concentration develop this complication. In women, urate concentration rises after menopause.

Postmenopausal women may develop Hyperuricemia and gout. In severe cases, deposit of crystalline uric acid and urate called tophi form in tissue, causing deformities (Bishop *et al*., 2010). Another common cause of elevated plasma uric acid concentration is increased metabolism of cell nuclei, as occurs in patients on chemotherapy for such proliferative disease as leukemia, lymphoma, multiple myeloma, and polycythemia. Monitoring uric acid concentration in these patients is important to avoid nephrotoxicity.

Chronic renal disease causes increased uric acid concentration because filtration and secretion are impaired. However, uric acid is not useful as indicator of renal function because many other factors affect its plasma concentration. Patients with hemolytic or megaloblastic anemia may exhibit elevated uric acid concentration.

Hyperuricemia is a common feature of toxemia of pregnancy (preeclampsia) and lactic acidosis, presumably as a result of competition for binding sites in the renal tubules. Increased urate concentration may be found following ingestion of a diet rich in purine (Liver, kidney, sweetbread, shellfish) or as a result of increased tissue catabolism due to inadequate dietary intake (starvation) (Bishop *et al*., 2010).

Hyperuricemia is generally divided into three pathophysiologic categories: uric acid underexcretion, uric acid overproduction, and combined causes.

Underexcretion

Causes of uric acid underexcretion include the following:

- Idiopathic
- Familial juvenile gouty nephropathy: This is a rare autosomal dominant condition characterized by progressive renal insufficiency. These patients have a low fractional excretion of urate (typically 4%). Kidney biopsy findings indicate glomerulosclerosis and tubulointerstitial disease but no uric acid deposition.
- Renal insufficiency: Renal failure is one of the more common causes of hyperuricemia. In chronic renal failure, the uric acid level does not generally become elevated until the creatinine clearance falls below 20 mL/min, unless other contributing factors exist. This is due to a decrease in urate clearance as retained organic acids compete for secretion in the proximal tubule. In certain renal disorders, such as medullary cystic disease and chronic lead nephropathy, hyperuricemia is commonly observed even with minimal renal insufficiency.
- Metabolic syndrome: This syndrome is characterized by hypertension, obesity, insulin resistance, dyslipidemia, and hyperuricemia,(69) and is associated with a decreased fractional excretion of urate by the kidneys.
- Drugs: Causative drugs include diuretics, low-dose salicylates, cyclosporine, pyrazinamide, ethambutol, levodopa, and nicotinic acid.

- Hypertension
- Acidosis: Types that cause hyperuricemia include lactic acidosis, diabetic ketoacidosis, alcoholic ketoacidosis, and starvation ketoacidosis.
- Preeclampsia and eclampsia: The elevated uric acid associated with these conditions is a key clue to the diagnosis because uric acid levels are lower than normal in healthy pregnancies.
- Hypothyroidism
- Hyperparathyroidism
- Sarcoidosis
- Lead intoxication (chronic): History may reveal occupational exposure (eg, lead smelting, battery and paint manufacture) or consumption of moonshine (ie, illegally distilled corn whiskey) because some, but not all, moonshine was produced in lead-containing stills)
- Trisomy 21

Overproduction

- Idiopathic
- Hypoxanthine guanine phosphoribosyltransferase (HGPRT) deficiency (Lesch-Nyhan syndrome): This is an inherited X-linked disorder. HGRPT catalyzes the conversion of hypoxanthine to inosinic acid, in which PRPP serves as the phosphate donor. The deficiency of HGPRT

results in accumulation of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP), which accelerates purine biosynthesis with a resultant increase in uric acid production. In addition to gout and uric acid nephrolithiasis, these patients develop a neurologic disorder that is characterized by choreoathetosis, spasticity, growth, mental function retardation, and, occasionally, self-mutilation.

- Partial deficiency of HGPRT (Kelley-Seegmiller syndrome): This is also an X-linked disorder. Patients typically develop gouty arthritis in the second or third decade of life, have a high incidence of uric acid nephrolithiasis, and may have mild neurologic deficits.

- Increased activity of PRPP synthetase: This is a rare X-linked disorder in which patients make mutated PRPP synthetase enzymes with increased activity. These patients develop gout when aged 15-30 years and have a high incidence of uric acid renal stones.

- Diet: A diet rich in high-purine meats, organ foods, and legumes can result in an overproduction of uric acid.

- Increased nucleic acid turnover: This may be observed in persons with hemolytic anemia and hematologic malignancies such as lymphoma, myeloma, or leukemia.

- Tumor lysis syndrome: This may produce the most serious complications of hyperuricemia.

- Glycogenoses III, V, and VII

- Exposure to persistent organic pollutants (eg, organochlorine pesticides)(70)

Combined causes

Alcohol(71): Ethanol increases the production of uric acid by causing increased turnover of adenine nucleotides. It also decreases uric acid excretion by the kidneys, which is partially due to the production of lactic acid.

- Fructose-sweetened soft drinks: Fructose raises serum uric acid levels by accentuating degradation of purine nucleotides and increasing purine synthesis, and epidemiologic studies have documented a link between sugar-sweetened soft drink intake and serum uric acid levels in several populations(72,73,74). More recently, Lecoultre et al found that fructose-induced hyperuricemia is associated with a decreased renal uric acid excretion. (75).

- Exercise: Exercise may result in enhanced tissue breakdown and decreased renal excretion due to mild volume depletion.

- Deficiency of aldolase B (fructose-1-phosphate aldolase): This is a fairly common inherited disorder, often resulting in gout.

- Glucose-6-phosphatase deficiency (glycogenosis type I, von Gierke disease): This is an autosomal recessive disorder characterized by the development of symptomatic hypoglycemia and hepatomegaly within the first 12 months of life. Additional findings include short stature, delayed adolescence, enlarged kidneys, hepatic adenoma, hyperuricemia, hyperlipidemia, and increased serum lactate levels.

HYPOURICEMIA

Hypouricemia is less common than Hyperuricemia and is usually secondary to sever liver disease or defective tubular reabsorption, as in fanconi syndrome. Hypouricemia can be caused by chemotherapy with 6-mercaptopurine or azathioprine, inhibitors of de novo purine synthesis, and as a result of overtreatment with Allopurinol (Bishop *et al*., 2010).

SERUM URIC ACID LEVEL IN DIABETES

In recent decades, serum uric acid has emerged as a potential risk factor for type 2 diabetes mellitus (T2DM). Elevated uric acid levels are often found in individuals with the metabolic syndrome, a collection of risk factors for T2DM often found to cluster together and including the following: truncal obesity, hypertriglyeridemia, decreased high density lipoprotein, hypertension,

and insulin resistance.1 While uric acid appears to increase the risk of T2DM, it remains unclear if this relationship is maintained after accounting for the other metabolic factors. If uric acid proves to be a novel screening tool that predicts future incidence of T2DM, it may have an application in risk stratification, especially for patients with few of the other established risk factors. Early identification of those who are likely to develop T2DM allows early implementation of interventions to mitigate their risk.

In the meta-analysis derived from 8 prospective cohort studies, found that high level of serum uric acid was associated with increased risk of developing type 2 diabetes in middle-aged and older people. For each 1 mg/dl increment in serum uric acid level, there was a 6% increase in the risk of incident type 2 diabetes. Importantly, the relationship between serum uric acid and incident diabetes was independent of other established risk factors of type 2 diabetes, especially metabolic syndrome components, which strongly supported high serum uric acid as a causal factor of type 2 diabetes.

Several underlying mechanisms might be involved in the association between hyperuricemia and the development of type 2 diabetes. For example, recent animal studies showed fructose-induced hyperuricemia play a pathogenic role in metabolic syndrome, and the conditions were improved by decreasing uric acid levels (76,77). Hyperuricemia has been shown to induce endothelial dysfunction and to reduce the production of nitric oxide (78,79). Nitric oxide reduction could lower insulin-stimulated glucose intake in skeletal

muscle, which contributes to insulin resistance and thus diabetes. In addition, hyperuricemia is associated with oxidative stress (80,81), which plays an important role in the pathogenesis of type 2 diabetes. These experimental evidence supports serum uric acid as a causal factor of diabetes.

Given the fact that type 2 diabetes has been a growing public health burden across the world and hyperuricemia is very common in the general population, early identification of hyperuricemia will be of importance. Moreover, serum uric acid levels can be easily measured and hyperuricemia is modifiable by medication. Therefore, controlling hyperuricemia might be a promising strategy for the prevention of type 2 diabetes.

MICROALBUMINURIA

Under normal conditions, daily albumin excretion is in the range of 5–10 mg and the urine albumin: creatinine ratio is in the range of 0–29 mg albumin/g creatinine. Forty years ago, technology for measuring small amounts of urine albumin was described to determine abnormal amounts of albumin excretion or albuminuria. Microalbuminuria is defined as an abnormal increase in albumin excretion rate within the specific range of 30–299 mg of albumin/g of creatinine. It is important to recognize that the term microalbuminuria specifically refers to an abnormal albumin excretion rate and not the presence of an abnormal (small) albumin molecule. The term was coined in the early 1980s, when technical advances made it possible to

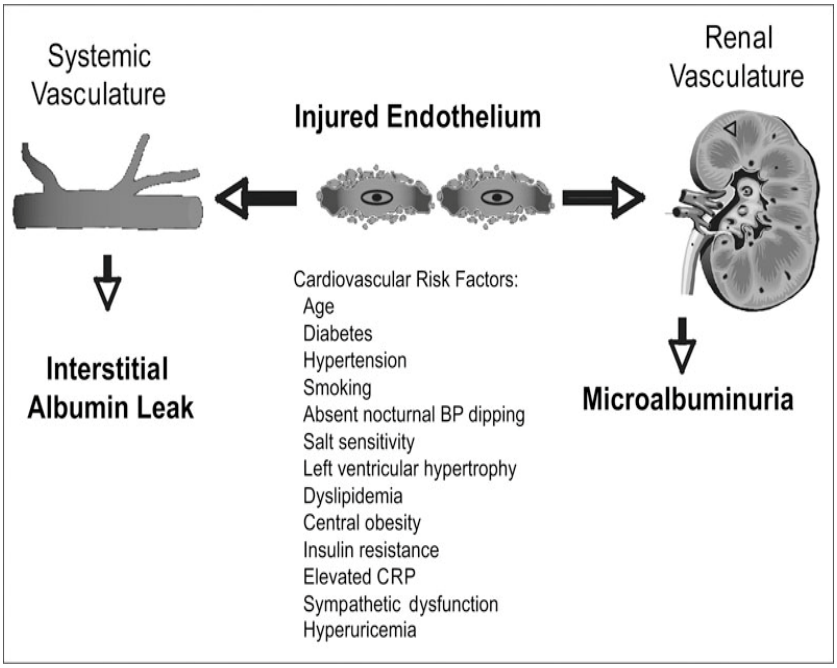
identify small, but abnormal, increases in albumin in the urine of patients with diabetes and other diseases—hence the term "microalbuminuria."

CLINICAL SIGNIFICANCE OF MICROALBUMINURIA

Microalbuminuria is a widely identified marker of endothelial dysfunction. microalbuminuria is associated with other cardiovascular risk factors, including markers of inflammation and markers of endothelial dysfunction. The presence of microalbuminuria markedly increases the risk for cardiovascular morbidity and mortality among diabetics and nondiabetics. It has been estimated that 6% of men and 10% of women in the United States have microalbuminuria; Its prevalence is 16% among hypertensives and as high as 28% among diabetics.

Observational studies in the general population have shown an increase in risk for total and cardiovascular mortality. In type 1 and type 2 diabetics, the presence of microalbuminuria is associated with increased cardiovascular and all-cause mortality and ischemic heart disease events. In addition, microalbuminuria is independently associated with angiographic evidence of coronary artery disease. Most studies indicate that the presence of persistent microalbuminuria imposes a two-fold increase in risk for cardiovascular mortality. Cross-sectional data indicate that microalbuminuria among hypertensive nondiabetics is associated with an increase in all-cause mortality among hypertensives. Furthermore, among hypertensives without diabetes

followed prospectively, microalbuminuria is associated with a four-fold increased risk for ischemic heart disease.



