



Biopsy Proven Non-diabetic Kidney Disease among Diabetic Patients; Report from a Single Center Registry

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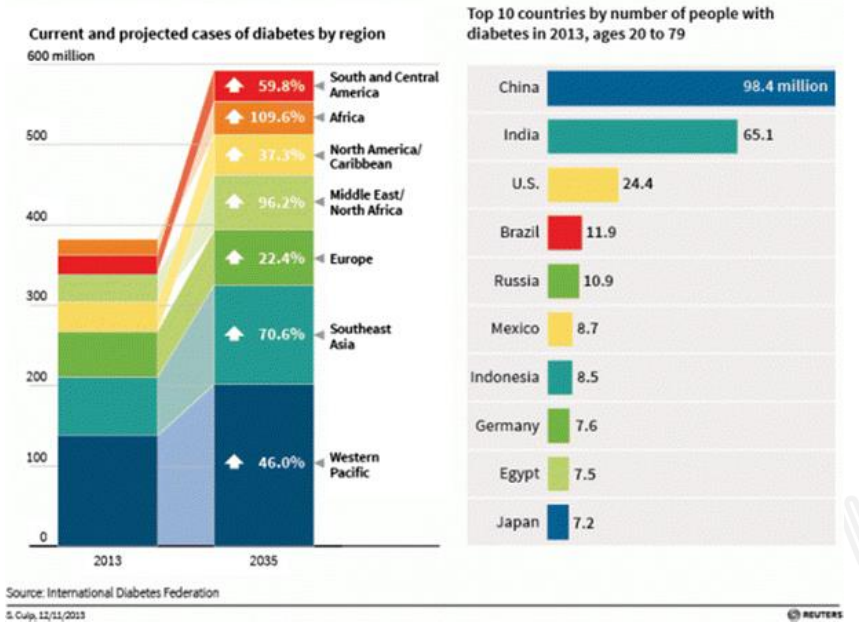
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Introduction

- The prevalence of **diabetes mellitus** (DM) is increasing worldwide, is expected to affect more than 350 million people by the year 2035.
- **Diabetic kidney disease (DKD):**
major complications
prevalence 20-40%
commonly progresses to kidney failure
- **Non-diabetic kidney disease (NDKD):**
occur in diabetic patients alone or simultaneously with DKD
prevalence reported of 3-82% .
- **Importance:** treatment of DKD and NDKD are different.
Specific VS conservative therapy .

World diabetes cases expected to jump 55 percent by 2035



M. Fiorentino et al. Nephrol Dial Transplant (2017)

Introduction. (continued)

- **kidney biopsy** should be considered when patients present with atypical features for DKD (NDKD is suspected.)
- **Indications of kidney biopsy** in diabetic patients (there is yet no consensus):
 - Sudden increase albuminuria
 - Rapid GFR decline
 - Active urine sediment
 - Presence of other systemic disease
 - Heavy albuminuria/ proteinuria in short diabetes duration (type-1 <5 yrs, Type-2 <10-15yrs)
 - Kidney disease in the absence of retinopathy

Uptodate.2023

Method and Material

- This **retrospective observational study** was conducted on 547 diabetic patients, who underwent kidney biopsy between 1998 and 2023 in HKC, Tehran, Iran.
- Demographic, laboratory features (serum creatinine level (SCr), 24-hour urine protein, hematuria), clinical syndromes at presentation and medical history including hypertension and DM, and histopathological diagnosis were extracted from the kidney biopsy registry of HKC.
- Patients with histopathologic diagnosis of DKD and NDKD were compared regarding clinical and laboratory characteristics.



Statistical analysis

- Mann-Whitney U test and Student's t-test were used for skewed and normally distributed data analysis respectively.
- The chi-square test was used for comparisons of categorical variables.
- Independent predictors of DKD were identified by univariate logistic regression analysis, with results reported as the odds ratio (OR) with 95% confidence interval (CI).
- Receiver operating characteristic (ROC) curve analysis were performed to determine the best cut-off value of HbA1c level and duration of DM for predicting the presence of DKD.
- A P-value of less than 0.05 was considered to be statistically significant.



