A STUDY ON PREVALENCE AND RISK FACTORS OF DIABETIC NEPHROPATHY IN NEWLY DETECTED TYPE 2 DIABETIC PATIENTS

submitted to

The Tamil Nadu Dr.M.G.R.Medical University

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BRANCH – I (GENERAL MEDICINE)

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

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BONAFIDE CERTIFICATE

This is to certify that **"A STUDY ON PREVALENCE AND RISK FACTORS OF DIABETIC NEPHROPATHY IN NEWLY DETECTED TYPE 2 DIABETIC PATIENTS"** is bonafide work done by **Dr.R.RAMPRASAD**, post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of **M.D.Degree Branch I (General Medicine)** during the academic period from May 2006 to March 2009.

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ETHICAL COMMITTEE OF
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KILPAUK, CHENNAI-10.
Venue: Dean Chamber, Date: 3.1.2008

Chair person
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Director of Medical Education (OSD)
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TO WHOMSOEVER IT MAY CONCERN

Dear Sir / Madam

Sub: Internal Medicine – MD PG's Dissertation Ethical Committee – Reg.

Ref: Requisition from H.O.D. Medicine.

This is in reference to the letter dated 2.1.2008 regarding Ethical committee meeting clearance with regard to the following topics

Sl.No	Name of the Post Graduate	Dissertation Topic
1	Dr. R.Ramprasad	A study on Prevalence and Risk Factors of Diabetic Nephropathy in Newly Detected Type 2 Diabetic Patients
2	Dr. V.Sakthivadivel	A study on Cardiac abnormalities in HIV infected individuals
3	Dr. K.S.Gopakumar	A study on Subclinical Hypothyroidism in females over 50 years of age
4	Dr. T.Karthikeyan	Inflammatory profile in Acute Myocardial Infarction

5	Dr. Maliyappa Vijay Kumar	A study on Prevalence of Microalbuminuria in HIV patients not on ART and Correlation with CD4 count
6	Dr. D.Radha	High sensitivity C - reactive protein as a determinant in the outcome of Acute ischemic stroke
7	Dr. Lakshmi Thampy M.S	A Study on the prevalence of increased LV mass & Proteinuria in newly diagnosed Hypertensive patients.
8	Dr. Manu Bhasker	A study on the effect of Intravenous Metoprolol along with Thrombolysis in Acute Myocardial infarction
9	Dr. P.Mohanraj	Evaluation of Lipid Profile in patients with non diabetic Chronic Kidney Disease Stage 3,4 and 5
10	Dr. P.Dhanalakshmi	A study On Metabolic Syndrome in Young Ischemic Stroke
11	Dr. V.Murugesan	A study on Electrocardiographic and Echocardiographic changes in Chronic Obstructive Airway Disease
12	Dr. M.Seetha	Effect of Right ventricular infarction on the immediate prognosis of Inferior wall Myocardial Infarction

We are glad to inform you that at the EC meeting held on 3.1.08 on the above topics were discussed and **Ethically approved**.

DEAN

Chair person
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Chairman & Members of the Ethical Committee:

Chairman

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We confirm that no member of the study team is on the Ethics Committee and no member of the study team voted.

The trial will also follow the Ethics Guidelines for Bio-Medical Research On Human subjects issued by ICMR, New Delhi and will not involve any expense to the Government and will not be detrimental to the normal functioning of the Institution.

The study will also satisfy the revised order issued by the Government of Tamil Nadu, Health and Family Welfare Department G.O.MS.No:319, H & FW, Dept. dated 30.11.2001.

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CONTENTS

INTRODUCTION

Diabetes mellitus is a major health problem and causes considerable morbidity and mortality, primarily due to micro and macro vascular complications. The prevalence of diabetes is increasing globally and the maximum increase is expected to be in developing countries like India. By the year 2010, it is estimated that nearly 220 million people world wide will have diabetes.

India is predicted to be the capital of diabetes. According to the most recent estimates published in the Diabetes Atlas 2006 (2), 'India has the largest number of diabetic patients in the world ,estimated to be about 40.9 million in the year 2007 and expected to increase to about 69.9 million by the year 2025'. Diabetes is preventable and so are its complications.

Type 2 diabetes usually starts in middle age or later. It is the common type of diabetes and is thought to be due to both impaired insulin secretion and resistance to the action of insulin at its target cells. Diabetes affects the small blood vessels (microangiopathy) at least is thought to be related to the duration and severity of hyperglycemia[1]. Micro vascular changes would have already started occurring in most of the DM type 2 patients at the time of diagnosis itself. This is because these patients remain symptom free for long periods before they are diagnosed clinically.

The diabetes control and complications trial (DCCT) showed that intensive control of the blood sugar over the seven year study interval reduced the progression of diabetic neuropathy, retinopathy and nephropathy[2]. The relationship between control and complications in type 2 diabetes mellitus was evaluated in UKPDS[3]. The study concluded that for every one percent decrease in HbA1c there was 35% reduction in the risk of micro vascular complications.

Nephropathy is a major cause of illness and death in diabetes. Indeed the excess mortality in diabetes occurs mainly in proteinuric diabetic patients and results not only from end-stage renal disease but also from cardiovascular disease (CVD), particularly in type 2 diabetic patients[4]. The risk for cardiovascular disease was 3 fold higher in South Indian Diabetic nephropathic patients when compared with their non-nephropathic counter parts[5]. A reduction of micro albuminuria in Type 2 diabetic patients is an integrated indicator for renal and cardiovascular risk reduction[6].

Although proteinuria had been demonstrated in diabetic patients since 18th century, it was Bright who in 1836 postulated that albuminuria could reflect a serious renal disease specific to diabetes[4]. One hundred years later Kimmelstiel and Wilson[7] described the nodular glomerular

intercapillary lesions in long-standing type 2 diabetes patients suffering from the clinical syndrome of heavy proteinuria and renal failure accompanied by arterial hypertension. The relationship between arterial blood pressure and diabetic nephropathy seems to be complex one, nephropathy increasing blood pressure and blood pressure accelerating the course of the nephropathy[8].

It is estimated that 20% of type 2 diabetes patients reach ESRD during their lifetime[9]. Detecting the patients in the early stage of nephropathy and thereby timely intervention prevents as well as retards the progression towards ESRD and also these patients should be screened for coronary heart disease and to be managed appropriately.

AIM

The aims of the study are:

1. To determine the prevalence of Diabetic Nephropathy in Newly Detected type 2 diabetic patients.

2. To analyze the risk factors associated with the development of Diabetic Nephropathy.

REVIEW OF LITERATURE

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) all over the world. It is the most disabling complication of diabetes which accounts for 20-40% of all causes of CKD. It is estimated that over 43% of the patients developing ESRD have diabetes as the cause[10].

Persistent albuminuria is the hallmark of diabetic nephropathy which can be diagnosed clinically if the following additional criteria are fulfilled: presence of diabetic retinopathy and the absence of clinical or laboratory evidence of other kidney or renal tract disease[4].

During the last decade several longitudinal studies have showed that raised urinary albumin excretion below the level of clinical albuminuria, so called microalbuminuria, strongly predicts the development of diabetic nephropathy.

According to the Mogensen's staging system, Diabetic nephropathy consists of five stages which include microalbuminuria as stage 3, also known as incipient nephropathy.

Microalbuminuria was first defined in 1982 by the Guys Hospital Group and referred as subclinical increase in urine albumin excretion in

insulin dependent diabetics which strongly predicted the subsequent development of overt diabetic nephropathy. Microalbuminuria was soon after reported to predict clinical proteinuria and also early mortality in type 2 diabetes.

Pathogenesis[11]

The pathogenesis of diabetic glomeruloscerosis is intimately linked with that of generalized diabetic microangiopathy.

- The bulk of the evidence suggests that diabetic glomerulosclerosis is caused by the metabolic defect, that is, the insulin deficiency, the resultant hyperglycemia, or some other aspects of glucose intolerance. These metabolic defects are responsible for biochemical alterations in GBM, including increased amount and synthesis of collagen type IV and fibronectin and decreased synthesis of the heparan sulfate proteoglycan.

- Nonenzymatic glycosylation of proteins is known to occur in diabetics and gives rise to advanced glycosylation end (AGE) products, may contribute to the glomerulopathy.

One hypothesis implicates hemodynamic changes in the initiation and progression of diabetic glomerulosclerosis. It is well known that the early stages of diabetic nephropathy are characterized by an increased GFR with increased glomerular capillary pressure and glomerular hypertrophy with increased glomerular filtration area.

Pathology[11]

The following morphological patterns are seen in diabetic nephropathy:

Glomerular Basement Membrane Thickening

Widespread thickening of the glomerular capillary basement membrane (GBM) occur virtually in all diabetics, irrespective of the presence of proteinuria. This thickening begins as early as 2 years after the onset of type 1 diabetes and by 5 years amounts to about a 30% increase. The thickening continues progressively and usually concurrently with mesangial expansion. Simultaneously there is thickening of the tubular basement membranes.

Diffuse Mesangial Expansion

This lesion consists of diffuse increase in mesangial matrix. As the disease progresses, the expansion of mesangial areas can extend to

nodular configurations. The progressive expansion of the mesangium has been shown to correlate well with measures of deteriorating renal function such as increasing proteinuria.

Nodular Glomeruloscerosis

This is known as intercapillary glomerlosclerosis or Kimmelstiel Wilson disease. The glomerular lesions take the form of ovoid or spherical, often laminated, nodules of matrix situated in the periphery of the glomerulus. The nodules are PAS positive. As the disease advances, the individual nodules enlarge and may eventually compress and engulf capillaries, obliterating the glomerular tuft. As a consequence of glomerular and arteriolar lesion, the kidney suffers from ischemia, develops tubular atrophy and interstitial fibrosis and usually undergoes overall contraction in size.

