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Non-Diabetic Kidney Disease in Type 2 Diabetic Patients: Assiut University Experience

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ABSTRACT

Background: Diabetic kidney disease (DKD) is regarded as the leading reason for inducing end-stage renal disease (ESRD), representing (34.7%) of hemodialysis patients in Egypt.

Also, the prevalence of non diabetic kidney disease (NDKD) is high in type 2 diabetes mellitus (T2DM). Consequently, renal biopsy is considered the gold standard for determining NDKD in T2DM.

This study investigated the potential reasons for triggering kidney disease in T2DM cases with atypical presentations of DKD. **Patients and Methods:** The present study was conducted in the Department of Internal Medicine, Nephrology Unit, Assiut University Hospital, Egypt, during the interval from January 2016 to May 2020. We recruited 60 patients with T2DM and investigated for the atypical presentation of DKD in this study.

Subjects underwent laboratory investigations, examination, detailed history, special investigations when indicated, fundus examination, and renal biopsy. **Results:** The current study showed that the NDKD either alone or coexisting with DKD, representing 81.7% of the studied patients. Subjects were categorized into three groups according to the findings of biopsy DKD, NDKD, and coexisting DKD with NDKD; the frequencies were 11 (18.30 %), 32 (53.30 %), and 17 (28.30 %), respectively. Amyloidosis is the most common renal disease, followed by acute tubular injury.

Conclusion: This study demonstrated that NDKD is prevalent in T2DM, and renal biopsy is considered the gold standard for diagnosing renal pathology in diabetic patients.

Keywords: Diabetic kidney disease, Renal biopsy, Non Diabetic Kidney disease.

Abbreviations: Diabetic kidney disease **(DKD),** end-stage renal disease **(ESRD),** non diabetic kidney disease **(NDKD),** type 2 diabetes mellitus **(T2DM),** glomerular filtration rate **(GFR),** the renin-angiotensin-aldosterone system **(RAAS),** focal segmental glomerulosclerosis **(FSGS),** estimated glomerular filtration rate **(eGFR),** modified diet in renal disease **(MDRD),** antinuclear antibody test **(ANA),** anti-double stranded deoxyribonucleic acid **(AntiDs-DNA),** antineutrophil cytoplasmic antibodies test **(ANCA),** hepatitis B surface antigen **(HBsAg),** hemoglobin A1C **(HbA1C),** blood pressure **(BP),** masson's trichrome stains **(MT),** immunoperoxidase **(IP),** leucocyte chemotactic factor type 2 **(LECT2),** amyloid light-chain **(AL),** amyloid A **(AA),** the global sclerosis score **(GS),** advanced glycation end products **(AGEs),** renal reactive amyloidosis **(RAAA),** acute kidney injury **(AKI),** diabetes mellitus **(DM),** diastolic blood pressure **(DBP),** systolic blood pressure **(SBP),** periodic acid–Schiff **(PAS),** eosin and hematoxylin **(H&E),** standard deviation **(SD),** hypertension **(HTN),** mean arterial pressure **(MAP),** Immunohistochemistry **(IHC).**

INTRODUCTION

DKD is regarded as the primary reason for inducing ESRD, representing (34.7%) of hemodialysis cases in Egypt [1]. The guidelines of KDOQI in 2007 defined DKD involvement as the existence of microalbuminuria or macroalbuminuria, along with diabetic retinopathy in both kinds of diabetes mellitus (DM) [2]. On the contrary, the properties that indicate the existence of NDKD were summarized as: a rapid decline in renal function, non-existence of diabetic retinopathy, rapid elevation in nephrotic syndrome or proteinuria, active urinary sediment, refractory hypertension, symptoms or signs of systemic disease, as well as decreased glomerular filtration rate (GFR) for more than 30% within 2–3 months following the blockade of the renin-angiotensin-aldosterone system (RAAS) [2].

In contrast, NDKD pervasiveness is increased in T2DM, and thus it is crucial to identify NDKD in T2DM [3]. Renal biopsy is considered the standard gold method to diagnose kidney disease in T2DM [4].

Several groups found that the most frequent NDKD diagnoses in diabetes patients' renal biopsies are focal segmental glomerulosclerosis (FSGS), membranous nephropathy, and IgA nephropathy [5].

In our study, we aimed at determining the potential reasons for inducing kidney disease in T2DM cases.

PATIENTS AND METHODS

Patients:

The current prospective cross-sectional study was conducted in the Department of Internal Medicine, Nephrology Unit, Assiut University Hospital, Egypt, during the interval from January 2016 to May 2020. We recruited 60 patients with T2DM and investigated for the atypical presentation of DKD.

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Methods:

All subjects underwent examination, history taking, fundus examination, laboratory investigations, as well as a renal biopsy.

