

## SPECTRUM OF NON DIABETIC RENAL DISEASE IN PATIENTS WITH TYPE 2 DIABETIS MELLITUS

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**ABSTRACT:** The progressive rise in the number of patients with end-stage renal disease (ESRD) due to Diabetic Nephropathy (DN)/ Diabetic kidney disease (DKD) is a major social and economic burden in several countries. Furthermore, prognosis in such patients is very poor compared with patients with ESRD due to other renal diseases. Our Study included 200 patients. Along with history and physical examination, we did investigations included proteinuria, active urine sediment, HbA<sub>1c</sub>, Serum Creatinine and Percutaneous renal biopsy.

**KEYWORDS:** Non Diabetic Renal Disease, Diabetic Nephropathy, End-stage renal disease, Renal Biopsy.

**INTRODUCTION:** Type 2 DM patients often experience diabetic nephropathy, they can also develop other renal diseases, pathologically unrelated to diabetes and known as non-diabetic renal disease (NDRD).<sup>(1)</sup> Precise diagnosis of these various diseases has obvious prognostic and therapeutic implications.<sup>(2)</sup> Diabetic nephropathy is the leading cause of chronic kidney disease worldwide, constituting 25-45% worldwide.

### Diabetic nephropathy is defined as:

- Presence of persistent albuminuria, (Either microalbuminuria or macroalbuminuria).
  - a) Micro albuminuria defined as AER 30-300 mg/24 hrs. (or) 30-300mg/gm creatinine (or) AER 20-200 µg/min in timed collection, in at least two of three consecutive non ketotic sterile urine samples.
  - b) Macro albuminuria defined as AER >300 mg/24 hrs. (or) 300mg/gm creatinine (or) AER >200µg/min in timed collection.

An elevated ACR should be confirmed in the absence of urinary tract infection with two additional first-void specimens collected during the next 3 to 6 months.

- Presence of diabetic retinopathy.
- Absence of clinical or laboratory evidence of other kidney or renal tract disease.

### Causes of Renal disease in Type 2 DM include:

1. Diabetic nephropathy.
2. Non-diabetic renal disease (NDRD).
  - a) Primary glomerulonephritis -- Membranous nephropathy, IgA nephropathy, Post infectious glomerulonephritis, Focal segmental glomerulosclerosis, Minimal change nephropathy, crescentic glomerulonephritis.
  - b) Acute kidney injury from various causes.

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- c) Tubulo interstitial diseases - Polycystic kidney disease, Reflux nephropathy, Pyelonephritis, Renal calculus disease, contrast nephropathy.
- d) Vascular lesions - Renal artery stenosis, Vasculitis, Benign nephrosclerosis, Atheroembolic renal disease.
- e) Systemic diseases - Amyloidosis, Systemic lupus erythematosus, Thrombotic microangiopathy.
- f) Obstructive causes - Neurogenic bladder, Benign prostatic hyperplasia.
- g) Malignancy - Renal cell carcinoma, bladder cell carcinoma.

Non-diabetic renal disease often develops in patients with Type 2 DM. On kidney biopsy studies, prevalence of NDRD among the Type 2 DM patients was 22% of European and 26.7% of Asian patients.<sup>(3)</sup> Since renal disease in the setting of diabetes is often ascribed to the diabetes, without further diagnostic efforts, the coincidence of non-diabetic renal disease in persons with diabetes may be underestimated.

**Epidemiology of Non-diabetic kidney disease in patients with type 2 diabetes mellitus:** There is no general agreement on prevalence of non-diabetic kidney disease among patients with type 2 diabetic mellitus. Consequently, it is not clear whether kidney biopsy should become a part of the standard evaluation of proteinuric patients with this type of diabetes mellitus. English publications on kidney biopsy in proteinuric patients with this type of diabetes mellitus were analysed. 665 cases of renal biopsies were included in the analysis that was performed separately for Caucasian and Asian populations. Prevalence of non-diabetic kidney disease among European patients with type 2 diabetes mellitus varied from 3% among Danish to 32% in Italian subjects. Coexistence of both non-diabetic nephropathy and diabetic nephropathy was the most infrequent result of kidney biopsies. On average, diabetic nephropathy was the most common pathology in proteinuric patients with type 2 diabetes mellitus (64.8%), followed by non-diabetic kidney diseases (18.7%), normal renal structure (13.2%) and non-diabetic nephropathy superimposed on diabetic nephropathy (3.3%).

Altogether, non-diabetic kidney disease was present in approximately 22% of patients with type 2 diabetes mellitus. Analysis of kidney biopsy results from Asian patients with type 2 diabetes mellitus (Subjects from Japan, China and India) provided consistent findings. A significant variation in prevalence of diabetic nephropathy (From 87.7% in subjects from India to 35.3% in Chinese patients) was evident across the studies. Non-diabetic nephropathy without coexistent diabetic nephropathy was found in 16.8% cases and superimposition of chronic non-diabetic renal pathology on diabetic nephropathy accounted for 9.9% cases. Altogether, non-diabetic renal disease affected 26.7% of Asian subjects with type 2 diabetes mellitus. Taken together, the results of this analysis indicate that, even after adjusting for differences in methodology among the studies, non-diabetic renal disease may affect a significant percentage of patients with type 2 diabetes mellitus. Therefore, kidney biopsy may become a useful diagnostic option among proteinuric patients with this type of diabetes mellitus.

**Clinical markers of non-diabetic kidney disease among patients with type 2 diabetes mellitus and renal affection:**

**Major clinical clues suggesting presence of Non-diabetic glomerular disease include:**

1. Acute onset of renal disease. Diabetic nephropathy characterized by slowly progressive increase in albuminuria & serum creatinine over a period of years.