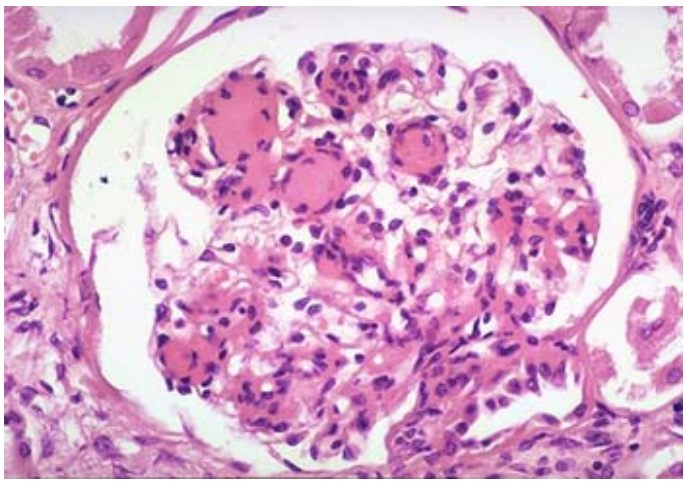


Fig. 1. Nodular Glomeruloscerosis

Pathology of Diabetic Nephropathy in Patients with Diabetes and Proteinuria (Table - 1)[4]

Always Present	Often or Usually Present	Sometimes Present
Glomerular basement membrane thickening[*]	Kimmelstiel-Wilson nodules (nodular glomerulosclerosis)[*]; global glomerular sclerosis; focal-segmental glomerulosclerosis, atubular glomeruli	Hyaline "exudative" lesions (subendothelial)[†]
Tubular basement membrane thickening[*]	Foci of tubular atrophy	Capsular drops[†]
Mesangial expansion with predominance of increased mesangial matrix (diffuse glomerulosclerosis)[*]		Atherosclerosis
Interstitial expansion with predominance of increased extracellular matrix material		Glomerular microaneurysms
Increased glomerular basement membrane, tubular basement membrane, and Bowman capsule staining for albumin and IgG[*]	Afferent and efferent arteriolar hyalinosis[*]	

[*] In combination, diagnostic of diabetic nephropathy.
[†] Highly characteristic of diabetic nephropathy

Nodular glomeruloscerosis and diffuse mesangial sclerosis are fundamentally similar lesions of the mesangium. The nodular lesion, however, is highly but not completely specific for diabetes, as long as care is taken to exclude MPGN, the glomerulopathy associated with light chain and monoclonal immunoglobulin deposition disease, amyloidosis and a few rare entities which can have a similar appearance. Approximately 15-30% of patients with long term diabetes develop Nodular glomeruloscerosis, and in most instances it is associated with renal failure.

Screening for diabetic nephropathy

Primary prevention of diabetic nephropathy is possible with vigorous glucose and blood pressure control. Screening for diabetic renal disease falls within the scope of secondary prevention.

Recommendation for screening

The American Diabetic Association in concert with National Kidney Foundation recommended screening for microalbuminuria starting at diagnosis of type 2 diabetes and patients with type 1 diabetes longer than 5 years[12]. Since microalbuminuria can present during an episode of urinary tract infection, exercise, stress and fluctuation of urine albumin excretion is well known, it is recommended to have at least 2 or 3 samples tested in the course of six months.

A suggested path for screening for diabetic nephropathy
(The American Diabetic Association)

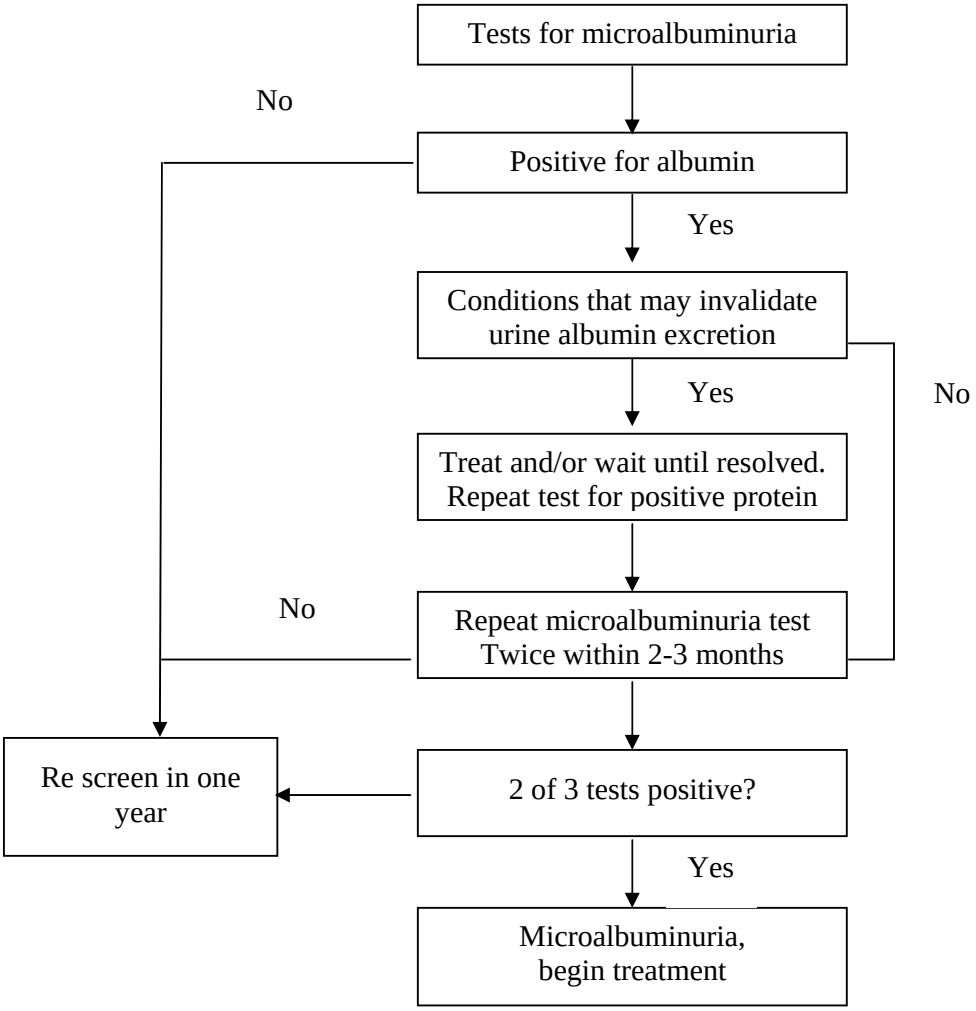


Fig. 2

Choice of screening test

At present two general classes of tests are used to screen for diabetic nephropathy: 1. GFR 2. Albuminuria.

GFR: It can be estimated conveniently with a creatinine value incorporating in to prediction equations such as MDRD[13] (Modification of Diet in Renal Disease) or CG (Cockrauft-Gault). In diabetic nephropathy the GFR can be normal even in stage of overt nephropathy. In addition when GFR is descended into clearly abnormal range, much of the course of diabetic nephropathy has been run and opportunity for intervention become minimal. Thus GFR decline is a late index of kidney damage especially in diabetic renal disease and it is not a very good early marker for screening.

MDRD Equation:

GFR ($mL/min/1.73m^2$) = 186.3 x Pcr ($e^{-1.154}$) x age($e^{-0.203}$) x (0.742 if female) x (1.21 if black)

Albuminuria: Urinary albumin excretion rate (UAER) remains the cornerstone of early detection of diabetic nephropathy and it is the recommended screening test for diagnosis of diabetic nephropathy[14]. Atleast 2 or 3 samples within six months period should be positive before designating a patient has microalbuminuria.

Diagnosis of diabetic nephropathy

The diagnosis of diabetic nephropathy can be made by 1) Urinary albumin excretion rate 2) GFR estimation 3) Serum creatinine 4) Renal biopsy

Urinary albumin excretion rate (UAER)

The total urinary protein excretion is not a good indicator of the macromolecular permeability defect in the early stages of diabetic kidney disease. Direct measurement of urine albumin excretion increases the accuracy. Persistent microalbuminuria is the earliest reliable predictor and marker of diabetic nephropathy. Microalbuminuria is defined as 24 hours urinary albumin excretion rate (UAER) between 30-300 mg/day or 20-200 μg/min, equivalent to 0.46-4.6 μmol/24 hours. If a timed collection of urine cannot be obtained a random sample index of albumin/creatinine (μg/mmol) can be calculated, and microalbuminuria is present at an index >3.5 (sensitivity>95%, specificity>65%). The detection of microalbuminuria denotes stage 3 nephropathy or incipient nephropathy.

Several methods are available to measure microalbuminuria such as radioimmunoassay, nephelometric immunoassay, Enzyme Linked Immuno Sorbent Assay (ELISA) and semi quantitative dipstick test (Micral test).

Once the urine albumin excretion rate (UAER) exceeds >300mg in 24 hrs or >200μg/min equivalent to 500 mg protein excretion per day, it is defined as macroalbuminuria or clinical or overt nephropathy. The detection of macroalbuminuria denotes stage 4 or Overt nephropathy.

Dipstick Detection of Microalbuminuria[15]

Micral-Test is an immunochemically based urinary dipstick for the semi quantitative determination of microalbuminuria. According to a study of 298 consecutive 24 hour collections performed in diabetic subjects[16], when compared with Radioimmunoassay a Micral test result of more than 20mg/L had a sensitivity of 92.2% , specificity of 92.3% in predicting an AER $\geq$ 20microgram/min.