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Clinical trials have also demonstrated an increased risk for cardiovascular events in individuals with microalbuminuria at baseline. In addition, these trials have demonstrated improved outcomes among both diabetics and nondiabetics treated with agents that block the renin-angiotensin system. For example, in the Heart Outcomes Prevention Evaluation (HOPE) study, type 2 diabetics with microalbuminuria had a two-fold higher rate of cardiovascular events, including myocardial infarction, stroke, and cardiovascular death, as compared with patients without microalbuminuria. In this trial, ramipril treatment was associated with improved cardiovascular outcomes in both diabetics and nondiabetics. In the Losartan Intervention For

Endpoints (LIFE) trial, patients with microalbuminuria also had increased stroke and myocardial infarction rates as compared with those without microalbuminuria. Patients treated with a losartan-based regimen, including microalbuminurics, had improved cardiovascular morbidity and mortality as compared with those treated with a treatment program based on atenolol.

SIGNIFICANT PROTEINURIA

Twenty-four hour urinary protein which is the gold standard investigation and it is significant when the total protein excretion of 300mg or more in 24 hours urine is present and severe proteinuria is diagnosed when total urinary protein is ≥ 3g/24hours. However, the limitations with this is that it is cumbersome, is expensive, there is delay in making diagnosis and interventions, sample collection is difficult and inaccurate, above all it requires admission. In visual dipstick urinary strips, two clean–catch midstream or catheter specimens of urine collected 4hours or more apart is used and is significant when there is proteinuria of 2+ or more i.e (1g/L) or 1+ (0.3g/L) if specific gravity is < 1.030 and PH < 8. The advantage of visual dipstick is that it is handy, cheap, fast, easy to administer, does not need special training, however it has poor sensitivity, specificity, negative predictive value and positive predictive value. The protein-creatinine ratio cut off ≥30mg/mmol has been used and it correlates with 24hour urinary protein in term of sensitivity, specificity, negative predictive value and positive predictive value, and should replace visual dipstick in clinical practise, however it is expensive and requires

training . Microalbumin cut off of 30mg/dL has been used. It correlates well with 24hour urine protein however the strips are not readily available, is more expensive than visual dipsticks.

Spot urinary microalbumin: creatinine ratio cut off of >30mg/g (3.4mg/mmol) is considered as positive for significant proteinuria and correlates well with 24hour urine protein with sensitivity of 94% and specificity of 98%. It also has good positive predictive value and negative predictive value and is a suitable substitute to visual dipsticks however is more expensive than visual dipstick and the technology is not yet embraced and few studies have been done to validate its benefits(Heerspink et al., 2006).

The gold standard for measuring proteinuria is 24 hours urine sample this is because of variation in protein excretion during the day, which is affected by factors such as water intake and excretion rate of diuresis, exercise, recumbency and diet (Price et al., 2005). However the major problem with 24 hour protein collection is that it is often impractical in the outpatient setting with problems of incomplete collection. Besides, the collection is cumbersome, often incomplete and difficult to administer, most time requiring admission, increase cost with possible prolonged hospital stay, hence there is need to find a method that is shorter, quick, easy to administer and correlates well with 24 hour urinary protein excretion. Unfortunately, the most widely used screening test for proteinuria, the dipstick test has been fraught with error and correlates poorly with 24 hour urinary protein excretion. Hence there remains therefore

the need for a reliable semi-quantitative measurement of urinary protein excretion that will be quick, easy to administer and also correlates well with 24hour urinary protein excretion .

Much more accurate is the use of spot urinary microalbumin to creatinine ration (UAC) of 30-300mg/g or 3.4- 33.9mg/mmol. Creatinine excretion rates are fairly constant provided the glomerular filtration rate (measured by creatinine clearance) is constant. Thus a ratio of the concentrations of urinary protein and creatinine in a single voided urine sample would reflect the cumulative excretion during the day since the ratio of two stable rates would cancel out the time factor. Thus a spot urinary microalbumin to creatinine ratio cut off of > 30mg/g (3.4mg/mmol) is considered as positive for significant proteinuria and correlates well with 24hours urine protein with sensitivity of 94%, specificity of 98% as against microalbuminuria alone which has sensitivity of 58% and specificity of 83%. Furthermore, the urinary microalbumin to creatinine ratio has a good negative predictive value and a result of <3.4mg/mmol rules out significant proteinuria and avoids unnecessary investigations. These improved sensitivity, specificity and NPV of (UAC) over the visual dipstick suggests that it may be a suitable substitute for visual dipstick in clinical practice for it has the potential to improve accuracy of screening for proteinuria and enhancing safety by preventing incorrect diagnosis and unnecessary investigations.

The clinician and the patient need to know what the probability is that a positive result is genuinely positive (positive predictive value) and what the probability is that a negative result is genuinely negative. This determines the confidence the clinician has in a positive or negative result and his willingness to base clinical judgements on the results. The positive predictive values for urinary microalbuminuria/creatinine ratio (96.7%), is higher than that for the dipstick test (88%). The positive predictive value is even higher when these indices are combined together. Hence the probability that a positive result with dipstick is false is higher than the probability that it is genuinely positive. This clearly shows the risk associated with making decisions based on a positive dipstick reaction. The positive predictive value demonstrates the unreliability of the dipstick test. This demonstrates that the possibility of mismanagement of patients based on decision made using a positive urinary microalbuminuria/creatinine ratio is low.

In terms of accuracy which is the measure of a test to accurately detect or rule out the disease, this was expectedly highest for the microalbuminuria/ creatinine ratio (93.8%) compared to the urine microalbumin dipstick test(83.8%) and visual dipstick test (71.3%) . The microalbuminuria/creatinine ratio especially is reliable, relatively faster and accurate for proteinuria correlating well with 24hour urinary protein excretion; they also show that it is much more reliable than the dipstick test on every test of effectiveness

measured, and therefore should substitute the urine dipstick test for protein estimation in clinical practice.

TREATMENT

Glycemic and blood pressure control, particularly with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), may reduce both moderately increased albuminuria (formerly called "microalbuminuria") and progression to severely increased albuminuria (formerly called "macroalbuminuria") . Nondihydropyridine calcium channel blockers (diltiazem and verapamil) also may be beneficial, while other classes of antihypertensive drugs have less or no antiproteinuric effect and are not specifically used for renal protection.

ACE inhibitors/ARBs — Renoprotective benefits with ACE inhibitors and ARBs compared with placebo have been noted in a number of trials . The potential magnitude of benefit can be illustrated by the results of a trial in which 590 hypertensive patients with type 2 diabetes and moderately increased albuminuria were randomly assigned to either irbesartan (150 or 300 mg/day) or placebo and then followed for two years .

The primary end point was the time from baseline to first detection of overt nephropathy (urine albumin excretion >200 mcg/min [severely increased albuminuria] and at least a 30 percent increase from baseline on two consecutive visits). This end point was significantly more common in the

placebo group compared with irbesartan (14.9 versus 9.7 and 5.2 percent with 150 and 300 mg of irbesartan). This benefit was not related to differences in blood pressure, although the systolic blood pressure was 3 mmHg lower with 300 mg irbesartan than with placebo or 150 mg irbesartan (141 versus 144 mmHg), a difference that was statistically significant.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have similar efficacy in type 2 diabetic patients with moderately increased albuminuria. The only randomized comparative trial (DETAIL) of these agents in type 2 diabetic patients compared enalapril with the ARB telmisartan in 250 patients with early nephropathy as defined by albuminuria (82 percent moderately increased and 18 percent severely increased albuminuria to a maximum of 1.4 g/day) and a baseline GFR (measured isotopically) of approximately 93 mL/min per 1.73 m2. A greater fall in GFR of at least 10.0 mL/min per 1.73 m2 at five years was predefined as suggesting a clinically significant difference between the two treatment groups.

At five years, there was a smaller decline in GFR with enalapril that was not significant (14.9 versus 17.9 mL/min per 1.73 m2 with telmisartan). Both groups had similar rates or findings for the secondary end points, which included annual changes in the GFR, blood pressure, serum creatinine concentration, urinary albumin excretion, end-stage kidney disease, cardiovascular events, and mortality.

Almost all of the moderately increased albuminuria trials involved hypertensive patients . Only one major trial involved "normotensive" patients . In this trial of 94 patients, enalapril was associated with stable albuminuria and serum creatinine, while increases in both parameters were noted with placebo at five and seven years.

In patients with type 2 diabetes and moderately increased albuminuria, we treat with either an ACE inhibitor or an ARB to slow or prevent progression to severely increased albuminuria and overt diabetic nephropathy. The renal goal of ACE inhibitor therapy is a modest reduction in urine albumin excretion.

Calcium channel blockers — Calcium channel blockers have less antiproteinuric effect than ACE inhibitors or ARBs, and the antiproteinuric effect is primarily seen with diltiazem and verapamil, not the dihydropyridines.

The difference between these drug classes in patients with type 2 diabetes and moderately increased albuminuria was evaluated in the MARVAL trial in which 332 such patients were randomly assigned to valsartan or amlodipine . Albumin excretion was reduced by 44 percent with valsartan compared to 8 percent with amlodipine, a difference that was highly significant. There was no difference in blood pressure between the two groups during the course of the study.

ASSOCIATION OF URIC ACID WITH PROTEINURIA

Despite the advances in the management of patients with diabetes, diabetic nephropathy (DN) remains the most common cause of end stage renal disease (ESRD) in the US and worldwide. Inflammation and endothelial dysfunction appear to play a central role in the onset and the progression of DN. Recent evidence has emerged in the last decade to suggest uric acid is an inflammatory factor and may play a role in endothelial dysfunction. This has lead our group and others to explore the role of uric acid in the onset and progression of DN.

Diabetic nephropathy (DN) is the most common cause of chronic kidney disease in the US and worldwide . Unfortunately, in the wake of the current epidemic of diabetes mellitus (DM), the prevalence of DN and ESRD are projected to rise . Different therapeutic strategies targeting DN have been explored such as tight glycemic control, tight blood pressure control , and various inhibitors of the renin angiotensin aldosterone system (RAAS) . While these therapies appear to slow the progression of kidney disease due to diabetes, none of them are curative. Hence there is a pressing interest to identify other potentially modifiable factors in the progression of DN.

Over the last 2 decades, an ample amount of scientific evidence has been generated and testifies to the role of cytokines in diabetic nephropathy . Specifically, hemodynamically- induced activation of transforming growth

factor β-1 (TGFβ-1) appears to play a major role in mesangial expansion ; in concert with the induction of ECM production . Several biochemical mechanisms have been identified to explain the adverse effects of hyperglycemia on the kidney, including protein kinase C (PKC), the (mitogen activate protein) MAP kinase pathway, in addition to activation of the polyol pathway, increased accumulation of advanced glycation products, and oxidative stress . Despite the strides that we have made in understanding the factors that contribute to the evolution and the progression of diabetic kidney disease, this growing knowledge has yet to culminate in new therapeutic approaches. This is partially due to the extreme complexity of the underlying process. But also, some potent mediators of diabetic kidney disease are not viable or safe therapeutic targets. For example, as enticing as it has been to target TGF β -1 for the treatment of diabetic nephropathy, TGF β-1 carries out multiple vital biologic functions . Importantly, it is a primary regulator of the immune system and mice with targeted disruption of TGF β -1 gene die within weeks of birth due to a generalized wasting syndrome characterized by multifocal mixed inflammatory cellular response and tissue necrosis . This explains the apprehension towards inhibiting TGF β -1 in humans and illustrates the need for other potentially modifiable factors in DN. One such factor that has made it onto the scene in recent years is uric acid.

Uric acid (Urate) is synthesized in the liver from purine compounds provided by the diet or by the endogenous pathway of purine synthesis de

novo. Some uric acid is also produced in peripheral tissues, especially the intestine and kidney. Uric acid that is produced in the liver is released into the circulation in its soluble form (monosodium urate), which is readily filtered by the glomerulus. The proximal tubular cells of the kidney reabsorb most of the uric acid resulting in a normal fractional excretion of approximately 10% . Uric acid accumulation beyond its solubility point (6.8 mg/dL) in water defines hyperuricemia. In general, hyperuricemia develops due to uric acid overproduction, undersecretion, or both . It is widely accepted that when uric acid levels are chronically elevated beyond their physiological levels, uric acid deposits in the joints and soft tissues leading to inflammatory arthritis and tophi (gout). Lowering uric acid levels is key to preventing recurrent acute gout attacks . Serum uric acid levels have also increased in Western populations where they have been found to predict the development of insulin resistance and diabetes . The potential causal relationship between uric acid and other conditions such as chronic kidney disease, however, remains controversial. Some authors indicate that uric acid is a potent antioxidant, and in a few studies when uric acid was administered acutely it appeared to improve endothelial function . Other experimental evidence however suggests that uric acid may induce oxidative stress once it enters cells, and as such it may be a mediator of disease . Consistent with this latter observation, data by our group demonstrates that even mild hyperuricemia, induced by the administration of a uricase inhibitor, causes endothelial dysfunction that resolves once uric acid levels are lowered. These findings when viewed in light of the importance of endothelial

dysfunction in the progression of DN prompted us to hypothesize that uric acid plays a role in diabetic induced kidney disease.