2. The presence of active urine sediment containing redcells & cellular casts. However active sediment can also be seen with diabetic nephropathy alone.<sup>(4)</sup>
3. Signs & symptoms of systemic disease.
4. Abrupt onset of overt proteinuria.
5. Significant reduction in gfr (>30 percent), within three months of initiation of Angiotensin converting enzyme inhibitors or Angiotensin II receptor blockers.
6. Absence of retinopathy & neuropathy, especially in Type 1 DM. But in Type 2 DM it may give clue to the presence of non-diabetic renal disease & as there is poor retino renal concordance.
7. Onset of proteinuria less than 5yrs from the documented onset of Type 1 Diabetes, since the latent period for overt diabetic nephropathy is usually at least 10 to 15 yrs. The latent period is probably similar in patients with Type2 diabetes, but the time of onset is often difficult to ascertain.

None of the proposed markers has either absolute sensitivity or 100% specificity for non-diabetic renal disease. Therefore, they cannot be used as sole indicators of non-diabetic renal disease in patients with type 2 diabetes mellitus. Nevertheless, some of these markers, particularly used in combination, may come useful when decisions about kidney biopsy in type2 diabetic patients are made.

The most common nondiabetic glomerular diseases were membranous nephropathy, IgA nephropathy, post infectious glomerulonephritis, focal segmental glomerulosclerosis& minimal change disease.

Tubulointerstitial renal disease was a relatively rare find in gon renal biopsy in patients with type 2 diabetes mellitus.<sup>(5)</sup>

In particular, pathology indicating chronic pyelonephritis was not common among diabetic patients undergoing kidney biopsy. This underrepresentation of chronic pyelonephritis among type 2 diabetic patients is surprising in light of the well-known tendency to asymptomatic bacteriuria among diabetic subjects.

In addition to nondiabetic glomerular diseases, renal insufficiency & proteinuria may also be induced by other diseases, particularly arteriosclerotic vascular disease (Nephrosclerosis) in older Type 2 diabetes. This disorder cannot usually be distinguished from diabetic nephropathy without performing a renal biopsy. This is rarely necessary since making this distinction is of no clinical value. One potential clue favouring the presence of nephrosclerosis is rise in serum creatinine following institution of ACEI. However this is also consistent with renal artery stenosis.

Therefore, kidney biopsy may become a useful diagnostic option among proteinuric patients with type 2 diabetes mellitus. However, it is generally agreed that renal biopsy cannot be used as a routine diagnostic test in all type 2 diabetic patients with proteinuria.

Diabetic subjects that may benefit from kidney biopsy should be rather identified on a case-by-case basis. Absence of diabetic retinopathy, particularly used in combination with a canthocyturia, may come useful in decisions about kidney biopsy in type 2 diabetic patients.

### **Screening and Diagnosis of DKD:**

1.1 Patients with diabetes should be screened annually for DKD. Initial screening should commence:

- 5 years after the diagnosis of type 1 diabetes; (A) or
- From diagnosis of type 2 diabetes. (B)

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### 1.1.1 Screening should include:

- Measurements of urinary albumin-creatinine ratio (ACR) in a spot urine sample; (B)
- Measurement of serum creatinine and estimation of GFR.(B)

1.2 An elevated ACR should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected over the next 3 to 6 months.(B)

- Microalbuminuria is defined as an ACR between 30-300mg/g.
- Macroalbuminuria is defined as an ACR>300 mg/g.
- 2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification.

1.3 In most patients with diabetes, CKD should be attributable to diabetes if:

- Macroalbuminuria is present; (B) or
- Microalbuminuria is present
- In the presence of diabetic retinopathy, (B)
- In type 1 diabetes of at least 10 years' duration. (A)
- 1.4 Other cause(s) of CKD should be considered in the presence of any of the following circumstances: (B)
- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;
- Presence of active urinary sediment;
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB.

**Renal Pathology Society classification:** A classification of type1 and type2 diabetic nephropathy was developed by the research committee of the Renal Pathology Society.

### Glomerular classification of DN:

Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes and EM-proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV. GBM > 395 nm in female and >430 nm in male individuals 9 years of age and older.
Ia	Mild mesangial expansion	Biopsy does not meet criteria for class III or IV Mild mesangial expansion in >25% of the observed mesangium
Ib	Severe mesangial expansion	Biopsy does not meet criteria for class III or IV Severe mesangial expansion in >25% of the observed mesangium
II	Nodular sclerosis (Kimmelstiel-Wilson lesion)	Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel-Wilson lesion
III	Advanced diabetic Glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli Lesions from classes I through III

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This classification scheme is based on glomerular lesions because these are relatively easy to recognize with good inter observer agreement and because glomerular lesions best reflect the natural course of progressive DN. Glomerular and interstitial lesions contribute to the decline in renal function in DN and may be independent factors in the progression of DN; however, many studies also show that severity of chronic interstitial and glomerular lesions are closely associated.

### Interstitial and vascular lesions of DN:

Lesion	Criteria	Score
<b>Interstitial lesions</b>		
IFTA	No IFTA	0
	<25%	1
	25-50%	2
	>50%	3
Interstitial inflammation	Absent	0
	Infiltration only in relation to IFTA	1
	Infiltration in areas without IFTA	2
<b>Vascular lesions</b>		
Arteriolar hyalinosis	Absent	0
	At least one area of arteriolar hyalinosis	1
	More than one area of arteriolar hyalinosis	2
Presence of large Vessels arteriosclerosis (score worst artery)		Yes/No
	No intimal thickening	0
	Intimal thickening less than thickness of media	1
	Intimal thickening greater than thickness of media	2

**Non-diabetic kidney disease in patients with type 2 diabetes mellitus:** There is no general agreement on prevalence of non-diabetic kidney disease among patients with type 2 diabetic mellitus. Consequently, it is not clear whether kidney biopsy should become a part of the standard evaluation of proteinuric patients with this type of diabetes mellitus. English publications on kidney biopsy in proteinuric patients with this type of diabetes mellitus were analysed. 665 cases of renal biopsies were included in the analysis that was performed separately for Caucasian and Asian populations.