A) Laboratory tests:

All subjects underwent the following tests: blood urea nitrogen, serum creatinine, estimated glomerular filtration rate (eGFR) by Modified Diet in Renal Disease (MDRD) equation, urine analysis, 24 hours proteins in urine, Hemoglobin A1C (HbA1c), serum albumin, complete blood picture, prothrombin time and concentration, and special investigations when indicated (Antinuclear antibody test (ANA), anti-double stranded deoxyribonucleic acid (AntiDs-DNA), antineutrophil cytoplasmic antibodies test (ANCA), serum protein electrophoresis, serum calcium, serum phosphorous, alkaline phosphatase, bone marrow biopsy, lymph node biopsy, viral markers: anti-hepatitis C virus and hepatitis B surface antigen (HBsAg)). Estimated glomerular filtration rate (eGFR in mL/min/1.73 m2) was evaluated based on the level of serum creatinine utilizing the study equation of MDRD [6]. Proteinuria was described as >0.15 g/24 h. Nephrotic syndrome was described as proteinuria (>3 g/24 h) along with hyperlipidemia, edema, as well as hypoalbuminemia (<30 g/L). Microscopic hematuria was described as >4 red blood cells per high-power field based on examination of urine. Hypertension was recognized as a diastolic blood pressure (DBP) > 90 mmHg or a systolic blood pressure (SBP) > 140 mmHg.

B) Renal biopsy:

Specimens from renal biopsy were obtained utilizing immunoperoxidase and light microscopy. It is noteworthy that electron microscopy was not routinely carried out. Light microscopy was used to examine all specimens using Masson's trichrome stains (MT), periodic acid–Schiff (PAS), eosin and hematoxylin (H&E), Congo red. Immunoperoxidase (IP) studies were carried out utilizing antihuman IgG, IgM, IgA, C3, kappa, as well as lambda light chains. In addition, the IP studies were done using Leica automated system. The same pathologist made all of the pathology diagnoses.

The most pervasive biopsy indication in our study was the presence of another systemic disease (28.3 %), followed by sub-nephrotic proteinuria (23.3 %), unexplained rapidly raised renal chemistry (21.7%), rapidly developed Nephrotic syndrome (18.3%), Nephritic syndrome (8.3 %), as depicted in **(Figure 2).**

Ethical approval and participation consent:

The Faculty of Medicine 's Human Ethics Review Committee in Assiut University approved the current study on 4/10/2016, with reference approval number 17200565. All subjects provided written informed consent before the renal biopsy. The clinical trial registration number is NCT05021705. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis of data

Analysis of data was performed utilizing the 20th version of IBM SPSS Statistics (SPSS Inc., Chicago, IL, USA). Furthermore, categorical data were expressed as percentages as well as frequencies, whereas Chi-square tests were utilized to compare between groups. With regard to continuous data, they were expressed as mean ± standard deviation (SD) and tested for normality based on the Shapiro-Wilkes test. In contrast, continuous data were normally distributed, the one-way ANOVA was utilized to compare groups, and the post hoc test was performed. In case data were non-normally distributed, the Kruskall Wallis test was utilized. Also, the Mann-Whitney test was utilized to compare continuous variables in case of comparison between two groups. The level of significance was set at P-value <0.05.

RESULTS

Sixty T2DM patients were recruited in the study, with a median age at the time of biopsy of 51.8 ± 9.7 years, males representing 50% of the study group. The demographic, as well as laboratory data, are displayed in **(Table 1);** it was grouped based on the presence of NDKD or not into three groups: DKD alone, NDKD alone, and DKD with superimposed NDKD. Fundus examination was done for 58 of the studied patients; the remaining two patients had cataracts, 13 patients had advanced stage diabetic retinopathy, as depicted in **(Table 2)**. NDKD was found in (53.3%) of the studied patients (28.3%) who had DKD with superimposed NDKD while only (18.3%) with DKD alone. Amyloidosis (16.3 %), Acute tubular injury (14.3 %), FSGS (12.2 %), Membranous (10.2 %), Minimal Change disease (10.2 %), and small-vessel vasculitis, infection-related glomerulonephritis, light chain case disease (8.2 %), Cryoglobulinemic vasculitis (4.1 %) were all found in both groups of NDKD, along with acute tubulointerstitial nephritis (2 %). Cases of Renal Amyloidosis were stained; amyloid light-chain (AL) and amyloid A (AA) amyloidosis were found in (6.1%), (6.1%) respectively, and leucocyte chemotactic factor type 2 (LECT2) Amyloidosis was found in (4.1%), as depicted in **(Table 3)**. The global sclerosis score (GS) was substantially elevated in the DKD patients. A substantial difference was detected between the three groups in relation to tubular atrophy and interstitial fibrosis. Also, arteriolar hyalinosis demonstrated a substantial difference between the three cohorts; nearly all patients in both groups of DKD had arteriolar hyalinosis **(Table 4)**.

Table (1): Demographic and laboratory data of 60 studied patients according to pathological diagnoses of kidney disease:

		pathological Diagnoses			Total *(n=60)*	P-value
		DKD *(n=11)*	**NDKD *(n=32)***	**DKD & NDKD *(n=17)***		
Age		53.7 ± 9.3	49.2±10.4 [a]	55.6 ± 7.0 [a]	51.8 ± 9.7	0.068^
Sex	Male	9 (81.8%)	12 (37.5%)	9 (52.9%)	30 (50%)	0.039 [s]
	Female	2 (18.2%)	20 (62.5%)	8 (47.1%)	30 (50%)	
Duration of DM (years)		8.5 ± 3.8	5.7 ± 5.9	8.4 ± 5.5	6.9 ± 5.6	0.056*
Presence of hypertension (HTN)		6 (54.5%)	17 (53.1%)	14 (82.4%)	37 (61.7%)	0.116
Duration of HTN (years)		2.5 ± 3.4	3.0 ± 4.9	2.9 ± 3.6	2.9 ± 4.3	0.500*
Blood Pressure:						
Systolic BP (SBP)		129.1 ± 21.2	124.2 ± 13.0	121.8 ± 8.8	124.4 ± 13.8	0.398*
Diastolic BP (DBP)		75.5 ± 11.3	77.8 ± 10.0	75.9 ± 7.1	76.8 ± 9.5	0.696*
Mean arterial pressure (MAP)		93.3 ± 14.4	93.3 ± 10.5	91.2 ± 6.8	92.7 ± 10.3	0.779*
Renal function tests						
Serum creatinine (mg/dl)		5.0 ± 1.6	3.9 ± 0.03	5.5 ± 1.1	4.9 ± 0.2	0.624*
Blood urea nitrogen (mg/dl)		71.8 ± 6.5	56.0 ± 4.8	44.0 ± 5.5	55.5 ± 4.1	0.342*
eGFR (ml/min)		24.5 ± 3.8	34.7 ± 8.9	45.7 ± 6.4	38.7 ± 5.9	0.770*
Urine analysis						
Microscopic Hematuria		7 (63.6%)	21 (65.6%)	9 (52.9%)	37 (61.7%)	0.678
Red cell Urinary casts		3 (27.3%)	3 (9.4%)	0	6 (10 %)	0.062
Pus cells		4 (36.4%)	17 (53.1%)	7 (41.2%)	28 (46.7%)	0.546
Crystals		1 (9.1%)	7 (21.9%)	0	8(13.3%)	0.090
Bacteriuria		4 (36.4%)	9 (28.1%)	1 (5.9%)	14 (23.3%)	0.114
Proteinuria (g/day)		2.5 ± 0.7	2.7 ± 0.9	4.9 ± 0.6	3.3 ± 0.8	0.688*
HbA1C (%)		8.6 ± 1.1	7.4 ± 0.88	7.8 ± 0.78	7.8 ± 0.98	0.003 [s*]
Serum Albumin (g/l)		28.9 ± 6.0	27.4 ± 5.0	27.3 ± 5.6	27.7 ± 4.6	0.567*
CBC						
WBCs (10^3)		7.5 ± 1.6	9.9 ± 2.5	7.6 ± 2.6	8.8 ± 1.5	0.117*
Hemoglobin (g/dl)		10.2 ± 1.8	10.7 ± 2.2	10.6 ± 1.4	10.6 ± 1.9	0.761*
Platelets (10^3/ul)		295.9±63.3	265.9±19.8	225.4±18.4	259.9±11.1	0.233*
Coagulation profile						
PT (sec)		13.1 ± 1.1	13.0 ± 1.3	12.6 ± 1.0	12.9 ± 1.2	0.382*
PC (%)		86.4 ± 1.5	89.9 ± 2.4	90.9 ± 14.2	89.5 ± 12.6	0.644*

Data are presented as mean ± SD or number & percentage n(%).
One-way ANOVA, Kruskal-Wallis as well as Chi-square tests were utilized.
^ P-value was calculated using One-way ANOVA to compare the age in the three groups. No statistically significant difference was detected. [a] Statistically significant difference in the age between NDKD and Coexisting DKD & NDKD groups. P-value *was calculated using One-way ANOVA test. *P-value for all other parameters were calculated using Kruskal-Wallis test to compare the three groups except for sex, presence of HTN, microscopic hematuria, red cell urinary casts, pus cells, crystals and bacteriuria were calculated using Chi-square test. [S] Significant p-value for sex and HbA1C when compared the three groups.*
Mean arterial pressure (MAP) =SBP+2(DBP)/3.

Table (2): Diabetic Retinopathy (advanced stage of diabetic retinopathy) in 58 studied patients:

	Diabetic Retinopathy		P-value
	Yes (n=13)	**No (n= 45)**	
Group			
DKD	4 (36.4%)	7 (63.6%)	0.004 [s*]
NDKD [a]	1 (3.1%)	29 (90.6%)	
DKD + NDKD	8 (47.1%)	9 (52.9%)	
Duration of DM	9.6 ± 5.3	6.4 ± 5.5	0.041 [s^]

Data are presented as mean ± SD or number & percentage n(%).
*Chi-square and Mann-Whitney tests were utilized.*P-value were calculated using Chi-square to test the association between the three groups and presence of retinopathy. Statistically significant difference was found.*
^P-value was calculated using Mann-Whitney to test the association between the duration of DM and presence of retinopathy and it showed statistically significant result. [S] Significant p-value.
[a] Two cases in the NDKD group have cataracts.

Table (3): pathological diagnoses of NDKDs in the studied groups:

Renal histology	NDKD (n=32)	Coexisting NDKD & DKD (n= 17)	Total (n=49)
Renal amyloidosis	6 (18.8%)	2 (11.8%)	8 (16.3%)
LECT2 amyloidosis	1 (3.1%)	1 (5.9%)	2 (4.1%)
AA amyloidosis	2 (6.3%)	1 (5.9%)	3 (6.1%)
AL amyloidosis	3 (9.4%)	0	3 (6.1%)
Acute tubular injury	3 (9.4%)	4 (23.5%)	7 (14.3%)
FSGS	6 (18.8%)	0	6 (12.2%)
Membranous glomerulonephritis	2 (6.2%)	3 (17.6%)	5 (10.2%)
Minimal change disease	5 (15.6%)	0	5 (10.2%)
Small vessel vasculitis *(Granulomatosis with polyangitis)*	4 (12.5%)	0	4 (8.2%)
Infection Related Glomerulonephritis	1 (3.1%)	3 (17.6%)	4 (8.2%)
Light Chain Cast Nephropathy	1 (3.1%)	3 (17.6%)	4 (8.2%)
Cryoglobulinemic vasculitis	1 (3.1%)	1 (5.9%)	2 (4.1%)
Acute infectious tubulointerstitial nephritis	1 (3.1%)	0	1 (2%)
Lupus glomerulonephritis (class v)	0	1 (5.9%)	1 (2%)
Mesangiocapillary glomerulonephritis	1 (3.1%)	0	1 (2%)
Thrombotic microangiopathy	1 (3.1%)	0	1 (2%)

Data are presented as numbers & percentages n (%).