POTENTIAL MECHANISMS BY WHICH URIC ACID COULD MEDIATE DN

Uric acid has several reported effects by which it may cause DN , including endothelial dysfunction, increased activity of the RAAS, and induction of inflammatory cascades, in addition to profibrotic cytokine activation all of which have been demonstrated to contribute to progression of microvascular disease and thereby renal injury in DN. The effects of uric acid on the endothelium are subject of a contentious debate. On the one hand, uric acid has been shown to decrease nitric oxide (NO) production by endothelial cells in vitro, and it does so in association with increased CRP expression . Uric acid can also react with NO irreversibly leading to the formation of 6-aminouracil and may thus lead to NO depletion . Furthermore, hyperuricemic rats develop endothelial dysfunction (as noted by reduced urinary nitrites), and if given early, L-arginine supplementation, can prevent both the systemic and glomerular hypertension in experimental hyperuricemia . These data by our group and others suggest that uric acid leads to endothelial dysfunction. On the other hand however, some studies suggest that oxidative stress due to increased xanthine oxidase activity rather than uric acid is the major factor contributing to endothelial dysfunction. An example of such findings can be found in 2 double- blind placebo- controlled studies by George et al. Patients with

congestive heart failure were randomized in the first study to allopurinol or placebo and in the second study to probenecid (a uricosuric agent) or placebo. Both treatment arms in both studies had lower serum uric acid levels, but endothelial function improved only in the study where allopurinol was administered. Direct comparisons between the allopurinol and the probenecid groups were not conducted in this study, hence, it remains unclear if the favorable outcomes noted with allopurinol treatment are secondary to xanthine oxidase inhibition, lowering uric acid, or perhaps both. In the kidney, experimental hyperuricemia causes an afferent renal arteriolopathy and tubulointerstitial fibrosis. This effect is largely mediated by activating the RAAS, as the renal injury was reversed with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers but not with thiazide therapy despite all treatments lowering blood pressure . In this study, uric acid was shown to induce vascular smooth muscle proliferation in vitro as well, and similar to the findings in the animal kidneys, the effects of uric acid on vascular smooth muscles was reversible with the use of losartan. In addition to a direct role for uric acid in the vasculature, such data suggest uric acid effects are mediated at least partially by activation of the RAAS.

On the inflammatory front, uric acid induces the interstitial inflammation and the local expression of chemokines such as MCP-1 in the kidney , as well as COX-2 in the blood vessels . A direct role for uric acid in inducing inflammation is further supported by the findings that when infused

into mice, uric acid increases cytokine production (TNF-α) . In humans with CKD, withdrawal of uric acid lowering therapy has been reported to increased urinary TGF β-1 suggesting that hyperuricemia may contribute to the fibrotic process in patients with kidney disease . In addition to stimulating TGF β-1 production, hyperuricemia may activate its downstream targets. Although the transcriptional effects of TGF β-1 are generally mediated by a group of proteins; the Smads , the expression ofcertain TGF β-1-induced genes is mediated via the mitogen activate protein (MAP) kinase pathway . This pathway has also been reported to mediate uric acid effects in cell culture . Although the results of these studies need confirmation, such findings raise the possibility that treatment of hyperuricemia may provide a safe venue for alleviating cytokine- mediated kidney disease progression.

OBJECTIVE:

To evaluate association between serum uric acid levels and urine albumin in type 2 diabetes mellitus patients.

MATERIALS and METHODS

OPERATIONAL DEFINITION

DIABETES MELLITUS

FBS >126 mg/dl

PPBS >200 mg/dl

Urine albumin categorised into no significant , Micro, Macro albuminuria.

Microalbuminuria – 30-300 mcg/mg creatinine

Macroalbuminuria - >300 mcg/mg creatinine

PLACE OF STUDY :- Department of Internal Medicine, Govt. Stanley Medical College.

STUDY DESIGN :- Cross sectional Study

STUDY PERIOD :- February 2016 to July 2016

SAMPLE SIZE: 100 patients

INCLUSION CRITERIA:

100 type 2 diabetic patients.

EXCLUSION CRITERIA:

Patients with arthritis, hypertension, hypothyroidism, myeloproliferative disorders, renal failure, heart failure, acute febrile illness, recent exercise, urinary tract infection, patients taking alcohol, diuretics.

DATA COLLECTION and METHODS

Material for the study taken from the patients visiting Diabetology OPD.

Data collected using a pre-tested profoma meeting the objectives of the study

- History
- Physical examination
- Investigations
- Purpose of the study explained to the patient
- Informed consent obtained

Using clinical methods and investigation diabetic patients who fulfill the inclusion criteria assessed.

All patients underwent serum uric acid and urine spot albumin creatinine ratio.

Blood samples for complete blood count, RBS, urea, creatinine, electrolytes , FLP , urine for urine routine obtained.

ALBUMIN TO CREATININE RATIO(ACR) ESTIMATION:

All patients were asked to report with early morning urine sample.

Spot urine collection was used for determination of Albumin creatinine Ratio.

In our study, modified immunoturbimetric assay known as 'turbilatex' test was used to measure microalbuminuria.

MICROALBUNINURIA ESTIMATION:

Various methods to detect microalbuminuria:

METHOD	DURATION	TIME OF ASSAY
Single radio immune diffusion[Manni 1965]	1.25mg/dl	1 day
Electro immune assay[Laurel 1966]	5mg/l	4-6hours
Immuno turbidimetric assay[tepper 1982]	5mg/l	20-30min
Radio immune assay[keen and chlouvervakis, 1963]	6.2 mcg/l	1-2 days
ELISA[Filding, 1983]	250mcg/l	12-18 min
Latex agglutinates immune nephrometry[Vasquez 1984]	750mcg/l	6hours
Fluorescent immune assay[Chavers 1984]	750mcg/l	4-6 hours
Immune chemical semi quantia dipstic [MICRAL]	20-300mg/l	5sec-5min

Microalbumin-turbilatex is a quantitative turbidimetric test for the measurement of microalbumin in human urine. Latex particles coated with specific antibodies,anti-human albumin are agglutinated when mixed with samples containing micoralbumin. The agglutination causes an absorbance

change, dependent upon the microalbumin contents of the patient sample that can be quantified by comparison from a calibrator of known microalbumin concentration.

Urine albumin level classified into 3 categories:

No significant albuminuria

Microalbuminuria

Macroalbuminuria

Serum uric acid levels association with no significant, micro, macroalbuminuria evaluated.

CREATININE:

Technology: Jaffe method-Rate blanked and compensated

Method : photometry

REFERANCE VALUES:

To define microalbuminuria in random urine specimens, we used theACR cutoff values of 30 to 300 mg/g for both men and women were used. Subjects with an ACR<30mg/g were defined as having normoalbuminuria; those with ACR >300 mg/g were defined as having overt proteinuria.

SERUM URIC ACID ESTIMATION:

PRINCIPLE:

The principle for the determination of Serum Uric Levels was devised by Trivedi and Kabasakalian with a modified Trinder peroxidase method using TBHB.

URIC ACID + O2 + H2O Uricase Allantoin + CO2 + H2O2

H2O2 + 4- AAP + TBHB Peroxidase Quinoneimine + H2O.

The intensity of chromogen (Quinoneimine) formed is proportional to the uric acid concentration in the sample when measured at 510 nm **(510 - 550nm).**

REFERANCE VALUES SERUM URIC ACID LEVELS:

In Males : 3.4 - 7.0 mg/dl

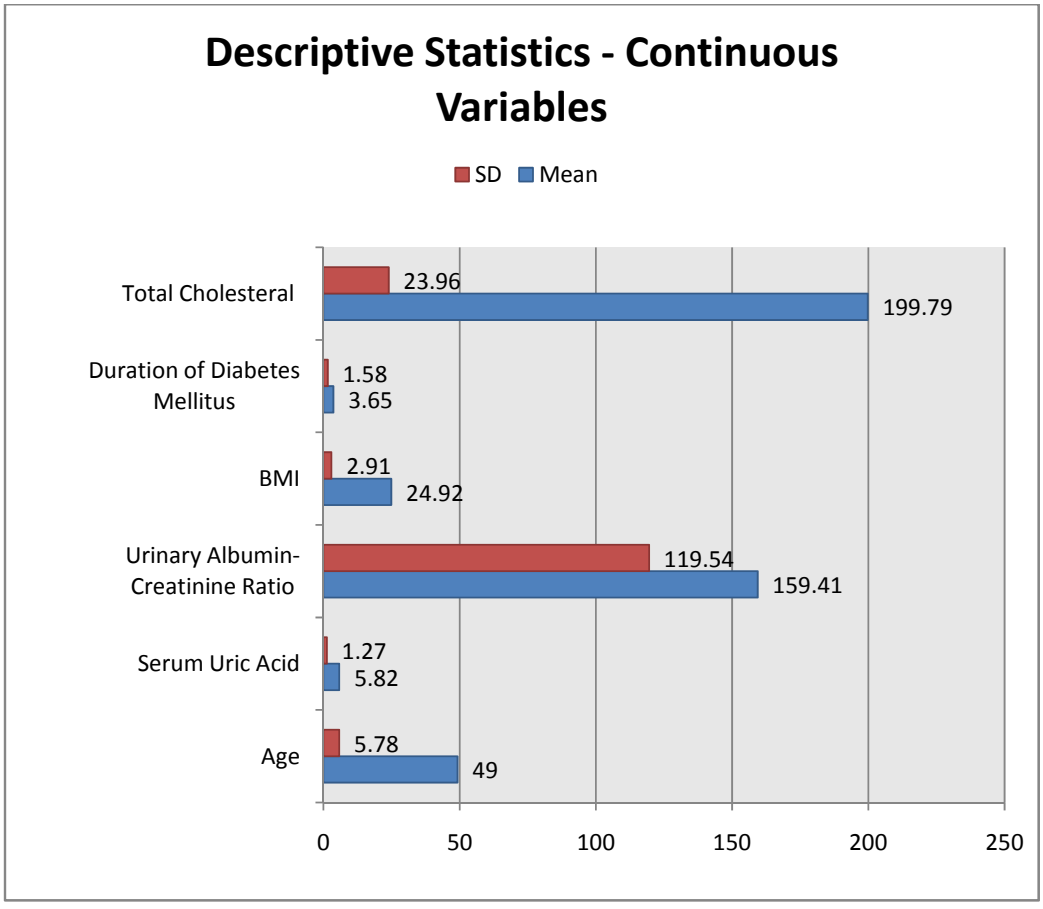
In females : 2.4 - 6.0 mg/dl

Hyperuricemia was defined as serum uric acid level of >7.0mg/dl for men and >6.0mg/dl for women.