Prevalence of non-diabetic kidney disease among European patients with type 2 diabetes mellitus varied from 3% among Danish to 32% in Italian subjects. Coexistence of both non-diabetic nephropathy and diabetic nephropathy was the most infrequent result of kidney biopsies. On average, diabetic nephropathy was the most common pathology in proteinuric patients with type 2 diabetes mellitus (64.8%), followed by non-diabetic kidney diseases (18.7%), normal renal structure (13.2%) and non-diabetic nephropathy superimposed on diabetic nephropathy (3.3%). Altogether, non-diabetic kidney disease was present in approximately 22% of patients with type 2 diabetes mellitus.

Analysis of kidney biopsy results from Asian patients with type 2 diabetes mellitus (Subjects from Japan, China and India) provided consistent findings. A significant variation in prevalence of

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**AIM OF THE STUDY:** Diagnosis of Diabetic nephropathy is almost always based on clinical grounds. The diagnosis was supported by long duration of Diabetes, evidence of target organ damage, proteinuria preceding azotemia.

The validity of this clinical approach is well established in Insulin dependent diabetes mellitus but not in non-insulin dependent diabetes mellitus. Therefore proteinuria in Type2 DM may reflect Diabetic nephropathy or concurrent non-diabetic renal disease super imposed on DN, or NDRD only. The detection of super imposed NDRD in diabetic patients has an obvious prognostic & therapeutic importance. It is generally believed that it is difficult to reverse DN, whereas some cases of NDRD are readily treatable & remittable.

Therefore it is important to determine which patients with Type 2 diabetes mellitus accompanied by non-diabetic renal disease. However, factors clinically associated with NDRD in Type 2 DM remains unclear.

Therefore AIM of the study is:

- To estimate prevalence of NDRD
- To study the clinical spectrum of non-diabetic renal disease in Type 2 DM patients with renal involvement (Proteinuria or renal impairment).
- And to assess factors that predict Non diabetic renal disease.

### **MATERIAL & METHODS:**

**STUDY PERIOD:** December 2011 to December 2013.

**STUDY DESIGN:** Single centre based prospective randomized controlled study.

**INCLUSION CRITERIA:** All individuals with Type 2 DM (Defined by American Diabetes Association) with renal involvement either in the form of Microalbuminuria or macroalbuminuria or renal insufficiency or both, those attending outpatient clinic, or admitted in the department of nephrology, King George Hospital, which is a tertiary care referral centre, not only from Andhra Pradesh but also from adjacent states.

Total number of patients enrolled was 200.

**EXCLUSION CRITERIA:** Patients with:

1. End stage renal disease.
2. Pregnancy.

**METHODOLOGY:** Study included data from 200 patients. Demographic, clinical & biochemical data from these patients collected.

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Through history & physical examination was done for all patients.

Major factors assessed include, Age, Age at the onset of DM, duration of DM, presence or absence of retinopathy, HTN, degree of proteinuria, presence or absence of Active urine sediment, Acute rise in serum creatinine, HbA1c.

Other biochemical parameters assessed were serum creatinine, creatinine clearance, blood urea, complete urine examination, complete blood picture, blood culture sensitivity, urine culture sensitivity, 24hr urine protein, serum electrolytes, serum albumin, serum uric acid, Fasting serum calcium, phosphorus, fasting lipid profile, Fasting thyroid profile, fasting & post prandial blood sugar. Chest x ray, ECG, U/S abdomen, 2D ECHO was performed routinely.

Special investigations like complete collagen profile, ASO titres, C-reactive protein, serum complement levels were done based on clinical circumstances.

CT abdomen was performed when obstructive etiology or malignancy was suspected. X-ray KUB performed when renal calculus disease or emphysematous pyelonephritis were suspected. Renal Doppler & renal angiography were done when renal artery stenosis was suspected under clinical grounds like.

1. Presence of refractory HTN,
2. Episodes of flash pulmonary edema,
3. Asymmetry in kidney sizes >1.5cm
4. >30% rise in serum creatinine over the base line following institution of ACI or ARBs.
5. Unexplained renal failure in an elderly patient.

Doppler study of lower limb arteries done in case of suspected peripheral vascular disease.

If patients had long history of Diabetes, associated diabetic retinopathy, other macro vascular complications, & proteinuria proceeding azotemia, diagnosis of Diabetic nephropathy was considered obvious and renal biopsy was deferred.

In all cases renal biopsy was performed because urinary abnormalities or renal function was inconsistent with the clinical expression or the natural history of DN. Percutaneous renal biopsy was performed as described by Veiga.<sup>(6)</sup>

### **Clinical scenario where biopsy was done in this study includes:**

- Presence of active urine sediment, after excluding infection, renal calculi.
- Rapidly progressive renal failure.
- Unexplained renal failure, after excluding reno vascular disease.
- Presence of signs & symptoms of systemic disease.
- Asymptomatic urinary abnormalities in the absence of diabetic retinopathy.
- Abrupt onset of heavy proteinuria.
- If the degree of renal failure not correlating with duration of diabetes.

Renal biopsy was performed under ultrasound guidance with a biopsy gun. (BARD GUN. 16/18gauge, 22mm cutting edge.) After biopsy obtained tissue was subjected to both light microscopy (LM) & immune florescence (IF). Tissue for LM was fixed in buffered formalin and processed on to Paraffin blocks. Processed tissue was stained with hematoxylin& Eosin, Periodic acid-shiff (PAS), Silver methanamine and Masson trichrome stain. Tissue for IF was stained with fluorescent labeled antisera to IgG, IgA, IgM, C3, C4, C1q. The intensity was semi quantitatively scored as 0 for negative, 1+ for present, 2+ for definite, 3+ for strongly positive. Electron microscopy was not used as this facility is not available to us.