Results

Table1. Demographic, Laboratory and Clinical Features in DKD and NDKD groups

	DKD ¹	Non-DKD	P value	Total
Patients Number (%)	261 (47.7)	286 (52.3)		547 (100)
Sex (male%)	55.9	51.4	0.28	53.6
Mean Age*	54.11 ± 13.6	54.4 ± 13	0.77	54.2± 13.3
Duration of diabetes (year)**	<u>10 (12)</u>	5.5 (8.25)	<0.001	7 (9)
Hypertension ² frequency (%)	<u>205 (78.5)</u>	178 (62.2)	<0.001	387 (70.7)
Mean SCr ³ level at admission*	<u>4.45 ± 3.04</u>	3.37 ± 2.99	<0.001	3.89± 3.06
Mean GFR ⁴ at admission (ml/min)	<u>24.6 ± 22.2</u>	40.4 ± 32.3	<0.001	32.9± 29
Mean Proteinuria amount (mg/24h)*	4810 ± 4192	4511 ± 4170	0.428	4652± 4179
Nephrotic range proteinuria ⁵ frequency(%)	139 (57)	136 (52.9)	0.334	275 (54.9)
Nephritic syndrome ⁶ frequency(%)	6 (2.3)	<u>20 (7)</u>	0.01	26 (4.8)

*Mean ± Standard Deviation

** Median (Inter Quartile Range)

1. Diabetic kidney disease,
2. Blood pressure ≥ 140/90 mmHg,
3. Serum Creatinine mg/dl,
4. Glomerular filtration rate according to CKD-EPI formula,
5. Proteinuria ≥ 3500 mg/24h
6. Hematuria, hypertension and creatinine rise from baseline

Table1. (continued)

	DKD ¹	Non-DKD	P value	Total
SCr > 1.4 at Admission (mg/dl) (%)	229 (88.1)	200 (70.4)	<0.001	429 (78.9)
Hematuria ² frequency (%)	139 (57.2)	138 (50.2)	0.11	77 (53.5)
Retinopathy frequency (%)	76 (76)	27 (28.4)	<0.001	103 (52.8)
Mean ESR level ³ *	64.5 ± 32.7	57.2 ± 35.4	0.03	60.7 ± 34.3
Mean Albumin level*	3.23 ± 0.61	3.12 ± 0.72	0.121	3.17 ± 0.67
Mean HbA1c level*	7.41 ± 1.55	6.89 ± 1.42	0.034	7.11 ± 1.49
Mean Hemoglobin level (g/dl)**	9.7 (2.3)	11.5 (3.1)	<0.001	10.4 (3.1)
Positive rheumatologic tests ⁴ frequency (%)	12 (4.6)	28 (9.8)	0.02	40 (7.3)

* Mean ± Standard Deviation

** Median (Inter Quartile Range)

1. Diabetic kidney disease,
2. Red blood cell \geq 3/ HPF in urine sediment.
3. Erythrocyte sediment rate.
4. Positive antinuclear antibody or anti ds-DNA antibody or antineutrophilic cytoplasmic antibody