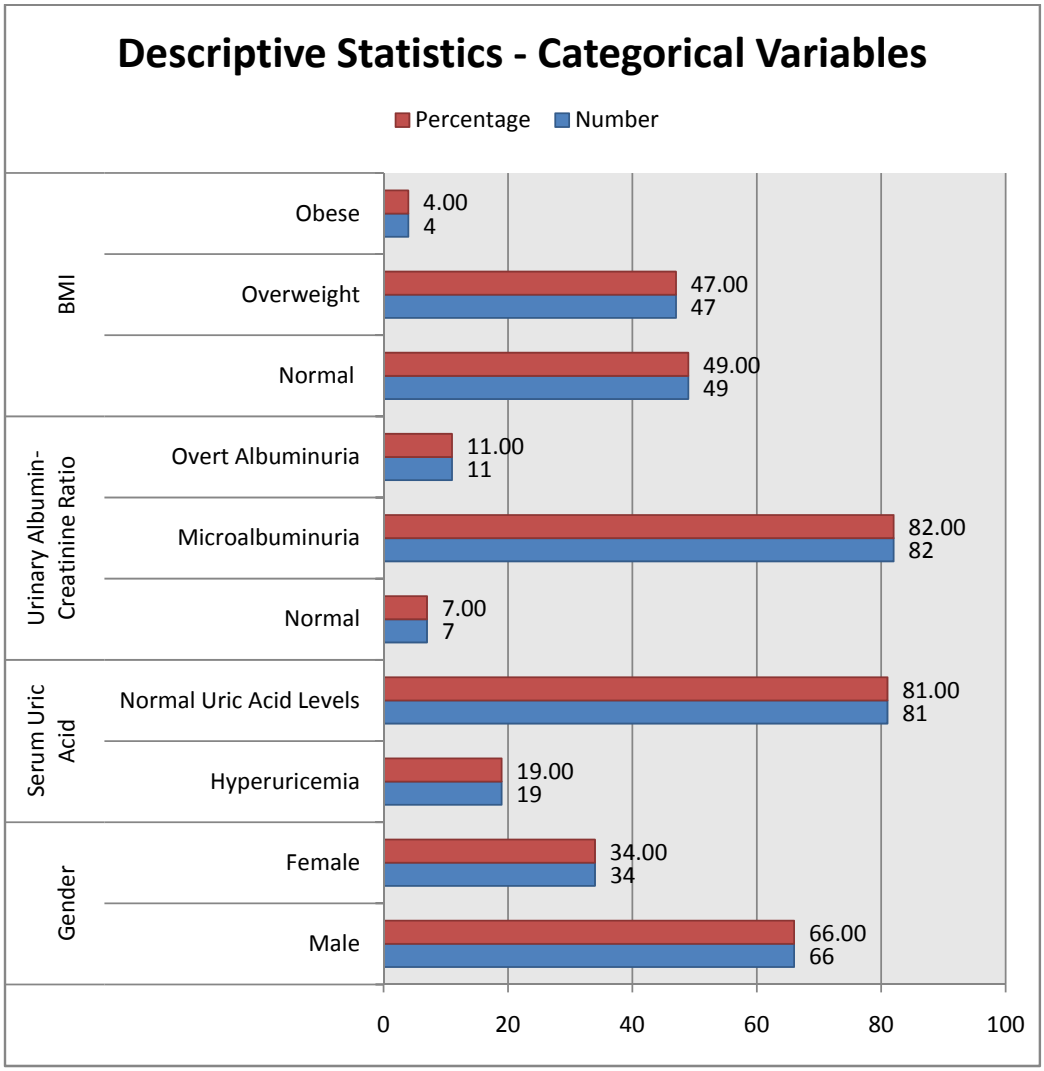
RESULTS & DISCUSSION

Data Analysis

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

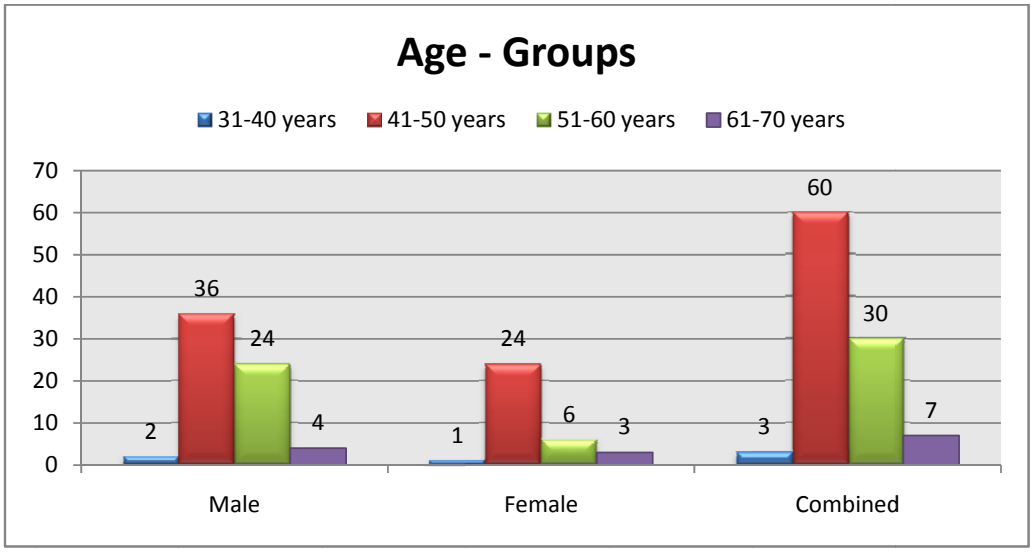


Descriptive Statistics - Continuous Variables	Age	Serum Uric Acid	Urinary Albumin-Creatinine Ratio	BMI	Duration of Diabetes Mellitus	Total Cholesteral
Mean	49.25	5.82	159.41	24.92	3.65	199.79
Standard Error	0.58	0.13	11.95	0.29	0.16	2.40
Median	48.00	5.70	128.00	25.15	3.20	196.00
Mode	48.00	5.50	128.00	27.40	2.60	183.00
Standard Deviation	5.78	1.27	119.54	2.91	1.58	23.96
Range	26.00	6.10	540.00	12.70	7.00	102.00
Minimum	38.00	3.10	21.00	19.50	1.50	163.00
Maximum	64.00	9.20	561.00	32.20	8.50	265.00
Confidence Level(95.0%)	1.15	0.25	23.72	0.58	0.31	4.75

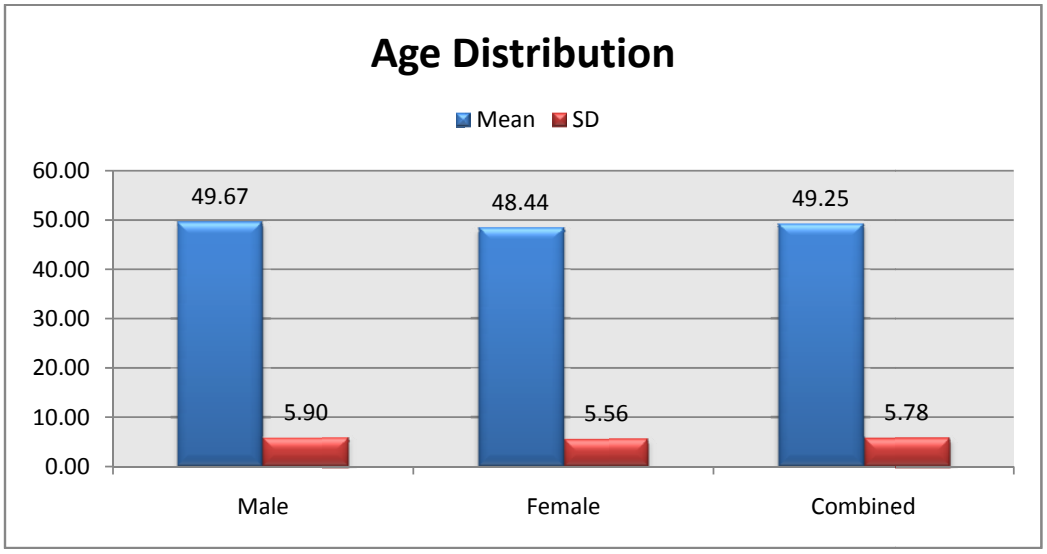


Descriptive Statistics - Categorical Variables		Number	Percentage
Gender	Male	66	66.00
	Female	34	34.00
Serum Uric Acid	Hyperuricemia	19	19.00
	Normal Uric Acid Levels	81	81.00
Urinary Albumin-Creatinine Ratio	Normal	7	7.00
	Microalbuminuria	82	82.00

	Overt Albuminuria	11	11.00
BMI	Normal	49	49.00
	Overweight	47	47.00
	Obese	4	4.00

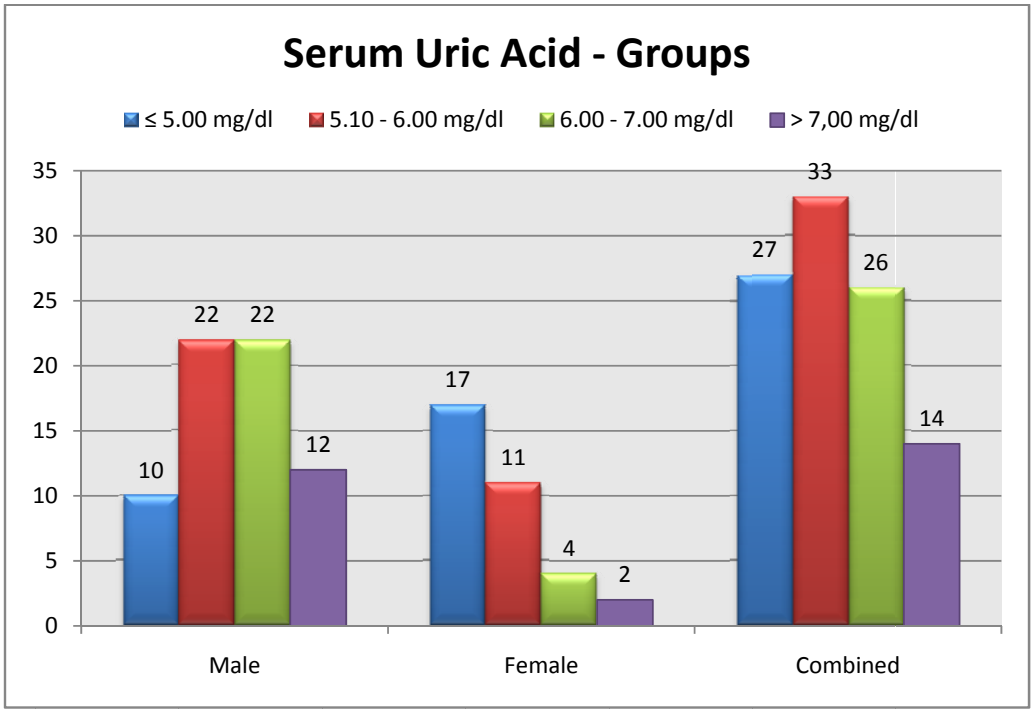


Age - Groups	Male	Female	Combined	Male %	Female %	Combined %
31-40 years	2	1	3	3.03	2.94	3.00
41-50 years	36	24	60	54.55	70.59	60.00
51-60 years	24	6	30	36.36	17.65	30.00
61-70 years	4	3	7	6.06	8.82	7.00
Total	66	34	100	100	100	100

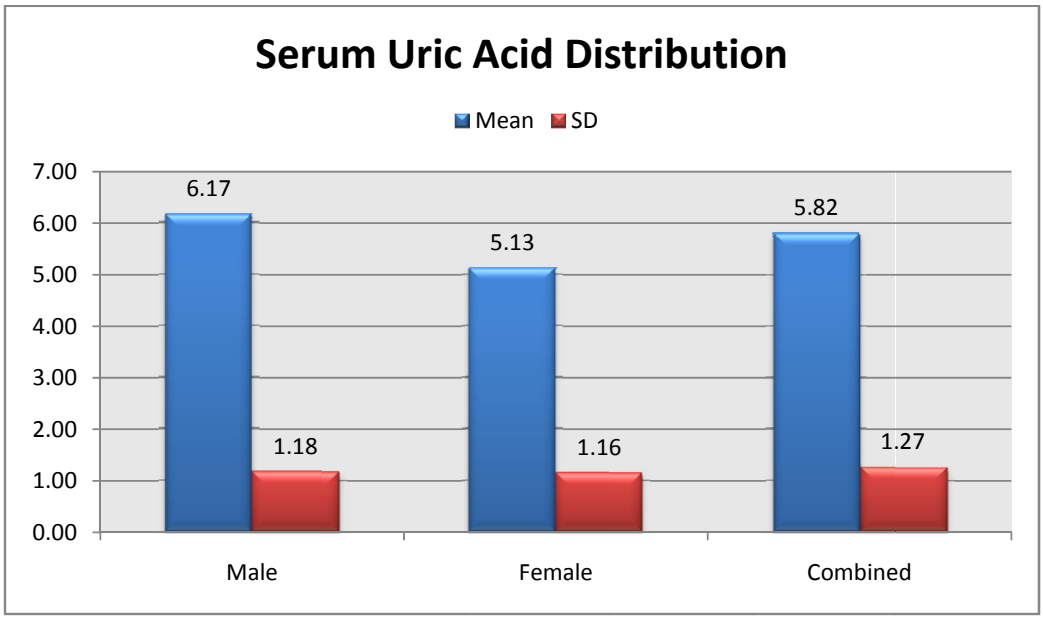


Age Distribution	Male	Female	Combined
Mean	49.67	48.44	49.25
SD	5.90	5.56	5.78
P value Unpaired t Test		0.3180	