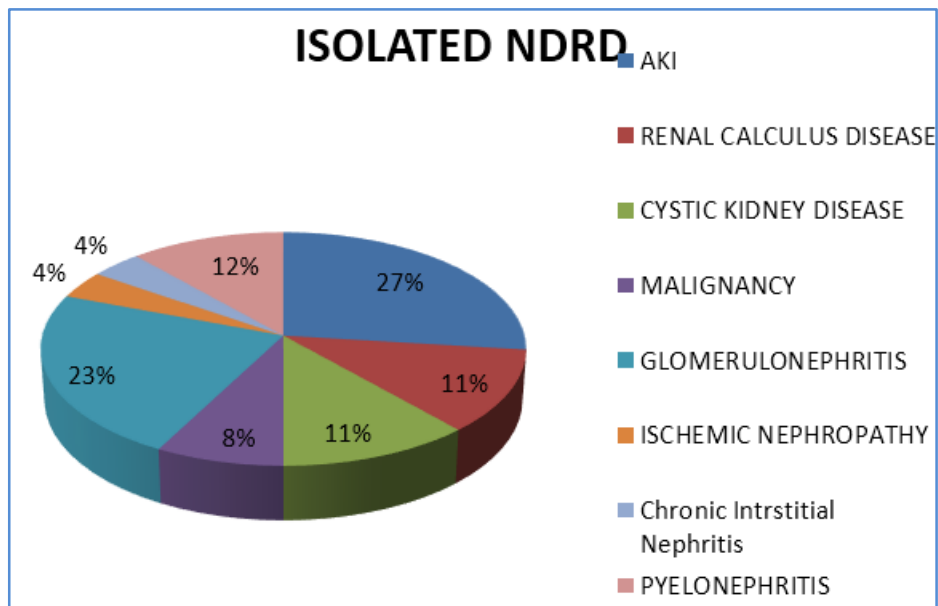
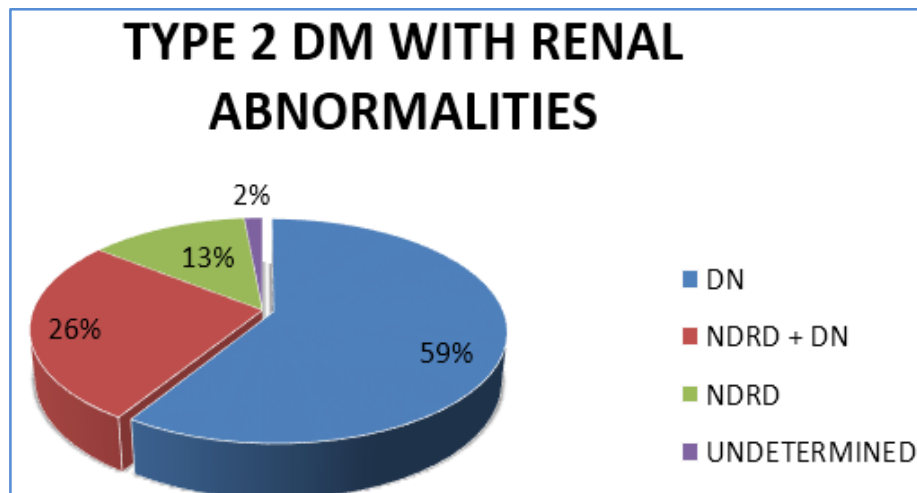
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In the post biopsy period, Packed cell volume and Ultrasound were done to exclude perirenal hematoma.

All patients after thorough evaluation categorized in to three groups based on clinical history & physical examination, lab parameters as mentioned above & renal biopsy as per indications.

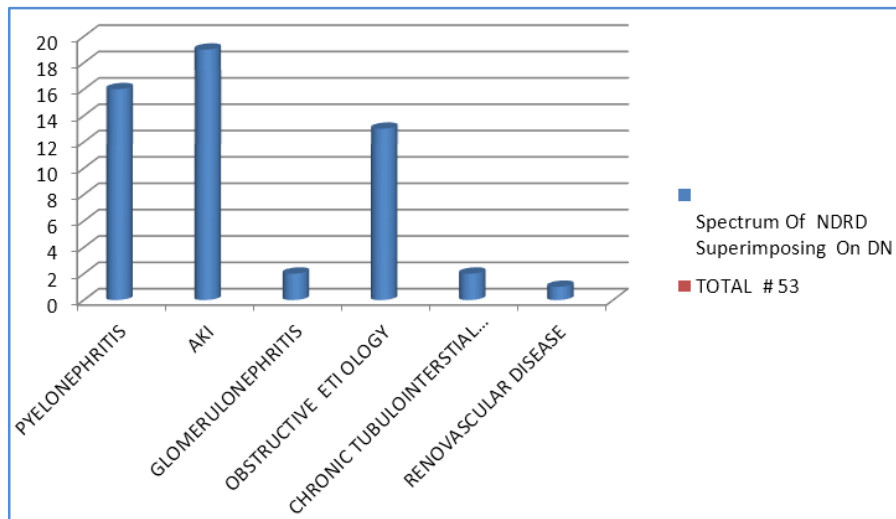
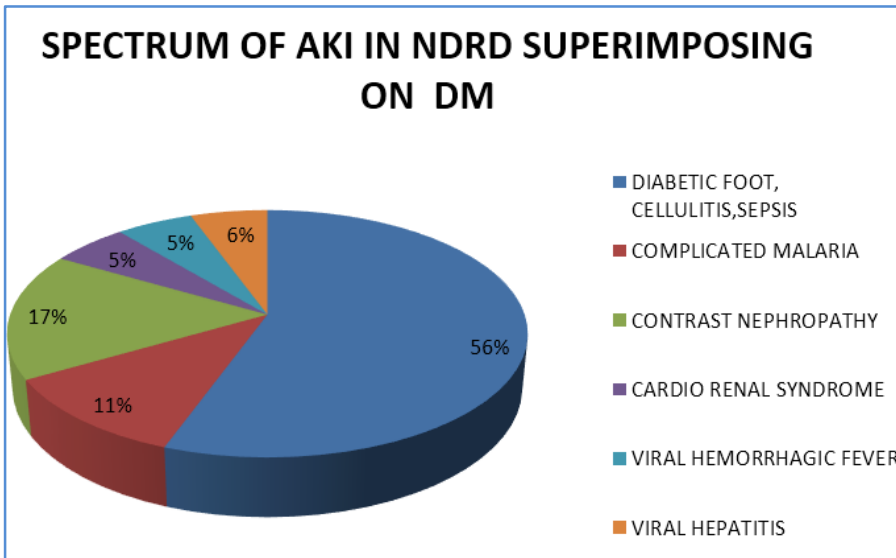
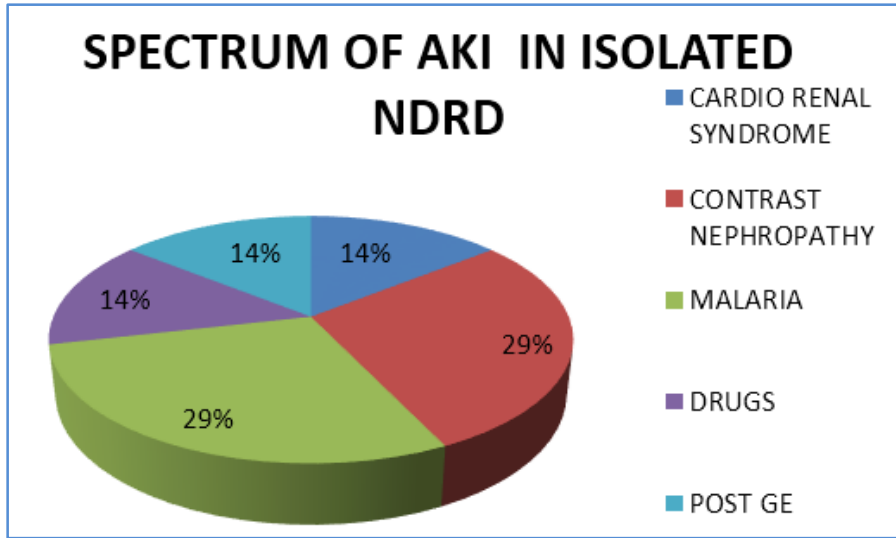
Diabetic glomerulosclerosis (DGS) was diagnosed by the presence of mesangial expansion, with or without the nodular Kimmelstiel – Wilson (KW) formation, basement membrane thickening, fibrin caps, or capsular drops. Vascular changes of DN included arteriolar hyalinosis, medial hyperplasia of smaller arteries, and intimal sclerosis of larger arteries. NDRDs were categorized as per WHO classification of 1995.