GFR estimation

The GFR can be high or high normal in the early stages of nephropathy (stage 1-3) and normal or low normal in the later stage (stage 4-5). GFR estimation in a diabetic patient is more useful to initiate intervention in the early stages especially in type 1 diabetes. The 4 variable MDRD equation is simple and used in most laboratories provide GFR based on a single creatinine value.

Serum creatinine

Serum creatinine is a simple test but relatively late marker of diabetic renal disease and usually not elevated until diabetic nephropathy is advanced (stage 4). Variations in calibration and improper standardization of the machines give high or low values which is a major limitation. An elevated creatinine in a diabetic nephropathy is the cause of renal failure when it is associated with significant proteinuria.

Renal biopsy

Renal biopsy is not usually done to diagnose diabetic nephropathy. Abnormal renal histology in diabetic nephropathy is seen from stage 2 disease where early basement thickening is seen. In subsequent stages (stage 3 and 4) there is progressive increase in the mesangial matrix and increased thickness of basement membrane. The classical lesion diffuse glomerulosclerosis is seen in stage 4 and 5 nephropathy and nodular sclerotic lesions (kimmelstiel-wilson). Though not pathognomonic, is an important pathological lesion in diabetic nephropathy. Additional findings such as fibrin cap, capsular drops along with hyaline lesions in afferent and efferent arteries may be seen in diabetic nephropathy. Immunoflorescence studies reveal no immune deposits or scanty linear IgG deposits in the capillary loops. Presence of these findings would support diagnosis of diabetic nephropathy in a diabetic patient who has 1) minimal proteinuria 2) active urine sediment with RBC casts in urine 3) the duration of diabetes is short 4) absence of diabetic retinopathy

On the basis of current knowledge, the following recommendations have been made for the use of renal biopsy on clinical grounds alone[15]. Biopsy on clinical grounds alone if,

a) IDDM<10 year and absence of any diabetic retinopathy with clinical evidence of renal disease,

b) NIDDM with clinical renal disease in absence of background or proliferative retionopathy independent of duration

c) If rate of decline of GFR or rise in AER falls outside established norms or when clinical and laboratory findings indicate increased likelihood of non-diabetic renal disease.

d) IDDM in whom a multisystem disease (eg.Systemic Lupus Erythematosis) is suspected or present.

Markers other than microalbuminuria

Microalbuminuria is relatively a late marker to diagnose nephropathy, because there have been studies demonstrated advanced renal lesions on renal biopsies by the time microalbuminuria is present. There is intensive research to identify earlier clinical/biochemical (phenotypic) or DNA defect (genotypic) that would predict with high sensitivity and specificity the susceptibility to diabetic nephropathy before actual development of the disease. Of these genes coding for renin angiotensin system and especially genes coding for ACE, have attracted most interest. Three genotypes of insertion /deletion ACE gene polymorphism (II, ID, DD) has been found in the population[17]. Studies on human kidneys revealed highest tissue ACE and mRNA levels in glomeruli and tubule of subjects with DD genotype compared with other genotypes. Marre et al.[18] demonstrated alterations in glomerular

hemodynamics with DD or ID ACE genotypes when acute hyperglycemia induced normotensive and normoalbuminuric type 1 diabetic patients. Based on the evidence patients with ID or DD genotype likely to develop severe renal disease, may be resistant ACE inhibitors or Angiotensin receptor blockers(ARB) therapy and thus progress rapidly to ESRD[19].

Natural course of Diabetic Nephropathy

The characteristic clinical stages of diabetic nephropathy are best understood in the setting of type 1 diabetes. Most of these young patients do not have any coexisting illness and time of onset of diabetes is abrupt, therefore the ensuing renal injury after a mean period of 10 years or longer can regularly attributed exclusively to diabetes. Type 2 diabetes patients may have other coexisting disease including hypertension, and renal disease in this patients can be attributed to diabetes only in 75% cases. Furthermore type 2 diabetes is usually diagnosed after actual onset of the disease , which is often indolent, so the characteristic of the early clinical stages of kidney involvement often difficult to delineate . However in pima Indians it has been shown that progression of the disease advances through the similar stages in as it does in type 1 diabetes. Diabetic nephropathy can be conveniently characterized into different stages as mentioned in the following (Table - 2)[20].

Table - 2

Stage	GFR	Albuminuria	Blood Pressure	Time Course
Stage 1 RenalHypertrophy	Elevated (20%-50%)	Absent	Normal	At diagnosis
Stage 2 Normoalbuminuria	Elevated	12 – 20 µg/min	Normal	5 years
Stage 3 Microalbuminuria	Elevated	20 – 200 µg/min	Normal or increased	6 – 15 years
Stage 4 Clinical or overt Nephropathy	Decreased	> 200 µg/min	Elevated	20 – 25 years
Stage 5 ESRD	<10 ml/min	> 200 µg/min	Elevated	25 – 30 years

Stage 1:

This early stage manifests renal hypertrophy, elevated renal biood flow, and increased GFR (20-40%). Urine albumin excretion and blood pressure is typically normal. In type 2 diabetes the elevation GFR is modest(15-20%). Aggressive pharmacological interventions to achieve good glycemic control at this stage reverse the changes.

Stage 2:

This stage is almost similar to stage 1 where almost all patients have normoalbuminuria (urinary AER less than 20 mic.gm/ min). The GFR is still elevated and blood pressure usually within the normal range or it may increase. The renal histology reveals basement membrane thickening. Pharmological interventions at this stage may reverse both the elevated GFR and the histological changes.

Stage 3:

This is the stage of microalbuminuria characterized by urine AER 20- 200 µg/min. It typically occurs 6 - 15 years after the onset of type 1 diabetes. The GFR is still elevated and the blood pressure usually starts rising (increase by 3mm Hg/year if untreated). The renal histology reveals basement membrane thickening and mesangial matrix expansion. Aggressive pharmacological interventions at this stage reduce microalbuminuria and may prevent developing overt nephropathy. The histological changes may partially reverse.

Stage 4:

This stage is called as stage of overt or clinical nephropathy which is usually seen after 15-25 years the onset of diabetes. It is characterized by urinary AER more than 200µg/min or proteinuria more than 500mg/day. The GFR starts declining at the rate of 10ml/min/year and blood pressure is often elevated (increase by 5mmHg/year if untreated). The renal histology reveals diffuse mesangial expansion and may have closure of glomerular capillaries. The disease is typically progressive even with interventions. Aggressive blood pressure control and modification dietary protein are the main stay of therapy. Once overt nephropathy develops there is a progressive decline in GFR that can be assessed as an absolute decline in ml/min/per year. In the absence of

glycemic control and blood pressure control albumin excretion increases at 20 to 40% per year and GFR decline at a rate of 10 ml/min/year.

Stage 5:

This stage is final outcome after 25-30 years after onset of the disease. The GFR is less than 10 ml/min and associated with marked proteinuria and the severity of hypertension has major impact on progression. The renal histology shows glomerular closure and advanced nephropathy.

Common Progression promoters of diabetic nephropathy

The promoters of progression are almost similar in both diabetic and non diabetic renal disease. However severity of proteinuria rather than the underlying disease per se predicts the outcome. The metabolic sequelae of chronic hyperglycemia comprise the central biochemical abnormalities of diabetes. Genetic and haemodynamic factors must be operative in patients at risk for development of diabetic nephropathy, because nephropathy does not develop in all diabetic patients. The factors predicting a high risk in addition to poor glycemic control include duration of diabetes (more than ten years), haemodynamic injury (systemic and intraglomerular hypertension), familial/genetic factors, and racial predisposition.

Patients with early diabetes –especially type 1, and lesser extent type 2 tend to have higher GFR. This occurs due to the increased vasodilators (prostanoids, nitric oxide) and increased sodium-glucose reabsorption in proximal tubule, which leads to reduced delivery of sodium to distal part of nephron, resulting in afferent arteriolar dilatation due to altered tubuloglomerular feedback. The increased vasodilatation of afferent arteriole increase the single nephron GFR (SNGFR) as a result of increased glomerular blood flow (QA) and glomerular capillary pressure (PGc). A host of metabolic consequences related to hyperglycemia (increased activity of polyol pathway, increased glucosamine metabolism and protein kinase C activity (PKC), non enzymatic glycation of proteins) contribute to development of nephropathy. Hyperlipidemia may lead to increased formation of oxidized LDL in the mesangial cells which result in activation of inflammatory response, subsequently fibrosis and sclerosis.

Genetic factors considered to play a role in progression. First one third of patients invariably develop diabetic nephropathy, even when blood glucose control is excellent. Second, the incidence of diabetic nephropathy decreases after 25-30 years in type 1 diabetes again suggesting genetic factor in the development of nephropathy.In addition there is strong evidence for familial clustering of diabetic nephropathy.

Siblings of type 1 diabetic patients with nephropathy have 2.5-5 times higher risk of developing diabetic kidney disease and similar findings in Pima Indians and African-Americans with type 2 diabetes. Pima Indians are at three fold increased risk for diabetic kidney disease if another family member has diabetic nephropathy[21].

Primary and Secondary prevention of diabetic nephropathy

It is well established that angiotensin converting enzyme (ACE) inhibitors delay the progression of Incipient Nephropathy to overt Diabetic Nephropathy (secondary prevention) either in type 1 or in type 2 Diabetes and remarkably decrease disease progression to uremia and overall cardiovascular mortality in patients with overt Diabetic Nephropathy. Whether early treatment with ACE inhibitors in normoalbuminuric diabetic patients may effectively prevent progression to microalbuminuria (primary prevention) is not established so far. However, preliminary evidence is available that the incidence of microalbuminuria may be reduced by ACE inhibition therapy in hypertensive type 2 Diabetes patients.