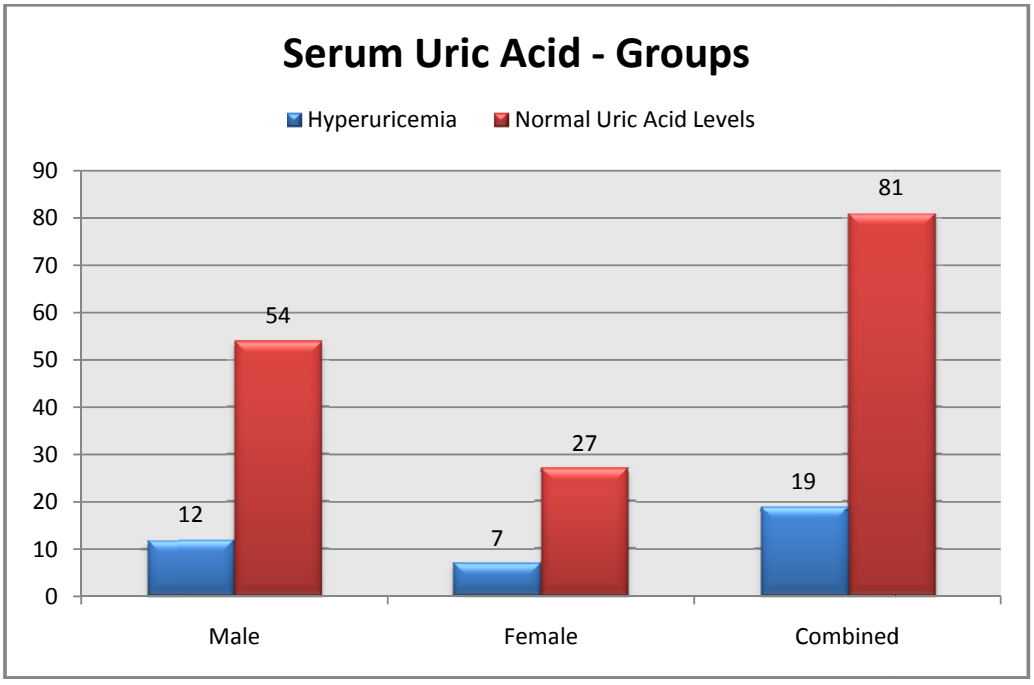
Majority of the male group patients belonged to the 41-50 years age class intervals (n=36, 54.55%) with a mean age of 49.67 years. In the female group patients, majority belonged to the 3-4 years age class interval (n=24, 79.59%) with a mean age of 48.44 years. The association between the stydy groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.



Serum Uric Acid - Groups	Male	Female	Combined	Male %	Female %	Combined %
≤ 5.00 mg/dl	10	17	27	15.15	50.00	27.00
5.10 - 6.00 mg/dl	22	11	33	33.33	32.35	33.00
6.00 - 7.00 mg/dl	22	4	26	33.33	11.76	26.00
> 7,00 mg/dl	12	2	14	18.18	5.88	14.00
Total	66	34	100	100	100	100



Serum Uric Acid Distribution	Male	Female	Combined
Mean	6.17	5.13	5.82
SD	1.18	1.16	1.27
P value Unpaired t Test		0.0001	



Serum Uric Acid - Groups	Male	Female	Combined	Male %	Female %	Combined %
Hyperuricemia	12	7	19	18.18	20.59	19.00
Normal Uric Acid Levels	54	27	81	81.82	79.41	81.00
Total	66	34	100	100	100	100

By conventional criteria the association between the study groups and serum uric acid distribution among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to male group, the mean serum uric acid level is 6.17 mg/dl. In female group the mean serum uric acid level is 5.13 mg/dl. The increased mean serum uric acid level in male group compared to the female group is statistically significant as the p value is 0.0001 as per unpaired t- test indicating a true difference among study groups.

Discussion

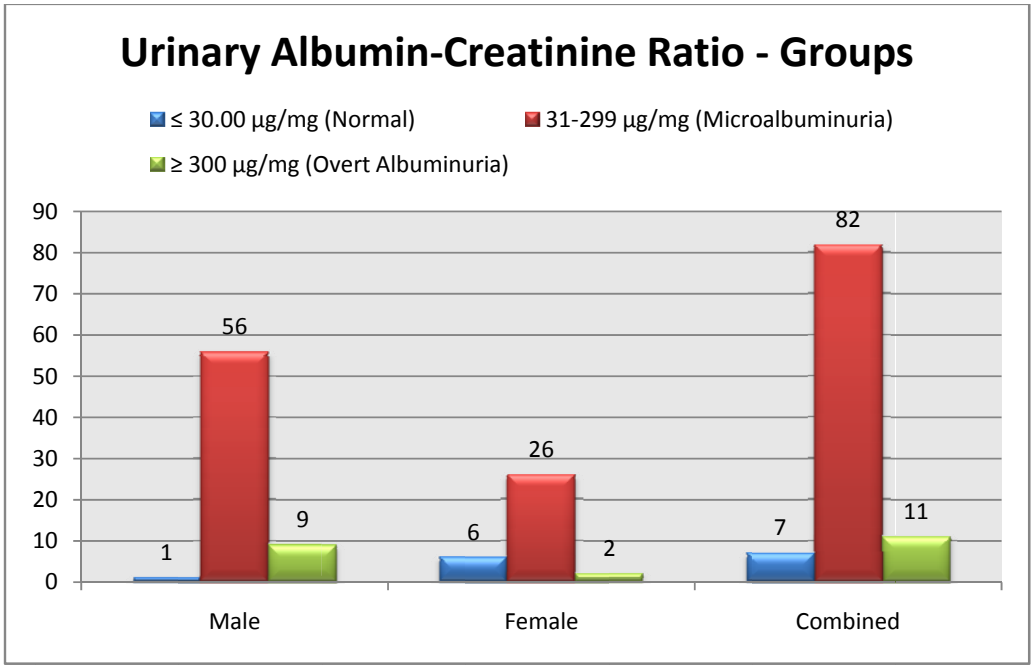
The mean serum uric acid level was meaningfully more in male group compared to the female group by 17% with a mean difference of 1.04 mg/dl. This difference is true and significant and has not occurred by chance.

Conclusion

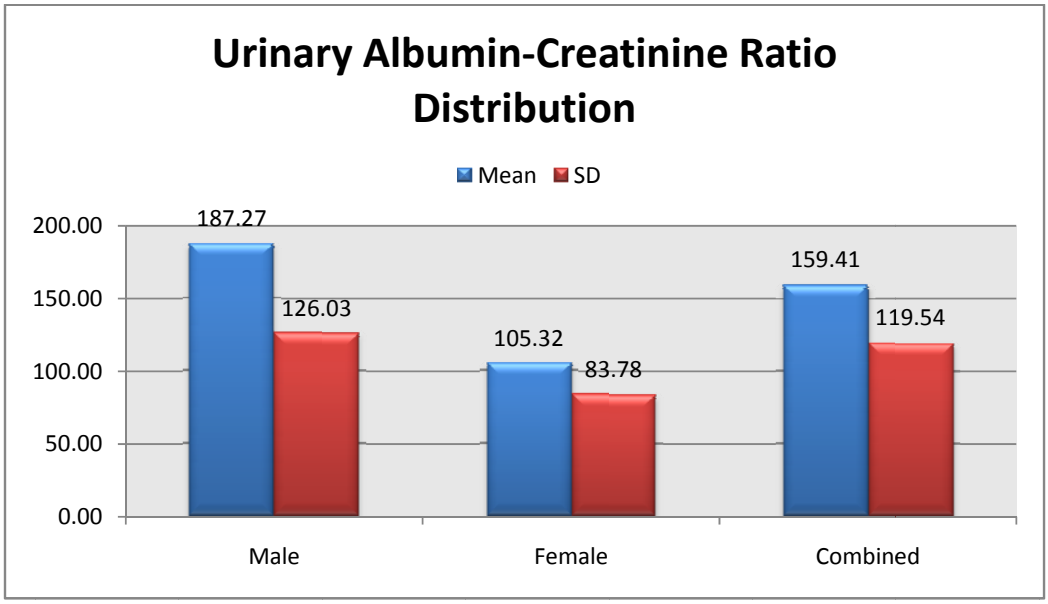
In this study we can safely conclude that the mean serum uric acid level was significantly and consistently higher among male study subjects compared to female study subjects in type 2 diabetes mellitus patients.

In other words among patients with type 2 diabetes mellitus, males have significantly 1.20 more times the level of serum uric acid compared to females

Urinary Albumin-Creatinine Ratio



Urinary Albumin-Creatinine Ratio - Groups	Male	Female	Combined	Male %	Female %	Combined %
≤ 30.00 µg/mg (Normal)	1	6	7	1.52	17.65	7.00
31-299 µg/mg (Microalbuminuria)	56	26	82	84.85	76.47	82.00
≥ 300 µg/mg (Overt Albuminuria)	9	2	11	13.64	5.88	11.00
0	0	0	0	0.00	0.00	0.00
Total	66	34	100	100	100	100



Urinary Albumin-Creatinine Ratio Distribution	Male	Female	Combined
Mean	187.27	105.32	159.41
SD	126.03	83.78	119.54
P value Unpaired t Test		0.0009	

By conventional criteria the association between the study groups and urinary albumin-creatinine ratio distribution among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to male group, the mean urinary albumin-creatinine ratio level is 187.27. In female group the mean urinary albumin-creatinine ratio level is 105.32. The increased mean urinary albumin-creatinine

ratio level in male group compared to the female group is statistically significant as the p value is 0.0009 as per unpaired t- test indicating a true difference among study groups.

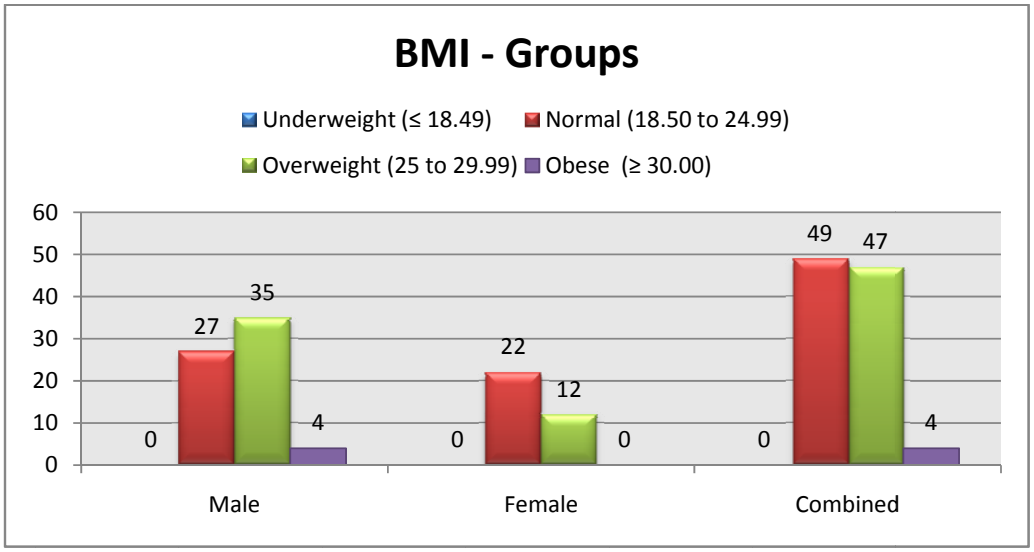
Discussion

The mean urinary albumin-creatinine ratio level was meaningfully more in male group compared to the female group by 44% with a mean difference of 81.95. This difference is true and significant and has not occurred by chance.

