“TO CORRELATE SERUM URIC ACID LEVELS AND MICROALBUMINURIA AS MARKERS OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES.”

By

Dr.ATISHAYA.G.V, MBBS

Dissertation submitted to

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Dr. RAVEESHA.A, M.D

PROFESSOR AND HOD

Department of General Medicine

DEPARTMENT OF GENERAL MEDICINE

SRI DEVARAJ URS MEDICAL COLLEGE

TAMAKA, KOLAR-563101

2022

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR, KARNATAKA.

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Dr. ATISHAYA.G.V
Postgraduate in General Medicine
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:

Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR, KARNATAKA.

CERTIFICATE BY THE GUIDE

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Dr. RAVEESHA.A
Professor and HOD
Department of General Medicine
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:

Place:

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR, KARNATAKA.

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Dr. RAVEESHA.A
Professor & HOD,
Department of General Medicine,
Sri Devaraj Urs Medical College,
Tamaka,Kolar.

Dr. P.N.SREERAMULU
Principal
Sri Devaraj Urs Medical College,
Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION &RESEARCH

TAMAKA, KOLAR, KARNATAKA.

ETHICS COMMITTEE CERTIFICATE

This is to certify that the Ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar, has unanimously approved

Dr ATISHAYA.G.V

Post graduate student, in the subject of

GENERAL MEDICINE

at Sri Devaraj Urs Medical College, Tamaka, Kolar,
to take up the dissertation work titled

"TO CORRELATE SERUM URIC ACID AND MICROALBUMINURIA AS MARKERS OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES ."

to be submitted to the

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

Member Secretary
Sri Devaraj Urs medical college
Tamaka,Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH, TAMAKA, KOLAR, KARNATAKA.

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Dr ATISHAYA.G.V

Post graduate

Department of General Medicine

Date:

Place: Kolar

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Prof & HOD of Medicine
SDUMC, Tamaka, Kolar

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LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
2-h PG	2-h plasma glucose
ACR	Albumin-creatinine ratio
AER	Albumin excretion rate
AKI	Acute kidney injury
AUC	Area under the curve
beta TP	Beta-trace protein
BMI	Body mass index
CAD	Coronary artery disease
CBC	Complete blood count
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein test
DCCT	Diabetes Control and Complications Trial
DKD	Diabetic kidney disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
ECG	Electrocardiogram
ESRD	End-stage renal disease
FPG	Fasting plasma glucose
GBM	Glomerular basement membrane
GDM	Gestational diabetes
GFR	Glomerular filtration rate
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
GLUT9	Glucose transporter 9
HbA1c	Hemoglobin A1C
HDL	High-density lipoprotein

HMGB 1	High mobility group box chromosomal protein 1
IFTA	Interstitial fibrosis and tubular atrophy
JAK-STAT	Janus Kinase and Signal Transducer and Activator of Transcription
LDL	Low-density lipoprotein
MALB	Microalbuminuria
MVC	Micro-vascular complications
NGAL	Neutrophil gelatinase-associated lipocalin
NO	Nitric oxide
OGTT	Oral glucose tolerance test
PVD	Peripheral vascular disease
RAAS	Renin-angiotensin-aldosterone system
RAGE	Receptor for advanced glycation end products
RBBB	Right bundle branch block
ROC	Receiver Operative curve
ROS	Reactive oxygen species
SUA	Serum uric acid
T2DM	Type 2 Diabetes mellitus
UA	Uric acid
UAE	Urinary albumin excretion
URAT1	Urate transporter 1
VEGF-A	Vascular endothelial growth factor

ABSTRACT

Background: Levels of “serum uric acid” are linked to the beginning and advancement of diabetic nephropathy and as a risk factor independently for early kidney disease, helping to predict the progression of microalbuminuria. This study is aimed at finding the link and correlating microalbuminuria and “serum uric acid” levels as markers of diabetic nephropathy.

Methods: This is a prospective observational study conducted in the Medicine Department of R. L. Jalappa Hospital and Research Center on subjects with type-2 diabetes mellitus. Patients who meet the exclusion and inclusion criteria are recruited sequentially by convenient sampling til the sample size is attained, with the agreement of the institutional ethics committee. The key outcome parameters are “serum uric acid” and microalbuminuria.

Results: The study comprised 120 type-2diabetes patients with an average age of 58.05± 12.3 years, with 65.83 percent men and 34.17 percent females. The mean duration of diabetes in the study population was 6.28 ± 4.2 years. Based on ACR levels, 79.17% had diabetic nephropathy, and 20.83% with no diabetic nephropathy. The mean “serum uric acid” is 6.6 ± 0.85 mg/dL.

Conclusion: The “serum uric acid” had a fair predictive validity in predicting diabetic nephropathy, as indicated by area under the curve of 0.767 (95% CI 0.66 to 0.88, p value < 0.001) in our study. It had a sensitivity of 63.16% (95% CI 52.64% to 72.83%), specificity 72.00% (95% CI 5.61% to 87.93%), false positive rate 28.00% (95% CI 12.07% to 49.39%), false negative rate 36.84% (95% CI 27.17% to 47.36%), positive predictive value 89.55% (95% CI 79.65% to 95.70%), negative predictive value 33.96% (95% CI 21.52% to 48.27%), with a total diagnostic accuracy of 65.00% (95% CI 55.76% to 73.48%). Between diabetic nephropathy and non-nephropathy, a statistically noteworthy difference in “serum uric acid”

was found. (p value<0.05). The connection between “serum uric acid” and microalbuminuria (r=0.564) was slightly positive and significant statistically (p=0.001).

Key words: Hyperuricemia, Type-2 diabetes mellitus, Diabetic nephropathy, Urine albumin-creatinine ratio (ACR), Microalbuminuria.

INTRODUCTION

INTRODUCTION:

Diabetes mellitus (DM) is a chronic and progressive disorder characterized by persistent hyperglycemia. It could possibly be linked to decreased insulin secretion, resistance to insulin's peripheral activities, or both.[1] Based on the aetiology and clinical presentation, diabetes is divided into three main categories: type 1 diabetes, type-2 diabetes, and gestational diabetes (GDM). Secondary diabetes and monogenic diabetes are two less prevalent kinds of diabetes.[2] Type 2 diabetes (T2DM), also known as non-insulin-dependent diabetes or adult-onset diabetes, affects 90–95 percent of people with diabetes. It is characterized by insulin resistance and a relative (rather than quantitative) insulin shortfall.[3] Type-2 diabetes is caused by a mix of genetic variables linked with decreased insulin resistance and reduced insulin synthesis, as well as ecological factors such as obesity, overeating, a lack of exercise, stress, and ageing. Increased insulin resistance and decreased insulin production are the primary pathophysiological characteristics of type 2 diabetes. Obesity, ageing, inadequate calorie consumption, alcohol use, smoking, and other risk factors of type-2 diabetes mellitus all contribute to the deterioration of pancreatic cell function.[4]

Diabetes consequences are classified into two types: microvascular complications (neuropathy, retinopathy, and nephropathy) and macrovascular disease (stroke, coronary artery disease (CAD), and peripheral vascular disease) (PVD).[5]

“Diabetic nephropathy” (DN) is a frequent chronic micro-vascular consequence (MVC) of type-2 diabetes. It is the commonest cause of end-stage kidney failure and one of the leading causes of mortality and disability in people with diabetes mellitus (DM).[6] Diabetic nephropathy (DN) is a phenomenon defined by abnormal amounts of urine albumin excretion, diabetic glomerular lesions, and loss of kidney function.[7]

Globally, the percentage of ESRD patients with diabetes climbed from 19.0 percent in 2000 to 29.7 percent in 2015, while the percentage of ESRD patients due to diabetes went from 22.1 percent to 31.3 percent. Between 2000 and 2015, the global yearly incidence of ESRD among diabetic individuals grew from 375.8 to 1,016.0 per million diabetic people. In the Western Pacific Region, the highest average rates were reported. In comparison, the rates of ESRD among European diabetic patients ranged from half (309.2 vs. 544.6) to one-third (419.4 vs. 1,245.2) of the rates seen in the Western Pacific population between 2000 and 2015.[8] In India, 34.4 percent of people have DKD, per a study conducted by our group.[9]

Age, poor glycemic management, high blood pressure, and smoking are some of the factors that contribute to T2DM patient's nephropathy progression. The two commonest factors in the pathogenesis of DN appear to be inflammation and endothelial dysfunction.[10] During the synthesis of UA, oxidants are produced, and they might contribute to kidney injury.[11] Free oxygen radicals produced by UA are shown to have a significant impact on endothelial dysfunction by causing inflammation, which contributes to diabetic nephropathy development.[12] According to recent research, UA is a component that can produce inflammation and contribute to endothelial dysfunction, which in turn can lead to the development of DN.[12] According to Zoppini et al.[13] In people with T2DM who have a normal renal function, hyperuricemia appears to represent a separate risk factor for the onset of incident CKD. Patients with hyperuricemia had a much higher rate of long-term kidney disease (in terms of overt proteinuria) than those who did not (29.5 vs. 11.4 percent, p-value 0.001).

Micro-albuminuria is an indicator of endothelial dysfunction and is considered a prognostic marker of kidney damage. Microalbuminuria (MALB) is the appearance of albumin in urine

>= 30 mg/day or 20 μg/min and has been documented to be the initial clinical evidence of DN in DM patients.[14] If hyperuricemia is also a standalone risk factor for CKD, the causality of hyperuricemia and micro-albuminuria can provide the evidence of hyperuricemia to be the risk factor of CKD. Several measurements provide an assessment of overall renal function, such as eGFR and urinary protein.[15] The best way to assess the role of UA in the pathogenesis of CKD is to determine whether UA level affects the development of micro-albuminuria by longitudinal follow-up. Several studies, including that done by Resl et al.[16] have demonstrated that Hyperuricemia and microalbuminuria have an independent relationship in diabetic patients. It is very important to identify a sensitive biomarker for the renal disease before the progression to obvious kidney damage. Micro-albuminuria may be a worthy surrogate marker for the onset of kidney damage. Broad population research of the relationship between serum UA and microalbuminuria could offer light on the role of UA in CKD.

NEED OF THE STUDY:

Diabetic nephropathy, often known as diabetic kidney disease, is a significant kidney-related consequence of type-2 diabetes. Diabetic kidney disease is the most frequent form of chronic kidney disease, which in turn can lead to ESRD and premature death. In addition, it negatively affects a patient's quality of life and social environment and poses a burden on national health care budgets. Even though various therapeutic approaches, such as hypoglycemic agents, antihypertensive drugs, and renin-angiotensin system inhibitors, have been tried in diabetics to slow the progression of nephropathy, the number of patients with DKD continues to rise with the prevalence of type-2 diabetes mellitus. Thus, early identification of patients at risk of developing diabetic nephropathy and initiation of appropriate therapy is important to improve patient outcomes. Screening for microalbuminuria with a spot urine albumin/creatinine ratio identifies the early stages of

nephropathy. UA, as it is a potential mediator for endothelial dysfunction, may be used as a simple and helpful clinical indicator of excessive oxidative stress, and thus microalbuminuria, Early detection and treatment of hyperuricemia in diabetic individuals can help them avoid developing overt nephropathy. The aim of the study is to see the correlation of UA with "microalbuminuria" as markers for diabetic nephropathy in type-2 diabetes mellitus.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES:

- To study microalbuminuria in T2DM.
- To study “serum uric acid” level in T2DM
- To correlate “serum uric acid” levels and microalbuminuria as markers of DN in type 2 diabetes.

REVIEW OF

LITERATURE

REVIEW OF LITERATURE:

Type II DM:

Type-2 DM is a condition in which insulin insensitivity is the characteristic feature which occurs as a result of insulin resistance, reducing insulin production, and finally pancreatic beta-cell failure.[17,18] This disorder causes a decrease in the transportation of glucose into muscle cells, liver cells, and fat cells. With hyperglycemia, there is a surge in fat breakdown. The hampered alpha-cell function has recently been linked to the pathogenesis of type-2 diabetes.[19]

As a result of this, hepatic glucose levels and glucagon, which rises during fasting, are not suppressed following a meal. Given lower than adequate insulin levels and increased insulin resistance, hyperglycemia results. The incretins are important agents which mediate insulin release, which will be released from the gut and, in the case of GLP-1, of glucagon suppression. Despite the fact that GIP activity is reduced in people with type-2 diabetes, GLP-1 insulinotropic effects remain intact, making GLP-1 a potentially effective treatment alternative.[19] However, like GIP, GLP-1 is rapidly converted to an inactive form by DPP-IV in vivo.

Epidemiology:

In 2017, approximately 462 million individuals were affected by type 2 diabetes, corresponding to 6.28% of the world's population (4.4% of those aged 15-49 years, 15% of those aged 50-69, and 22% of those aged 70+), or a prevalence rate of 6059 cases per 100,000. Diabetes alone is responsible for about 1 million deaths per year, making it the tenth-largest cause of death.[20] A systematic and critical review of literature search in PubMed, EMBASE, and Web of Science from articles published during January 1994-December 2018 reported the prevalence of T2DM in India ranged from 1.9% to 25.2%.[21]

Diagnosis:

Glycosylated hemoglobin criteria or plasma glucose criteria, in plasma glucose, either the fasting plasma glucose (FPG) or the 2-hour post prandial plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT), can be used to diagnose diabetes.[22]

Criteria for the diagnosis of diabetes.[22]

Glycosylated haemoglobin ≥6.5%. The test must be carried out in a laboratory with an NGSP-certified method that is standardized to the DCCT assay. * Or FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as nill caloric intake for 8 hours at least.* Or 2-h PG ≥200 mg/dL (11.1 mmol/L) while doing OGTT. The test must be performed as described by the WHO; while doing the test, a glucose load containing the dose equivalent of 75 g anhydrous glucose dissolved in water should be used.* Or In a patient with typical symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L). * In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Complications:

Diabetes is a progressive disorder leading to complications, which are broadly divided into a small vessel or microvascular disease and a large vessel or macrovascular disease. Microvascular complications affect the inner part of the eye—the retina known as diabetic retinopathy, the kidney termed as diabetic nephropathy, and the peripheral nerves termed as diabetic neuropathy. The macrovascular complications affect the heart, the brain, and the peripheral arteries termed the cardiovascular disease, cerebrovascular disease, and peripheral vascular disease, respectively.[23]

Diabetic Nephropathy in T2DM:

Diabetic kidney disease affects 20-40% of people with type 1 or type-2 diabetes. It is a clinical condition defined by chronic albuminuria (> 300 mg/24 h or 300 mg/g creatinine), a steady drop-in glomerular filtration rate, elevated arterial blood pressure, and increased cardiovascular morbidity and mortality. In a case with typical diabetic nephropathy, the normal course is defined by microalbuminuria or moderately elevated urine albumin excretion (30–300 mg/g creatinine). If microalbuminuria goes untreated, then it may rise gradually, reaching severely levels of albuminuria (macroalbuminuria) over 5 to 15 years. Glomerular filtration rate then begins to decline, and end-stage renal failure is reached without treatment in 5 to 7 years.[24]

Diabetic nephropathy is divided based on the hierarchy into four glomerular lesions with a separate evaluation for degrees of interstitial and vascular involvement.