Calcium channel blockers (CCBs) inhibit the vasoconstrictor as well as both the hypertrophic and hyperplastic effects of angiotensin II and other mitogens on mesangial and vascular smooth muscle cells

through blockade of calcium dependent mechanisms. Early studies, however, demonstrate marked differences between the antiproteinuric effects of dihydropyridine. CCBs and nondihydropyridine CCBs (verapamil and diltiazem).

Recent data support the concept that differences in antiproteinuric response subclasses relate to their differential effects on glomerular permeability, that is, dihydropyridine CCBs do not ameliorate glomerular barrier perm-selectivity whereas nondihydropyridine CCBs attenuate it. Failure to restore the sieving properties of the glomerular barrier increases protein ultrafiltration and enhanced protein traffic in the long-term contributes to the progression of renal injury independently of the underlying renal disease.[22]

Recent studies found that nondihydropyridine CCBs may have the same reno-protective potential of ACE inhibitors either in experimental models of Progressive renal disease and in type 2 Diabetes patients. The association of ACE inhibitors with nondihydropyridine CCBs may even more effectively than the two agents alone decrease, at comparable level of blood pressure control, proteinuria and prevent glomerulosclerosis in experimental diabetes and in hypertensive stroke-prone rats.[22]

Additionally, recent studies document that the association of ACE inhibitors with nondihydropyridine CCBs reduces urinary albumin excretion rate more effectively than the two agents alone in hypertensive type 2 Diabetes patients either with incipient or overt nephropathy. Furthermore, in proteinuric type 2 Diabetes patients, the combination of these classes of agents appears to slow GFR decline and to yield the lowest side effect profile over either agent alone in diabetic patients with overt nephropathy.[22]

Lastly, the association of a calcium channel blocker to ACE inhibition therapy in hypertensive diabetics may reduce the need for additional diuretic therapy that has been associated with an excess mortality in diabetes mellitus. However, whether the association may more effectively than ACE inhibitors alone prevent the onset of microalbuminuria (primary prevention) or delay the progression from microalbuminuria to macroalbuminuria (secondary prevention) is not established so far.

UKPDS-74[3] states that development of Albuminuria or renal impairment was independently associated with increased base line systolic blood pressure , urinary albumin, plasma creatinine, and Indian-Asian ethnicity. Additional independent risk factors for Albuminuria

were male sex, increased waist circumference, plasma triglycerides, LDL cholesterol, HbA1C, increased white cell count, ever having smoked and previous retinopathy. Intensive measures are to be taken to control above mentioned risk factors so that the development of Diabetic Nephropathy can be prevented .

Risk Factors/Markers for Development of Diabetic Nephropathy in Type 1 and Type 2 Diabetic Patients (Table - 3)[4]

Risk Factors/Markers	Type 1	Type 2
Normoalbuminuria (above median)	+	+
Microalbuminuria	+	+
Sex	M > F	M > F
Familial clustering	+	+
Predisposition to arterial hypertension	+/-	+
Increased sodium/lithium counter transport	+/-	-
Ethnic conditions	+	+
Onset of IDDM before 20 years of age	+	?
Glycemic control	+	+
Hyperfiltration	+/-	+/-
Prorenin	+	?
Smoking	+	+

Treatment of Diabetic Nephropathy[23]

The optimal therapy for diabetic nephropathy is prevention by control of glycemia. As part of comprehensive diabetes care, microalbuminuria should be detected at an early stage when effective therapies can be instituted. Annual measurement of the serum creatinine to estimate GFR is recommended. Interventions effective in slowing progression from microalbuminuria to macroalbuminuria include: (1) normalization of glycaemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors or ARBs. Dyslipidemia should also be treated.

Improved glycemic control reduces the rate at which microalbuminuria appears and progresses in type 1 and type 2 DM. However, once macroalbuminuria exists, it is unclear whether improved glycemic control will slow progression of renal disease. During the phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. Furthermore, many glucose-lowering medications (sulfonylureas and metformin) are contraindicated in advanced renal insufficiency.

Many individuals with type 1 or type 2 DM develop hypertension. Numerous studies in both type 1 and type 2 DM demonstrate the effectiveness of strict blood pressure control in reducing albumin excretion and slowing the decline in renal function. Blood pressure should be maintained at <130/80 mmHg in diabetic individuals without proteinuria. A slightly lower blood pressure (125/75) should be considered for individuals with microalbuminuria or macroalbuminuria.

Either ACE inhibitors or ARBs should be used to reduce the progression from microalbuminuria to macroalbuminuria and the associated decline in GFR that accompanies macroalbuminuria in individuals with type 1 or type 2 DM. Although direct comparisons of ACE inhibitors and ARBs are lacking, most experts believe that the two classes of drugs are equivalent in the patient with diabetes. ARBs can be used as an alternative in patients who develop ACE inhibitor–associated cough or angioedema. After 2–3 months of therapy in patients with microalbuminuria, the drug dose is increased until either the microalbuminuria disappears or the maximum dose is reached. If use of either ACE inhibitors or ARBs is not possible, then calcium channel blockers (non-dihydropyridine class), beta blockers, or diuretics should be used. However, their efficacy in slowing the fall in the GFR is not proven. Blood pressure control with any agent is extremely important, but a drug-specific benefit in diabetic nephropathy, independent of blood

pressure control, has been shown only for ACE inhibitors and ARBs in patients with DM.

The ADA suggests modest restriction of protein intake in diabetic individuals with microalbuminuria (0.8 g/kg per day) or macroalbuminuria (<0.8 g/kg per day, which is the adult Recommended Daily Allowance, or ~10% of the daily caloric intake).

Once macroalbuminuria ensues, the likelihood of ESRD is very high. As compared to nondiabetic individuals, hemodialysis in patients with DM is associated with more frequent complications, such as hypotension (due to autonomic neuropathy or loss of reflex tachycardia), more difficult vascular access, and accelerated progression of retinopathy. Survival after the onset of ESRD is shorter in the diabetic population compared to nondiabetics with similar clinical features. Atherosclerosis is the leading cause of death in diabetic individuals on dialysis, and hyperlipidemia should be treated aggressively. Renal transplantation from a living-related donor is the preferred therapy but requires chronic immunosuppression. Combined pancreas-kidney transplant offers the promise of normoglycemia and freedom from dialysis.

MATERIALS AND METHODS

1. **Study group:** Newly detected type 2 Diabetes subjects (n=200) from Diabetes clinic, Department of Diabetology, Kilpauk Medical college, Chennai. The study was conducted over a 8 month period from Jan 2008 to Aug 2008.

2. **Study design:** Cross sectional study.

3. **Materials:** Questionnaire, BMI calculation, Blood pressure, Lipid profile, Blood Urea, Serum creatinine, , GFR calculation, Urinalysis, urine PCR (Protein Creatinine Ratio), Micralbuminuria (MICRAL strip test), Fundus examination, Ultrasound KUB.

BMI calculation

Body mass index (BMI) is calculated with height and weight of the subject using the following formula.

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

Blood pressure

Right upper arm blood pressure is taken in supine position by using sphygmomanometer under appropriate condition.

Lipid Profile

Triglyceride (TGL), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) levels were estimated and calculated using standard methods in the early morning fasting Blood Sample.

Renal function test

Blood samples are collected for blood urea and serum creatinine and analyzed in the laboratory at KMCH, Chennai. The Blood Urea in this study was estimated using DAM method (Diacetyl Monoxime). Serum creatinine was estimated using Modified Jaffe's method.

GFR calculation

GFR is calculated using MDRD formula.

GFR (mL/min/1.73m^2) = 186.3 x Pcr ($e^{-1.154}$) x age($e^{-0.203}$) x (0.742 if female) x (1.21 if black).

The following website was used for doing the calculation: www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

Urinalysis

Urine sample is collected for urine routine analysis which includes sugar, protein, cytology and urinary sediments, and also for culture and sensitivity.

Urine spot PCR

Urine sample is collected to estimate protein creatinine ratio. Sulfo salicylic precipitation method used for protein estimation.

Urine Dipstick test

MICRAL test strips used to detect the presence of microalbuminuria in the early morning sample.

Fundus examination

Fundus examination is done for all the subjects with direct ophthalmoscope.

USG KUB

Ultrasound KUB was done to find out renal size and to rule out non-diabetic causes of nephropathy.

Inclusion criteria

Newly detected type 2 diabetes mellitus subjects.

Exclusion criteria

- Patients not willing for study
- Patients with uncontrolled hypertension
- Patients with poor glycemic control.
- Patients with urinary tract infection.
- Patients with cardiac failure.
- Patients suspected to have non-Diabetic Nephropathy like USGKUB showing contracted kidney, cystic renal disease etc.
- Patients with other medical illness

DEFINITIONS

Diabetes Mellitus

The WHO in consultation with an expert committee of the American Diabetes Association has approved the following diagnostic criteria for Diabetes Mellitus. OGTT was done with 75gm glucose in 250ml of water as per WHO recommendation.

Table – 4

CATEGORY	FPG	PPG
Normal	<100 mg/ dL (5.6 mmol/L)	<140 mg/dL (7.8 mmol/L)
IFG	100-125 mg/ dL (5.6-6.9 mmol/L)	-
IGT	-	140-199 mg/ dL (7.8-11.0 mmol/L)
Diabetes	≥ 126 mg/dL (7.0 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)

Fasting: No caloric intake for atleast 8 hours.
2-3 days of unrestricted carbohydrated diet prior to the test.
No physical activities during the procedures.