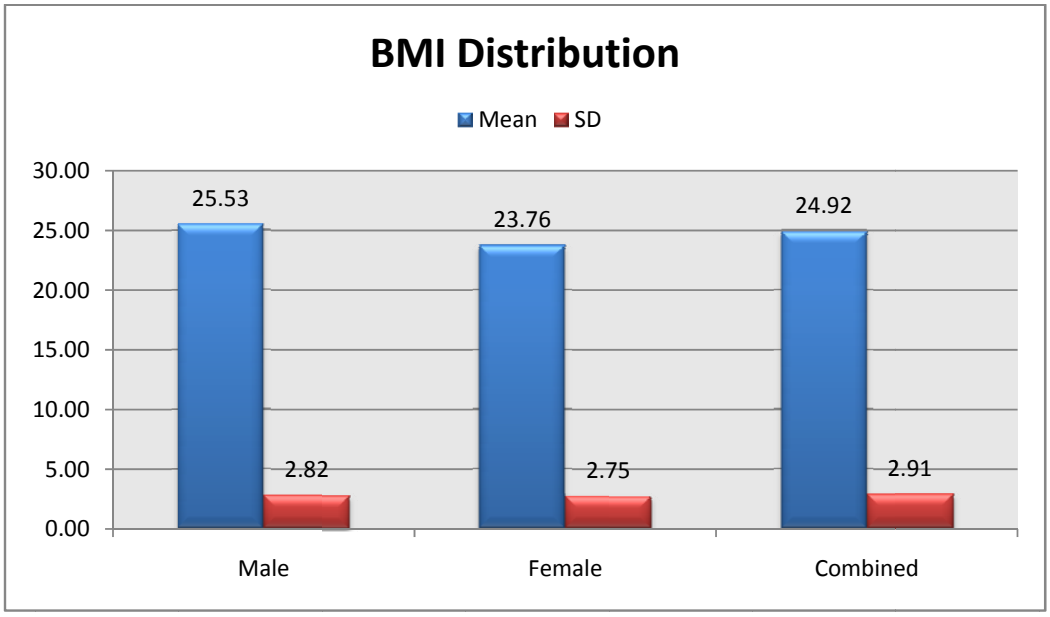
Conclusion

In this study we can safely conclude that the mean urinary albumin-creatinine ratio level was significantly and consistently higher among male study subjects compared to female study subjects in type 2 diabetes mellitus patients.

In other words among patients with type 2 diabetes mellitus, males have significantly 1.78 more times the level of urinary albumin-creatinine ratio compared to females.



BMI - Groups	Male	Female	Combined	Male %	Female %	Combined %
Underweight (≤ 18.49)	0	0	0	0.00	0.00	0.00
Normal (18.50 to 24.99)	27	22	49	40.91	64.71	49.00
Overweight (25 to 29.99)	35	12	47	53.03	35.29	47.00
Obese (≥ 30.00)	4	0	4	6.06	0.00	4.00
Total	66	34	100	100	100	100



BMI Distribution	Male	Female	Combined
Mean	25.53	23.76	24.92
SD	2.82	2.75	2.91
P value Unpaired t Test		0.0035	

By conventional criteria the association between the study groups and BMI distribution among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to male group, the mean BMI level is 25.53. In female group the mean BMI level is 23.76. The increased mean BMI level in

male group compared to the female group is statistically significant as the p value is 0.0035 as per unpaired t- test indicating a true difference among study groups.

Discussion

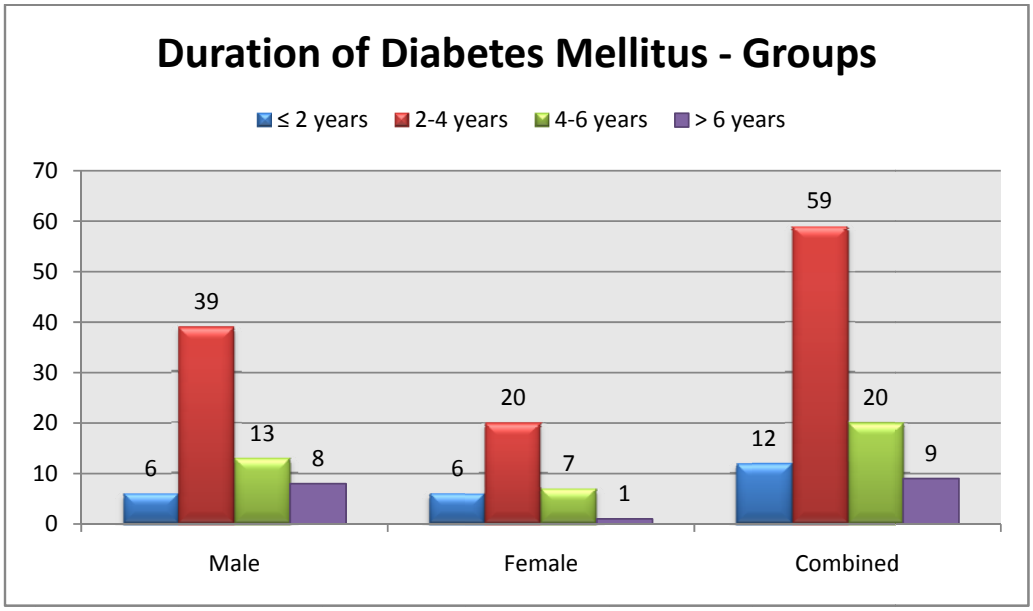
The mean BMI level was meaningfully more in male group compared to the female group by 7% with a mean difference of 1.77. This difference is true and significant and has not occurred by chance.

Conclusion

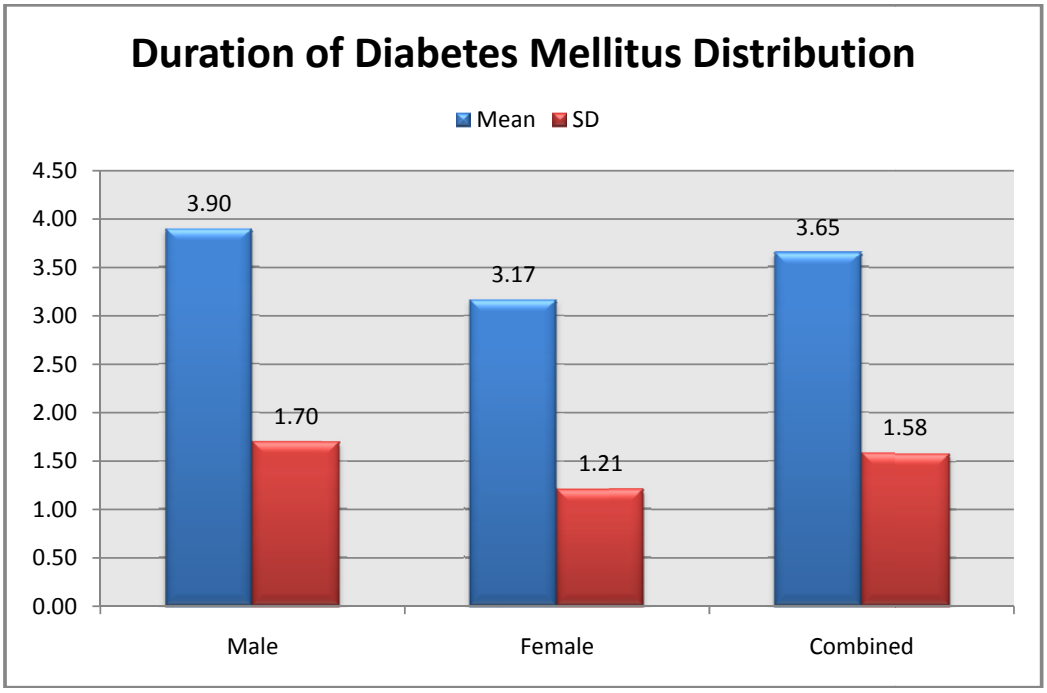
In this study we can safely conclude that the mean BMI level was significantly and consistently higher among male study subjects compared to female study subjects in type 2 diabetes mellitus patients.

In other words among patients with type 2 diabetes mellitus, males have significantly 1.07 more overweight and obese compared to females.

Duration of Diabetes Mellitus

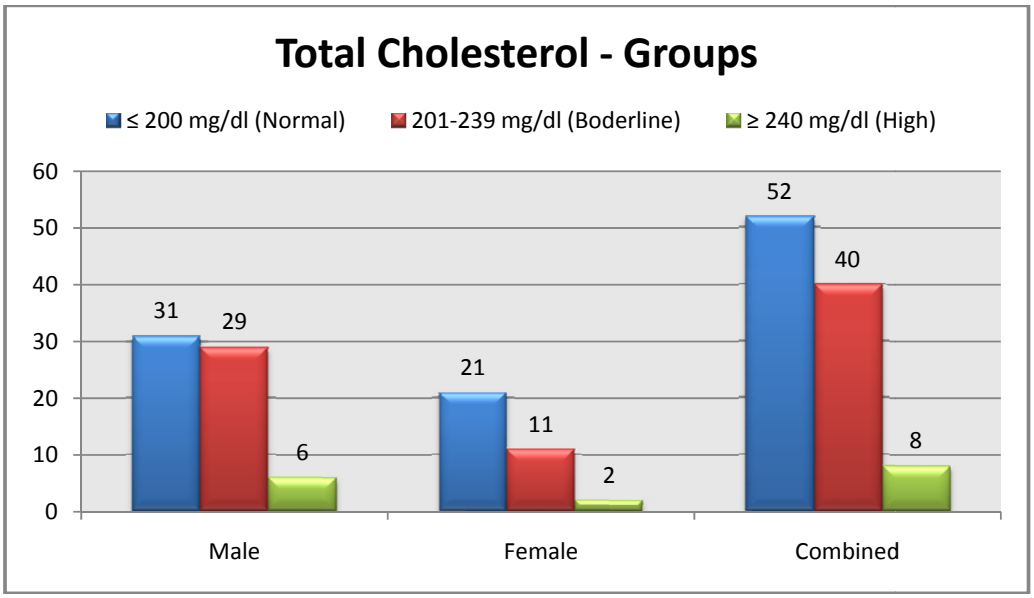


Duration of Diabetes Mellitus - Groups	Male	Female	Combined	Male %	Female %	Combined %
≤ 2 years	6	6	12	9.09	17.65	12.00
2-4 years	39	20	59	59.09	58.82	59.00
4-6 years	13	7	20	19.70	20.59	20.00
> 6 years	8	1	9	12.12	2.94	9.00
Total	66	34	100	100	100	100

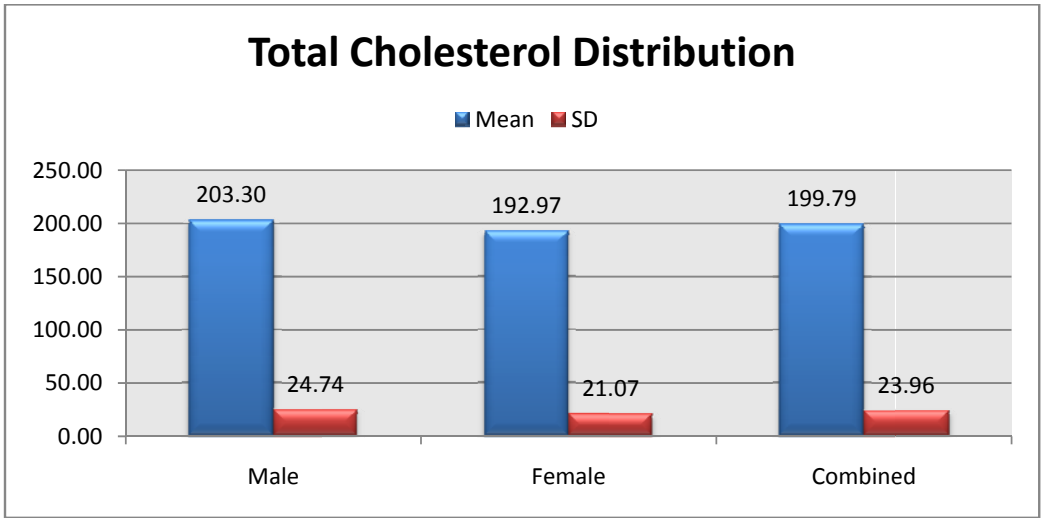


Duration of Diabetes Mellitus Distribution	Male	Female	Combined
Mean	3.90	3.17	3.65
SD	1.70	1.21	1.58
P value Unpaired t Test		0.0284	

Majority of the male group patients belonged to the 2-4 years duration of diabetes class intervals (n=39, 59.09%) with a mean duration of 3.90 years. In the female group patients, majority belonged to the 2-4 years duration of diabetes class intervals (n=20, 58.82%) with a mean duration of 3.17 years. The association between the stydy groups and duration of diabetes distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.



Total Cholesterol - Groups	Male	Female	Combined	Male %	Female %	Combined %
≤ 200 mg/dl (Normal)	31	21	52	46.97	61.76	52.00
201-239 mg/dl (Boderline)	29	11	40	43.94	32.35	40.00
≥ 240 mg/dl (High)	6	2	8	9.09	5.88	8.00
Total	66	34	100	100	100	100



Total Cholesterol Distribution	Male	Female	Combined
Mean	203.30	192.97	199.79
SD	24.74	21.07	23.96
P value Unpaired t Test		0.0404	

By conventional criteria the association between the study groups and total cholesterol distribution among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to male group, the mean total cholesterol level is 203.30 mg/dl. In female group the mean total cholesterol level is 192.97 mg/dl. The increased mean total cholesterol level in male group compared to the female group is statistically significant as the p value is 0.0404 as per unpaired t- test indicating a true difference among study groups.