Table2. Predictive factors of DKD

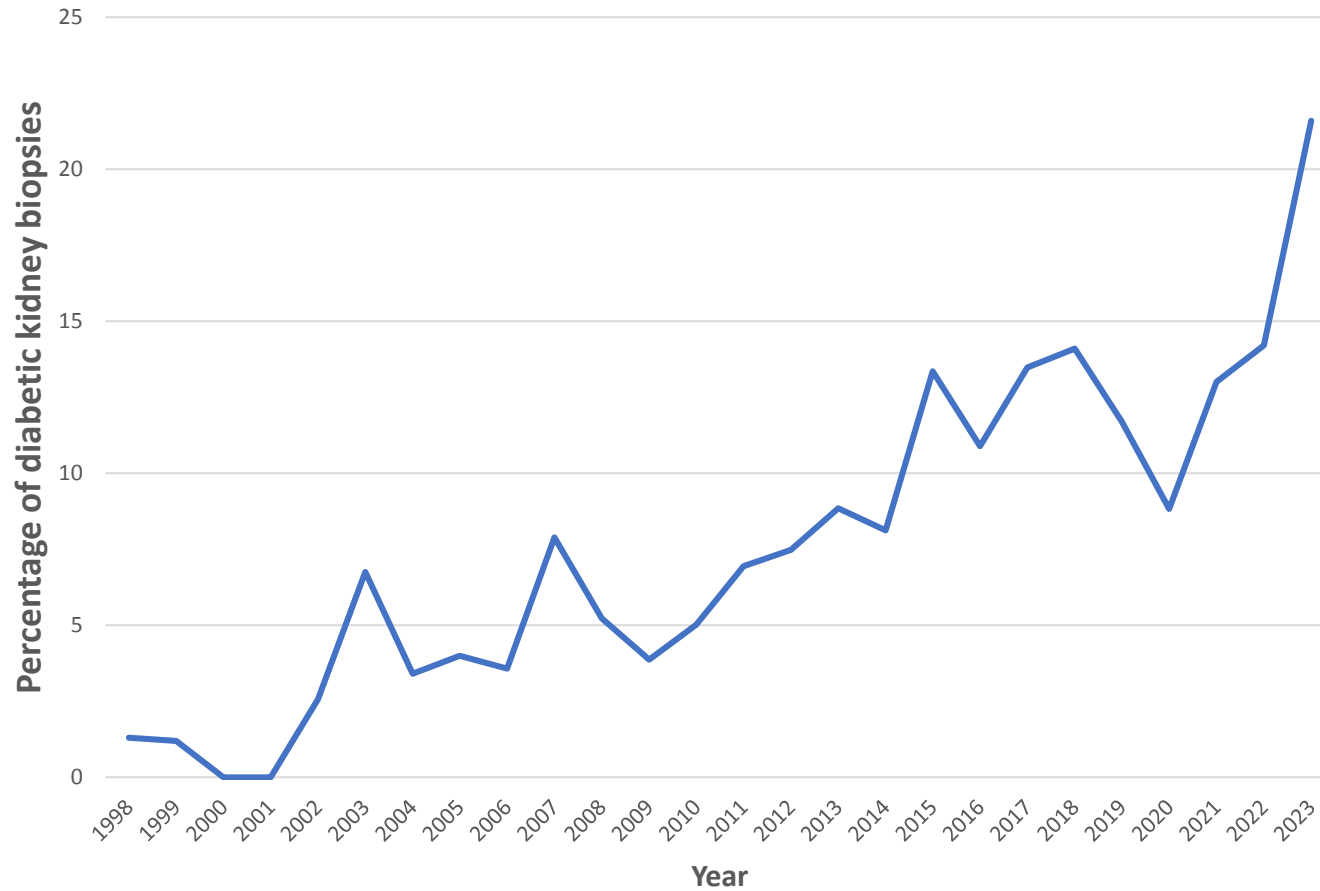
	OR (95% CI)*	P value	AUC**	Cut-off point
Duration of diabetes (year)	1.12 (1.07 - 1.16)	<0.001	0.69	9.5 years
retinopathy	7.97 (4.2 - 15.1)	<0.001		
HbA1c	1.26 (1.013 - 1.57)	0.038	0.6	7.35

*Odd’s Ratio (95% Confidence Interval)