Newly detected type 2 Diabetes

Type 2 diabetic patients of less than 6 months duration from the diagnosis are taken as the study subjects.

Microalbuminuria

It is defined as urinary albumin excretion greater than 30 mg/24 hours (20 μg/min), and less than or equal to 300 mg/24hours (200μg/min) irrespective of how the urine is collected. Atleast two out of three samples collected within 6 months period under optimal conditions should be positive to call it as persistent microalbuminuria (stage 3 diabetic Nephropathy)[2].

In this study Micral dip stick showing positivity more than 20 mg/L has taken as Microalbuminuria. Protein creatinine ratio also considered and correlated with this result. PCR Value of >0.03 to 0.3 is considered as excretion of about 30 mg to 300 mg in 24 hours. Both showed one/ one correlation in our study.

Macroalbuminuria

It is defined as persistent albuminuria greater than 300 mg/24 hours or 200 μg/min (AER).[2]

Diabetic Retinopathy

The minimum criterion for diagnosis of diabetic retinopathy is the presence of atleast one definite microaneurysm in any of the visualized fields.

Systemic Hypertension (As per the JNC VII Guidelines)

Subjects with self reported hypertension and those who had a systolic blood pressure of ≥ 140 mmHg and / or diastolic blood pressure ≥ 90 mmHg were considered to have hypertension. JNC VII recommends cut off value of ≤ 130/80 mmHg for good control of systemic hypertension in diabetic subjects.

Controlled Hypertension

Subjects with systemic hypertension having blood pressure ≤130/80 mmHg with therapeutic intervention.. ACE Inhibitors and nondihydropyridine CCBs were not used for the control of blood pressure since they have modifying effect on proteinuria.

In this study only Normotensive and controlled hypertensive patients are taken as study subjects. Those who had uncontrolled hypertension are not included in this study so that false positivity due to uncontrolled hypertension while the detection of Albuminuria is eliminated.

Dyslipidemia

Adult Treatment Panel III (ATP III) guidelines developed by the National Cholesterol Education Program have been used to detect dyslipidemia in the study subjects. According to the guidelines:

Table - 5

TYPE	Cut off values (mg/ dl)
TGL Dyslipidemia	≥ 150
LDL Dyslipidemia	> 100
HDL Dyslipidemia	< 40

Overweight and Obesity

The following classification adopted from National Institute of Health, National Heart, Lung and blood Institute recognized by WHO is used for classifying the subjects according to the weight status.

Table - 6

BMI GROUP	BMI(kg/m^2)
Underweight	< 18.5
Healthy weight (normal)	18.5-24.9
Overweight	25.0-29.9
Obesity	≥ 30.0

Stastistical Analysis

The statistical methods used for analysis were

1) Chi-square test
2) Two sample ‘t’ test
3) Binary logistic regression model

All Analysis was done using Windows- based SPSS statistical package (version 11.5).

RESULTS

Total No. of subjects in the study – 200.

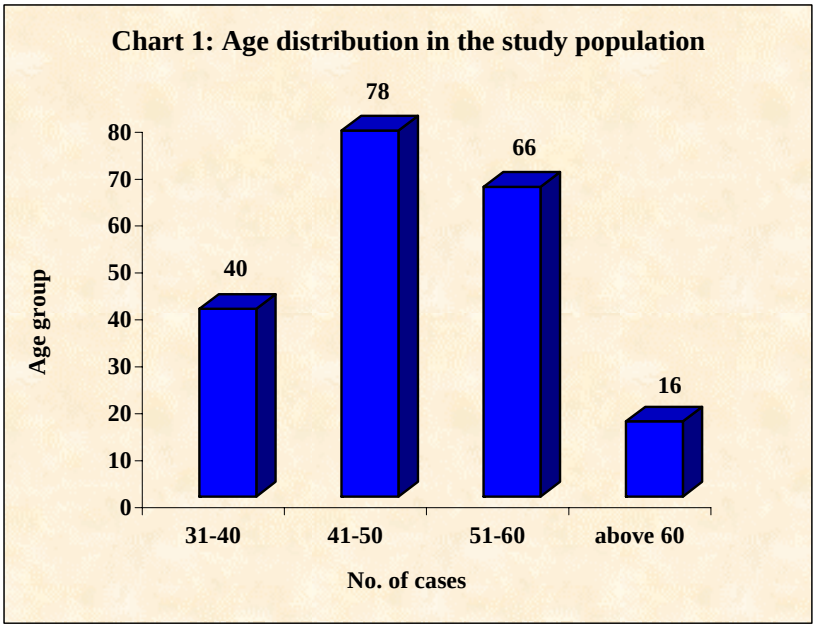
No. of Males – 70 (35%).

No. of Females – 130 (65%).

Age distribution in the study population

Table - 7

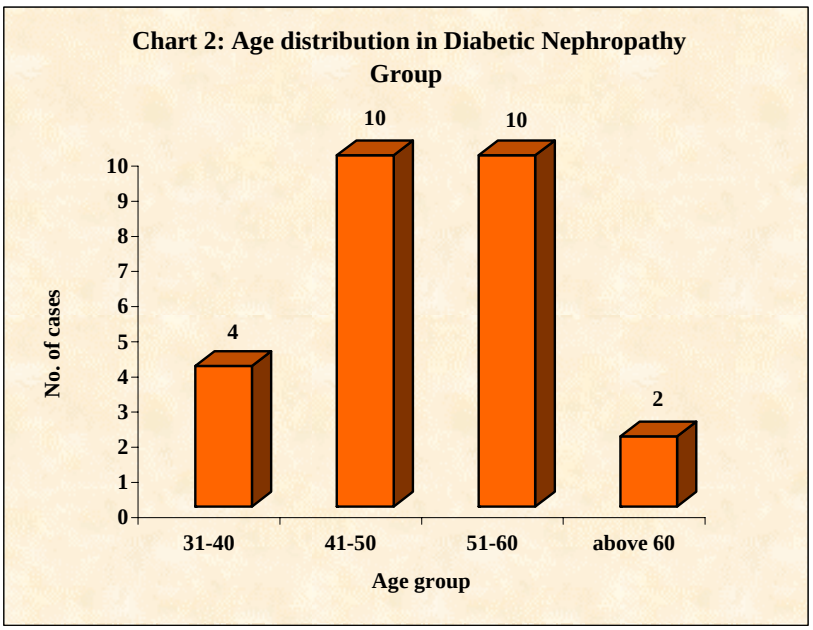
Age group (Yrs)	No. of subject	Percentage
31-40	40	20.0
41-50	78	39.0
51-60	66	33.0
above 60	16	8.0
Total	200	100



Age distribution in the Diabetic Nephropathy Group

Table - 8

Age group (Yrs)	No. of subject	Percentage
31-40	4	15.4%
41-50	10	38.5%
51-60	10	38.5%
above 60	2	7.7%
Total	26	100%

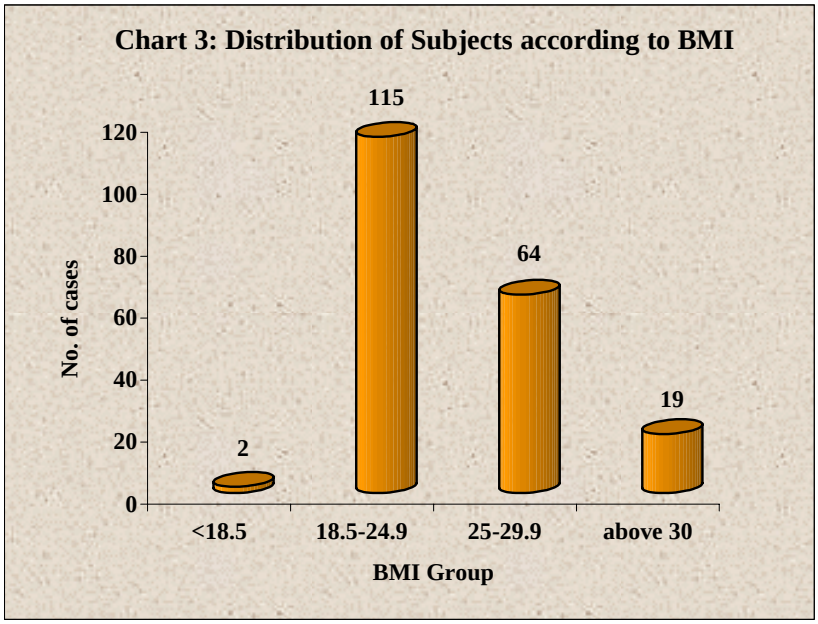


Distribution of Subjects according to B.M.I.