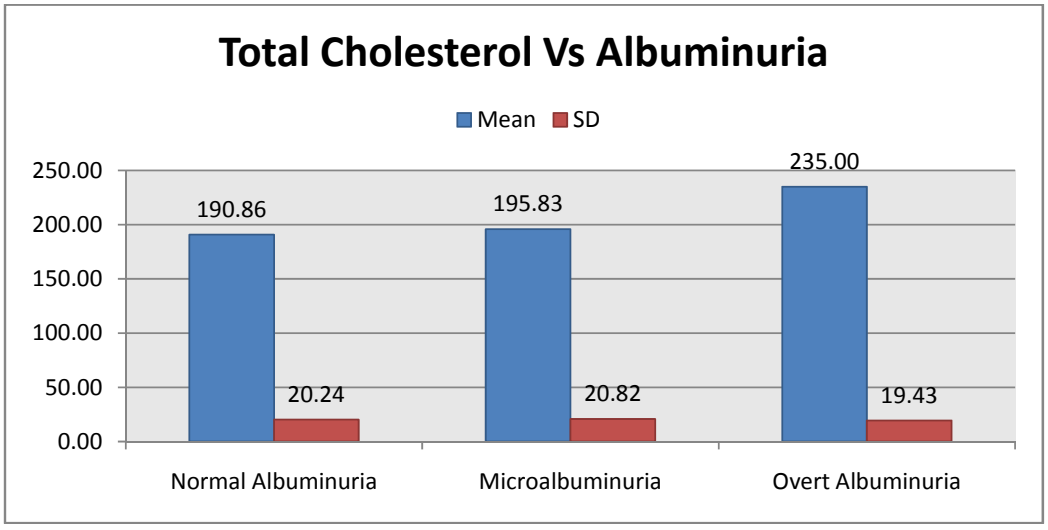
Discussion

The mean total cholesterol level was meaningfully more in male group compared to the female group by 5% with a mean difference of 10.33 mg/dl This difference is true and significant and has not occurred by chance.

Conclusion

In this study we can safely conclude that the mean total cholesterol level was significantly and consistently higher among male study subjects compared to female study subjects in type 2 diabetes mellitus patients.

In other words among patients with type 2 diabetes mellitus, hypercholesterolemia is found 1.05 significantly more among males compared to females.



Total Cholesterol Vs Albuminuria	Normal Albuminuria	Microalbuminuria	Overt Albuminuria
N	7	82	11
Mean	190.86	195.83	235.00
SD	20.24	20.82	19.43
P value Single Factor ANOVA			<0.0001

By conventional criteria the association between the total cholesterol levels and albuminuria status among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to normal albuminuria, microalbuminuria and overt albuminuria groups, , the mean total cholesterol level is 190.86, 195.83 and 235.00 mg/dl respectively. The increased mean total cholesterol level as per increasing albuminuria status is statistically significant as the p value is <0.0001 as per single factor ANOVA test indicating a true difference among study groups.

Discussion

The mean total cholesterol level was meaningfully more in, microalbuminuria group compared to the normal albuminuria group by 3% with a mean difference of 4.97 mg/dl

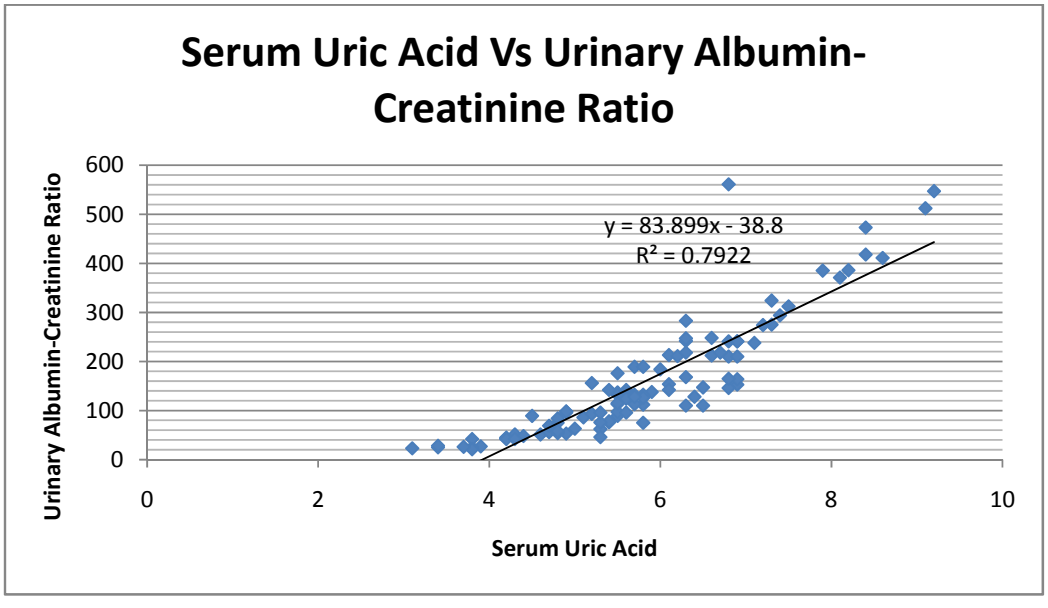
The mean total cholesterol level was meaningfully more in overt albuminuria group compared to the microalbuminuria group by 17% with a mean difference of 39.17 mg/dl

This difference is true and significant and has not occurred by chance.

Conclusion

In this study we can safely conclude that the mean total cholesterol level was significantly and consistently higher in microalbuminuria patients compared to normal albuminuria and consistently higher in overt albuminuria patients compared to microalbuminuria in type 2 diabetes mellitus patients.

In other words among patients with type 2 diabetes mellitus, elevated total cholesterol levels are a strong predictor of the development of albuminuria



Regression Statistics	
Multiple R	0.890043
R Square	0.792176
Adjusted R Square	0.790055
Standard Error	0.581066
Observations	100

ANOVA	***df***	***SS***	***MS***	***F***	***Significance F***
Regression	1	126.1254	126.1254	373.5523	<0.0001
Residual	98	33.08851	0.337638		
Total	99	159.2139			

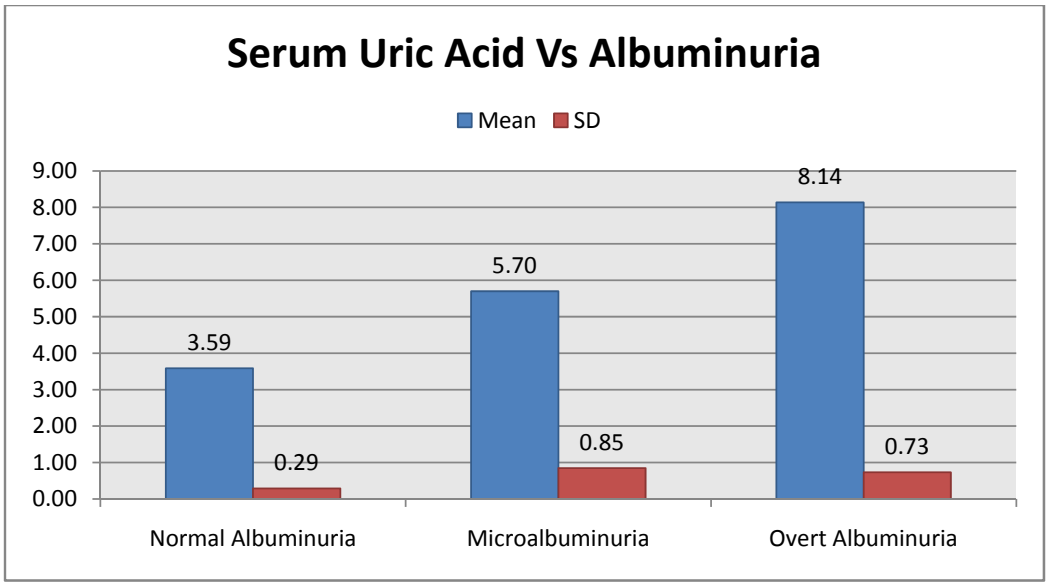
	Coefficients	***Standard Error***	***t Stat***	***P-value***	***Lower 95%***	***Upper 95%***	***Lower 95.0%***	***Upper 95.0%***
Intercept	4.313841	0.097166	44.39683	0.0000	4.121019	4.506662	4.121019	4.506662
Urine Albumin Creatinine Ratio	0.009442	0.000489	19.3275	0.0000	0.008473	0.010412	0.008473	0.010412

There is a strong positive correlation between increase in serum uric acid levels and corresponding increase in urine albumin creatinine ratio. This is indicated by the Pearson's R Correlation value of 0.890043. This means as serum uric acid levels increases the urine albumin creatinine ratio increases. As per Pearson's R Correlation this increase in urine albumin creatinine ratio due to corresponding increase in serum uric acid levels happens 89% of times.

This direct positive and high correlation is significant with a p value of <0.0001 as per analysis of variance test. The percentage change is also explained in the scatter plot. This linear model explains all the variability of the response data around its mean. Since $R^2$is 0.792176, "the fitted regression equation explains 79% of the variation in Y"(Y= 83.899 (uric acid measurement) – 38.8).

Thus 1 mg/dl increase in serum uric acid causes 45.10 points increase in urine albumin creatinine ratio. This variation in serum uric acid in relation to urine albumin creatinine ratio correlates 89% of times and this variation is truly accounted 79% of times.

So we can conclude that serum uric acid is an independent positive and strong correlate of urine albumin creatinine ratio in patients with type 2 diabetes mellitus.



Serum Uric Acid Vs Albuminuria	Normal Albuminuria	Microalbuminuria	Overt Albuminuria
N	7	82	11
Mean	3.59	5.70	8.14
SD	0.29	0.85	0.73
P value Single Factor ANOVA			<0.0001

By conventional criteria the association between the serum uric acid levels and albuminuria status among study subjects is considered to be statistically significant since $p < 0.05$.

Results

In patients belonging to normal albuminuria, microalbuminuria and overt albuminuria groups, the mean serum uric acid level is 3.59, 5,70 and 8.14 mg/dl repectively. The increased mean serum uric acid level as per increasing albuminuria status is statistically significant as the p value is <0.0001 as per single factor ANOVA test indicating a true difference among study groups.

Discussion

The mean serum uric acid level was meaningfully more in overt albuminuria, group compared to the microalbuminuria group by 37% with a mean difference of 2.44 mg/dl.

The mean serum uric acid level was meaningfully more in microalbuminuria group compared to the normal albuminuria group by 30% with a mean difference of 2.11 mg/dl.

This difference is true and significant and has not occurred by chance.

Conclusion

In this study we can safely conclude that the mean serum uric acid level was significantly and consistently higher in microalbuminuria patients compared to normal albuminuria and consistently higher in overt albuminuria patients compared to microalbuminuria in type 2 diabetes mellitus patients.

In other words among patients with type 2 diabetes mellitus, elevated serum uric acid levels are a strong predictor of the development of albuminuria

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CONCLUSION

- Total number of 100 diabetic patients were studied . Mean age group is 49.25 years.

- Mean serum uric acid levels were 5.8 mg/dl.

- Mean urine albumin creatinine ratio was 159.41.

- Mean duration of diabetes was 3.65 years.

- Majority of the male group patients belonged to the 41-50 years age class intervals (n=36, 54.55%) with a mean age of 49.67 years. In the female group patients, majority belonged to the 41-50 years age class interval (n=24, 79.59%) with a mean age of 48.44 years.

- In patients belonging to normal albuminuria, microalbuminuria and overt albuminuria groups, the mean total cholesterol level is 190.86, 195.83 and 235.00 mg/dl respectively. In this study we can safely conclude that the mean total cholesterol level was significantly and consistently higher in microalbuminuria patients compared to normal albuminuria and consistently higher in overt albuminuria patients compared to microalbuminuria in type 2 diabetes mellitus patients.

- In patients belonging to male group, the mean serum uric acid level is 6.17 mg/dl. In female group the mean serum uric acid level is 5.13 mg/dl. In this study we can safely conclude that the mean serum uric acid level was

significantly and consistently higher among male study subjects compared to female study subjects in type 2 diabetes mellitus patients.