Table (4): Renal biopsy data of 60 studied patients according to histological diagnoses of kidney disease:

		Histological Diagnoses			Total *(n=60)*	P-value
		DKD *(n=11)*	**NDKD *(n=32)***	**DKD & NDKD *(n=17)***		
***Global sclerosis* (GS) score (%)**		56.1±28.6 ^{b,c}	18.1±19.1 ^{a,c}	35.6±30.1 ^{a,b}	30.1 ± 28.1	0.001 ^{s}*
Interstitial fibrosis & Tubular atrophy	**No**	0	18 (46.9%)	2 (11.8%)	17 (28.3%)	0. 001 ^{s}^
	Mild < 25%	1 (9.1%)	9 (28.1%)	3 (17.6%)	13 (21.7%)	
	Moderate > 25% - <50%	4 (36.4%)	7 (21.9%)	5 (29.4%)	16 (26.7%)	
	Marked >50%	6 (54.5%)	1 (3.2%)	7 (41.2%)	14 (23.3%)	
Arteriosclerosis	**No**	0	5 (15.6%)	1 (5.9%)	6 (10%)	0.218^
	Unremarkable	2 (18.2%)	10 (31.2%)	1 (5.9%)	13 (21.7%)	
	Mild < 25%	1 (9.1%)	4 (12.5%)	4 (23.5%)	9 (15%)	
	Moderate > 25% - <50%	7 (63.9%)	13 (40.6%)	10 (58.8%)	30 (50%)	
	Marked >50%	1 (9.1%)	0	1 (5.9%)	2 (3.3%)	
Arteriolar hyalinosis	**No**	0	7 (21.9%)	1 (5.9%)	8 (13.3%)	<0.001^{s}^
	Mild < 25%	1 (9.1%)	8 (25%)	3 (17.6%)	12 (20%)	
	Moderate > 25% - <50%	6 (54.5%)	5 (15.6%)	11 (64.7%)	22 (36.7%)	
	Marked >50%	4 (36.4%)	1 (3.1%)	1 (5.9%)	6 (10%)	
***Immunohistochemistry* (IHC)**	**Yes**	0	5 (15.6%)	3 (17.6%)	8 (13.3%)	0.348^
	No	11 (100%)	27 (84.4%)	14 (82.4%)	52 (86.7%)	

Data presented as mean ± SD or number & percentage n(%).
*Kruskal-Wallis and Chi-square tests were used. ^P-value for all parameters except GS were calculated using Chi-square to test the association between the three groups and presence of interstitial fibrosis &tubular atrophy, arteriolar hyalinosis, arteriosclerosis and IHC. Statistically significant differences were detected for interstitial fibrosis &tubular atrophy and arteriolar hyalinosis when compared the three groups. *P-value for GS was calculated using Kruskal-Wallis to test the association between the three groups and presence of GS. Also, compared every two groups with each other showed statistically significant differences.*
^{a,b,c} post hoc analysis for GS compared every two groups with each other showed significant results.^{s} Significant p-value.

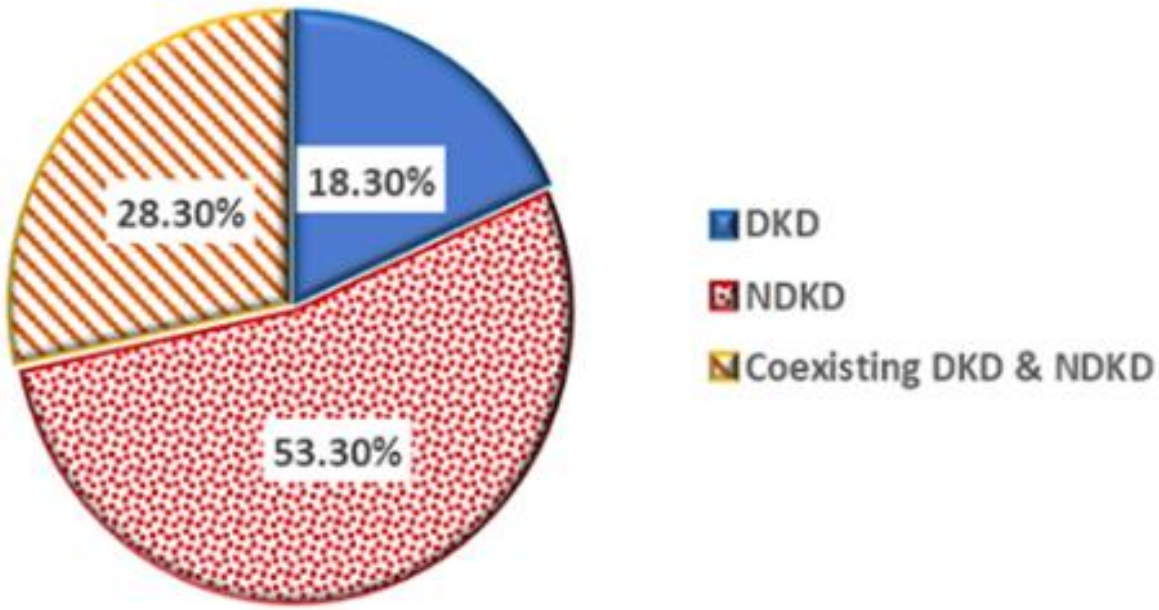

Fig. (1): The Studied groups according to renal biopsy.