Table - 9

BMI Group (Kg/m^2)	No. of subject	Percentage
< 18.5	2	1.0
18.5-24.9	115	57.5
25-29.9	64	32.0
≥ 30	19	9.5
Total	200	100

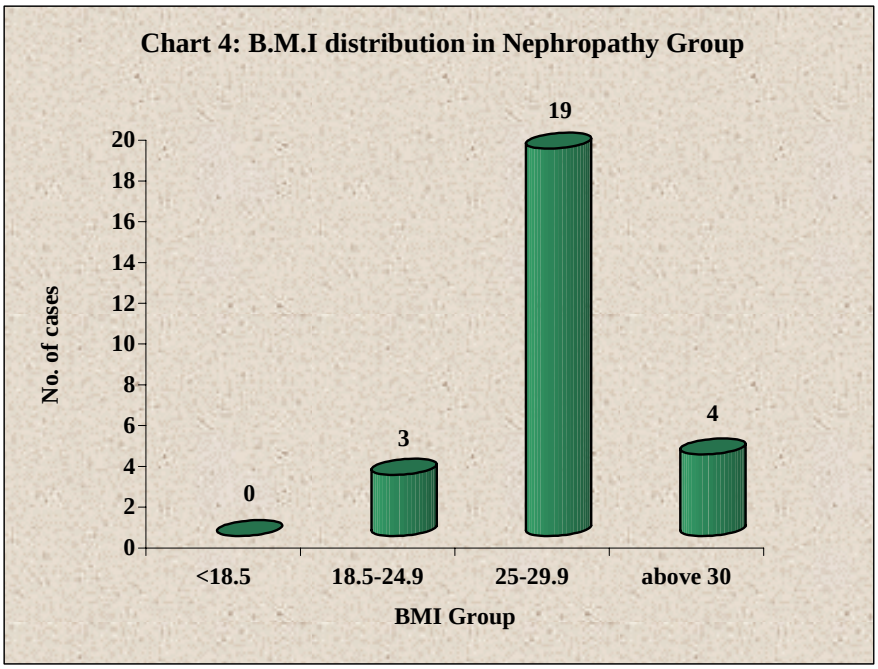
- 57.5% of the subjects had normal B.M.I.
- 32% were overweight and 9.5% were obese.



BMI distribution in Nephropathy Group

Table - 10

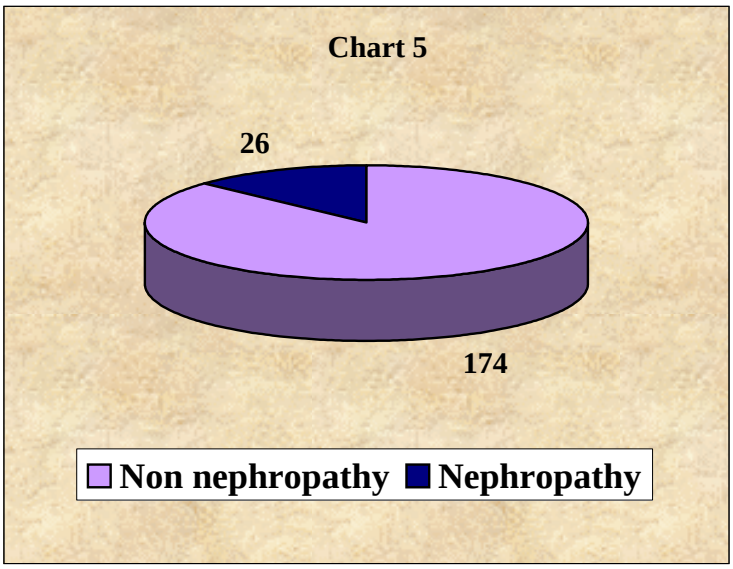
BMI group (Kg/m^2)	No. of subject	Percentage
< 18.5	0	0%
18.5-24.9	3	11.5%
25-29.9	19	73.1%
≥ 30	4	15.4%
Total	26	100%

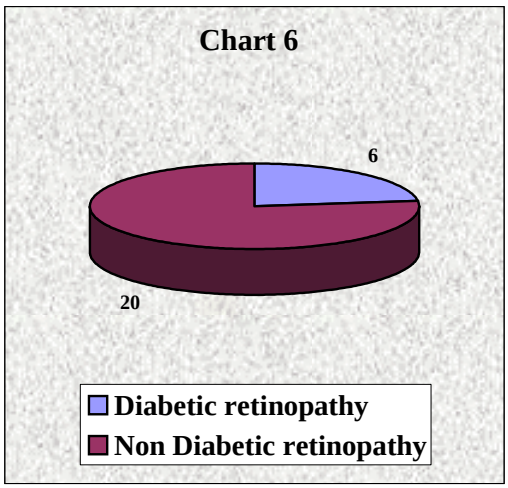


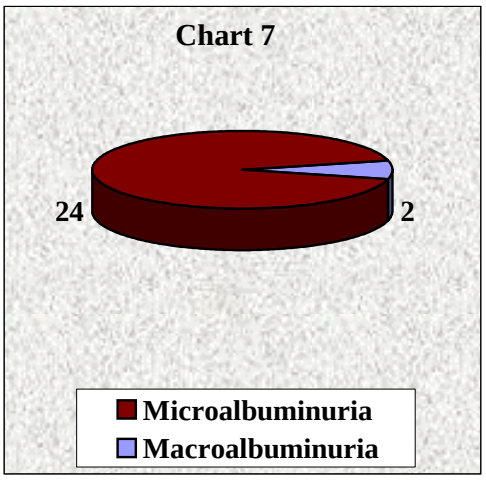
- Subjects having weight above the desired normal B.M.I. were 88.5% in the Nephropathy group. Among them 73.1% and 15.4% were overweight and obese respectively.

- 26 Patients were diagnosed to have Diabetic Nephropathy, 24 of them had Microalbuminuria (Stage 3 Diabetic Nephropathy) and two of them had Macroalbuminuria (Stage 4 Diabetic Nephropathy).

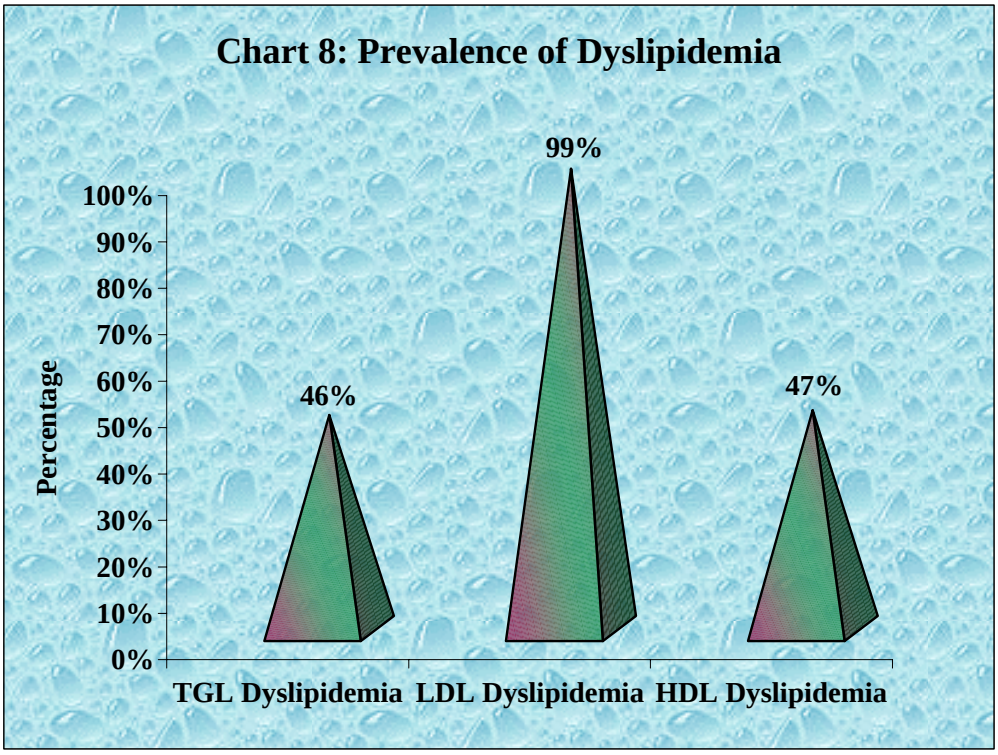
- Among the nephropathy group, 6 Patients had Diabetic Retinopathy.







- Among the study group of newly detected Diabetes Mellitus 46% of subjects had hypertriglyceridemia and subjects having raised LDL level and low HDL level were respectively 99% and 47%



Age and Diabetic Nephropathy

Table - 11

Nephropathy	N	Age Mean	Std. Deviation	Std. Error Mean
Yes	26	48.46	8.33	1.63
No	174	49.17	9.18	0.70

P=0.710 **Not significant**

BMI and Diabetic Nephropathy

- Mean BMI among the non Nephropathy Group is 24.52.
- Among the Nephropathy Group 26.79.

Table. 12

Nephropathy	N	BMI Mean	Std. Deviation	Std. Error Mean
Yes	26	26.79	2.34	0.46
No	174	24.52	3.58	0.27

P=0.002 **significant**

Table - 13

BMI group (Kg/m^2)		Nephropathy		Total
		No	Yes	
< 18.5	Count	2	0	2
	% Within Non Nephropathy & Nephropathy	1.1%	0.0%	1.0%
	% of Total	1.0%	0.0%	1.0%
18.5-24.9	Count	112	3	115
	% Within Non Nephropathy & Nephropathy	64.4%	11.5%	57.5%
	% of Total	56.0%	1.5%	57.5%
25-29.9	Count	45	19	64
	% Within Non Nephropathy & Nephropathy	25.9%	73.1%	32.0%
	% of Total	22.5%	9.5%	32.0%
30 & above	Count	15	4	19
	% Within Non Nephropathy & Nephropathy	8.6%	15.4%	9.5%
	% of Total	7.5%	2.0%	9.5%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

Serum creatinine and Diabetic Nephropathy

Table - 14

Nephropathy	N	Serum creatinine Mean	Std. Deviation	Std. Error Mean
Yes	26	0.82	0.11	0.02
No	174	0.77	0.10	0.01

P=0.019 **Significant**

The mean Serum creatinine value in non-Nephropathy subjects is 0.7 mg/dl and in Nephropathy group is 0.8 mg/ dl.