Table 1: Biopsies diagnosed as diabetic nephropathy are classified as follows.[25]

I	GBM thickening confirmed by electron microscopy and mild or nonspecific alterations on light microscopy: GBM > 395 nm (female), GBM > 430 nm (male).
IIa	Mild mesangial expansion in >25% of the mesangium observed; Area of mesangial proliferation < area of the capillary cavity.
IIb	Severe mesangial expansion in >25% of the mesangium observed. Area of mesangial proliferation < area of the capillary cavity.
III	At least one convincing nodular sclerosis (Kimmelstiel-Wilson lesion).
IV	Advanced diabetic glomerulosclerosis in >50% of glomeruli

Table 2: The separate scoring system of interstitial and vascular lesions of DN:

Lesion	Criteria	Score
Tubulointerstitial lesions	No IFTA IFTA < 25% 25% < IFTA < 50% IFTA > 50%	0 1 2 3
Interstitial inflammation	Absent Relate to IFTA In areas without IFTA	0 1 2
Arteriolar hyalinosis	Absent One hyaline arteriole More than one hyaline arteriole	0 1 2
Arteriosclerosis (most severely affected artery	No intimal thickening is observed Intimal thickening is less than the thickness of the media Intimal thickening is more than the thickness of the media	0 1 2

IFTA: tubulointerstitial fibrosis and tubular atrophy.[25]

Epidemiology:

DN is highly prevalent across the globe. The odds of diabetes patients developing CKD were reported around 1.75 (95% CI: 1.62–1.89).[26] Despite the fact that rates of diabetes-related complications such as diseases of the cardiovascular system have decreased dramatically over the last two decades, kidney issues have not. Diabetes-related CKD is well-known as the most common cause of end-stage kidney disease (ESKD) in T2DM patients around the world.[27 28] Between 2013 and 2016, about 36% of diabetic patients in the United States developed diabetic kidney disease, resulting in chronic albuminuria, a lower eGFR, or both.[28]

Risk factors:

DN is caused by a complex interplay of genetic and environmental factors. The important risk factors include hyperglycemia, hypertension, and genetic predisposition. Exacerbating hyperglycemia is also a critical risk factor for microvascular problems.[29] DN risk factors can conceptually be classified as susceptibility factors (e.g., age, sex, race/ethnicity, and family

history), initiation factors (e.g., hyperglycemia and AKI), and progression factors (e.g., hypertension, dietary factors, and obesity). Two of the most prominent established risk factors are hyperglycemia and hypertension.[30]

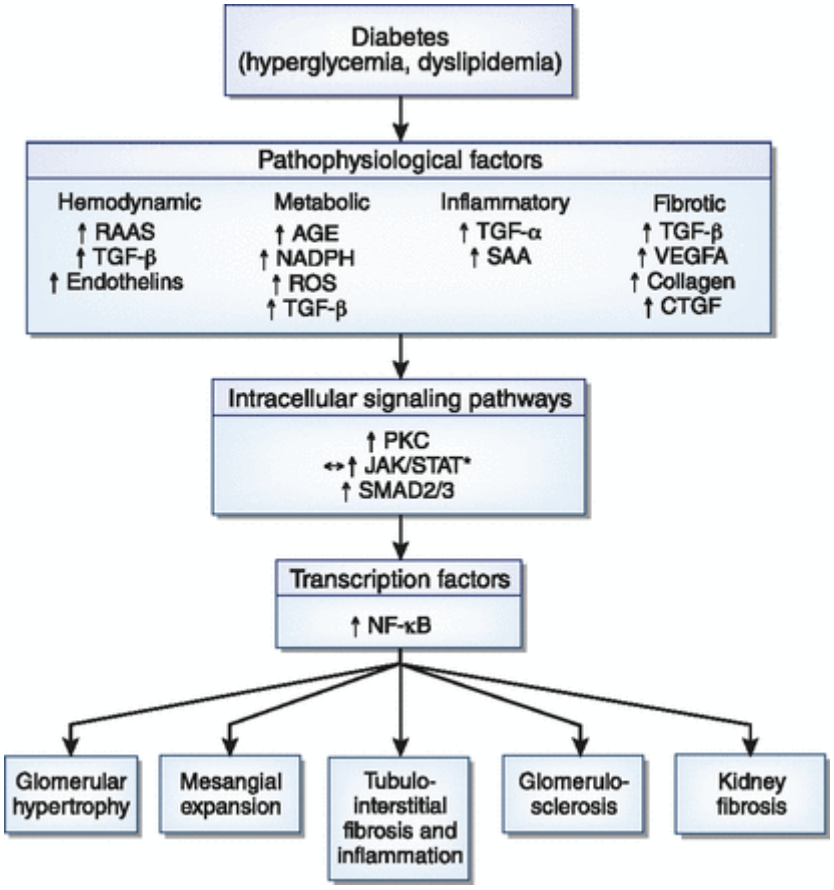
Pathophysiology:

The pathogenesis of diabetes Mellitus microvascular complications is not completely understood; however, hyperglycemia is always a beginning and sustaining element in the continual destruction of target tissues and organs. As a result of substantial micro vasculopathy and interstitial inflammation, tissue vulnerability rises. Hyperglycemia with its glucotoxicity produces hyaline degeneration and fibrinoid degeneration in arterioles and micro vessels, which appears to be activating a vicious cycle and causing damage to renal mitochondria since the kidney is an organ of high metabolic needs, culminating in bioenergetic deficit in renal tubular epithelial cells.[31]

Hyper aminoacidemia, which promotes glomerular hyperfiltration and hyper perfusion, and hyperglycemia are two key metabolic changes in early diabetes that affect kidney hemodynamics and promote inflammation, later fibrosis.[31] Both hypertension and obesity, through processes such as higher transmitted systemic BP and glomerular hypertrophy, contribute to an abnormal increase in glomerular filtration rate in T2DM.[31] Abnormal increase in glomerular filtration rate is a well-known early diabetic complication. Overall, it is found in 10%–40%, or up to 75%, of individuals with DM1 and up to 40% of patients with T2DM. The mechanisms underpinning the abnormal increase in glomerular filtration rate in diabetes are unknown[33]; However, one possible mechanism is enhanced proximal tubular glucose reabsorption via sodium-glucose cotransporter 2, which lowers the distal supply of solutes to the macula densa, particularly sodium chloride.[34] [35] The afferent arteriole may dilate as a

result of the reduced tubuloglomerular feedback, enhancing glomerular perfusion, but enhanced local angiotensin II production at the efferent arteriole induces vasoconstriction. High intraglomerular pressure and an abnormal rise in glomerular filtration rate are the overall effects.[32,33]

Figure 1: Different pathways and networks involved in the initiation and advancement of diabetic nephropathy.



AGE stands for advanced glycation end product; CTGF stands for connective tissue growth factor; JAK-STAT stands for Janus kinase/signal transducer and activator of transcription; PKC stands for protein kinase C; RAAS stands for the renin-angiotensin-aldosterone system; ROS stands for reactive oxygen species; SAA stands for serum amyloid A; VEGF-A stands for vascular endothelium.[34 36]

Diagnosis:

eGFR and albuminuria values, as well as clinical features such as diabetes duration and diabetic retinopathy, are used to make a clinical diagnosis of DN.[27,34] A consistently high urine albumin-to-creatinine ratio of 30 mg/g and/or a sustained drop in eGFR < 60 ml/min per 1.73 m2 are clinical signs of DN.[35] Patients with T2DM should be screened for DN once a year, starting at the time of diagnosis. The occurrence of diabetic retinopathy in patients with albuminuria is significantly predictive of DN. A urine albumin-to-creatinine ratio test conducted on a spot sample, ideally in the morning, is the preferred test for albuminuria.[34 27] The serum creatinine concentration is used to determine the eGFR. Although the Chronic Kidney Disease-Epidemiologic Prognosis Initiative equation is more accurate, especially at eGFR levels in the normal or near-normal range, clinical laboratories commonly report using the Modification of Diet in Renal Disease equation.[27] Two abnormal values taken at least three months apart are required to confirm albuminuria or low eGFR. Other causes for the renal disease should be considered if features atypical of DN are present. Sudden onset of low eGFR or rapidly decreasing eGFR, an abrupt increase in albuminuria or development of nephrotic or nephritic syndrome, refractory hypertension, signs or symptoms of another systemic disease, and >30% eGFR decline within 2–3 months of starting a renin-angiotensin system inhibitor are all atypical features.[35]

Complications and Management:

Weight loss, increased physical activity, dietary sodium reduction, and quitting of smoking are all non-pharmacological therapies that must be included in any attempt to enhance outcomes in individuals with DKD. Unfortunately, these objectives are notoriously difficult to fulfil; therefore, patients must be encouraged to participate actively in their own care and receive help in achieving mutually agreed-upon treatment objectives.[36]

The emergence of renal disease in adults with diabetes will lead to a considerable increase in the risk of death from cardiovascular disease; hence all patients should undergo intensive risk factor reduction. This includes quitting smoking and lowering cholesterol; the relevance of controlling blood pressure will be covered later. The question of whether the lipid-lowering treatment has a direct advantage in delaying the progression of DN is still being debated. Hyperlipidemia has been linked to glomerulosclerosis in people with CKD, and while some research has suggested that reducing cholesterol can assist preserve eGFR or reduce albuminuria, this has not been demonstrated clearly.[37–39] Improving glycemic management has a positive impact on the onset and course of DN.[40]

Markers of Diabetic nephropathy in Type II DM:

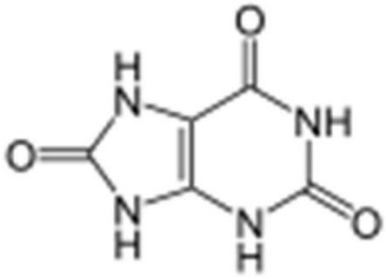
In recent years, a number of biochemical indicators linked to diabetic nephropathy have been discovered, which can help anticipate the onset and progression of the illness. Although absolute albumin excretion rate (AER) and GFR measurements are important biomarkers, AER classification often lacks the required specificity and sensitivity, and estimates of declining GFR are hampered by methodological limitations for GFRs in the normal-to-high range. Oxidative and inflammatory indicators, profibrotic cytokines, UA, advanced glycation end products, functional and structural markers of vascular dysfunction, kidney structural alterations, and tubular biomarkers are all becoming risk markers for the progressive loss of kidney function. Serum.UA and soluble tumor necrosis factor receptor (type 1 and type 2) levels are the most promising, especially in relation to GFR alterations.[41] Motawi et al.[42] estimated three new promising biomarkers: neutrophil gelatinase-associated lipocalin (NGAL), beta-trace protein (beta TP), and microRNA-130b (miR-130b) in type 2 DM. They concluded that serum NGAL and betaTP were significantly elevated in T2DM patients and can serve as early biomarkers of tubular and glomerular markers, respectively.

Studies have shown that a decline in the number of podocytes and the disappearance of foot processes often occur in the early stages of DN due to apoptosis or shedding of podocytes. Therefore, urinary podocytes and their specific protein products may be regarded as potential biomarkers of podocyte injury.[43] Researchers found that urinary levels of a1-microglobulin and RBP4 in patients with normoalbuminuria were significantly higher than those in control subjects and were both associated with the levels of HbA1c, so that detection of two biomarkers may be helpful for early diagnosis of diabetic nephropathy.[44,45]

SUA levels as a marker of diabetic nephropathy in type 2 DM:

UA is synthesized mainly in the liver, intestines, and other tissues such as muscles, kidneys, and the vascular endothelium as the end product of an exogenous pool of purines, derived largely from animal proteins. In addition, live and dying cells degrade their nucleic acids, adenine, and guanine into UA. Deamination and dephosphorylation convert adenine and guanine to inosine and guanosine, respectively. The enzyme purine nucleoside phosphorylase converts inosine and guanosine to the purine bases, respectively hypoxanthine and guanine, which are both converted to xanthine via xanthine oxidase-oxidation of hypoxanthine and deamination of guanine-by-guanine deaminase. Xanthine is further oxidized by xanthine oxidase to UA.[46,47]

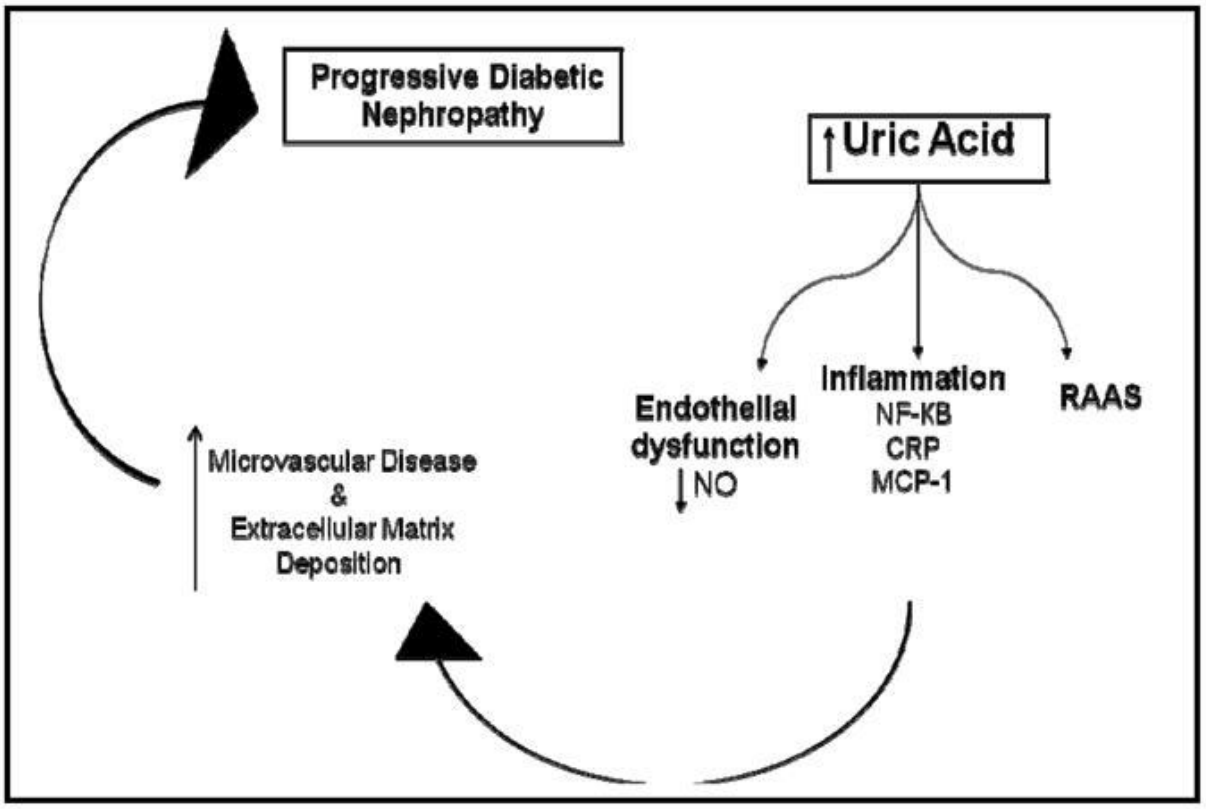
Figure 2: Uric acid, C5H4N4O3, 7,9-dihydro-1H-purine-2,6,8(3H)-trione, molecular mass 168 Da, is a product of the metabolic breakdown of purine nucleotides (adenine and guanine).[46]