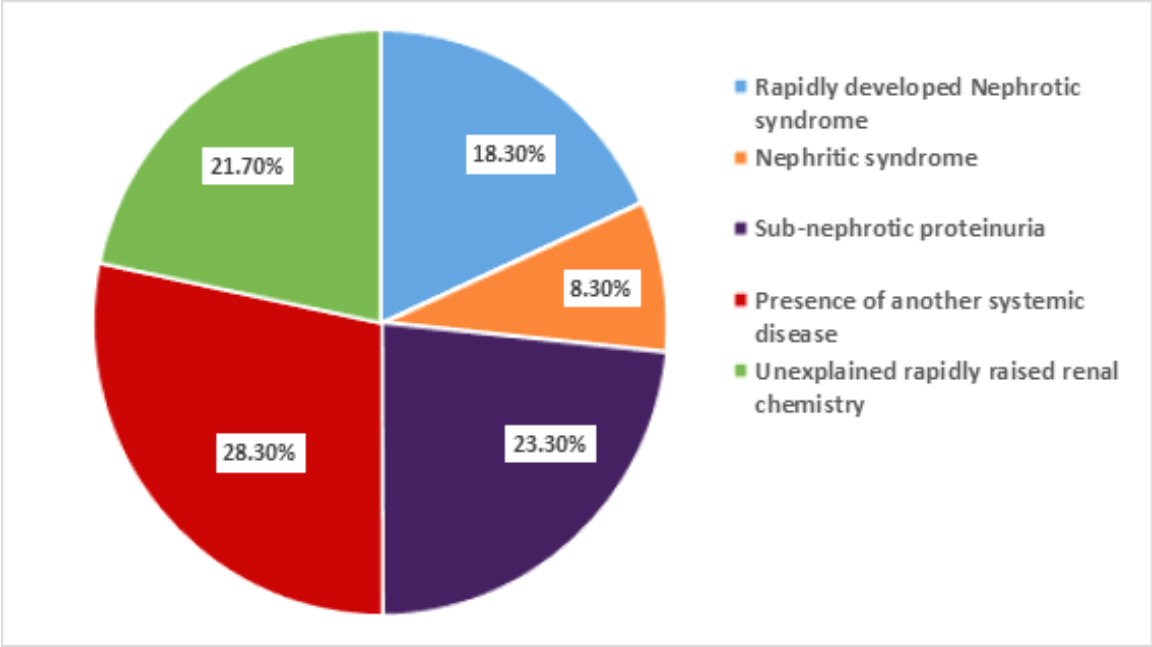

Fig. (2): Indications for renal biopsy in the studied group.