- In patients belonging to male group, the mean urinary albumin-creatinine ratio level is 187.27. In female group the mean urinary albumin-creatinine ratio level is 105.32. In this study we can safely conclude that the mean urinary albumin-creatinine ratio level was significantly and consistently higher among male study subjects compared to female study subjects in type 2 diabetes mellitus patients.

- In patients belonging to normal albuminuria, microalbuminuria and overt albuminuria groups, the mean serum uric acid level is 3.59, 5,70 and 8.14 mg/dl repectively The mean serum uric acid level was meaningfully more in overt albuminuria group compared to the microalbuminuria group by 37% with a mean difference of 2.44 mg/dl . The mean serum uric acid level was meaningfully more in microalbuminuria group compared to the normal albuminuria group by 30% with a mean difference of 2.11 mg/dl.

- The association between serum uric acid levels and urine albumin levels in patients with Diabetes Mellitus is found to be statistically significant.

- Hence serum uric acid levels can be considered as an marker for Diabetic nephropathy .

SUMMARY

This study " ASSOCIATION OF URIC ACID LEVELS WITH PROTEINURIA IN DIABETIC PATIENTS" was carried out in government Stanley medical college and hospital , Chennai from march 2016 to august 2016

100 Diabteic patients were selected and their serum uric acid levels and urine albumin levels were studied.

In diabetic patients serum uric acid levels and urine albumin levels were studied and it was found that in patients who had micro±macroalbuminuria had elevated serum uric acid levels.

Thus serum uric acid levels can be considered as an marker for Diabetic nephropathy.

LIMITATIONS OF THE STUDY

First, it involved only a single collection of urine, which did not completely conform to the requirement of multiple urine collections over 3 to 6 months for the diagnosis of microalbuminuria.

Second, the validity to extrapolate the relationship between uric acid and urinary albumin excretion rate to nondiabetic subjects requires confirmation.

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PROFORMA

NAME: AGE: SEX:

ADDRESS: CONTACT NO:

OCCUPATION :

COMPLAINTS:

PAST H/O

CARDIAC ILLNESS 1. Yes 2. No If yes specify_____

STROKE 1.Yes 2. No If yes specify

PERSONAL H/O:

H/O SMOKING:

FAMILY HISTORY:

RELEVANT CLINICAL EXAMINATION

BP: PR: RR: BMI:

CVS: RS:

PA:

CNS:

INVESTIGATIONS:

COMPLETE BLOOD COUNT:

URINE ROUTINE:

URIC ACID:

URINE ALBUMIN CREATININE RATIO:

RENAL FUNCTION TEST:

SERUM ELECTROLYTES:

LIVER FUNCTION TEST:

FASTING LIPID PROFILE:

COURSE OF PRESENT ILLNESS:

COMPLICATIONS :

COMMENT:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

"A STUDY ON THE ASSOCIATION OF SERUM URIC ACID AND MICROALBUMINURIA IN DIABETES" AT GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL, CHENNAI**.**

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

“A STUDY ON THE ASSOCIATION OF SERUM URIC ACID AND MICROALBUMINURIA IN DIABETES”

நான்இந்தஆராய்ச்சியில்விவரங்களைமுற்றிலும்புரிந்துகொண்டேன்.

ஆய்வில்பங்குஎடுத்துபோது,

சாத்தியமானஅபாயங்கள்மற்றும்பயன்களைபற்றிநான்அறிந்துள்ளேன்.

நான்எந்தவொருவேளையிலும்ஆய்வில்இருந்துதிரும்பமுடியும்,

அதன்பின்னர்,

நான்வழக்கம்போல்மருத்துவசிகிச்சைபெறமுடியும்என்றுபுரிந்துகொள்கறேன்.

நான்ஆய்வில்பங்குஎடுத்துபணம்எதையும்பெறமுடியாதுஎன்றுஅறிந்துள்ளேன்.

இந்தஆய்வின்முடிவுகள்எந்தமெடிக்கல்ஜர்னலில்வெளியிடப்படஇருந்தால்

நான்எதிர்க்கவில்லை,

என்தனிப்பட்டஅடையாளத்தைவெளிப்படுத்தப்பட்டுஇருக்ககூடாது.

நான்இந்தஆய்வில்பங்கெடுப்பதன்மூலம்நான்என்னசெய்யபோகிறேன்

என்று தெரியும்.

நான்இந்தஆய்வில்என்முழுஒத்துழைப்பையும்கொடுப்பேன்என்றுஉறுதிய

ளிக்கிறேன்.

தன்னார்வளர்	**சாட்சி**
பெயர்மற்றும்முகவரி	பெயர்மற்றும்முகவரி
கையொப்பம் /விரல்ரேகை:	கையொப்பம்
விரல்ரேகை:	

ஆராய்ச்சியாளர்
கையொப்பம்மற்றும்தேதி

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Study on association of Serum Uric Acid level with Uric Albumin level in Type 2 Diabetes Mellitus.

Principal Investigator : Dr. P N Karthigeyan

Designation : PG, MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.03.2016 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

MASTER CHART

Name	Age/Sex	Serum Uric Acid	Urine Alb, Creat Ratio	BMI	Duration of DM	total Cholesteral
Ramalingam	52/m	6.3	283	26	6	212
Govindaraj	57/m	5.2	156	25	4.6	225
Venkatesan	48/m	5.7	189	27.3	5.2	232
Santhanam	43/m	7.4	294	28.3	3.7	186
Vanitha	61/f	4.8	75	21.5	2.6	189
Annadurai	53/m	5.5	113	22.7	4.5	178
Valarmadhi	48/f	4.9	53	20.2	3.2	174
Perumal	53/m	5.8	75	24.7	4.3	212
Jodhi bai	45/f	5.3	46	28.3	4.8	247
Mohan	52/m	5.5	89	26.8	2.2	232
Ramesh	51/m	6.9	153	27.4	4.7	213
Shanmugam	49/m	8.2	386	31.2	7.8	265
Malliga	63/m	5.6	128	26.5	3.2	194
Boomidevi	56/f	4.7	69	25.7	4.7	187
Lakshmi	62/f	5.2	93	19.8	3.7	179
Pudhiyannan	64/m	6.8	146	21.5	4.9	207
Jayammal	47/f	3.4	25	23.1	3.2	208
Ramasamy	56/m	9.2	547	32.1	8.5	249
Venkatachalam	49/m	7.1	238	26.8	6.5	214
Rajasekar	38/m	4.2	43	23.3	2.6	184
Kesavan	42/m	5.8	189	28.4	5.3	239
Selvi	54/f	3.8	25	25.3	2.9	198
Dayalan	52/m	5.5	137	23.7	3.7	173
Rajalakhsmi	41/m	4.9	98	24.5	2.5	184
Umapathy	53/m	6.6	212	25.3	4.3	204

Name	Age/Sex	Serum Uric Acid	Urine Alb, Creat Ratio	BMI	Duration of DM	total Cholesteral
Jayaraman	46/m	7.3	324	29.3	5.7	238
Padmavathy	39/f	5.5	176	24.8	6.8	178
Gopal	47/m	6.1	213	23.8	3.4	185
Suguna	42/f	5.3	76	21.4	1.6	167
Suresh babu	49/m	8.4	473	32.2	8.4	253
Thangavelu	57/m	6.8	210	24.9	5.2	178
Mylavathy	52/f	5.8	132	27.4	2.5	212
Jayanthi	48/f	3.1	23	21.4	4.2	168
Karunakaran	46/m	5.4	76	26.4	1.8	221
Malathi	52/f	6.5	110	27.3	3.2	203
Panneerselvam	48/m	6.9	241	26.3	3.8	185
karihalan	43/m	4.3	51	23.2	2.6	178
Mariyammal	47/f	5.6	142	24.9	4.7	194
Palani	49/m	6.8	561	28.5	7.9	208
Mayavathy	48/f	4.9	96	23.2	2.8	187
Nagaraj	48/m	5.5	132	21.8	3.7	168
Velmurugan	43/m	7.9	385	27.4	7.4	231
Ravi	51/m	6.2	211	25.7	2.6	214
Sumadhi	45/f	3.4	28	22.6	1.7	168
Mani	47/m	4.5	89	21.5	2.8	182
Dhanapal	54/m	6.8	241	25.7	3.4	207
Savithri	46/f	5.3	96	26.7	2.7	206
Manoharan	44/m	9.1	512	29.7	6.7	253
Saradha	48/f	4.8	54	23.6	2.9	184
Amsaveni	42/f	6.9	210	27.3	3	218

Name	Age/Sex	Serum Uric Acid	Urine Alb, Creat Ratio	BMI	Duration of DM	total Cholesteral
Nagammal	50/f	5.6	124	27.4	2.3	204
Pandian	46/m	8.6	411	30.6	6.4	243
Kumar	46/m	4.2	45	23.6	2	168
Sivakumar	44/m	6.7	218	24.1	3.6	183
Kandhasamy	50/m	3.9	27	21.3	2.9	205
Paramasivam	41/m	6.3	242	28.4	3.5	221
Usha	49/f	3.8	42	20.8	2.6	169
Murugeasan	52/m	4.6	51	24.6	2	183
Punniyakotti	48/m	5.4	78	28.3	2.5	204
Sujatha	46/f	7.5	312	28.2	4	214
Fathima	48/f	4.2	42	20.2	1.6	184
Rajeshwari	43/f	4.9	98	21.7	3	192
Sultan	54/m	5.8	112	25.7	2.3	185
Pushpalatha	47/f	8.1	371	26.9	5.8	213
Raja	46/m	5.5	97	21.8	2.6	176
Kamatchi	49/m	6.9	241	25.8	3.6	203
Rathakrishnan	38/m	8.4	418	29.3	6	218
Murali	44/m	5.3	62	21.6	2.5	183
Shanthi	42/f	3.8	21	20.3	1.8	174
Kanniyappan	46/m	6.5	147	26.4	3	215
Gopinath	48/m	5.7	132	25.8	2.6	176
Nagavendhan	49/m	7.3	275	24.6	5.2	183
Chinnasamy	45/m	5.1	86	22.3	2.9	172
Thangaraj	53/m	6.3	168	27.6	3	217
Chinnasamy	64/m	5.4	142	21.8	3.5	178

Name	Age/Sex	Serum Uric Acid	Urine Alb, Creat Ratio	BMI	Duration of DM	total Cholesteral
Krishnan	52/m	6	184	25.3	2.6	197
Subburaj	57/m	5.9	138	25.9	3.4	184
venkatammal	49/f	4.8	84	20.6	1.6	173
Saraswathy	53/f	6.3	247	26.3	2.9	208
Gurumoorthy	42/m	4.7	56	19.5	2	179
Sampath	55/m	6.9	164	23.4	3.6	183
Angaiyan	62/m	6.4	128	24.1	3	204
Raja	47/m	5.8	128	26.3	2.6	251
Narayanan	54/m	5	63	21.6	1.5	195
Valarmathy	61/f	6.3	218	26.3	4.2	243
Eswaran	57/m	6.1	154	26.8	3.6	203
Balamurugan	46/m	5.5	115	21.6	2.6	186
Dhanapal	57/m	7.2	274	28.7	4	218
Thangaraj	45/m	4.4	48	21.4	3	175
Latha	43/f	5.7	113	23.6	4.2	182
Manjula	48/f	3.7	26	20.9	2	215
Parthasarathy	53/m	6.6	248	27.5	3.9	227
Sasikala	42/f	5.8	126	21.3	2.6	189
Ayyapan	54/m	6.1	142	25.8	4	183
Gurusamy	43/m	5.6	96	23.4	2	174
Vanitha	46/f	4.3	42	22.6	2.2	168
Padmavadhy	52/f	4.8	58	21.3	2.8	163
Anjalai	46/f	5.7	128	24.8	3	203
Thondaiman	55/m	6.8	165	26.1	2.6	228
Devaraj	48/m	6.3	110	25.8	3	214

ABBREVIATION

SUA	:	SERUM URIC ACID
CVD	:	CARDIO VASCULAR DISEASE
T2DM	:	TYPE2 DIABETES MELLITUS
T1DM	:	TYPE1 DIABETES MELLITUS
UAC	:	URINE ALBUMINE CREATININE ratio
BMI	:	BODY MASS INDEX
HDL	:	HIGH DENSITY LIPOPROTEIN
LDL	:	LOW DENSITY LIPOPROTEIN
eGFR	:	ESTIMATED GLOMERULAR FILTRATION RATE