The soluble form of uric acid generated in the liver (monosodium urate) is discharged into the circulation and is easily filtered by the glomerulus. Most of the UA secreted by the glomerulus will be reabsorbed by proximal convoluted tubule resulting in a normal fractional excretion of approximately 10%.[48] Hyperuricemia is defined as a condition in which uric acid will accumulate in the blood beyond the solubility point(6.8 mg/dL). In general, hyperuricemia develops due to overproduction, under secretion of UA, or both.[48]

UA has several known effects by which it may cause DN, which is illustrated in the figure below, increased activity of the RAAS, including endothelial dysfunction, and induction of inflammatory cascades, in addition to activation of profibrotic cytokine, all of which have been demonstrated to contribute to the progression of microvascular disease and thereby kidney injury in DN.[49]

Figure 3: Mechanisms by which UA may cause diabetic nephropathy.[49]



The effects of UA on the endothelium are the topic of continuous debate. On the one hand, in vitro studies have shown to decrease nitric oxide (NO) production by endothelial cells, and it does so in association with increased CRP expression. UA may also react with NO in a way that the binding cannot be reversed, leading to the formation of 6- amino uracil and may thus lead to depletion of NO.[49] Data from Jalal et al.[49] According to the study; uric acid causes endothelial dysfunction. However, some research suggests that oxidative stress caused by elevated xanthine oxidase activity is the primary cause of endothelial dysfunction rather than elevated uric acid. An example of such findings can be found in 2 double-blind placebo-controlled studies done by George et al.[50]

In endothelial cells, UA promotes the synthesis with the extracellular release of the high mobility group box chromosomal protein 1 (HMGB1). HMGB1 is an inflammatory cytokine

that causes inflammation and oxidative stress by interacting with the RAGE receptor, resulting in endothelial dysfunction.[12]

The circulating uric acid is easily filtered from the glomeruli into the renal tubule. About 90% of filtered UA is reabsorbed by the middle of the proximal convoluted tubule, mainly by urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9)[51], and the remaining excreted 10% is responsible for 60–70% of total body uric acid excretion.[52,53] A small amount of UA secreted in the intestine is responsible for 30–40%.[53] The production and excretion rate of UA is relatively constant in healthy people. Changes in the uric acid content in body fluids can reflect the state of metabolism, immunity, and other functions of the human body. If the body produces too much UA or the excretion mechanism is degraded, the body will retain excessive UA. UA levels in the circulation greater than 5.7 mg/dl in women and 7.0 mg/dl in men were characterized as hyperuricemia.[54]

Role as a marker for diabetic nephropathy in type 2 DM:

High-normal blood UA levels may predict the likelihood of CKD stage 3 or greater, according to a retrospective observational longitudinal study of patients with type-2 diabetes mellitus and intact renal function (eGFR 60 mL/min/1.73 m2).[55] One retrospective study reported that the levels of UA in patients in the diabetic nephropathy and non-nephropathic groups were 6.3 (4.2-9.6) mg/dl and 4.9 (3-8.5) mg/dl, respectively, with a difference which is statistically significant with $p<0.001$. The best cut-off value for UA in detecting diabetic nephropathy was 5.2 mg/dl (AUC=0.749, $p<0.001$), and according to ROC analysis, UA predicted diabetic nephropathy with 80.6% sensitivity and 64.1% specificity.[56] In the general prevalence of DKD was significantly higher (68.3% vs. 41.5%, $p<0.0001$) in the hyperuricaemic group than in the normouricaemic group, and the difference remained

significant after classification by gender in a cross-sectional study. Logistic regression analysis revealed that serum UA, whether treated as a continuous (OR = 1.381, 95%CI = 1.293–1.476, p <0.0001) or a stratified variable (OR = 1.435, 95%CI = 1.335–1.543, p <0.0001), remained strongly associated with DKD.[57]

A cross-sectional study reported that patients with elevated uric acid (SUA) levels (≥420 μmol/L for males and ≥360 μmol/L for females) had a significantly higher prevalence of DN (UAE ≥30 mg/24 h, 39.3% vs 26.3%; p < 0.001), higher UAE levels (140 ± 297 vs 63 ± 175 mg/24 h; p < 0.001), and lower eGFR ; 79.3 ± 26.8 vs 96.8 ± 19.6 mL/min/1.73 m2; p < 0.001), when compared with patients with normal SUA levels.[58] A case-control study demonstrated that that solely 32% of diabetic patients were hyperuricemic, but in contrast to healthy control subjects, SUA levels were higher in T2DM patients with onset of diabetes <5 years and continue to rise with the progression of the disease and clinical presentation of DN.[59]

Microalbuminuria as a marker of diabetic nephropathy in type 2 DM:

Albumin is the most abundant plasma protein and is produced in the liver. It has a molecular weight of B65 kDa and is an anionic, flexible, heart-shaped molecule.[60] Human serum albumin has amino acids 585 in number, which forms a single polypeptide which is of known sequence. Genetic variants which have been well characterized have been reported. The Physico-chemical characteristics of the protein are well-established. By contrast, the complete secondary and tertiary structures are not known; information about major structural features only has been obtained. The albumin molecule seems to have an overall ellipsoidal shape (about 140 x 40 A) and to be composed of domains.[61] Although it is not required for life, this protein has a number of important and diverse functions, including maintaining oncotic

pressure and blood volume, acid/base buffer functions, antioxidant functions, and the transport of a variety of substances, including fatty acids, bilirubin, ions such as Ca2+ and Mg2+, drugs, hormones, and lipophilic as well as hydrophilic vitamins, such as vitamin A, riboflavin, Vitamin B6, Vitamin c and folate. In renal disease, both serum and urine albumin levels are important prognostic markers.[62]

Under normal conditions, the glomerulus, an intricate vascular structure in the kidney, limits the transport of albumin from blood to the urine.[63] The barrier through which glomerular filtration takes place is made up of glomerular endothelial cells on the blood vessel side, the glomerular basement membrane, and podocytes with interdigitating foot processes on the urine side of the barrier.[62] In diseases such as diabetic nephropathy, the integrity of the barrier for glomerular filtration is compromised by chronic hyperglycemia, leading to increased albumin filtration into the urine (and detectable albuminuria).[64]

The glomeruli filter albumin, which is thought to be the main source of urine albumin. Albumin filtration is followed by tubular reabsorption, and albuminuria is the consequence of the combined contribution of these two processes. Both glomerular damage and tubular impairment have been involved in the earliest events leading to proteinuria.[62]

End-stage renal disease is distinguished by irreversible kidney damage. Because renal impairment, particularly in Type 2 diabetes, is not always accompanied by albuminuria and can occur in persons with normal eGFR[68], microalbuminuria must be used in conjunction with traditional nephropathy markers to evaluate renal function. Increased urine protein excretion might be an early clinical sign of diabetic nephropathy.[69] The urine dipstick, on the other hand, is a somewhat insensitive diagnostic for initial increases in protein excretion, only

appearing positive when protein excretion surpasses 300 to 500 mg/day. (Upper limit of normal less than 150 mg/day, with most individuals excreting less than 100 mg/day). Cross-sectional research of Type-2 diabetes mellitus patients discovered a positive relationship between UA and microalbuminuria, with mean SUA levels of 6.991.01 mg/dL and microalbuminuria levels of 5.631.08 mg/mmol and an R-value of 0.0838.75.

Using a particular albumin test is a better sensitive technology that is now widely acknowledged. Albumin excretion should not exceed 30 mg/day (20 mcg/min); chronic albumin excretion between 30 and 300 mg/day (20 to 200 mcg/min) is referred to as moderately elevated albuminuria (the new terminology for what was formerly called "microalbuminuria").[65] Albumin excretion more than 300 mg/day (200 mcg/min) is considered to represent severely increased albuminuria (the new terminology for what was earlier called "macroalbuminuria").[65]

Role as a marker for diabetic nephropathy in type 2 DM:

Early morphologic lesions of diabetic nephropathy, such as thickening of glomerular basement membrane and mesangial expansion, develop in practically all insulin-dependent diabetics within a few years once metabolic abnormality develops.[66] Nonetheless, clinical diabetic nephropathy with proteinuria, hypertension, and renal function decline develops eventually in only about 45% of insulin-dependent diabetics, the remainder being spared clinically important renal disease. Several benefits could be derived from knowing early in the course of diabetes whether a patient is likely to develop clinical diabetic nephropathy.[66]

Proteinuria is the laboratory hallmark of diabetic nephropathy and is highly predictive of uremia and early mortality.[67] However, proteinuria comes as positive only when urine

albumin concentration (and excretion) is increased from normal by a factor of approximately 20. Recent studies using more sensitive techniques have revealed the existence of early abnormalities in protein excretion, termed either "subclinical proteinuria" or "microalbuminuria." These studies have documented that even a slight elevation of urine albumin excretion—far below the level found in "clinical proteinuria"—is a strong predictor of future overt diabetic nephropathy. Diabetic patients devoid of microalbuminuria have only a small risk of developing clinical proteinuria over the next 10 to 14 years; therefore, the excess mortality of such patients in comparison with the nondiabetic population is likely to be small.[67]

A cross-sectional study to find glycated albumin and microalbuminuria as early risk markers along with the duration of Uncontrolled Diabetes Mellitus in type-2 diabetic nephropathy noted that the Microalbuminuria increased significantly with a glycemic control which is poor and it correlated with elevated serum creatinine levels, which indicated a renal damage ($p<0.0001$). In Type 2 DM patients, glycemic control and microalbuminuria showed a significant linear correlation with duration of diabetes ($p<0.0001$).[68]

Correlation between serum uric acid levels and microalbuminuria in T2DM:

In a retrospective study group on diabetic nephropathy patients, the correlation between _microalbuminuria and UA was reported as significant with a p-value of 0.017 and r value 0.238.[56] The level of SUA was notably higher in the macroalbuminuria group than in the normoalbuminuria (6.9 2.3 versus 5.6 1.6, p 0.001) and microalbuminuria (6.9 2.3 versus 6.1 1.7, p 0.001) groups in a cross-sectional study to evaluate the relationship between increases in serum uric acid level and albuminuria. SUA levels were considerably greater in the microalbuminuria group than in the normoalbuminuria group (6.1 1.7 versus 5.6 1.6, p

0.001).[69] A cross-sectional investigation of Type-2 diabetes mellitus patients indicated a strong correlation between UA and microalbuminuria, with mean SUA levels of 6.991.01 mg/dL and microalbuminuria levels of 5.631.08 mg/mmol and an R-value of 0.0838.[75]

Hyperuricemia is a risk factor for renal insufficiency, and it correlates to intima-media thickness and microalbuminuria. A prospective observational study on logistic regression analysis indicated that each 1 mg/dL increase of UA was associated with a 1.42-times increased risk of micro-albuminuria after adjustment for the 8 factors (age, sex, and 6 metabolic metrics) (OR=1.42, 95% CI: 1.27–1.59, p<0.01). A Cox regression model using subjects with serum UA less than 5 mg/dL as reference group indicated higher hazard ratios (HRs) only found in subjects with serum UA more than 7 mg/dL (HR=3.54, 95% CI: 2.11–5.93, p<0.01) and not in subjects with serum UA of 5 to 7 mg/dL (HR=1.30, 95% CI: 0.82–2.07, p=0.15).[75]

A cross-sectional study in type-2 diabetes patients looked at the relationship between SUA concentration and urinary albumin excretion and found that level of SUA was positively linked with urine ACR (P =0.04). Patients with normoalbuminuria, microalbuminuria, and macroalbuminuria had SUA levels of 4.49 1.22 mg/dL, 4.84 1.52 mg/dL, and 6.15 1.68 mg/dL, respectively (P = 0.004). Even after accounting for predicted GFR, the link between blood uric acid content and urine albumin excretion was substantial.[70]

According to a single-center observational study conducted on type II diabetic patients to assess the association of HbA1c (a glycemic control marker) with SUA and microalbuminuria in type II DM, microalbuminuria showed a significant correlation with serum uric acid (r = 0.338) when Pearson's correlation was applied.[71] The concentration of UA in the blood was greater in patients with microalbuminuria (7.54 1.39 mg/dL, P = 0.009) than in individuals

with normoalbuminuria (6.44 1.23 mg/dL), according to a cross-sectional study done to evaluate the relationship between "serum uric acid" concentration, degree of urinary albumin excretion (UAE) in T2DM patients.[72] Khan et al.[73] in their observational study, reported a significant relationship between U.ACR (Normo-Albuminuria, Microalbuminuria, and Macro-Albuminuria) with respect to "Serum Uric Acid" with a P-value < 0.05.

According to a cross-sectional study, the odds of micro albuminuria were 1.02 times (95 percent CI 0.58 to 1.79, p-value 0.944) higher in people with UA levels between 5 and 7.49 mg/dl and 1.855 times (95 percent CI 0.56 to 6.081, p-value 0.30) higher in people with uric acid levels of 7.5 and above, when compared to people with uric acid levels below 5 mg/dl.[74]

Evidence suggests that both elevated UA and microalbuminuria levels were significantly associated with diabetic chronic micro/macro-vascular complications.

MOST RELEVANT STUDIES:

Jain et al.[75] **(2020)** assessed the significance of microalbuminuria as well as UA for an early finding of kidney and cardiovascular involvement in type-2 Diabetes mellitus in a cross-sectional case-control study. It was seen that the prevalence of microalbuminuria was 37% in cases and 8% in control. The mean value of age, BMI, fasting glucose, post-meal plasma glucose, SUA, microalbuminuria in patients of diabetes mellitus was found to be highly significant as compared to the control group ($p< 0.0001$)). The study concluded that microalbuminuria may also be used as a predictor for early kidney involvement in type 2 diabetes. In patients with diabetes mellitus, UA can be used to screen for diabetic nephropathy.

Xia et al.[58] **(2020**) aimed to look into the connection between serum uric acid (SUA) and the severity of diabetic nephropathy (DN) and diabetic retinopathy (DR) in individuals with type-2 diabetes mellitus (T2DM). SUA was linked significantly with UAE ($r = 0.069$, $p < 0.001$). They concluded that for patients with T2DM, higher SUA levels are associated with higher UAE, lower eGFR, and higher prevalence of DN, but not DR.

Khan et al.[73] **(2020)** studied the link between SUA & albuminuria among patients with T2DM in an observational study. Most of the patients were found to have Micro-Albuminuria 72 (45.3 %), followed by Normo Albuminuria 65(40.9%) and Macro-Albuminuria 22(13.8%). There was a significant relationship noted between U.ACR (Normo-Albuminuria, Microalbuminuria, and Macro-Albuminuria) with respect to SUA with P-value <0.05. The study summarized that hyperuricemia is commonly associated with albuminuria which is an early sign of diabetic nephropathy.

Kocak et al.[56] **(2019**) The aim of this study was to look at the association between "serum uric acid" (UA) and microalbuminuria as a measure of renal damage in people with type-2 diabetes. Serum UA levels of diabetic nephropathy patients were profoundly higher than those in the non-nephropathy group (UA in patients with DN groups: 6.3 (1.82) mg/dl, UA in patients of the non-nephropathic group: 4.85 (1.92) mg/dl) (p<0.001). There was a relation between microalbuminuria and UA (r=0.238). This correlation was statistically significant (p=0.017). They concluded that UA levels may be an important predictor of nephropathy in diabetic patients.