**RESULTS:** All patients included in the study & analysed were 200. Patients were divided into three categories, based on presence of whether Diabetic nephropathy is superimposing on Non-diabetic renal disease (or) isolated presence of Non-diabetic renal disease & isolated Diabetic nephropathy.





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	<b>SPECTRUM OF NDRD SUPERIMPOSING ON DN</b>	<b>NO</b>	<b>PREVALENCE</b>
1	<b>PYELONEPHRITIS</b> a) Perinephric Renal Abscess b) Emphysematous pyelonephritis c) Pyelonephritis	<b>16</b> 1 5 10	30.19%
2	<b>AKI</b>	<b>19</b>	35.85%
3	<b>GLOMERULONEPHRITIS</b> a) Post infectious glomerulonephritis b) HIV Associated Nephropathy	<b>2</b> 1 1	3.77%
4	<b>OBSTRUCTIVE ETI OLOGY</b> a) Renal Calculus b) Malignancy I. Cervical Carcinoma II. Bladder Carcinoma III. Prostatic Carcinoma c) BPH d) Stricture Urethra e) Neurogenic Bladder	<b>13</b> 3 4 2 1 1 2 2 2	24.53%
5	<b>CHRONIC TUBULOINTERSTITIAL NEPHRITIS</b>	<b>2</b>	3.77%
6	<b>RENOVASCULAR DISEASE</b>	<b>1</b>	1.88%

**Table 1**

<b>CLINICAL PARAMETERS</b>	<b>GROUP1 (η =26)</b>	<b>POSITIVE PREDICTIVE VALUE</b>	<b>GROUP2 (η =53)</b>	<b>POSITIVE PREDICTIVE VALUE</b>	<b>GROUP3 (η =118)</b>	<b>NEGATIVE PREDICTIVE VALUE</b>
DURATION OF DIABETES	4.9±2.3	100%	11 ±4.16	50%	12 ± 6.8	90%
ACTIVE URINE SEDIMENT	13	50%	25	47.16%	Nil	100%
ABSENCE OF RETINOPATHY	22	84.6%	2	3.77%	Nil	100%

**Table 2: Clinical Markers Associated With Non Diabetic Renal Disease**

<b>Parameter</b>	<b>Group I (η=26)</b>	<b>Group II (η=53)</b>	<b>Group III (η=118)</b>
<b>Retinopathy present</b>	4	51	109
<b>HTN present</b>	9	26	87
<b>Duration &lt;10 yrs.</b>	26	50	50
<b>Average Degree of Proteinuria</b>	1.43	1.14	1.2

**Table 3**

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CLINICAL PARAMETER	GROUP 1 ( $\eta = 8$ , no. of patients who underwent biopsy)	GROUP 2 ( $\eta = 5$ , no. of patients who underwent biopsy)	GROUP 3 ( $\eta = 3$ , no. of patients who underwent biopsy)
Active urine sediment	4	2	
Unexplained acute deterioration of renal function	2		
Abrupt onset of proteinuria	1		3
Presence of systemic disease	1	1	
Absence of retinopathy	All 8 cases	2	

*Table 4: Indications for Renal Biopsy*

Group 1 includes patients with Isolated Non diabetic renal disease. Patients in group 1 were 26, which comprise 13%. Group 2 include patients with Non-diabetic renal disease superimposing on diabetic nephropathy. Patients in Group 2 include 53, which comprise 26%. Group 3 include patients with Diabetic nephropathy only, these comprise 118, constitutes 59%.

The numbers of patients in Isolated Non Diabetic Renal disease were 26. Mean age of the patients is 51 yrs. ( $\pm$ ) 6yrs. Male patients in the study 17, female patients 9. Male to female ratio 2:1.