** Area Under Curve.



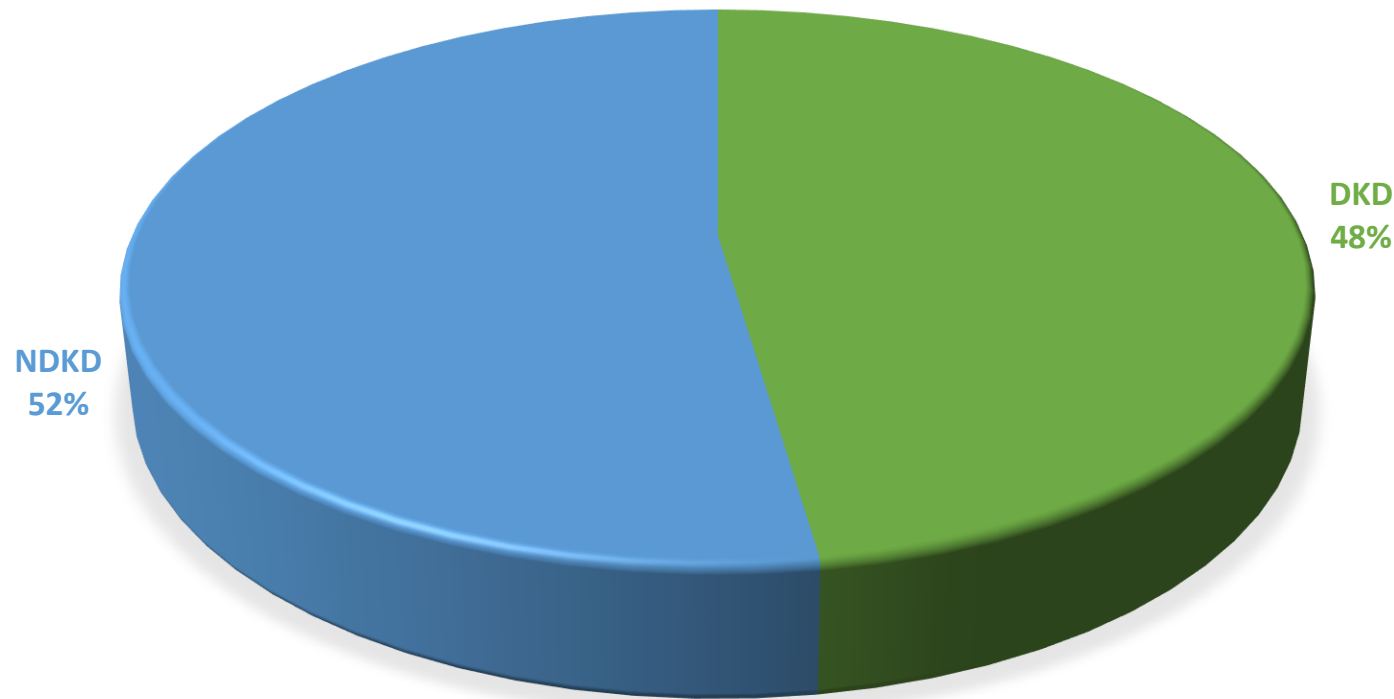
Figure1. Temporal trend of kidney biopsies among diabetic patients



We identified significant annually increase in kidney biopsy frequencies in diabetic patients over 24 years.