Kiconco et al.[76] **(2019)** a cross-sectional study was undertaken to identify the prevalence of microalbuminuria in diabetic persons and to determine its relationship with traditional renal

indicators in the assessment of incipient nephropathy. The overall prevalence of microalbuminuria was 22.9%. The prevalence of microalbuminuria in diabetic patients was high in this study. The study suggests the need to screen for microalbuminuria early to reduce the possible burden of ESRD. When serum creatinine is used as a renal function marker among diabetic patients, it should be combined with microalbuminuria for better assessment of incipient nephropathy

Li et al.[5] **(2018)** conducted a study to evaluate the relationships between blood uric acid (BUA) level and the incidence, progression, and deterioration of diabetic nephropathy (DN) in people with type-2 diabetes mellitus (T2DM). Multiple linear regression analysis depicted that UA level was the main factor affecting ACR ($R2=0.636$, $p< 0.001$). According to the findings from the study, UA level is itself a stand-alone risk factor for early renal disease in T2DM patients, which might hasten the progression and deterioration of the renal disease.

Latif et al.[77] **(2017)** In this cross-sectional study, researchers looked at the relationship between microalbuminuria and the levels of SUA in Type-2 diabetic nephropathy. The mean blood UA level was 6.991.01 mg/dL, whereas microalbuminuria was 5.631.08 mg/mmol, with an R-value of 0.0838, indicating a positive connection. According to the findings, the SUA levels and microalbuminuria levels are substantially linked to nephropathy in Type-2 diabetic patients.

Fiza et al.[71] **(2017**) The intention of this study was to examine if there was a connection between SUA and microalbuminuria in Type 2 Diabetes Mellitus patients. Overall odds of microalbuminuria were 1.02 times (95 percent CI 0.58 to 1.79, p-value 0.944) in people with uric acid levels between 5 and 7.49 and 1.855 times (95 percent CI 0.56 to 6.081, p-value

0.30) in those with UA levels above 7.5. (HbA1c). The concentration of UA in the blood was associated with UAE (r = 0.323, P 0.05), age (r = 0.337, P 0.05), and age at onset (r = 0.341, P 0.05).

Idowu et al.[78] **(2017)** a study was done to see if there was a link between microalbuminuria and other predictors of morbidity as well as mortality in people with type 2 diabetes. Diabetics with a disease duration of >10 years were the oldest (65.861.71), had the highest systolic blood pressure (147.123.39), and the lowest BMI (27.200.711kg/m2); they had the worst lipid control (TC:5.540.26mmol/L), but the lowest TG (0.970.09mmol/L); and they had the most severe microalbuminuria (33.638.03g/L) and ACR (65.85±10.38mg/gm). Glycemic control was poorest among patients with diabetes for 5–10 years (FPG-7.820.47mmol/L; HbA1c-13.090.74%). In patients with 5–10 years disease, there are significant negative correlations between microalbuminuria, HBA1c (r=2.28, p=0.028), and serum creatinine (r=2.11, p=0.042); a positive correlation between the ACR and TC (r=1.00, p0.01) in those with >10 years disease. In multivariate analysis, independent predictors of microalbuminuria were disease duration (OR 2.2, p< 0.001); HBA1c (OR 7.3, p=0.02); LDL/HDL ratio (OR 13.4, p< 0.001). The severity and progression of albuminuria are linked to a longer duration of diabetes and poor glycemic control, according to the study.

Prabhuswamy et al.[74] **(2017)** The purpose of this particular study was to see if there was a link between SUA and microalbuminuria in Type 2 Diabetes Mellitus patients. The odds of microalbuminuria were 1.02 times (95 percent CI 0.58 to 1.79, p-value 0.944) in people with UA levels between 5 and 7.49 and 1.855 times (95 percent CI 0.56 to 6.081, p-value 0.30) in people with uric acid levels above 7.5 Researchers looked examined the relationship between SUA, urine albumin excretion (UAE), and glycated hemoglobin in Type-2 diabetes (T2DM)

patients (HbA1c). The concentration of UA in the blood linked favorably with UAE (r = 0.323, P 0.05), age (r = 0.337, P 0.05), and age at onset (r = 0.341, P 0.05).

Neupane et al.[72] **(2016**) Researchers looked examined the relationship between SUA level, urine albumin excretion (UAE), and glycated hemoglobin in Type-2 diabetes (T2DM) patients (HbA1c). SUA concentration (r = 0.323, P 0.05), age (r = 0.337, P 0.05), age at onset (r = 0.341, P 0.05), and duration of DM (r = 0.312, P 0.05) were associated favorably. In T2DM patients, SUA levels is linked to microalbuminuria and HbA1c.

Hayashino et al.[79] **(2016)** conducted a study to see if there was a link between baseline SUA levels and the risk of developing or progressing albuminuria later on. The multivariable-adjusted hazards ratios for the progression from microalbuminuria to macroalbuminuria were 2.17 [95 % confidence interval (CI) 1.15–4.08; p = 0.016], 3.04 (95 % CI 1.67–5.53; p < 0.001), and 3.56 (95 % CI 1.83–6.93; p < 0.0011) for the first, third, and fourth quartiles of SUA levels, respectively, as compared to that for the second quartile. Low and high SUA, independent of possible confounders, were associated with a subsequent risk of progression, not development, in albuminuria in type 2 diabetes patients. Therefore, levels of SUA may be useful for predicting the future risk of progression of microalbuminuria.

Fouad et al.[59] **(2016**) conducted a study to find the link between SUA and hypertension, early nephropathy, and progression of chronic kidney disease (CKD) in type 2 diabetes mellitus (T2DM). SUA at level of > 6.1 mg/dl, > 6.2 mg/dl and > 6.5 mg/dl had a greater sensitivity and specificity for identifying hypertension, early nephropathy and decline eGFR respectively. The study demonstrated that that solely 32% of patients with diabetes were hyperuricemic, but in contrast to healthy control subjects, SUA levels were higher in T2DM

patients with onset of diabetes less than 5 years and continue to rise with disease worsening and clinical presentation of DN.

Liang et al.[69] **(2016)** a research in Taiwanese people with diabetes mellitus to examine if there was a relationship between high blood UA levels and the severity of albuminuria In multivariate logistic regression analysis, a high UA concentration was determined to be a risk factor for albuminuria (odds ratio (OR), 1.227; 95 percent confidence interval (CI) = 1.015–1.482; p = 0.034). They also discovered that individuals with more severe albuminuria had higher blood UA concentrations. A higher blood UA level was shown to be significantly linked with the severity of albuminuria in Taiwanese individuals with type-2 diabetes.

Yan et al.[57] **(2015)** a study was done to see if there was a link between hyperuricemia and diabetic renal disease (DKD). The prevalence of DKD was higher in hyperuricaemic patients than in patients with normoglycemia (68.3% vs. 41.5%). The prevalence of DKD increased with increasing UA (p <0.0001). The logistic analysis identified UA as a standalone predictor of DKD (p <0.0001; adjusted OR (95%CI) = 1.005 (1.004–1.007), p <0.0001). After correcting for confounding factors, UA was positively correlating with albuminuria and creatinine levels (p0.0001) but negatively correlating with eGFR (p0.0001). The study concluded that hyperuricemia is a risk factor for DKD. SUA levels within the high-normal range are independently associated with DKD.

Kim et al.[55] **(2014)** Researchers investigated whether high-normal (SUA) levels might predict the development of CKD in individuals with type-2 diabetes mellitus who had preserved renal function at baseline in a retrospective observational longitudinal study. According to the data,

high-normal SUA may indicate the chance of CKD stage 3 or more in persons with type-2 diabetes mellitus and intact renal function.

Ali et al.[80] **(2014)** undertook a study to determine the prevalence of microalbuminuria in type II diabetics and to discover its relationship with blood pressure, illness duration, and anthropometric measures. Microalbuminuria was discovered to affect 58.2 percent of the population. Blood urea and creatinine levels were found to be high in 13.2 percent of the 53 individuals with microalbuminuria. Microalbumin has been associated to high systolic blood pressure, increased circulating glucose levels, and the duration of diabetes. As a result, diabetic individuals should be routinely screened for microalbuminuria at least once a year.

Behradmanesh et al.[81] **(2013)** analyzed the connections between serum uric acid (SUA) levels and proteinuria levels in type 2 diabetic (T2D) individuals in cross-sectional research. Body mass index (BMI) and SUA levels had a significant positive relationship (r = 0.428, P = 0.001). After adjusting for weight, there was a significant positive relationship between SUA and proteinuria (r = 0.47, P 0.001). The study concluded that SUA had a significant positive association with diabetic nephropathy. It might be hypothesized that SUA plays a role in diabetic nephropathy in T2D.

Chang et al.[82] **(2013)** state that elevated SUA is associated with the development of microalbuminuria in the general population and conducted a community-based prospective cohort study. Logistic regression analysis indicated that each 1 mg/dL increase of UA was associated with a 1.42-times increased risk of micro-albuminuria after adjustment for the same 8 factors (OR=1.42, 95% CI: 1.27–1.59, p<0.01). Hyperuricemia is substantially linked with microalbuminuria in middle-aged and elderly males and females from a general

population in Taiwan, according to the findings. In this cohort, increased serum UA is a standalone predictor of the development of microalbuminuria.

Kundu et al.[83] **(2013)** did research to investigate the levels of microalbuminuria in type 2 89 diabetics and to correlate changes in microalbuminuria levels with glycosylated hemoglobin levels and diabetes duration. The cases had significantly higher levels of urinary microalbumin and HbA 1c. Microalbumin levels were found to be linearly related to diabetes duration and HbA1c. Significant increases in urine microalbumin levels are linked to poor glycemic management. Furthermore, increasing urine microalbumin levels are associated with a longer duration of diabetes, implying that early diagnosis of elevated urinary microalbumin levels can prevent or lessen the clinical and economic burden of diabetic complications such as nephropathy in the future.

Kondaveeti et al.[68] **(2013)** conducted a cross-sectional study to find GA and microalbuminuria as early risk markers along with the duration of Uncontrolled Diabetes Mellitus in type-2 diabetic nephropathy. When compared to Controlled DM, the mean GA, microalbuminuria, and serum creatinine were all higher in Uncontrolled DM. Microalbuminuria and GA had a significant correlation with the duration of diabetes ($p<0.0001$). The present study identified that the risk of microalbuminuria increased with poor glycemic control. A persistent increase in GA and microalbuminuria may be considered risk markers in diabetic nephropathy.

Zoppini et al.[13] **(2012)** In research to see if baseline blood UA levels predict the development of CKD in type-2 diabetic patients, hyperuricemia was related with an increased risk of incident CKD (adjusted OR 2.10 [1.16-3.76], P 0.01). In a continuous study, a 1-SD rise in blood UA level was found to be associated with a 21% increased risk of CKD. According to

the data, hyperuricemia appears to be just a standalone risk factor for the development of incident CKD in type-2 diabetics with intact renal function.

Bonakdaran et al.[70] **(2011)** In a cross-sectional investigation, researchers looked at the relationship between hyperuricemia and albuminuria in diabetic individuals. Patients with normoalbuminuria, microalbuminuria, and macroalbuminuria had SUA levels of 4.49 1.22 mg/dL, 4.84 1.52 mg/dL, and 6.15 1.68 mg/dL, respectively. The urine albumin-creatinine ratio linked positively with SUA level (P =.04). In patients with type-2 diabetes, higher SUA concentrations were linked to a higher risk of albuminuria, according to the study.

LACUNAE OF LITERATURE:

Diabetic nephropathy presents in its earliest stage with low levels of albumin (microalbuminuria) in the urine. The pathogenesis of renal disease has been linked to UA. If there is a relation between hyperuricemia and microalbuminuria in Type-2 diabetes mellitus and diabetic nephropathy, then controlling hyperuricemia in diabetic patients could assist them in avoiding developing overt nephropathy. The current study is aimed to find the correlation between these two in the Indian context.

MATERIALS & METHODS

MATERIALS AND METHODS:

Study site: This study was done in the department of General Medicine at Sri Devaraj URS Academy of Higher Education and Research, Tamaka, Kolar-563101

Study population: All the eligible with diabetes who presented in the department of General Medicine at Sri Devaraj URS Academy of Higher Education and Research were considered as the study population.

Study design: This research was a prospective observational study.

Sample size: 114

Formula:

Formula

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{[FZ(\rho_1) - FZ(\rho_0)]^2} + 3$$

$$FZ(\rho_1) = \frac{1}{2}\ln\left[\frac{1+\rho_1}{1-\rho_1}\right] \qquad FZ(\rho_0) = \frac{1}{2}\ln\left[\frac{1+\rho_0}{1-\rho_0}\right]$$

Where,

ρ_0 : Population correlation coefficient

ρ_1 : Sample correlation coefficient

$Z_{1-\alpha/2}$: Desired confidence level

$1-\beta$: Power

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection for the study was done between August 2019 to August 2021 for a period of 2 years.

Inclusion Criteria:

- Patients more than 18 years of age with type 2 diabetes mellitus.

Exclusion criteria:

1. Patients with gout.
2. Patients with established chronic kidney disease.
3. Patients with acute illness, fever, urinary tract infection.
4. Pregnant and Lactating females.
5. Operated patients within a Month.
6. Patient with other causes of hyper uricemia and microalbuminuria.

Methodology:

- Patients were selected as per the exclusion and inclusion criteria.
- They were explained about the procedure, and their consent was taken, and they were subjected to examination and relevant investigations.
- Clinical, laboratory and sociodemographic data were elicited and recorded in a predefined proforma.

Ethical considerations: The study was approved by the institutional human ethics committee. All study participants were asked to sign an informed consent form, and only those who were willing to do so were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining written consent. The confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

STATISTICAL METHODS:

The major outcome measures were uric acid and microalbuminuria. Diabetic nephropathy was used as an explanatory variable.

Mean, and standard deviation was employed for quantitative variables, whereas frequency and percentage were utilized for categorical variables.

For regularly scattered quantitative parameters, the Pearson rank (rp) correlation coefficient was used to analyze the relationship between quantitative explanatory variables.

ROC curve analysis: The usefulness of serum uric acid in predicting diabetic nephropathy was evaluated using Receiver Operative curve (ROC) analysis. The area under the ROC curve, as well as the 95 percent CI and p-value, are displayed. The sensitivity, specificity, predictive values, and diagnostic accuracy of screening tests were given with predetermined cut-off values and their respective 95% confidence intervals. Pie charts, scatter plots, and bar charts were also used to represent data. SPSS V.22 was used to analyze the data.[84]

OBSERVATIONS AND RESULTS

Result:

A total of 120 participants were included in the final analysis.