Non-diabetic renal diseases include eight categories. These were acute kidney injury, renal calculus disease, cystic kidney diseases, Malignancy, Glomerulonephritis, Ischemic nephropathy, chronic tubulointerstitial nephritis with distal RTA, Pyelonephritis. Leading cause being acute kidney injury, followed by primary glomerulonephritis, pyelonephritis, cystic kidney disease, renal calculus disease.

Causes of AKI include, tropical diseases like complicated malaria, acute diarrheal disease, followed by contrast nephropathy, cardio renal disease, drug induced ATIN.

Hypertension is present in 9 members, out of 26. Therefore positive predictive value of absence of Hypertension in correlation with non-diabetic renal disease is 88.46%.

Retinopathy is present in 4 out of 26. Therefore Absence of retinopathy better correlate with non-diabetic renal disease. Positive predictive value of Absence of retinopathy is 84.6%.

Active urine sediment is present in 13 members out of 26. Positive predictive value of presence of active urine sediment is 50%, for the whole group. But if we consider the group of Non-diabetic renal disease due to primary glomerulonephritis, all are having active urine sediment. Therefore positive predictive value of Active urine sediment in primary glomerulonephritis as Non-diabetic renal disease is 100%.

Proteinurias are present in 7 out of 26. Positive predictive value of this in total Non-diabetic renal disease group is 26.9%. But if we consider primary glomerulonephritis group, it is present in all cases. Therefore positive predictive value of proteinuria in primary glomerulonephritis of Non-diabetic renal disease is 100%. And even abrupt onset of proteinuria is present in all primary glomerulonephritis cases compromising positive predictive value of 100%.

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Renal biopsy is performed in eight cases. In six cases indication for biopsy was, active urine sediment with abrupt onset of proteinuria, the biopsy reports were turned out to be PIGN in two cases, MPGN type 1 in two cases, HIV associated nephropathy in one case, Membranous nephropathy in one case. Abrupt onset of proteinuria is present in four cases & insidious onset of proteinuria is present in one case i.e. HIV Associated nephropathy.

Unexplained renal failure was the indication for biopsy in two cases. One case presented with rapidly progressive renal failure, with history of 10yrs Diabetes & absence of retinopathy, normotensive with no active urine sediment, in which biopsy suggestive of Acute tubule interstitial nephritis. In another case with 5yrs duration of Diabetes, normotensive with no evidence of micro or macro vascular complications, bland urine sediment, biopsy was suggestive of chronic interstitial nephritis.

Group 2 include 53 patients. Mean age of patients 55.6yrs $\pm$ 5.45 yrs. Mean duration of Diabetes is 11.06 yrs $\pm$ 4.16 yrs. Total number of male patients 35 & female patients 18. Hypertension is present in twenty six patients & absent in 27 members. Positive predictive value of Hypertension 50%.

Retinopathy is present in 51 patients. Absent in 2 patients. Non-proliferative retinopathy is present in twenty patients & proliferative retinopathy is present in 31 patients. Positive predictive value of retinopathy in the prediction of underlying Diabetic nephropathy is 96.2%.

Active urine sediment present in 25 patients, absent in 28 patients. Therefore positive predictive value of active urine sediment, in the prediction of Non-diabetic renal disease is 47.16%. Proteinuria is present in 42, Average degree of proteinuria is 1.14gm/24hrs, and positive predictive value of proteinuria in prediction of underlying diabetic nephropathy is 79.24%.

Renal biopsy performed in five cases. Biopsy was performed in those with unexplained rapid deterioration of renal function (In two cases) & In whom renal failure could not be attributed to underlying Diabetes because of absence of retinopathy & absence of proteinuria ,other micro & macrovascular complications (In two cases) & presence of associated comorbid condition like Retroviral disease.

The biopsy findings include Post-streptococcal glomerulonephritis super imposing on Diabetic glomerulosclerosis, Acute tubulointerstitial nephritis superimposing on Diabetic glomerulosclerosis & chronic interstitial nephritis, HIVAN superimposing on Diabetic glomerulosclerosis.

Group 3 include patients with Diabetic nephropathy only. It includes total 118 patients. Average duration of Diabetes is 12yr $\pm$ 6.8yrs. Total number of male patients 79, total number of female patients 39. . Male to female ratio 2:1. Average degree of proteinuria 1gm $\pm$ 0.6gm.

Retinopathy is present in 109 patients. Non-proliferative retinopathy is present in 38 patients & Proliferative retinopathy is present in 71. Positive predictive value of retinopathy in the prediction of Diabetic nephropathy is 92%.

None of the patients in diabetic nephropathy had active urine sediment. Therefore positive predictive value of absence of active urine sediment, in the prediction of isolated Diabetic nephropathy is 100%.

Hypertension is present in 86 patients, absent in 32 patients. Positive predictive value of Hypertension in the prediction of diabetic nephropathy is 72.8%.

Renal biopsy was performed in three cases of Group 3 in whom nondiabetic renal disease is suspected because of abrupt onset of proteinuria, all are having retinopathy (One is having non-

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proliferative retinopathy, other two are having proliferative retinopathy). Biopsy of all three cases showing diffuse nodular glomerulosclerosis.

The most common lesion found in Non-diabetic renal disease without concurrent Diabetic nephropathy was Acute kidney injury (27%) from various causes including malaria, cellulitis, cardiorenal syndrome, contrast nephropathy, sepsis. Other causes of Non-diabetic renal disease include Glomerulonephritis (23%), Pyelonephritis (12%), Cystic kidney disease (11%), renal calculus disease (11%), Malignancy (8%), Ischemic nephropathy (4%), Chronic interstitial nephritis (4%).

The most common lesion found in Non-diabetic renal disease superimposing on Diabetic nephropathy is AKI (35.85%) from various causes including cellulitis, malaria, contrast nephropathy, cardiorenal syndrome. Other causes include pyelonephritis (30.19%), Obstructive uropathy (24.53%), Glomerulonephritis (3.8%), chronic interstitial nephritis (3.8%), Renovascular disease (1.9%).

Out of 200 cases, cause of renal insufficiency remains undetermined in three cases as their renal abnormalities couldn't be attributed to Diabetic nephropathy. Renal biopsy couldn't be performed as one is having contracted kidneys & remaining two cases didn't give consent.