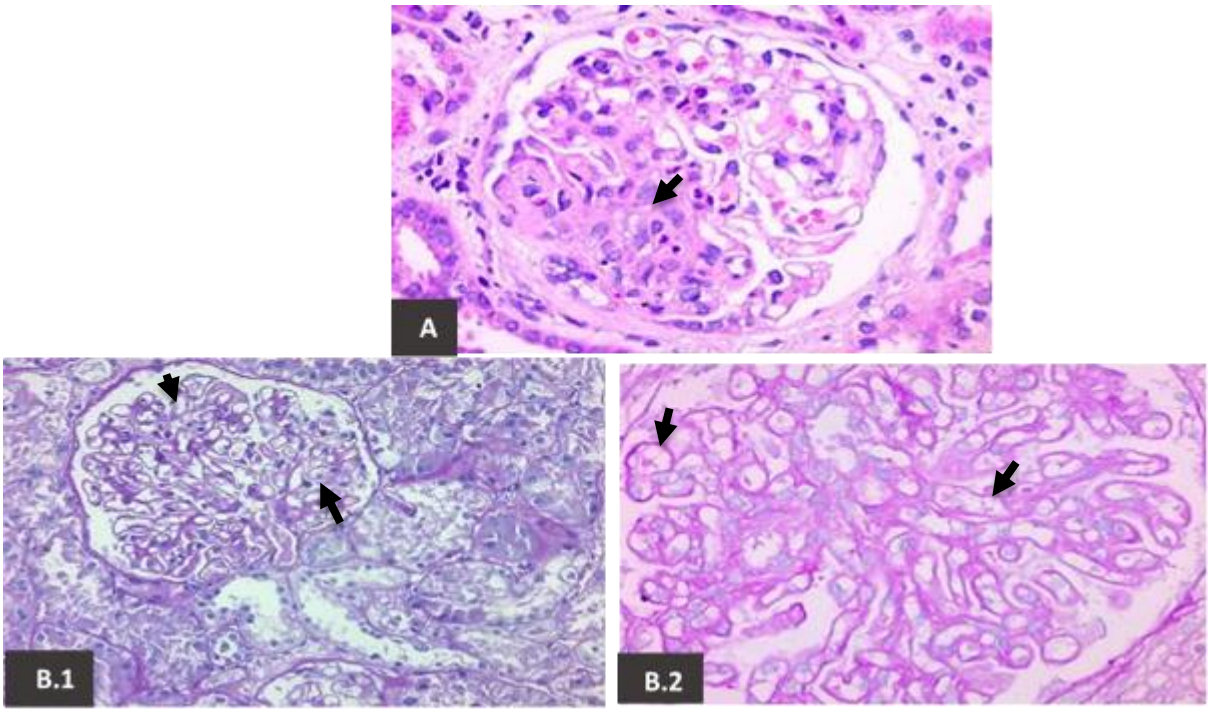

Fig. (3): A) Illustrate a case of FSGS under light microscopy using H&E stain showed segmental tuft sclerosis with histocytic proliferation (×400); **B)** Illustrate a case of membranous glomerulonephritis under light microscopy using H&E stain (×400) in **(B.1)** and PAS stain (×400) in **(B.2)** showed diffuse capillary basement membrane thickening.

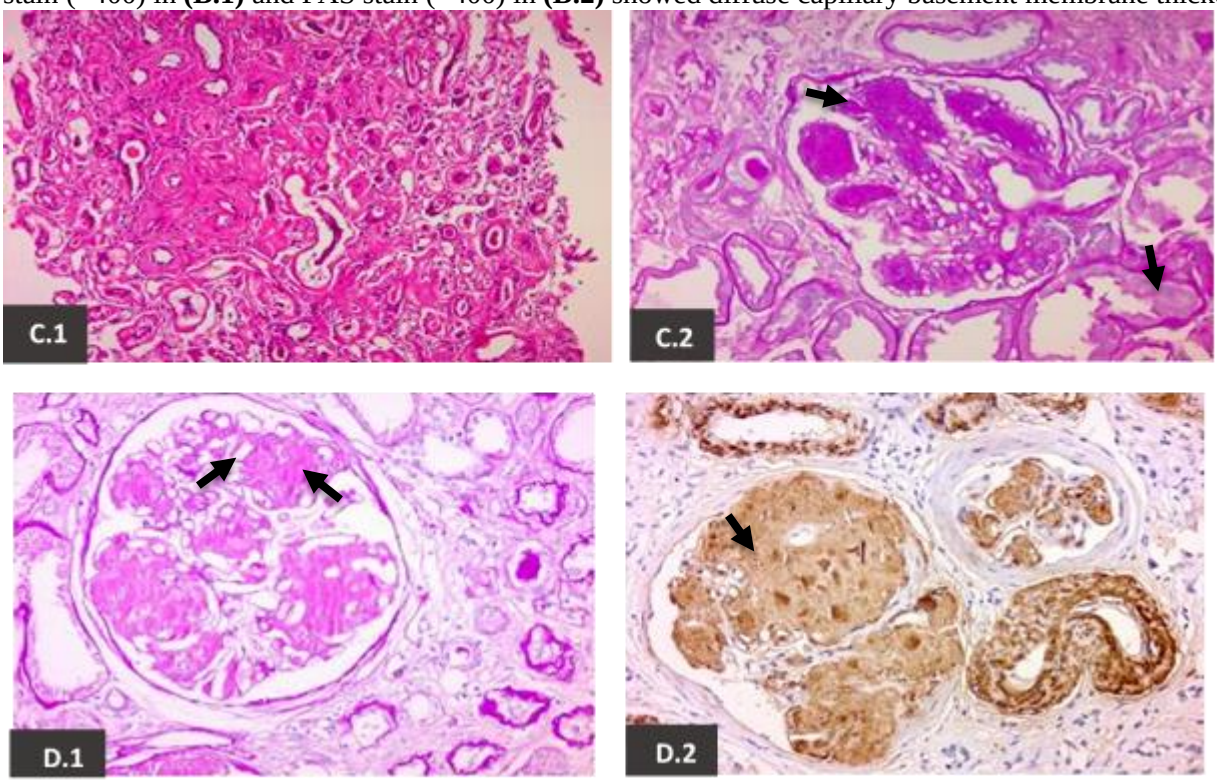

Fig. (4): C) Illustrate a case of advanced diabetic nodular glomerulosclerosis (class IV DKD) and LECT2 Amyloidosis under light microscopy using H&E stain (×100) in **(C.1),** PAS stain (×200) in **(C.2),** The glomerulus showed diffuse mild capillary basement membrane thickening with numerous hypocellular mesangial nodules.Tubules showed diffuse marked atrophy with thickened and wrinkled basement membranes. Interstitium showed diffuse extensive pink homogenous deposits with weak PAS reactivity; **D)** Illustrate a case of AA amyloidosis **(D.1)** under light microscopy utilizing PAS stain showed diffuse capillary basement membrane thickening and marked mesangial matrix expansion by homogenous pink deposits with weak PAS reactivity (×200) and **(D.2)** AA amyloid positive by immunoperoxidase staining (×200).