Table 3: Descriptive analysis of age in the study population (N=120)

Parameter	Mean ± SD	Median	Minimum	Maximum
Age (in years)	58.05 ± 12.3	57.0	30.0	90.0

The mean age in the study population was 58.05 ± 12.3 years, with minimum age as 30 years and maximum age as 90 years. (Table 1)

Table 4: Descriptive analysis of gender in the study population (N=120)

Gender	Frequency	Percentages
Female	41	34.17%
Male	79	65.83%

Among the study population, there were 41 (34.17%) females and 79 (65.83%) males. (Table 4 & Figure 4)

Figure 4: Pie chart for gender (N=120)

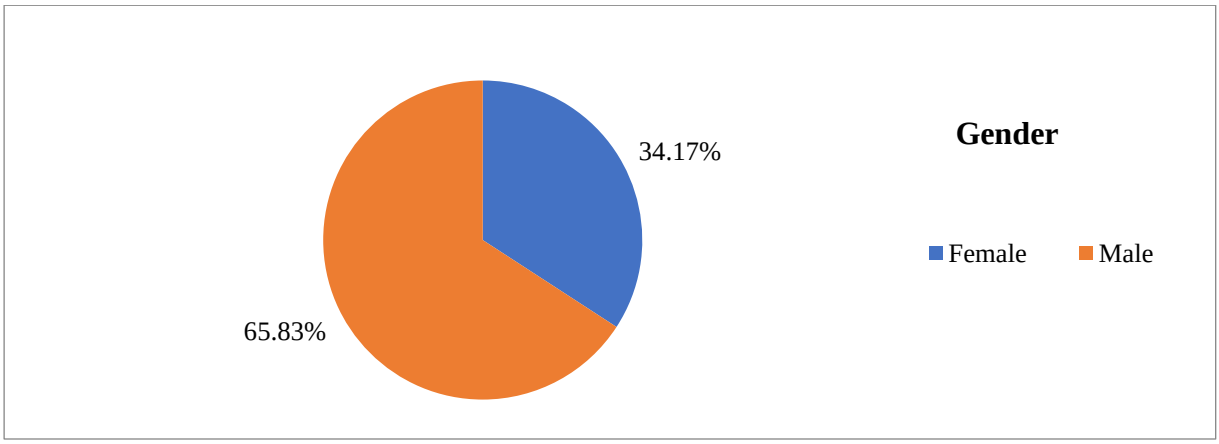


Table 5: Descriptive analysis of vital parameters in the study population (N=120)

Parameter	Mean ± SD	Median	Minimum	Maximum
Pulse Rate (bpm)	80.23 ± 9.11	81.0	62.0	110.0
Systolic blood pressure (mm/hg)	131.03 ± 7.96	130.0	110.0	152.0
Diastolic blood pressure (mm/hg)	79.67 ± 7.75	80.0	62.0	96.0

The mean pulse rate in the population studied was 80.23 ± 9.11 bpm, with a minimum pulse rate as 81 bpm and maximum pulse rate as 110 bpm. The mean systolic blood pressure in the population studied was 131.03 ± 7.96 mm/hg, with minimum systolic blood pressure as 110 mm/hg and maximum systolic blood pressure as 152 mm/hg. The mean diastolic blood pressure in the population studied was 79.67 ± 7.75 mm/hg, with minimum diastolic blood pressure as 62 mm/hg and maximum diastolic blood pressure as 96 mm/hg. (Table 5)

Table 6: Descriptive analysis of CBC in the study population (N=120)

CBC	Frequency	Percentages
Normal	103	85.80%
Abnormal	17	14.20%

The CBC report was normal for 103 (85.80%) participants and abnormal for 17 (14.20%) participants. (Table 6 & Figure 5)

Figure 5: Bar chart for CBC Report (N=120)

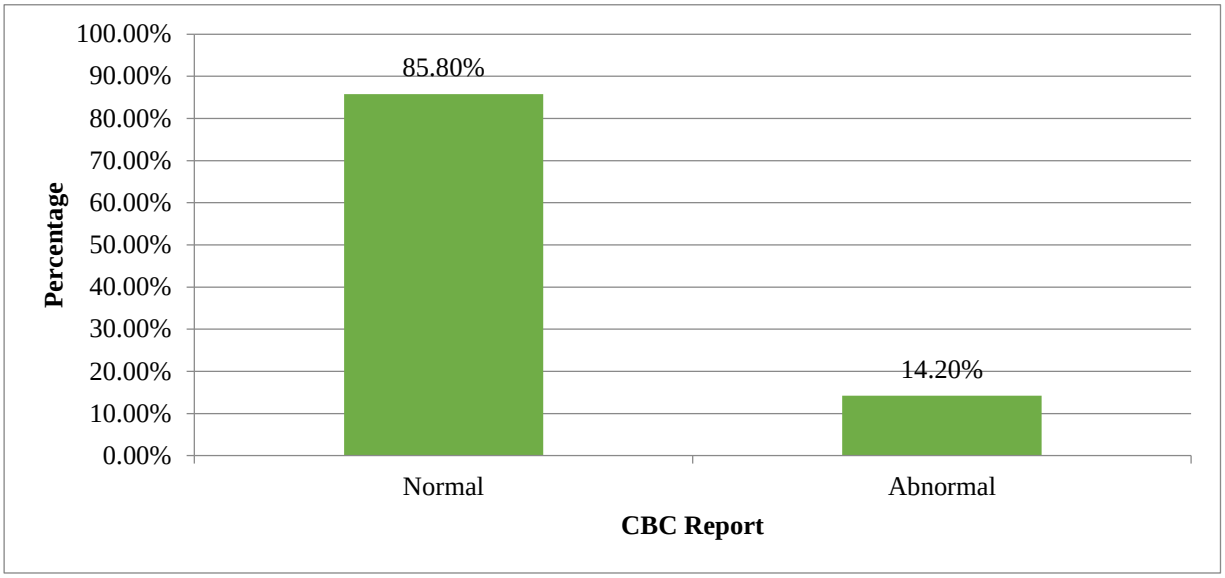


Table 7: Descriptive analysis of CBC-abnormalities in the study population (N=17)

Abnormalities	Mean ± SD (Min, Max)
Mean Hemoglobin (N=8)	10.55 ± 1.01 (9.20, 12.00)
Elevated TLC (IN T) (N=8)	12.47 ± 0.81 (11.40, 14.00)
Platelets (N=1) (in lakhs)	1.49

Among the 17 abnormalities in the population studied, the mean hemoglobin in the population studied was 10.55 ± 1.01 g/dl, with minimum hemoglobin as 9.20 g/dl and maximum hemoglobin as 12 g/dl. The mean elevated TLC in the population studied was 12.47 ± 0.81 T, with minimum elevated TLC as 11.40 T and maximum elevated TLC as 14 T. (Table 7)

Table 8: Descriptive analysis of lab parameters in the study population (N=120)

Parameter	Mean ± SD	Median	Minimum	Maximum
Urea (mg/ dL)	28.58 ± 5.91	28.0	12.0	42.0
Creatinine (mg/ dL)	0.8 ± 0.27	0.8	0.1	1.2
UACR (Mg/G)	103.47 ± 75.97	82.0	14.2	400.0
Uric Acid(mg/dl)	6.6 ± 0.85	6.6	4.1	9.0
Fasting blood sugar (mmol/L)	201.73 ± 57.52	192.0	100.0	360.0
Postprandial glucose test (mg/ dL)	247.94 ± 59.12	250.0	136.0	400.0

The mean urea in the population studied was 28.58 ± 5.91 mg/ dL, with minimum urea as 12 mg/ dL and maximum urea as 42 mg/ dL. The mean creatinine in the population studied was 0.8 ± 0.27 mg/ dL, with minimum creatinine as 0.1 mg/ dL and maximum creatinine as 1.2 mg/ dL. The mean UACR in the population studied was 103.47 ± 75.97 Mg/G, with minimum UACR as 14.2 Mg/G and maximum UACR as 400 Mg/G. The mean serum uric acid (SUA) in the population studied was 6.6 ± 0.85 mg/ dL, with minimum SUA as 4.1 mg/ dL and maximum SUA as 9.0 mg/ dL. The mean fasting blood sugar in the study population was 201.73 ± 57.52 mmol/ L, with minimum fasting blood sugar as 100 mmol/ L and maximum fasting blood sugar as 360 mmol/ L. The mean postprandial glucose test in the study population was 28.58 ± 5.91 mg/ dL, ranging from 136 mg/ dL to 400 mg/ dL. (Table 8)

Table 9: Descriptive analysis of glycosylated hemoglobin in the study population (N=120)

Parameter	Mean ± SD	Median	Minimum	Maximum
Glycosylated Hemoglobin (%)	7.91 ± 1.22	7.7	6.4	16.1

The mean glycosylated hemoglobin in the population studied was 7.91 ± 1.22%, ranging from 6.4% to 16.1%. (Table 9)

Table 10: Descriptive analysis of duration of diabetes (in years) in the study population (N=120)

Parameter	Mean ± SD	Median	Minimum	Maximum
Duration of diabetes (in years)	6.28 ± 4.2	5.0	0.1	22.0

The mean duration of diabetes in the population studied was 6.28 ± 4.2 years, ranging from 0.1 years to 22 years. (Table 10)

Table 11: Descriptive analysis of ECG in the study population (N=120)

ECG	Frequency	Percentages
Normal	100	83.33%
Poor progression of R wave	8	6.67%
Low voltage complexes	3	2.50%
Left axis deviation	2	1.67%
RBBB	2	1.67%
T wave inversions in leads I, AVL	2	1.67%
QT Prolonged	1	0.83%
Non-specific ST-T changes	1	0.83%

Among the study population, the ECG was normal for 100 (83.33%) participants and abnormal for 20 (16.67%) participants. The major abnormality was Poor progression of R wave for 8 (6.67%) participants, low voltage complexes for 3 (2.50%) participants, left axis deviation, RBBB, T wave inversions in leads for 2 (1.67%) participants, QT prolonged, and Non-specific ST-T changes for 1 (0.83%) participant. (Table 11)

Table 12: Descriptive analysis of fundoscopy in the study population (N=120)

Fundoscopy	Frequency	Percentages
Normal fundus	76	63.33%
Mild non-proliferative diabetic retinopathy	26	21.67%
Moderate non-proliferative diabetic retinopathy	12	10.00%
Severe non-proliferative diabetic retinopathy	6	5.00%

The fundoscopy was normal fundus for 76 (63.33%) participants. The fundoscopy was not normal fundus for 44 (36.67%) participants. The fundoscopy was mild non-proliferative diabetic retinopathy for 26 (21.67%) participants, moderate non-proliferative diabetic retinopathy for 12 (10.00%) participants, and severe non-proliferative diabetic retinopathy for 6 (5.00%) participants. (Table 12)

Table 13: Descriptive analysis of DN in the study population (N=120)

Fundoscopy	Frequency	Percentages
Diabetic nephropathy (UACR>=30)	95	79.17%
No diabetic nephropathy (UACR<30)	25	20.83%

Among the study population, 95 (79.17%) participants had diabetic nephropathy, and 25 (20.83%) participants did not have diabetic nephropathy. (Table 13 & Figure 6)

Figure 6: Bar chart for diabetic nephropathy (N=120)

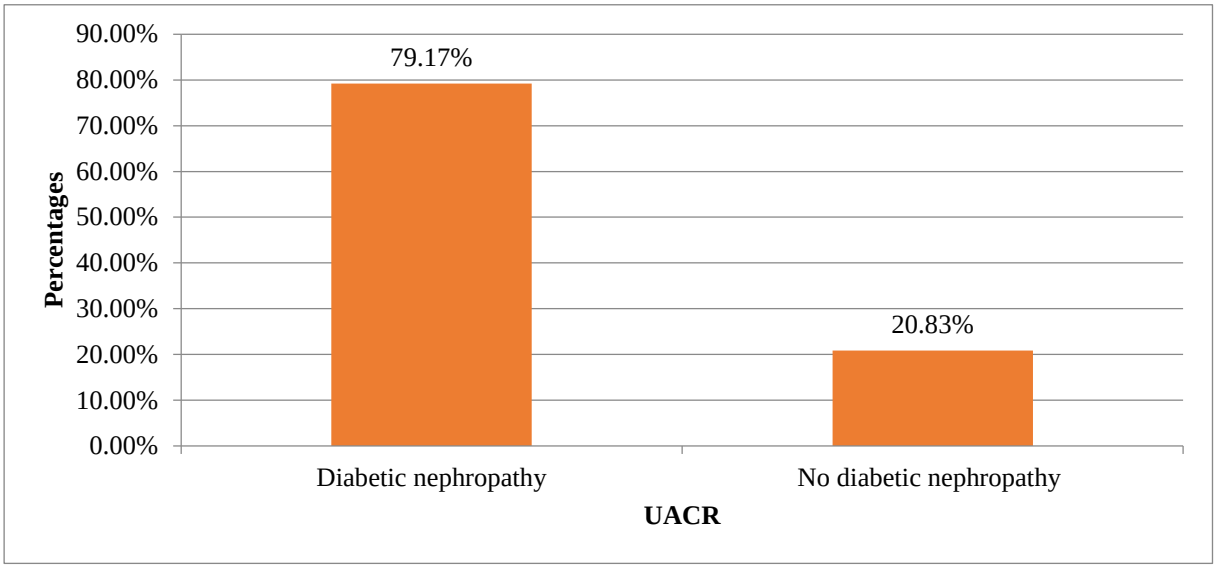


Figure 7: Predictive validity of SUA in predicting diabetic nephropathy (N=120)

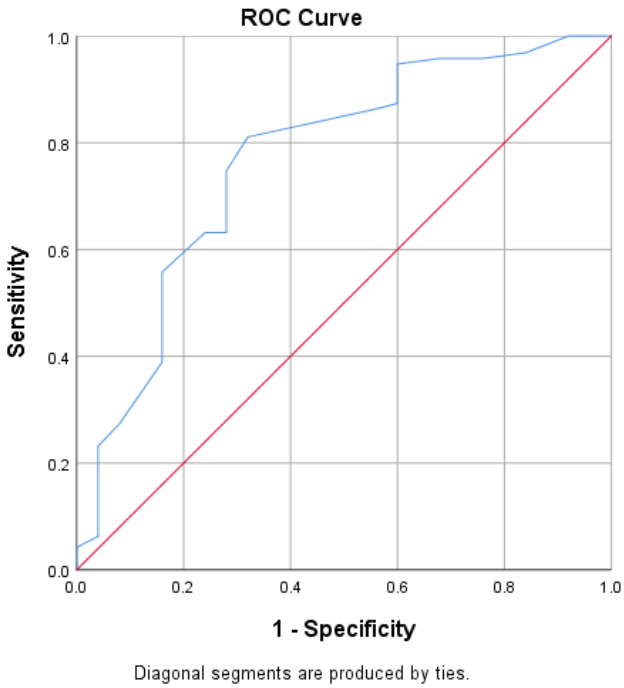


Table 14: Area under the curve for the predictive validity of SUA in predicting diabetic nephropathy (N=120)

Test Result Variable(s): **Serum uric acid in predicting diabetic nephropathy**				
Area Under the Curve	Std. Error	95% Confidence Interval of AUC		**P-Value**
		Lower Bound	Upper Bound	
0.767	0.057	0.66	0.88	<0.001

The serum uric acid had fair predictive validity in predicting diabetic nephropathy, as indicated by the area under the curve of 0.767 (95% CI 0.66 to 0.88, P-value <0.001). (Table 14 & Figure 7)

Table 15: Comparison of serum uric acid between diabetic nephropathy (N=120)