**DISCUSSION:** In the present study all patients had Diabetes mellitus with renal abnormalities and the overall prevalence of Non-diabetic renal disease is 39%. Isolated Non diabetic renal disease constitutes 13% & prevalence of Non-diabetic renal disease superimposing on Diabetic nephropathy is 23%.

This was in accordance with previous studies conducted by Beck & Evans et al (26%);<sup>(7)</sup> Chawamkul et al (12 – 33.3%).<sup>(8)</sup>

But different from other studies where the prevalence of NDRD was around 63.9 %to 75.5%. Studies were conducted by Soniet al., south India (72.5%);<sup>(9)</sup> Pham et al., USA (72.5%);<sup>(10)</sup> Chang et al., Korea (63.9%);<sup>(11)</sup> and Li et al., China (75.5%).<sup>(12)</sup>

The large variation is presumably due to different selection criteria for doing renal biopsy in these patients. The other cause being some studies included only Non-diabetic glomerular diseases only whereas some studies included Non-glomerular causes also.

Some studies recruited patients for biopsy, those having renal abnormalities in the absence of retinopathy, some included any degree of proteinuria, some included those with >1gm proteinuria. All the studies included patients with unexplained renal failure, those with rapid deterioration of renal function and those with Active urine sediment.

In some cases there is isolated Non diabetic renal disease and in others it is Non diabetic renal disease superimposing on Diabetic nephropathy.

We found male predominance in all three groups. There is no significant difference in Age between the three groups.

The duration of Diabetes is significantly less in Isolated non-diabetic renal disease than other two groups.

Short duration of Diabetes has a very high predictive value for the diagnosis of non-diabetic renal disease. Duration of Diabetes less than 10yrs had 100% positive predictive value.

Lee et al also concluded that a shorter duration of diabetes was significantly associated with NDRD.<sup>(13)</sup> Similar results were reported by Wong, Tone and Huang et al.<sup>(14)</sup>

Soni et al from India also reported that a short duration of diabetes was a predictor of NDRD.

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However, Bertani et al and Mak et al found no significant difference in the duration of diabetes among the different groups.<sup>(15)</sup>

There was significant difference in the prevalence of Hypertension between three groups, in the current study. Absence of hypertension is more predictive of Non-diabetic renal disease. This was different from previous studies by Soni & Matias et al.<sup>(16)</sup>

There was no significant statistical difference in the degree of proteinuria between the three groups, in the present study. This was different from study by Mak et al, which showed higher degree of proteinuria in Non-diabetic renal disease. Lin et al also reported lower proteinuria in patients with NDRD thus making it a significant factor indicative of renal biopsy.<sup>(17)</sup>

In the present study in which renal biopsy was performed because of abrupt onset of proteinuria had mixed results showing both Diabetic nephropathy & Non diabetic nephropathy.

But the significance of association of Abrupt onset of proteinuria with either Diabetic nephropathy or Nondiabetic renal disease was increased when combined with duration of diabetes.

Patients with abrupt onset of proteinuria & short duration of Diabetes had Isolated Non diabetic renal disease. Those with abrupt onset of proteinuria & long duration of Diabetes had diffuse mesangial sclerosis on renal biopsy.

Therefore duration of diabetes along with onset of proteinuria has high predictive value than degree of proteinuria alone.

Acute deterioration of renal function is more useful marker in detection of Non-Diabetic renal disease. In the present study 63.3% had acute deterioration of renal function & has high predictive value. This was statistically more significant, when compared to Group 3 which are having DN alone, in whom acute deterioration of renal function constitutes 12%.

This was in concordance with Yip-Boon Chong et al study from Malaysia. Taft et al study shown that coexisting Non diabetic renal disease along with DN was associated with more severe renal failure.<sup>(18)</sup>

Mak and Lin et al found that patients with both isolated DN and NDRD did not have any difference in serum creatinine levels.<sup>(19)</sup>

Presence of Active urine sediment is highly predictive of Nondiabetic renal disease in the present study. Mak and Matias et al found a strong correlation between NDRD and microscopic hematuria.<sup>(20)</sup>

On the contrary, Serra et al reported that DN was most commonly found in diabetic patients manifesting microscopic hematuria.<sup>(21)</sup> Other authors also found that the frequency of microscopic hematuria was similar in those with DN and NDRD (Isolated and superimposed).

A Japanese study by Tone showed that microscopic hematuria had lower sensitivity and specificity for the prediction of NDRD compared with the other parameters, suggesting that microscopic hematuria is not a good predictor of NDRD.

In the current study absence of retinopathy has very highly predictive of Non-diabetic renal disease. Positive predictive value of Absence of retinopathy, In the prediction of NDRD is 84.6%, in Isolated Non diabetic renal disease group.

The shorter duration of diabetes and seemingly low frequency of retinopathy in the NDRD group in the present study are correlations that cannot be simply attributed to a selection bias as the patients underwent renal biopsy irrespective of the ophthalmological status and disease duration.

Thus absence of retinopathy in diabetics with renal disease necessitates renal biopsy to rule out potentially treatable nondiabetic causes.

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Castellano et al.<sup>(22)</sup> found that retinopathy had a predictive value of 100% in predicting DN and concluded that its existence makes renal biopsy procedure to rule out NDRD unnecessary.

In contrast, several studies report that diabetic patients without retinopathy may have diabetic glomerulopathy or nephropathy at a rate of 44 to 70%, indicating that the possibility of DN cannot be excluded confidently by the absence of diabetic retinopathy, although the absence of retinopathy strongly favors NDRD.

In the current study prevalence of retinopathy in Nondiabetic renal disease is 69.62%. (Including both isolated non-diabetic renal disease & Non diabetic renal disease super imposing on Diabetic nephropathy). However as even 15% of Isolated Nondiabetic renal disease patients have retinopathy.

Therefore retinopathy existence does not obviate the need for renal biopsy, especially if the clinical presentation is a typical. Retinopathy strongly correlates with presence of DN, however discordance in the occurrence of these two micro vascular complications has been reported and dissimilar genetic predispositions have been suggested.