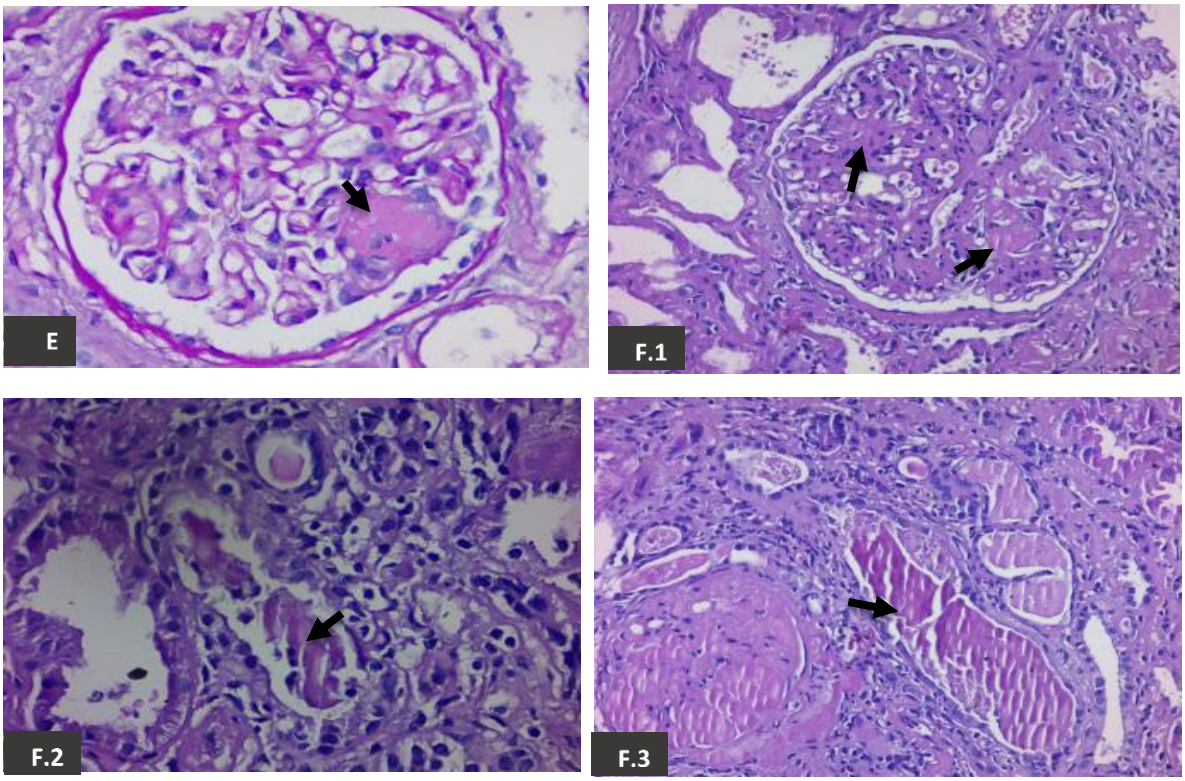

Fig. (5): E) Illustrate a case of Granulomatosis with Polyangiitis Consistent with Pauci-immune Small Vessel Vasculitis (Possibly Wegener's Granulomatosis) under light microscopy using H&E stain showed glomerulus with segmental fibrinoid necrosis surrounded by granulomatous reaction formed of lymphocytes, plasma cells, numerous neutrophils and eosinophils (×400); **F)** Illustrate a case of advanced diabetic nodular glomerulosclerosis (class IV DKD) and Light chain cast nephropathy under light microscopy using H&E stain **(F.1(×200), F.2(×400), F.3(×200))**. The glomerulus showed diffuse mild capillary basement membrane thickening, moderate to marked mesangial matrix increase with formation of hypocellular nodules **(F.1)**. Tubules showed diffuse marked atrophy with focal dilatation and hyaline fractured casts showed a mild cellular reaction, interstitium showed diffuse marked fibrosis **(F.2, F.3).**

DISCUSSION

In our study, we had renal biopsy from 60 patients with type 2 DM with atypical presentation of DKD. NDKD was found in 49 patients (81.7%); 17 had associated DKD. The most common renal pathology of NDKD in our study was Amyloidosis (16.3%) followed by acute tubular injury (14.3%), focal segmental glomerulosclerosis (12.2%), membranous glomerulonephritis, minimal change disease, small vessel vasculitis, infection-related glomerulonephritis, light chain, cryoglobulinemia, acute infectious tubulointerstitial nephritis, lupus nephritis, mesangiocapillary nephritis, and thrombotic microangiopathy.

Hyperglycemia was correlated with increased secretion of advanced glycation end products (AGEs) and markers of inflammation [7], which contributes to the progression of diabetic vasculopathy and nephropathy [8]. Furthermore, AGEs were probably involved in amyloidogenesis or amyloid deposition-associated complications [9]. Since T2DM is an inflammatory condition, and renal reactive amyloidosis (RAAA) is a disease induced by chronic inflammation, so higher prevalence of RAAA may occur in T2DM [10].

Diabetes is regarded as a significant predictor of acute kidney injury (AKI)[11]. Diabetic patients are more likely to develop normotensive ischemic AKI because of decreased renal autoregulation and atherosclerotic vasculature [12]. Furthermore, immunocompromised diabetic patients are prone to have infections. Diabetics are more likely to develop nephrotoxic acute tubular necrosis and acute interstitial nephritis as a result of herbals as well as nonsteroidal anti-inflammatory medications. Sharma et al. detected an elevated prevalence of acute tubular necrosis as a superimposed illness on DKD in a significant number of type 2 diabetic patients [4].