Serum uric acid	**UACR**		**Chi square**	**P value**
	Diabetic Nephropathy (N=95)	**No Diabetic Nephropathy (N=25)**		
>=6.45 mg/dl	60 (63.16%)	7 (28%)	9.921	0.002
<6.45 mg/dl	35 (36.84%)	18 (72%)		

Out of 95 participants having diabetic nephropathy, the SUA was >=6.45 mg/dl for 60 (63.16%) participants and <6.45 mg/dl for 35 (36.84%) participants. Out of 25 participants having no diabetic nephropathy, the SUA was >=6.45 mg/dl for 7 (28%) participants and <6.45 mg/dl for 18 (72%) participants. A statistically significant difference was observed in SUA between UACR (P Value<0.05). (Table 15)

Table 16: Predictive validity of serum uric acid in predicting diabetic nephropathy (N=120)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	63.16%	52.64%	72.83%
Specificity	72.00%	50.61%	87.93%
False positive rate	28.00%	12.07%	49.39%
False negative rate	36.84%	27.17%	47.36%
Positive predictive value	89.55%	79.65%	95.70%
Negative predictive value	33.96%	21.52%	48.27%
Diagnostic accuracy	65.00%	55.76%	73.48%

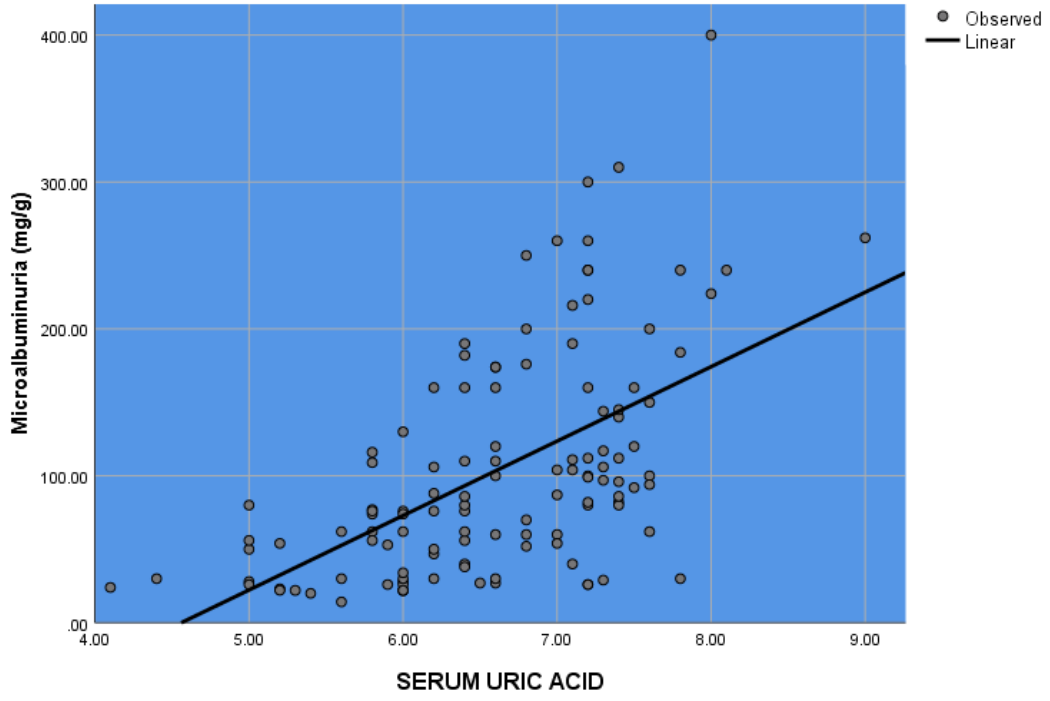
The serum uric acid of 6.45 and above had sensitivity of 63.16% (95% CI 52.64% to 72.83%) in predicting diabetic nephropathy. Specificity was 72.00% (95% CI 5.61% to 87.93%), false positive rate was 28.00% (95% CI 12.07% to 49.39%), false negative rate was 36.84% (95% CI 27.17% to 47.36%), positive predictive value was 89.55% (95% CI 79.65% to 95.70%), negative predictive value was 33.96% (95% CI 21.52% to 48.27%), and the total diagnostic accuracy was 65.00% (95% CI 55.76% to 73.48%). (Table 16)

Table 17: Correlation of serum uric acid with microalbuminuria in the study population (N=50)

Parameters		Microalbuminuria (mg/g)
Serum uric acid (mg/dl)	Pearson Correlation Coefficient	0.564
	P value	<0.001

There was a moderate positive correlation between SUA and microalbuminuria in the study population (r value= 0.564), which was statistically significant (P value0.001). (Table 17 & Figure 8)

Figure 8: Scatter plot for correlation of serum uric acid with microalbuminuria (N=50)



DISCUSSION

DISCUSSION:

A number of research studies have been conducted to investigate the complex interrelationships between blood UA levels and diabetes micro- and macrovascular issues, such as diabetic nephropathy. Uric acid (UA), which contributes to oxidative stress, has been related to the progression of diabetic nephropathy and may potentially be used to predict the disease. The pathophysiologic relevance of UA in CKD is debatable. While some studies have shown that UA is an essential antioxidant, others have shown that it can produce oxidative stress in cells. [52] ACR detection in diabetes patients' morning urine is a common method for clinically diagnosing the onset of renal problems in diabetic patients. Diabetic nephropathy problems and development can be avoided if diagnosed and treated early. There really are various therapy treatments for diabetic nephropathy, but none of them are effective enough to entirely stop the development. If we know the relationship between serum uric acid and microalbuminuria, we can employ supplementary treatments such as xanthine oxidase inhibitors to treat diabetic nephropathy. This seems to be observational research in type 2 diabetics to explore if blood UA levels and microalbuminuria may be utilized as indicators of diabetic nephropathy. UA and microalbuminuria are the most important outcome parameters. The explanatory measure of diabetic nephropathy is albumin to creatinine ratio (ACR) greater than 30 mg/mmol.

A total of 120 participants suffering from type-2 diabetes with a mean age of 58.05 ± 12.3 years were taken in the study. This group is a male dominant one with 65.83% males and 34.17% females. The mean duration of diabetes in the study population was 6.28 ± 4.2 years. Latif et al.[77] had a much younger population in their study with a mean age of 48.1±10.26 years and an almost equal gender distribution with 48.5% males and 51.5% females. 58% of them had ≤5 years of duration of diabetes, while 42% had >5 years of duration. Kocak et al.[56]

had an age group similar to ours with the mean age of the patients in the diabetic nephropathy, and non-nephropathy groups were 62.4±7.6 and 59.3±9.3 years, respectively (p=0.1). The gender distribution was 49% males and 51% females. Fouad et al.[59] study group also had a younger population with a mean age of 49.8 ± 10.6 years with 49.08% males and 50.9% females. Their study had 25.37% with no diabetes, 35.69% with <5 years of duration of diabetes, and 38.94% with >5 years of duration of diabetes. In a case-control study, Jain et al.[75] had the mean age of cases at 54.2 ± 10.94 with a predominantly female population with 70% females among the cases. Neupane et al.[72] had a similar age group with mean age 58.94±3.80 with a much longer duration of diabetes at 9.26±6.48, and 58% males and 42% females in their study.

The mean systolic blood pressure is 131.03 ± 7.96 mm/Hg, mean diastolic blood pressure is 79.67 ± 7.75 mm/Hg. The mean creatinine is 0.8 ± 0.27 mg/ dL with mean fasting blood sugar at 201.73 ± 57.52 mmol/L. The mean HbA1c is 7.91 ± 1.22; the mean serum creatinine is 0.8 ± 0.27. Latif et al.[77] study population had a mean systolic blood pressure of 128.99± 10.665, mean diastolic blood pressure 74.48 ± 9.0, mean HbA1c 7.619 ± 0.4774, mean serum creatinine 0.8431± 0.191. Kocak et al.[56] reported median systolic blood pressure 130 (120-180), median diastolic blood pressure 80 (70-105), median Serum creatinine level was 0.92 (0.65-1.2) mg/dl, median HbA1c 9.6 (6.1-15.5), median fasting blood sugar 225.5(62-466) in cases. In Fouad et al.[59] study mean systolic BP in those with less than 5 years of duration of diabetes was 126.88 ± 14.95, greater than 5 years was 141 ± 18.72, mean diastolic BP in < 5 years 78.75 ± 5.04, > 5 years 84.88 ± 9.19, mean HbA1c < 5 years 7.72 ± 1.44, > 5 years 8.83 ± 1.99, serum creatinine < 5 years 1.1 ± 0.21, > 5 years 2.04 ± 1.44. Jain et al.[75] study population had a mean serum creatinine in cases at 1.14± 0.41, mean fasting blood sugar 194.76± 68.83. Yan et al.[57] reported that elevated serum uric acid levels were correlated with

increased BMI, systolic blood pressure, diastolic blood pressure, microalbuminuria, creatinine, and triglycerides (p<0.0001) in their study. Systolic BP in normoglycemia and hyperuricemia was 130 (120,145) 140 (125,150) with p<0.0001; diastolic BP in normoglycemia and hyperuricemia was same, serum creatinine was 65 (55,78) and 78 (63,105) with p<0.0001; HbA1c was 9.1 (7.5,10.8) and 8.1 (6.8,10.0) with p<0.0001, respectively. Neupane et al.[72] reported a mean systolic BP of 137.60±28.10, mean diastolic BP of 84.80±15.01, mean HbAc of 8.12±2.14 in their study.

Table 18: Comparison of clinical and metabolic characteristics across studies.

Study	Mean systolic blood pressure (mm/Hg)	Mean diastolic blood pressure (mm/Hg)	Mean serum creatinine (mg/dL)	Mean fasting blood sugar (mmol/L)	Mean HbA1c (%)
Current study	131.03 ± 7.96	79.67 ± 7.75	0.8 ± 0.27	201.73±57.52	7.91 ± 1.22
Latif et al.[77]	128.99±10.665	74.48 ± 9.0	0.8431± 0.191		7.619±0.4774
Fouad et al.[59]	126.88 ± 14.95 (< 5) 141 ± 18.72 (>5)		1.1 ± 0.21 (<5) 1.2 2.04 ± 1.44 (>5)		7.72 ± 1.44 (<5) 8.83 ± 1.99 (>5)
Jain et al.[75]			1.14± 0.41	194.76±68.83	
Neupane et al.[72]	137.60±28.10	84.80±15.01			8.12±2.14

On complete blood picture, 14.20% had abnormal values in our study, with 6.66% having a decreased mean hemoglobin at 10.55 ± 1.01 g/dl, 6.66% have elevated total leukocyte count at 12.47 ± 0.81 T, and 0.83% have 1.49 lakh, platelet count. On fundoscopic exam, 63.33% had a normal exam, 21.67% had mild non-proliferative diabetic retinopathy, 10% had moderate non-proliferative diabetic retinopathy, and 5% had severe non-proliferative diabetic retinopathy.

Based on ACR levels, 79.17% had diabetic nephropathy, and 20.83% of participants did not have diabetic nephropathy in our study. The mean SUA in our study is 6.6 ± 0.85 mg/dL, which was similar to that noted in Latif et al.[77] study at 6.99±1.01 (mg/ dL). In Jain et al.[75] study UA was significantly higher (p=0.0382) in diabetic females (5.90±1.64mg/dl) as compared to diabetic males (5.22±1.43mg/dl) in cases. It has been shown that the genetic basis of uric acid production has a major sex-specific impact, indicating probably a genetic basis for gender differences even in the metabolism of glucose.[85] Kocak et al.[56] reported the median SUA in patients in the diabetic nephropathy and non-nephropathic groups were 6.3 (4.2-9.6) mg/dl and 4.9 (3-8.5) mg/dl, respectively; this difference was statistically significant (p<0.001). In Fouad et al.[59] study among those with <5 years duration, the mean SUA was 5.26 ± 1, and it was 7.40 ± 1.32 in patients with >5 years duration of diabetes. The controls had a much less value at 4.61 ± 1.8. Mean SUA concentration was 6.75 ± 1.36 mg/dL in Neupane et al.[72] study.

Table 19: Mean serum uric acid across studies.

Study	**Mean serum uric acid (**mg/dL)
Current study	6.6 ± 0.85
Latif et al.[77]	6.99±1.01
Jain et al.[75]	5.90±1.64 (females); 5.22±1.43 (males)
Fouad et al.[59]	5.26 ± 1 (< 5 years); 7.40 ± 1.32 (> 5 years)
Neupane et al.[72]	6.75 ± 1.36

Hyperuricemia is defined as serum uric acid (SUA) >=6.45 mg/dL, and at this value, the SUA had a fair predictive validity in predicting diabetic nephropathy, as indicated by the area under the curve of 0.767 (95% CI 0.66 to 0.88, p-value < 0.001) in our study. A statistically significant difference was observed in SUA between diabetic nephropathy and non-nephropathy patients (p value<0.05). Our findings revealed a considerable positive correlation

(r value= 0.564) between SUA and microalbuminuria, which was statistically significant (p-value 0.001). This is consistent with the result of Latif et al.[77] who discovered that SUA and microalbuminuria levels are highly associated to nephropathy in type-2 diabetes mellitus patients. Their study discovered a positive link with an (R-value of 0.0838) and a p-value of 0.0001.75. Early in the disease process of diabetes, SUA levels are connected to the later development of chronic macroalbuminuria in diabetics. 91 This was evidenced in the Latif et al.[77] study, where mean UA level and microalbuminuria were 7.070.98 (mg/dL) and 5.661.07 (mg/mmol) respectively (r value=0.164) in patients with diabetes <5 years, and 6.87+1.05 (mg/dL) and 5.581.09 respectively in patients with diabetes >5 years (R-value 0.060). Fouad et al.[59] study showed that the SUA had good predictive validity in predicting early diabetic nephropathy, as indicated by the area under the curve of 0.94.

Neupane et al.[72] found that the concentration of SUA has a strong correlation with ACR, with an R-value of 0.323 and a p-value <0.05. Age (r value=0.337, p-value 0.05), age at onset (R-value = 0.341, p-value 0.05), and total duration of diabetes (r value=0.312, p-value 0.05) all had positive correlations. Multiple regression studies demonstrated that SUA concentration, systolic blood pressure, HbA1c, and total diabetes mellitus duration were all independent predictors of UAE. Microalbuminuria and SUA were also shown to be associated in the study by Kocak et al.[56] with an R-value of 0.238 and a p-value of 0.017. According to Li et al.[5] study. SUA is highly associated with type-2 diabetes and is a standalone risk factor for the pathogenesis and progression of diabetic nephropathy.[5] Jain et al.[75] showed a positive and significant correlation of microalbuminuria with age, duration of diabetes, BMI, fasting blood sugar (FBS), post-meal blood sugar (PMBS), and UA (r value=0.32, p-value=0.0013) in patients of diabetes mellitus. After adjustment, SUA remained significantly associated with diabetic nephropathy with r value 0.069 and $p < 0.001$ as reported by Xia et al.[58]

Our observations are compatible with Fouad et al.[59] study who demonstrated that not only a higher level of SUA in patients with ACR ≥ 30 mg/g, but also a positive correlation with ACR ≥ 30 mg/g, and at a cutoff level of > 6.2 mg/dl identify the onset of early nephropathy in type-2 diabetic patients. With an R-value of 0.51 and a p-value of 0.001, their investigation found a positive connection between microalbuminuria and SUA. Yan et al.[57] showed that SUA, whether treated as a continuous (OR = 1.381, 95% CI = 1.293–1.476, p<0.0001) or a stratified variable (OR = 1.435, 95% CI = 1.335–1.543,p<0.0001), remained strongly associated with diabetic nephropathy after adjusting for confounding factors, including age, sex, BMI, duration of diabetes, blood pressure, serum lipids, andHbA1c. Multiple linear regression demonstrated a significant correlation between SUA and microalbuminuria and creatinine levels but a negative correlation with eGFR. Furthermore, higher UA levels were linked to lower HbA1c and a significantly higher prevalence of diabetic nephropathy.