Retinopathy is considered as an important predictor for adverse renal outcome and disease progression.<sup>(23)</sup> In the present study Patients with NDRD with retinopathy had rapid deterioration of renal failure following various clinical insults, in both isolated NDRD & NDRD superimposing on DN groups. There is no correlation of presence of retinopathy & degree of proteinuria in the Isolated Non diabetic renal disease group. However in the group 3 i.e. isolated diabetic nephropathy, there is statistically significant correlation between retinopathy & degree of proteinuria.

This correlation has been reported by Lee et al, who showed that absence of retinopathy was one of the significant factors that predicts NDRD.<sup>(24)</sup> Tone et al reported that absence of retinopathy showed the highest sensitivity(87%) and specificity (93%) for the prediction of NDRD. Similar findings have been reported by others.

Wong et al showed that absence of retinopathy with hematuria and/or proteinuria  $\geq 2\text{g/day}$  constitutes the most sensitive marker for NDRD and is thus a strong indication for biopsy. However, studies by Mak & Lin et al have demonstrated lack of correlation between NDRD and presence of retinopathy.

In the present study Acute kidney injury from various causes (As mentioned in Figure 2 & 3 & 5) constitutes major group of Nondiabetic renal disease. AKI comprises 27% in Non-diabetic renal disease group, & 35.85% in Non-diabetic renal disease superimposing on Diabetic nephropathy.

Glomerulonephritis being the second most common cause of Non-diabetic renal disease, constitutes 26.7%. Post infectious glomerulonephritis is most common primary glomerulonephritis followed by Membranoproliferative glomerulonephritis, Membranous nephropathy, HIVAN.

Other causes of Non-diabetic renal disease include obstructive causes (As mentioned in table. 1), Pyelonephritis, Chronic interstitial nephritis, Ischemic nephropathy.

In a study from Taiwan, AIN was the most prevalent NDRD (46.5%), followed by membranous nephropathy and IgA nephropathy.<sup>(25)</sup>

In another study from Pakistan also showed prevalence of AKI as cause of Nondiabetic renal disease, was 40%.

An Indian study also found AIN due to AKI be the most common NDRD, found in 18.1% of the patients with mixed renal disease (NDRD superimposed on DN), while membranous nephropathy (19.2%) was the most frequent diagnosis in patients with isolated NDRD.<sup>(26)</sup>

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Membranous glomerulonephritis was the commonest glomerular NDRD and in accordance with Prakash et al., & chronic tubulointerstitial nephritis was the commonest NDRD detected in the studied biopsies. Various studies in different populations have demonstrated crescentic glomerulonephritis, IgA nephropathy, acute interstitial nephritis, focal segmental glomerulosclerosis,<sup>(27)</sup> membranous glomerulonephritis, and proliferative glomerulonephritis as the most frequent causes of NDRD.

It is important to keep in mind that interstitial inflammatory cell infiltration is often prominent in advanced diabetic glomerulosclerosis. Thus, it is hard to know whether this is secondary to DN or superimposed with AIN, particularly when there is no prominent eosinophil interstitial infiltration. These tubulointerstitial changes in DN are said to be related to the renal microvascular alterations characteristic of long-term diabetes, and it is now generally held that they are due to chronic ischemia.

Information regarding the mechanisms implicated in the development of NDRD in diabetes remains suboptimal and speculative.<sup>(28)</sup>

Current knowledge suggests that hyperglycemia, advanced glycation end products, immune complexes, and other biochemical alterations in the diabetic milieu activate renal cells via stress-activated protein kinase signaling culminating in the upregulation of cell adhesion molecules and release of proinflammatory cytokines with consequent glomerular leukocyte recruitment and activation.<sup>(29)</sup> A number of modified proteins, like oxidized low density lipoproteins that develop in diabetes are potentially immunogenic resulting in immune complex penetration and inflammation. Circulating immune complexes and glomerular IgG deposits especially the proinflammatory subtypes IgG1 and IgG3 iso types are recognized in diabetic experimental models. Enhanced exposure of antigenic cellular components and pre-existing glomerular alterations might favor an immune reaction in the sub epithelial space. However, some authors found no difference in the prevalence of NDRD between patients with and without diabetes and suggest that the coexistence of a different glomerulonephritis in the diabetic kidney may be merely coincidental.<sup>(30)</sup>

**CONCLUSION:** The study demonstrates that renal complications in type 2 diabetics may be due to heterogeneous Nondiabetic renal diseases.

In the present study the overall prevalence of Non-diabetic renal disease is 39%. Isolated Non diabetic renal disease constitutes 13% & prevalence of Non-diabetic renal disease superimposing on Diabetic nephropathy is 23%.

As males outnumber the females, in 2:1 ratio, in study population, there is no statistically significant gender difference in the occurrence of Non-diabetic renal disease.

The major predictor of Non-diabetic renal disease is short duration of diabetes, which is having very high positive predictive value.

Other predictors are Absence of hypertension, presence of Acute deterioration of renal function & Active urine sediment and absence of retinopathy.

The degree of proteinuria has less significance in the prediction of non-diabetic renal disease. But the degree of proteinuria in combination with short duration of diabetes has highly predictive of non-diabetic renal disease.

Spectrum of Non-diabetic renal diseases acute kidney injury, Obstructive causes, Pyelonephritis, glomerulonephritis, Malignancy, chronic interstitial nephritis, Renovascular disease.



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Spectrum of Non-diabetic glomerular diseases include, Post infectious glomerulonephritis, Membrano proliferative glomerulonephritis, Membranous nephropathy.

In view of clinically significant prevalence of Non-diabetic renal disease, the emphasis is, Not to attribute every case of Type 2 DM with renal abnormalities as Diabetic nephropathy and there is every need to rule out underlying Non diabetic renal disease.

As Non-diabetic renal diseases have different prognostic & therapeutic implications, diagnosis & treatment of underlying Non diabetic renal disease will improve renal survival.

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