In T2DM, glomerular hyperfiltration occurs due to systemic hypertension and obesity [13] . Independent of diabetic status, obesity induces a secondary type of FSGS [14]. Activation of RAAS, podocyte injury, sodium retention, sympathetic nervous system activation, elevated intra-glomerular capillary pressure, resulting in hyperfiltration, and adaptive (i.e., secondary) FSGS lesions are clinical manifestations and pathogenic features

found with obesity-related glomerulopathy and DKD [15]. Primary FSGS is a sporadic disease (<1%) in diabetic patients [4].

The pervasiveness of NDKD in T2DM cases mutates significantly based on the studied populations from 12 to 75.5% [16]. Two large studies revealed that most subjects (63–72.5%) suffered NDKD lesions either isolated or superimposed on DKD based on renal biopsy retrospective examinations of diagnosed diabetic patients. In addition, it was found that FSGS was the most prevalent in the isolated NDKD group, then hypertensive nephrosclerosis, IgA nephropathy, acute tubular necrosis, as well as membranous nephropathy [4].

Racial predisposition and hereditary to multiple glomerulopathies, various indication criteria of renal biopsy in T2DM [17], in addition to geographic and ethnic factors, may also contribute to variability [18].

In the current study, a shorter DM duration was detected in the NDKD group only, which is an expected finding as DKD develops over a more extended interval; this is compatible with **Soni *et al*. [19], Chang *et al*. [20], and Wilfred et al. [5]**.

Also, HbA1C was statistically significantly higher in the DKD group, which may explain the development of DKD because of uncontrolled diabetes. This result aligns with **Byun *et al.* [3], Liu *et al.* [17], and Erdogmus *et al.* [21].**

Hyperglycemic exposure over an extended interval is the most crucial risk factor for developing DKD, leading to unique structural abnormalities in DKD, which developed only with increased glucose levels[22]. Many changes within the kidney induced by hyperglycemia lead to functional and structural abnormalities such as overexpression of humoral factors, cytokines, and growth factors. Complex alterations in renal cells, such as smooth muscle cells, glomerular endothelial cells, mesangial cells, podocytes, tubular cells, as well as collecting duct cells, are activated by chronic hyperglycemia for a longer duration[22].

No substantial difference has been detected between the three groups regarding the presence of hypertension, which agrees with previous studies [23]. This finding can be explained that renal diseases, whatever etiology, cause hypertension as there is a vicious cycle between blood pressure (BP) and the kidney. Renal impairment and renal disease increase BP, whereas elevated BP leads to a progressive decline in the diseased kidney function. The reasons for BP rise in the renal illness may be explained by salt retention, impaired endothelial cell-mediated vasodilatation, the improper activity of RAAS, as well as sympathetic nervous system [24].

The coexisting DKD, and NDKD showed higher levels of proteinuria despite being not significantly different from the other two groups. This finding is in concordance with the findings of **Castellano *et al*. [25], Li *et al*. [26], and Wilfred *et al.* [5].**

In our study, advanced diabetic retinopathy was detected in only one patient with isolated NDKD, while all other positive cases were diabetic (either isolated DKD or coexisting DKD with NDKD). Diabetic retinopathy was found in only 92.3% of cases with DKD (either isolated DKD or coexisting DKD with NDKD). This finding agrees with most of the studies [21], as all these studies showed that retinopathy was significantly less in patients with NDKD. On the contrary, Li *et al*. [26], and Lin *et al*. [27] revealed no association between NDKD and the absence of retinopathy. In our study, 63.6% of isolated DKD patients had no diabetic retinopathy, 77.6% of NDKD (either isolated NDKD or coexisting DKD with NDKD) had no diabetic retinopathy, which denotes the lack of diabetic retinopathy predicts the existence of NDKD but does not rule out DKD. This finding agrees with **Prakash *et al.* [28].**

Surprisingly, 27.3 % of patients with DKD alone showed red cell casts, and 63.6% had microscopic hematuria. A study done by Okada et al. reported a correlation between the existence of microscopic hematuria in type 2 diabetic patients and arteriolar hyalinosis in their renal biopsies [29]. Also, **Matsumura *et al.*** found advanced diffuse lesions, crescent formation, nodular lesions, capsular adhesion, microaneurysms, and interstitial lesions in renal biopsy type 2 diabetic cases suffering from microscopic hematuria compared to patients without microscopic hematuria [30].

The GS score was substantially elevated in DKD than NDKD as well as coexisting DKD & NDKD, which returns to longer-standing diabetes in this group. Unexpectedly, 53.13% of the NDKD alone group had varying degrees of tubular atrophy and interstitial fibrosis, which may be due to the pathology of the disease. 43.7% of NDKD showed arteriolar hyalinosis, implying hypertension's effect on renal vessels.

Our study limitations were mainly: the small number of the study group, which is because renal biopsy in diabetic patients is still not widely done to diagnose renal disease. In addition, the selection bias where the renal biopsy was done for those who presented with atypical criteria for DKD and lastly lack of long term follow up for the cases to conclude the renal outcomes of each group.

CONCLUSION

This study showed that NDKD is prevalent in T2DM and that renal biopsy is the gold standard for diagnosing renal pathology in diabetic patients.

CONFLICT OF INTEREST: There is no conflict of interest**.**

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