Table 20: Correlation of serum uric acid with diabetic nephropathy across studies.

Study	Pearson Correlation Coefficient (r)	p-value
Current study	0.564	<0.001
Latif et al.[77]	0.0838	0.0001
Neupane et al.[72]	0.323	0.05
Kocak et al.[56]	0.238	0.017
Jain et al.[75]	0.32	0.0013
Xia et al.[58]	0.069	< 0.001

In our study, a cut-off value of SUA >=6.45 mg/dL had a sensitivity of 63.16% (95% CI 52.64% to 72.83%), specificity 72.00% (95% CI 5.61% to 87.93%), false positive rate 28.00% (95% CI 12.07% to 49.39%), false negative rate 36.84% (95% CI 27.17% to 47.36%), positive predictive value 89.55% (95% CI 79.65% to 95.70%), negative predictive

value 33.96% (95% CI 21.52% to 48.27%), with a total diagnostic accuracy of 65.00% (95% CI 55.76% to 73.48%). Fouad et al.[59] study demonstrated that SUA at a level of > 6.1 mg/dl, > 6.2 mg/dl, and > 6.5 mg/dl had greater sensitivity and specificity for identifying hypertension, early nephropathy, and decline eGFR, respectively. Fouad et al.[59] study showed that SUA at a level of > 6.1, > 6.2, and > 6.5 had a greater sensitivity of predicting early diabetic nephropathy 81.25%, specificity 85.94%, PPV of 74.3, NPV 90.2, and total diagnostic accuracy of 84.4%. This higher sensitivity and diagnostic accuracy may be due to a much younger population in their study supporting the hypothesis that serum uric acid might be involved in the early stages of metabolic imbalance leading to prediabetes and to a lesser extent in the advanced stages when diabetes is diagnosed.[86] In Kocak et al.[56] study blood uric acid anticipated diabetic nephropathy with 80.6 percent sensitivity and 64.1 percent specificity, according to ROC analysis. [59] Urine ACR is determined mostly by serum uric acid, which is an independent predictor for the early pathological alterations of DN in type-2 diabetes mellitus patients. Patients with type-2 diabetes with hyperuricemia exhibited more severe renal impairment than those with only type-2 diabetes. Thus, in type-2 diabetes patients, hyperuricemia might exacerbate the advancement and severity of renal impairment.

SUMMARY

SUMMARY:

Diabetic nephropathy is a long-term microvascular consequence of diabetes that is the major cause of kidney failure. UA enhances oxidative stress and promotes the activation of the renin-angiotensin-aldosterone pathway as an inflammatory agent. As a result, UA levels have been related to the beginning and progression of diabetic nephropathy and are independent risk factors for early kidney disease, aiding in the prediction of microalbuminuria progression. [93] This is prospective observational research on type 2 diabetes- mellitus patients undertaken at the Medicine Department of R..L.Jalappa Hospital and Research Center to connect SUA levels and microalbuminuria as markers of diabetic nephropathy. The analysis included 120 people with type 2 diabetes, with an average age of 58.05 12.3 years. In our study, 79.17 percent of patients had diabetic nephropathy, and 20.83 proportion did not have diabetic nephropathy based on ACR values. In our study, the mean blood uric acid level approximately was 6.6 0.85 mg/dL. There had been a statistically significant difference in blood uric acid levels between diabetic nephropathy and non-nephropathy individuals (p value0.05). The correlation between blood uric acid and microalbuminuria was somewhat favorable (r value= 0.564) and statistically significant (p-value 0.001). In our investigation, serum uric acid showed a sensitivity of 63.16 percent, a specificity of 72.00 percent, and a total diagnostic accuracy of 65.00 percent for predicting diabetic nephropathy. In conclusion, elevated SUA levels are not a fortuitous finding; they are connected to microalbumin levels in diabetic nephropathy patients. SUA levels in diabetic individuals may be a significant predictor of nephropathy.

CONCLUSIONS

CONCLUSIONS:

- A total of 120 participants suffering from type-2 diabetes with a mean age of 58.05 ± 12.3 years are taken in the study.
- This group is a male dominant one with 65.83% males and 34.17% females.
- The mean duration of diabetes of the study population was 6.28 ± 4.2 years.
- The mean systolic blood pressure is 131.03 ± 7.96 mm/Hg, mean diastolic blood pressure is 79.67 ± 7.75 mm/Hg. The mean creatinine is 0.8 ± 0.27 mg/ dL with mean fasting blood sugar at 201.73 ± 57.52 mmol/L. The mean HbA1c is 7.91 ± 1.22; the mean serum creatinine is 0.8 ± 0.27.
- Based on ACR levels, 79.17% had diabetic nephropathy, and 20.83% of participants did not have diabetic nephropathy in our study.
- The mean SUA in our study is 6.6 ± 0.85 mg/dL.
- Hyperuricemia is defined as SUA >=6.45 mg/dL and at this value, the serum uric acid had a fair predictive validity in predicting diabetic nephropathy, as indicated by area under the curve of 0.767 (95% CI 0.66 to 0.88, p value < 0.001) in our study. It had a sensitivity of 63.16% (95% CI 52.64% to 72.83%), specificity 72.00% (95% CI 5.61% to 87.93%), false positive rate 28.00% (95% CI 12.07% to 49.39%), false negative rate 36.84% (95% CI 27.17% to 47.36%), positive predictive value 89.55% (95% CI 79.65% to 95.70%), negative predictive value 33.96% (95% CI 21.52% to 48.27%), with a total diagnostic accuracy of 65.00% (95% CI 55.76% to 73.48%).
- The difference in SUA between diabetic nephropathy and non-nephropathy individuals was statistically significant (p-value 0.05).
- The association between SUA and microalbuminuria was moderately positive (r value= 0.564) and statistically significant (p-value 0.001) in our study.

LIMITATIONS:

As our study is confined to a single facility with small sample size, the findings may be specific and cannot be applied to the general population. The causal correlation between serum uric acid (SUA) and microalbuminuria cannot be proven since this is an observational investigation.

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ANNEXURES

TO CORRELATE SERUM URIC ACID AND MICROALBUMINURIA AS MARKERS OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES

PROFORMA FOR DATA COLLECTION

NAME:

AGE:

SEX:

RESIDENTIAL ADDRESS

MOBILE NUMBER

CASE HISTORY

OTHER KNOWN ILLNESS

BP: **PULSE RATE:**

CVS-

CNS-

RS-

P/A-

OTHER MEASURES

FASTING BLOOD SUGAR	
POST PRANDIAL BLOOD SUGAR	
GLYCOSYLATED HAEMOGLOBIN	
RENAL FUNCTION TEST	
URINE ALBUMIN CREATININE RATIO	
COMPLETE BLOOD COUNT	
ELECTROCARDIOGRAM	
FUNDOSCOPY	

SIGNATURE:

INFORMED CONSENT FORM

SUBJECT'S NAME:

TITLE: TO CORRELATE SERUM URIC ACID LEVELS AND MICROALBUMINURIA AS MARKERS OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES.

If you agree to participate in the study, we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. This study has been reviewed by the institutional ethical committee. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for publication.

Subject name:

(Parents / Guardians name)

DATE:

SIGNATURE /THUMB IMPRESSION

PATIENT INFORMATION SHEET

STUDY TITLE:TO CORRELATE SERUM URIC ACID LEVELS AND MICROALBUMINURIA AS MARKERS OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES MELLITUS.

Principal investigator: Dr.Atishaya.G.V

Study site : R.L Jalappa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Purpose of the study: Diabetic nephropathy is the leading cause of chronic kidney disease recent evidence shows that early recognition and treatment prevents the complications and progression of nephropathy.recent evidence suggests thet uric acid levels are a strong predictor of albuminuria.many theraupetic stratergies have been explored for the treatment of diabetic nephropathy but none of them are good enough to stop progression completely.so adjunctive treatment methods in the form of xanthine oxidase inhibitors can be tried if we come to know that the patient has raised serum uric acid levels or microalbuminuria .and can we daelay the progreesion of albuminuria and development of chronic kidney disease.so this study will be taken up to access and correlate the markers of nephropathy that is serum uric acid and microalbuminuria.

Voluntary Participation: Your participation in this study is entirely voluntary. There is no compulsion to participate in this study. You will be no way affected if you do not wish to participate in the study. You are required to sign only if you voluntarily agree to participate in this study. Further you are at a liberty to withdraw from the study at any time. We assure you that your withdrawal will not affect your treatment by the concerned physician in any way.

Procedure : we will take detailed history and send your blood samples for Complete blood picture, FBS, PPBS, glycosylated haemoglobin ,Renal function test,ECG and fundoscopy will be done for screening cardiac issues and retinopathy respectively,this information is intended to give you the general background of the study.please read the following information and discuss with your family members .you are free to ask any questions regarding the study,if you agree to participate in the study we will collect the information from you or a person responsible for taking care of you or both.

Confidentiality: All information collected from you will be strictly confidential & will not be disclosed to anyone except if it is required by the law. This information collected will be used only for research. This information will not reveal your identity.

We would not compel you any time during this process; also we would greatly appreciate your cooperation to the study. We would like to get your consent to participate in the study.

For any information you are free to contact investigator. This study has been approved by the Institutional Ethics Committee & has been started only after their formal approval. The sample collected will be stored in the institute and I request you to permit us to store and use this sample for any future study.

***

For any further clarification you can contact the study investigator:

Dr.Atishaya.G.V (Post graduate)
Department of General Medicine
SDUMC , KOLAR ,Contact No : 9986722473

ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿ

ಮುಖ್ಯ ಸಂಶೋಧಕರು:ಡಾ||ಅತಿಶಯ.ಜಿ.ಎ

ನಾನುಡಾ||ಅತಿಶಯ.ಜಿ.ಎಶ್ರೀ ದೇವರಾಜ್ಅರಸ್ಮೆಡಿಕಲ್ ಕಾಲೇಜಿನ ಮೆಡಿಸಿನ್ವಿಭಾಗದಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿನಾನು.ಟೈಪ್ 2 ಡಯಾಬಿಟಿಸ್‌ನಲ್ಲಿ ನೆಫ್ರೋಪತಿಯ ಗುರುತುಗಳಾಗಿ ಸೀರಮ್ ಯೂರಿಕ್ ಆಸಿಡ್ ಮತ್ತು ಮೈಕ್ರೊಅಲ್ಬ್ಯುಮಿನೂರಿಯಾ ನಡುವಿನ ಪರಸ್ಪರ ಸಂಬಂಧ

ನನ್ನಮಹಾಪ್ರಬಂಧಕ್ಕಾಗಿಡಾ||ರವೀಶ.ಎ, ಪ್ರೊಫೆಸರ್,ಮೆಡಿಸಿನ್ವಿಭಾಗಮಾರ್ಗದರ್ಶನದಲ್ಲಿಮಾಡುತ್ತೇನೆ.

ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿದಲ್ಲಿ ನಾವು ನಿಮ್ಮ ಆಸ್ಪತ್ರೆಯ ದಾಖಲೆಗಳಿಂದ ನಿಮ್ಮ ಬಗ್ಗೆ ಸಂಬಂಧಿಸಿದ ವಿವರಗಳನ್ನು ಸಂಗ್ರಹಿಸುತ್ತೇವೆ. ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಮಾತ್ರ ಸಂಶೋಧನೆಯ ಉದ್ದೇಶಕ್ಕಾಗಿ ಬಳಸಲಾಗುತ್ತದೆ. ಈ ಅಧ್ಯಯನವು ಸ್ಥಳೀಯ ನೈತಿಕ ಬೋರ್ಡ್ ವಿಮರ್ಶೆ ಮಾಡುತ್ತದೆ ಮತ್ತು ಕೇವಲ ಅವರ ಔಪಚಾರಿಕ ಅನುಮೋದನೆ ನಂತರ ಪ್ರಾರಂಭಿಸಲಾಗುವುದು. ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ಮಾತ್ರ / ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ಸೈನ್ ಅಗತ್ಯವಿದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಯಾವುದೇ ವೆಚ್ಚದಲ್ಲಿ ಒಳಗೊಳ್ಳುವಂತಿಲ್ಲ.

ಸಂಪರ್ಕ ವಿವರಗಳು:
ಡಾ||ಅತಿಶಯ.ಜಿ.ಎ
ದೂರವಾಣಿ:9986722473
ಡಾ|| ರವೀಶ.ಎ

ಸಮ್ಮತಿ ಪತ್ರ:

ಈ ಕೆಳಗೆ ಸಹಿ ಮಾಡಿರುವ ---------- ಆದ ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವ ಸಲುವಾಗಿ ವೈದ್ಯಕೀಯ ಪ್ರಯೋಗ ಪರೀಕ್ಷೆಗೆ ಒಳಪಡಲು ನನ್ನ ವೈಯ್ಯಕ್ತಿಕ ವಿವರಗಳನ್ನು ನೀಡಲು ಸಮ್ಮತಿಸಿರುತ್ತೇನೆ.

ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ಅಧ್ಯಯನದ ಸಂದರ್ಭದಲ್ಲಿನೀಡುವ ಮತ್ತು ಸಂಗ್ರಹಿಸುವ ಮಾಹಿತಿಯಗೋಪ್ಯತೆಯ ಬಗ್ಗೆ ನನಗೆ ನನ್ನ ಸ್ಥಳೀಯ ಭಾಷೆಯಲ್ಲಿ ಓದಿ ಹೇಳಲಾಗಿದೆ/ವಿವರಿಸಲಾಗಿದೆ ಮತ್ತು ನಾನು ಇದನ್ನು ಅರ್ಥ ಮಾಡಿಕೊಂಡಿರುತೇನೆ. ಈ ಅಧ್ಯಯನದ ವಿವಿಧ ಅಂಶಗಳ ಬಗ್ಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳುವ ಅವಕಾಶವನ್ನು ನನಗೆ ನೀಡಲಾಗಿದೆ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ತೃಪ್ತಿಕರವಾದ ಉತ್ತರಗಳು ದೊರೆತಿರುತವೆ. ಈ ಅಧ್ಯಯನದ ಮೂಲಕ ಸಂಗ್ರಹಿಸಿರುವ ಮಾಹಿತಿಯನ್ನು ಸಂಶೋಧನೆಯ ಉದ್ದೇಶಕ್ಕೆ ಮಾತ್ರ ಬಳಸತಕ್ಕದ್ದು.