Gender and Diabetic Nephropathy

Table - 15

Gender		Nephropathy		Total
		No	Yes	
Male	Count	68	2	70
	% Within Non Nephropathy & Nephropathy	39.1%	7.7%	35.0%
	% of Total	34.0%	1.0%	35.0%
Female	Count	106	24	130
	% Within Non Nephropathy & Nephropathy	60.9%	92.3%	65.0%
	% of Total	53.0%	12.0%	65.0%
Total	Count	175	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 9.796$

P = 0.002 **Significant**

Family History of Diabetes and Diabetic Nephropathy

Table - 16

FH/D		Nephropathy		Total
		No	**Yes**	
No	Count	130	18	148
	% Within Non Nephropathy & Nephropathy	74.7%	69.2%	74.0%
	% of Total	65.0%	9.0%	74.0%
Yes	Count	44	8	52
	% Within Non Nephropathy & Nephropathy	25.3%	30.8%	26.0%
	% of Total	22.0%	4.0%	26.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 0.353$

P = 0.632 **Not Significant**

- In total 26% of the Patients (52) were having family history of Diabetes.

- Among the Nephropathy Patients 30.8% had family history of Diabetes mellitus.

Family History of Kidney diseases and Diabetic Nephropathy

- Two of the Patients were having family history of Kidney diseases among the Nephropathy Group.

- No such history was found in non-nephropathy group.

Table - 17

FH/KD		Nephropathy		Total
		No	Yes	
No	Count	174	24	198
	% Within Non Nephropathy & Nephropathy	100.0%	92.3%	99.0%
	% of Total	87.0%	12.0%	99.0%
Yes	Count	0	2	2
	% Within Non Nephropathy & Nephropathy	0.0%	7.7%	1.0%
	% of Total	0.0%	1.0%	1.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 13.520$

P = 0.016 **Significant**

Smoking and Diabetic Nephropathy

- Six subjects were found to be smokers in the subjects under the study and belonged to the non Nephropathy Group.

Table - 18

Smoking		**Nephropathy**		**Total**
		No	**Yes**	
No	Count	168	26	194
	% Within Non Nephropathy & Nephropathy	96.6%	100.0%	97.0%
	% of Total	84.0%	13.0%	97.0%
Yes	Count	6	0	6
	% Within Non Nephropathy & Nephropathy	3.4%	0.0%	3.0%
	% of Total	3.0%	0.0%	3.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 0.924$

P = 0.429 **Not Significant**

Dyslipidemia and Diabetic Nephropathy

- TGL Group: 46% of the subjects had Hypertriglyceremia in the study group. It was 61.5% in the Nephropathy Subjects.

- LDL Group: 99% of the subjects had LDL – Cholesterol dyslipidemia in the study group. It was 100% in the Nephropathy subjects.

- HDL Group: 47% of the subjects had HDL – Cholesterol dyslipidemia in the study group. It was 61.5% in the Nephropathy subjects.

TGL Dyslipidemia

Table - 19

TGL Dyslipi-demia		Nephropathy		Total
		No	Yes	
No	Count	98	10	108
	% Within Non Nephropathy & Nephropathy	56.3%	38.5%	54.0%
	% of Total	49.0%	5.0%	54.0%
Yes	Count	76	16	92
	% Within Non Nephropathy & Nephropathy	43.7%	61.5%	46.0%
	% of Total	38.0%	8.0%	46.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 2.905$

P = 0.096 **Not Significant**

LDL Dyslipidemia

Table - 20

LDL Dyslipi-demia		Nephropathy		Total
		No	Yes	
No	Count	2	0	2
	% Within Non Nephropathy & Nephropathy	1.1%	0.0%	1.0%
	% of Total	1.0%	0.0%	1.0%
Yes	Count	172	26	198
	% Within Non Nephropathy & Nephropathy	98.9%	100.0%	99.0%
	% of Total	86.0%	13.0%	99.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 0.302$

P = 1.000 **Not Significant**

HDL Dyslipidemia

Table - 21

HDL Dyslipi-demia		Nephropathy		Total
		No	Yes	
No	Count	96	10	106
	% Within Non Nephropathy & Nephropathy	55.2%	38.5%	53.0%
	% of Total	48.0%	5.0%	53.0%
Yes	Count	78	16	94
	% Within Non Nephropathy & Nephropathy	44.8%	61.5%	47.0%
	% of Total	39.0%	8.0%	47.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 2.536$

P = 0.141 **Not Significant**

Hypertension and Diabetic Nephropathy

- 11.5% of the study subjects were found to be Hypertensive.
- 34.6% of Nephropathy Patients were Hypertensive.

Table - 22

Hyper-tension		Nephropathy		Total
		No	Yes	
No	Count	160	17	177
	% Within Non Nephropathy & Nephropathy	92.0%	65.4%	88.5%
	% of Total	80.0%	8.5%	88.5%
Yes	Count	14	9	23
	% Within Non Nephropathy & Nephropathy	8.0%	34.6%	11.5%
	% of Total	7.0%	4.5%	11.5%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 15.690$

P = 0.001 **Significant**

GFR and Diabetic Nephropathy

- 23% of the subjects in the study group had Hyperfiltration.
- One percent of Nephropathy group had Hyperfiltration.
- Among the Nephropathy Patients 46.2% had a normal G.F.R. The same percentage of the Nephropathy subjects had decreased G.F.R.

Table - 23

GFR Group (ml/min./ 1.73m^2)		**Nephropathy**		**Total**
		No	**Yes**	
Low <90	Count	0	12	12
	% Within Non Nephropathy & Nephropathy	0.0%	46.2%	6.0%
	% of Total	0.0%	6.0%	6.0%
Normal 90-125	Count	130	12	142
	% Within Non Nephropathy & Nephropathy	74.7%	46.2%	71.0%
	% of Total	65.0%	6.0%	71.0%
Hyper filteration >125	Count	44	2	46
	% Within Non Nephropathy & Nephropathy	25.3%	7.7%	23.0%
	% of Total	22.0%	1.0%	23.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

Table - 24

Nephropathy	N	GFR Mean	Std. Deviation	Std. Error Mean
Yes	26	100.42	19.29	3.78
No	174	117.47	17.31	1.31

P=0.000 (<0.001) **Significant**

Retinopathy and Diabetic Nephropathy

- All the Six subjects found to have Retinopathy were under the Nephropathy group.

Table - 25

Retino-pathy		Nephropathy		Total
		No	Yes	
No	Count	174	20	194
	% Within Non Nephropathy & Nephropathy	100.0%	76.9%	97.0%
	% of Total	87.0%	10.0%	97.0%
Yes	Count	0	6	6
	% Within Non Nephropathy & Nephropathy	0.0%	23.1%	3.0%
	% of Total	0.0%	3.0%	3.0%
Total	Count	174	26	200
	% Within Non Nephropathy & Nephropathy	100.0%	100.0%	100.0%
	% of Total	87.0%	13.0%	100.0%

$\chi^2 = 41.396$

P = 0.000 (<0.001) **Significant**

BINARY LOGISTIC REGRESSION

- Nephropathy has been taken as dependent variable.

- The following variables are taken as models and Binary Logistic Regression model was applied to find out Correlation of the risk factors.

1. Age Group
2. Gender
3. Family history of diabetes
4. Family history of Kidney Diseases
5. Smoking
6. Body Mass Index
7. Body Mass Index group
8. Hypertension
9. TGL Group
10. LDL Group
11. HDL Group

Table - 26

Variables	$\chi 2$	Significant
Age	2.803	0.423
31-40 (Years)	1.898	0.168
41-50 (Years)	2.718	0.099
51-60 (Years)	1.623	0.203
Male gender	**5.725**	**0.017**
Family H/o Diabetes Mellitus	0.978	0.323
Family H/o kidney diseases	0.000	0.999
Smoking	0.000	0.999
BMI	**12.923**	**0.005**
Normal	0.000	1.000
Overweight	**3.935**	**0.047**
Obese	1.229	0.268
Hypertension	**9.325**	**0.002**
TGL Group	0.090	0.764
LDL Group	0.000	1.000
HDL Group	0.016	0.898

Binary regression model showed significant correlation between diabetic nephropathy and the following risk factors : Male sex, body mass index esp. over weight and hypertension.

DISCUSSION

The prevalence of diabetic nephropathy in this study is compared with studies done in various races. A study, done in the Chennai urban region by Unnikrishnan et al. showed 23.9% prevalence of microalbuminuria and 2.2% of macroalbuminuria. In our study it is 12% of microalbuminuria and 1% of macroalbuminuria. The lesser prevalence may be because of uncontrolled hypertensive patients are excluded from our study, while in other studies they were included. And also in other studies highly sensitive methods like Immunoturbidometric assay were used for AER detection. In addition, the sample size is small in our study. Prevalence of macroalbuminuria is higher in the western population.

Table - 27

Study	Place & Year	Micro albuminuria (Stage 3 nephropathy)	Macro albuminuria (Stage 4 nephropathy)	Nephropathy (Total)
Unnikrishnan et al[24]	Chennai, India,2004	26.90%	2.20%	29.10%
Wirta et al[25]	Finland, 1995	29.00%	4%	33.00%
Collins et al [26]	Wetern samoa, 1995	22%	3.90%	25.90%
This study	KMCH, Chennai,2008	12%	1%	13.00%

Correlation with various risk factors

Micro albuminuria and macroalbuminuria are both considered together as diabetic nephropathy and its correlation with the study variables are analysed. It has been compared with available datas of Unnikrishnan et al.[24], Chennai study (Chennai Urban Rural Epidemiology Study- CURES 45), and with studies done in western population like WIRTA et al.[25], Finland 1995; COLLINS et al[26]; Western Samoa, 1995 & UKPDS Studies[3].

Correlation Between AGE and Diabetic Nephropathy

Mean age in this study group is comparable with CURES study.

Table - 28

Study	Mean Age
This study	**49 ± 9**
Unnikrishnan et al	**51 ± 11**

In this study no correlation between Age and Diabetic Nephropathy was found. This is in contrast to the observation noted in Unnikrishnan et al study where as the age advances the risk of Diabetic nephropathy had increased.

Table - 29

	AGE MEAN		
Study	**Non Nephropathy (Yrs)**	**Nephropathy (Yrs)**	**P value**
Unnikrishnan et al	50 ± 11	52 ± 11*/ 57 ± 9**	< 0.0001
This study	49 ± 9	48 ± 8	0.710

* Microalbuminuria
** Macroalbuminuria

No significant difference is seen between the Age of the Diabetic patient and development of Diabetic Nephropathy.

Correlation Between Gender and Diabetic Nephropathy

In this study it was found that there is a significant correlation noted in between Gender and Diabetic Nephropathy. Binary regression model showed that significant correlation exists between male sex and Diabetic Nephropathy (P = 0.017).

In contrast, Unnikrishnan et al study showed no correlation between Gender and Diabetic Nephropathy. Various western studies had shown that male patients had increased risk of development of diabetic nephropathy[4].

Correlation Between Family History of Diabetes and Diabetic Nephropathy

In this study there is no significant correlation between Family History of Diabetes and development of Diabetic Nephropathy.

Table - 30

Family History of Diabetes		
Non Nephropathy	**Nephropathy**	**P value**
44	8	0.632

Correlation Between Family History of Kidney Diseases and Diabetic Nephropathy

There is a significant correlation between Family History of Kidney Diseases and development of Diabetic Nephropathy.

Table - 31

Family History of Kidney Diseases		
Non Nephropathy	**Nephropathy**	**P value**
0	2	0.016

Correlation Between Smoking and Diabetic Nephropathy

In this study there is no significant correlation between Smoking and development of Diabetic Nephropathy.

Table - 32

Smoking		
Non Nephropathy	**Nephropathy**	**P value**
6	0	1.000

In contrast in Unnikrishnan et al study there was a significant correlation was found. The small size of the study population and with less number of patients had the history of smoking are the major limitations in our study.

Correlation Between BMI and Diabetic Nephropathy

Patients having over weight showed significant development of Diabetic nephropathy.

Table - 33

BMI Mean		
Non Nephropathy	**Nephropathy**	**P value**
24.51± 3	26.78± 2	0.002

Correlation Between Hypertension and Diabetic Nephropathy

There is a highly significant correlation exist between Hypertension and Diabatic Nephropathy in this study and also in Unnikrishnan et al study.

Table - 34

Hypertension			
Study	**Non Nephropathy**	**Nephropathy**	**P value**
Unnikrishnan et al	40.80%	59.70%	<0.001
This study	14(8%)	9(34.6%)	0.001

In our study hypertensive subjects having optimum controlled Blood pressure are only included .So the bias of Albuminuria caused by hypertension itself is avoided in this study. Even then also the hypertensive patients had increased risk of nephropathy due to hypertensive vascular pathology caused by previously uncontrolled or delayed detection of Hypertension as well as type 2 diabetes. So this study signifies that screening and early detection of hypertensive subjects and also the effective control of systemic pressure in spite of diabetic status (including Latent Diabetes) is must.

Correlation Between Dyslipidemia and Diabetic Nephropathy

Table - 35

TGL Dyslipidemia		
Non Nephropathy	**Nephropathy**	**P value**
76	16	0.096

Table - 36

LDL Dyslipidemia		
Non Nephropathy	**Nephropathy**	**P value**
172	26	1.000

Table - 37

HDL Dyslipidemia		
Non Nephropathy	**Nephropathy**	**P value**
78	16	0.141

The subjects presented with Nephropathy had TGL, LDL & HDL Dyslipidemia with the prevalence of 61.5%, 100% and 61.5% respectively.

The prevalence in total subjects (Newly detected Diabetes Melitus) is 46%, 99% & 47% respectively.

This shows high prevalence of hypertryglyceridemia, high LDL cholestrol levels and low HDL cholesterol levels in Type II diabetes mellitus as well as in Diabetic nephropathy subgroup.

There is no statistical significance has been seen in this study between Dyslipidemia and diabetic nephropathy.

Various other studies had shown significant relation between dyslipidemia and nephropathy. This may be because of the small size of our study population and also the high prevalence of the Dyslipidemia among the all newly detected Diabetes mellitus patients in our study.

Correlation Between GFR and Diabetic Nephropathy

GFR has significant correlation with Diabetic Nephropathy in this study.

Table - 38

GFR Mean	GFR Mean	P value
Non Nephropathy	Nephropathy	
117(± 17)	100 (±19)	0.000 (<0.001)

50 percent of the Nephropathy subjects had lower GFR depending on the severity of the disease.

Among non –nephropathic subjects one fourth had Hyperfiltration suggestive of stage I Diabetic Nephropathy.

The mean GFR in total subjects (Newly detected type 2 Diabetes mellitus) is 115 $\pm$ 18 ml/min/ 1.73 sq.m.

Correlation Between Retinopathy and Diabetic Nephropathy

Retinopathy was found to have highly significant correlation between Nephropathy. Retinopathy patients had increased risk of developing Nephropathy.

About one fourth of the Nephropathy subjects in this study had presented with Diabetic Retinopathy.

The prevalence of retinopathy in this study is lesser and it may be because of using direct opthalmoscope for the fundus examination whereas fundul photography was used in other studies.

Table - 39

STUDY	Prevalence of retinopathy
Mohan Rema et al	5.10%
This Study	3%

CONCLUSION

1. In this study the prevalence of Diabetic Nephropathy in newly deducted type 2 diabetes mellitus is found to be significant. The study signifies the early screening of all Newly diagnosed type 2 Diabetic patients for Diabetic Nephropathy.

2. This study has shown significant association between the development of Nephropathy and risk factors like Family history of kidney diseases, Body Mass Index esp. with overweight, gender, systemic Hypertension, Serum creatinine, Glomerular filtration rate and Retinopathy. Binary regression model analysis showed significant association with male sex, over weight and hypertension.

3. This study has not shown significant association of smoking and dyslipidemia with the development of Diabetic Nephropathy.

4. Albumin Excretion Rate is the gold standard screening as well as diagnostic tool for the early diagnosis of Diabetic Nephropathy. Micral dip stick test method and the cost effective protein creatinine Ratio can be used as the valuable screening test in setting like our country where most of the population are in the low socio economic status.

5. Effective measures to control the risk factors and early detection of diabetic nephropathy to prevent it from progressing towards End Stage Renal disease is the key in maintaining the quality of life in Diabetic population. This not only decreases the morbidity and mortality among the Diabetic patients but also lessen the Financial burden faced on treating such complications enormously, in the developing countries like India.

6. The presence of complications at the time of diagnosis of type 2 diabetes itself shows that intensive screening for early detection of diabetes mellitus and tight glycaemic control as well as Blood pressure control will prevent the development of microvascular complications.

SUMMARY

This study was aimed to find out the prevalence of Diabetic Nephropathy in newly detected type 2 Diabetic patients and also the risk factors associated with the development of the Diabetic nephropathy.

The prevalence found in this study was 13 percent. Among these patients 12 percent had microalbuminuria and one percent had macroalbuminuria.

The risk factors found to be having significant association are family history of kidney diseases, overweight, male gender, systemic hypertention, serum creatinine, glomerular filtration rate and retinopathy.

The active screening and early detection of type 2 diabetes is necessary. Hence the measures to create awareness among the people and educate them for a healthy life style are to be taken.

The effective control of the risk factors in type 2 diabetic patients will prevent the development of nephropathy and also retards it’s progression.

ABBREVIATION

ACE Inhibition	-	Angiotensin converting enzyme inhibitor
AER	-	Albumin Excretion Rate
BMI	-	Body mass Index
CCBs	-	Calcium channel blockers
CVD	-	Cardiovascular disease
DM	-	Diabetes mellitus
DNA	-	Deoxyribonucleic acid
ESRD	-	End Stage Renal Disease
GBM	-	Glomerular Basement Membrane
GFR	-	Glomerular Filtration Rate
HDL	-	High Density Lipoprotein
IDDM	-	Insulin Dependent diabetes mellitus
LDL	-	Low Density Lipoprotein
MDRD	-	Modification of diet in renal disease
MPGN	-	Membrano Proliferative Glomerular Nephritis
NIDDM	-	Non insulin dependent diabetes mellitus
OGTT	-	Oral Glucose Tolerance Test
PCR	-	Protein creatinine ratio
TGL	-	Triglyceride
UAER	-	Urinary Albumin Excretion Rate
UKPDS	-	United Kingdom Prospective Diabetes Study

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PROFORMA

Name of the patient :

IP/OP No :

Age :

Sex :

Address :

H/O smoking :

H/O hypertension :

Family H/O diabetes :

Family H/O kidney disease :

Height :

Weight :

BMI :

Blood pressure :

Lipid profile :

- TGL :
- LDL :
- HDL :

RFT

Blood urea :

Serum creatinine :

GFR :

Urine routine :

Sample 1

Sample 2

Sample 3

Urine culture :

Urine PCR :

Sample 1

Sample 2

Sample 3

Dipstick(MICRAL)test :

Sample 1

Sample 2

Sample 3

USG KUB :

Fundus examination :