ಈ ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಂದರ್ಭದಲ್ಲಿಹಿಂದೆ ಸರಿಯುವ ಸ್ವಾತಂತ್ರ್ಯ ನನಗಿದೆ ಎಂಬುದನ್ನೂ, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವುದರಿಂದ ನನಗೆ ಯಾವುದೇ ಹೆಚ್ಚುವರಿ ವೆಚ್ಚ ತಗಲುವುದಿಲ್ಲವೆಂಬುದನ್ನು ತಿಳಿದಿರುತ್ತೇನೆ.

ಪರೀಕ್ಷಾರ್ಥಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ/ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು

ಸಾಕ್ಷಿಗಳಹೆಸರುಮತ್ತು ಸಹಿ

1. ದಿನಾಂಕ:
2. ದಿನಾಂಕ:

ಸಂದರ್ಶಕರಹೆಸರುಮತ್ತು ಸಹಿ

ದಿನಾಂಕ:

ಪ್ರಧಾನಪರೀಕ್ಷಕರಹೆಸರುಮತ್ತು ಸಹಿ

ದಿನಾಂಕ:

KEY TO MASTER SHEET:

Parameter	Key of the parameter
Sex/Gender	1=Male, 2=Female
Diabetic nephropathy	1=Yes, 2=No
Fundoscopy	1=Normal fundus, 2= Mild NPDR, 3= Moderate NPDR, 3=Severe NPDR

MASTER SHEET

S. no.	Age	Sex	PR	SBP	DBP	CBC	Hb	TLC (in T)	PLT	Urea	Creatinine	UACR (mg/g)	Diabetic nephropathy	URIC ACID	FBS	PPBS	Glycosylated hemoglobin	ECG	Fundoscopy	Duration of diabetes (in years)
1	65	1	86	140	96	Normal				26	0.6	26	2	7.2	170	180	7.1	Normal	1	5
2	62	2	74	144	90	Hb 9.6	9.6			28	0.4	60	1	6.8	164	200	7.4	Normal	1	2
3	75	1	78	146	94	Normal				30	0.8	260	1	7.2	190	240	7.6	Normal	2	8
4	62	2	64	136	82	Normal				27	0.9	29	2	7.3	200	260	7.4	poor progression of R wave	1	5
5	52	1	75	146	72	Normal				28	0.6	120	1	7.5	146	190	7.2	Normal	1	6
6	75	1	88	150	84	Normal				34	0.6	224	1	8	190	210	7.8	Normal	3	10
7	74	1	90	144	80	Normal				28	0.5	150	1	7.6	158	176	6.9	Normal	1	5
8	60	2	72	138	82	Hb 9.2	9.2			26	0.8	27	2	6.5	180	196	7	Normal	1	3
9	55	2	81	148	90	Normal				36	0.6	262	1	9	240	290	8.1	low voltage complexes	3	12
10	58	2	92	130	80	TLC 12T		12		28	0.9	26	2	5.9	201	240	7.4	Normal	1	2
11	51	1	66	128	76	Normal				36	1	240	1	8.1	174	256	7.7	Normal	2	8
12	70	2	84	142	90	Normal				32	0.8	200	1	7.6	162	194	7.2	Normal	2	9
13	90	1	76	138	86	Normal				24	0.4	22	2	6	168	180	6.8	Normal	1	4
14	78	1	67	140	90	Normal				18	0.6	27	2	6.6	178	190	7.3	Normal	1	5
15	85	2	75	144	80	Hb 10	10			28	0.4	92	1	7.5	190	242	7.6	Normal	1	7
16	67	2	83	152	94	Normal				27	0.4	100	1	7.6	154	206	7.5	Normal	1	6
17	66	2	95	124	80	Normal				30	0.9	184	1	7.8	175	224	7.7	Normal	2	8
18	42	1	77	130	70	Normal				28	0.4	160	1	7.5	182	250	8	left axis deviation	1	10
19	55	1	87	126	80	TLC12T		12		26	0.6	140	1	7.4	160	242	7	Normal	1	6
20	42	1	80	136	90	Normal				27	0.9	80	1	7.2	136	174	7.1	Normal	1	7
21	55	1	84	126	80	Normal				26	0.8	23	2	5.2	304	320	8	Normal	1	4
22	70	2	89	130	90	Normal				30	1	46.8	1	6.2	220	350	9.1	Normal	1	6
23	45	2	92	126	84	Normal				33	1	22	2	5.3	260	300	10	Normal	1	4
24	56	1	84	122	80	Hb 11	11			24	0.4	100	1	7.2	340	400	12	Normal	3	10
25	55	2	94	142	90	Normal				30	0.9	62	1	5.8	200	240	8	Normal	1	5
26	63	1	74	144	92	Normal				32	0.8	200	1	6.8	260	300	10	Normal	2	8

27	70	2	86	136	80	Normal				32	1.2	30	2	7.8	240	270	7.4	Normal	1	5
28	85	1	110	124	82	Normal				40	0.6	97	1	7.3	200	220	7.6	poor progression of R wave	1	8
29	54	2	96	126	70	Normal				20	0.7	50	1	5	160	200	7.2	Normal	1	5
30	50	1	68	132	90	Normal				42	1	30	2	4.4	220	300	8.4	Normal	1	1
31	52	2	70	128	66	Normal				26	0.8	80	1	5	182	260	7.8	Normal	1	4
32	75	1	76	122	80	Normal				22	1.2	216	1	7.1	120	309	10	Normal	4	6
33	65	1	81	116	66	Normal				28	0.7	28	2	6	163	179	11.5	Normal	1	3
34	65	1	82	132	84	Normal				30	0.9	82	1	7.4	172	200	9.4	Normal	1	8
35	36	2	88	124	80	Normal				36	0.7	53	1	5.9	164	156	7.2	Normal	1	10
36	51	1	74	120	80	Normal		12.6		22	0.6	22	2	6	156	190	7.7	Normal	1	2.4
37	65	1	62	126	74	TLC-12.6T				30	1	104	1	7.1	200	242	8	QT Prolonged	2	12
38	90	1	75	132	80	Normal				33	1	112	1	7.2	250	300	9	Normal	3	16
39	45	1	78	124	76	Normal				22	0.6	40	1	6.4	210	180	7.2	Normal	1	2.6
40	57	1	81	140	90	Normal				26	0.9	80	1	7.4	250	292	8	Normal	1	14
41	65	2	84	132	88	Normal				30	0.7	144	1	7.3	220	280	8.4	Normal	1	6
42	30	2	68	126	70	Normal				30	0.9	116	1	5.8	260	300	8	Normal	2	10
43	60	1	70	132	72	Normal				28	0.5	190	1	6.4	300	320	9	t wave inversions in leads I,AVL	4	18
44	47	2	78	134	90	Normal				26	0.9	56	1	5.8	196	210	7.1	Normal	1	12
45	42	1	62	126	80	Normal				30	0.8	94	1	7.6	156	190	7.4	Normal	1	7
46	55	2	64	132	82	Normal				26	0.9	76	1	6	166	212	7.6	Normal	1	5
47	45	1	70	134	80	Normal				33	0.9	38	1	6.4	190	209	6.9	Normal	1	4.4
48	34	1	76	116	64	Normal				26	0.7	26	2	6	164	192	6.7	Normal	1	6
49	63	1	68	142	88	Normal				40	1.1	174	1	6.6	170	200	7.1	Normal	2	18
50	55	2	80	136	88	Normal				36	1.1	109	1	5.8	200	266	8	Normal	3	7.3
51	61	1	84	126	72	Normal				26	1.1	111	1	7.1	212	256	7.8	Normal	1	11
52	50	2	76	124	80	Hb-11.8	11.8			33	1.1	62	1	6	184	200	6.9	low voltage complexes	1	14
53	51	1	78	110	70	Normal				24	0.8	30	2	6.6	154	182	7.2	Normal	1	3
54	68	1	66	118	80	Normal				18	1.1	40	1	7.1	190	240	7.6	Normal	1	0.1
55	60	1	70	124	80	Normal				24	1.1	88	1	6.2	266	324	8.6	Normal	1	4
56	60	1	80	136	90	Plt 149			149	36	1.1	117	1	7.3	280	322	8.8	Normal	2	22
57	49	1	90	124	70	Normal				24	1.1	74	1	6	254	300	9	RBBB	3	6.2
58	46	1	85	130	80	Normal				30	1.1	99	1	7.2	196	254	6.8	Normal	1	8.1
59	80	1	71	124	66	Normal				24	1.24	190	1	7.1	240	212	6.4	Normal	3	12
60	68	1	78	126	70	TLC-11.4T		11.4		33	1.1	106	1	6.2	266	272	7.3	Normal	2	4.5
61	65	1	94	126	74	Normal				26	1.1	24	2	4.1	300	346	8	poor progression of R wave	1	3
62	60	1	64	140	90	Normal				40	1.1	28	2	5	352	288	7.5	Normal	1	1.4
63	42	2	81	132	86	Normal				32	1.1	77	1	5.8	247	282	7.1	Normal	1	5
64	45	1	86	134	82	Normal				34	1.1	20	2	5.4	264	297	7.5	Normal	1	4.2

65	55	2	75	130	80	Normal				30	1.1	130	1	6	192	254	7.6	Normal	2	10
66	65	2	82	128	72	Normal				38	1.1	240	1	7.8	200	216	8.2	Normal	2	16
67	45	1	76	142	84	Normal				42	1.1	62	1	7.6	192	236	7.4	Normal	1	7.5
68	49	2	78	134	82	Normal				34	1.1	54	1	5.2	300	364	8.8	Normal	1	3
69	48	2	83	126	82	Normal				26	1.1	76	1	6.4	250	286	7.8	low voltage complexes	1	6
70	54	1	69	122	70	Hb-10	10			33	1.1	87	1	7	292	314	8.4	Normal	1	7.5
71	35	1	87	120	62	Normal				20	1.1	22	2	6	320	368	8.6	Normal	1	2
72	45	2	91	134	70	Normal				34	1.1	70	1	6.8	360	375	7.9	Normal	2	10
73	80	1	89	138	90	Normal				36	0.9	112	1	7.4	198	290	7.8	Normal	2	12
74	60	2	75	128	84	Normal				25	1.1	145	1	7.4	360	400	11.2	left axis deviation	3	9
75	37	2	65	136	88	Normal				36	1.1	76	1	6.2	224	275	7.4	Normal	1	10
76	46	1	74	140	90	TLC-12.8T		12.8		33	1.1	30	2	6	340	300	7.7	poor progression of R wave	1	3.5
77	38	1	76	128	90	Normal				28	1.1	80	1	6.4	185	228	6.8	Normal	2	3
78	65	1	86	126	82	Normal				24	1.1	82	1	7.2	224	282	7.8	Normal	2	8
79	45	1	85	130	90	Normal				30	0.9	96	1	7.4	198	258	7.8	Normal	4	6
80	54	1	90	136	80	Normal				26	0.6	100	1	6.6	300	340	9	Normal	1	2
81	66	1	86	140	84	Normal				28	0.8	260	1	7	240	300	8.6	Normal	3	10
82	70	1	94	126	82	HB-10.8	10.8			34	0.4	176	1	6.8	240	282	8	Normal	2	8
83	72	1	74	134	80	Normal				28	0.7	120	1	6.6	220	266	7.8	Normal	2	5
84	48	1	82	130	74	Normal				20	0.3	60	1	7	140	190	7.1	poor progression of R wave	1	2
85	60	1	66	126	72	Normal				12	0.4	56	1	6.4	136	184	7	Normal	1	1
86	62	1	80	134	74	TLC-14		14		34	0.4	160	1	7.2	182	266	7.8	Normal	2	6
87	56	2	72	136	72	Normal				32	0.5	62	1	5.6	128	170	6.9	Normal	1	1.5
88	80	1	90	118	64	Normal				28	0.9	104	1	7	156	200	7.2	t wave inversions in leads I,AVL	1	4
89	40	1	73	122	72	Normal				22	0.7	34	1	6	150	190	7	Normal	1	1
90	42	1	65	128	80	Normal				40	0.8	26	2	5	110	140	6.7	Normal	1	1
91	50	1	77	138	88	HB-12	12			34	0.3	86	1	6.4	100	136	6.6	Normal	1	2
92	56	1	82	144	76	Normal				26	1	110	1	6.6	144	192	7.1	Normal	2	5
93	68	1	86	122	76	Normal				14	0.9	220	1	7.2	246	294	8.8	poor progression of R wave	4	8
94	54	2	85	126	80	Normal				38	0.5	74	1	5.8	152	200	7.2	Normal	1	2.5
95	72	1	96	132	70	Normal				25	0.9	400	1	8	260	300	9	Non specific ST-T changes	4	20
96	50	2	70	126	70	Normal				24	0.7	76	1	5.8	220	250	8	Normal	1	1
97	52	1	100	136	74	Normal				28	0.1	54	1	7	160	210	7.1	Normal	2	4
98	46	1	91	124	86	Normal				32	0.9	50	1	6.2	106	170	6.8	RBBB	1	2
99	44	1	93	136	88	Normal				28	1	62	1	6.4	132	180	6.6	Normal	1	2
100	40	2	95	140	72	TLC-12		12		34	0.4	56	1	5	124	162	7	Normal	1	2
101	64	2	84	116	70	Normal				32	0.7	160	1	6.4	250	312	8	Normal	2	3
102	59	1	83	126	72	Normal				18	0.1	86	1	7.4	200	250	7.4	Normal	1	5

103	56	1	76	124	68	Normal				30	0.4	26	2	7.2	144	176	7.2	Normal	1	4
104	70	2	78	128	76	Normal				16	0.6	310	1	7.4	200	284	7.6	INCOMPLETE LBBB	4	12
105	57	1	81	126	80	Normal				22	0.5	160	1	6.6	226	292	7.7	Normal	3	5
106	62	2	84	130	84	Normal				28	0.8	110	1	6.4	188	146	7.8	poor progression of R wave	2	4
107	42	1	89	138	84	Normal				26	0.6	30	2	6.2	112	146	7	Normal	1	3
108	53	1	90	136	72	Normal				34	1.1	106	1	7.3	220	300	8	Normal	2	4
109	67	1	74	126	80	Normal				28	0.7	240	1	7.2	212	280	7.6	Normal	3	5
110	73	1	77	122	72	Normal				30	0.5	174	1	6.6	198	296	8	Normal	1	3
111	70	2	72	124	76	Normal				28	0.7	182	1	6.4	160	224	7.4	Normal	2	7
112	65	1	82	126	80	Normal				14	0.9	22.1	2	5.2	164	363	9.2	Normal	1	4
113	62	1	86	124	76	Normal				22	1	14.2	2	5.6	169	264	9.1	Normal	1	2
114	55	1	90	130	80	Normal				26	0.8	300	1	7.2	100	250	16.1	Normal	3	8
115	60	1	76	126	80	Normal				24	0.6	52	1	6.8	160	200	8.1	Normal	1	4.5
116	66	1	82	134	62	Normal				30	0.8	60	1	6.6	180	254	8.2	Normal	1	3
117	50	2	90	140	76	Normal				32	1	30	2	5.6	112	166	7	Normal	1	2
118	70	2	86	126	80	Normal				22	0.4	160	1	6.2	166	300	9	Normal	1	5
119	57	2	70	136	90	TC-13T		13		34	0.6	250	1	6.8	140	220	8.2	poor progression of R wave	2	7
120	70	1	82	132	80	Normal				18	0.1	240	1	7.2	210	260	7.8	Normal	1	5