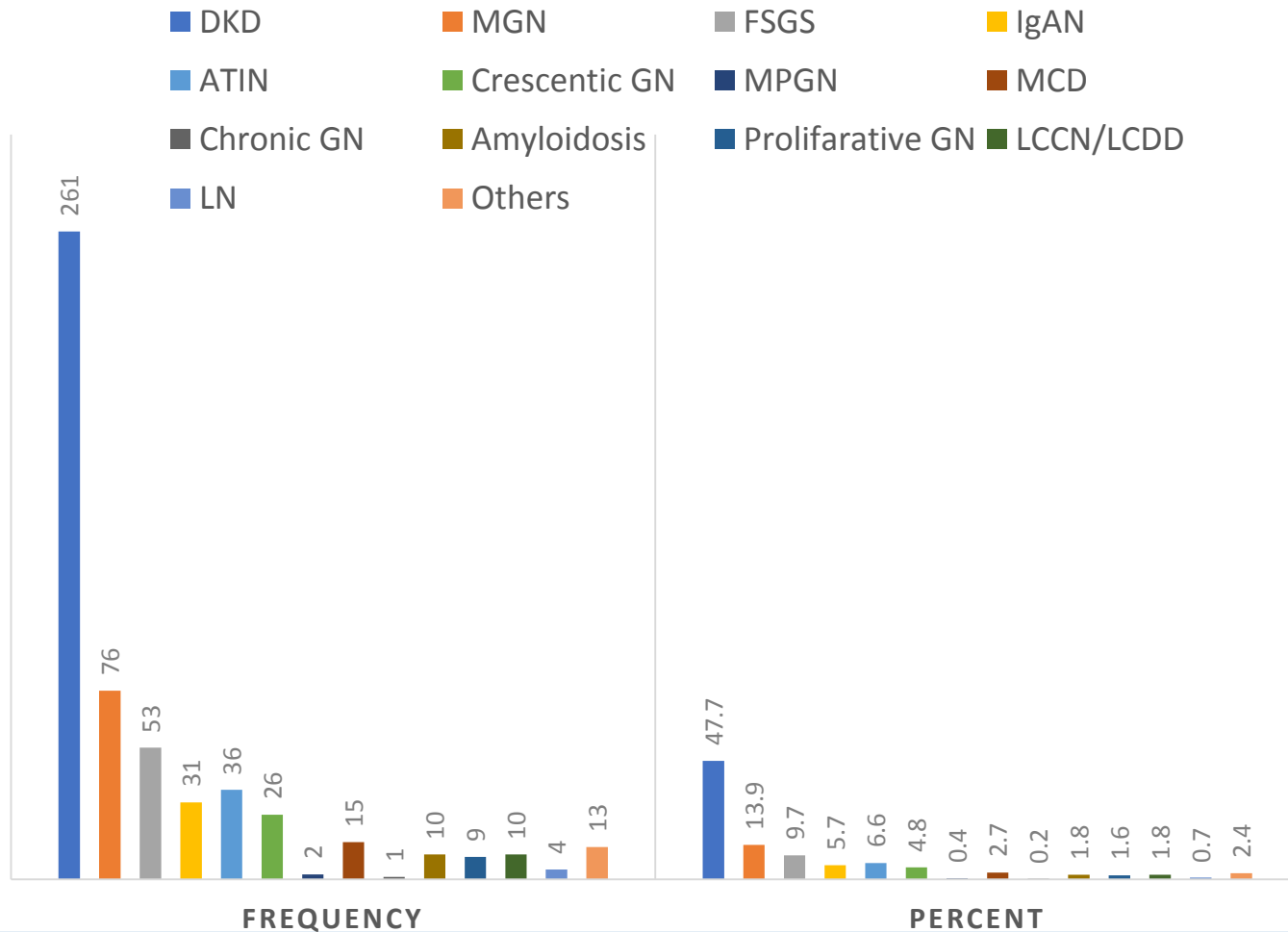
Figure 2. distribution of histopathological diagnosis

Diabetic patient undergone kidney biopsy

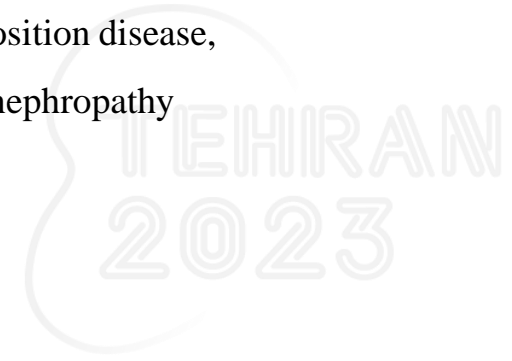


In our series, nearly the half of the performed biopsies were compatible with diagnosis of NDKD (52%).

Figure 3. Distribution of renal histopathologic diagnosis in diabetic patients



DKD: Diabetic kidney disease,
 MGN: Membranous Glomerulonephritis,
 FSGS: Focal Segmental Glomerulosclerosis,
 IgAN: Immunoglobulin A Nephropathy,
 ATIN: Tubulointerstitial nephritis without diabetic kidney disease
 GN: Glomerulonephritis
 MPGN: Membranoproliferative Glomerulonephritis,
 MCD: Minimal Change disease,
 LCDD: Light chain deposition disease,
 LCCN: light chain cast nephropathy
 LN: Lupus nephritis



Discussion

In our study:

- Frequency of NDKD among diabetic patients was 52.3%
- AKI, hematuria, amount of proteinuria and annual GFR decline were not distinctive factors between DKD and NDKD

Other series:

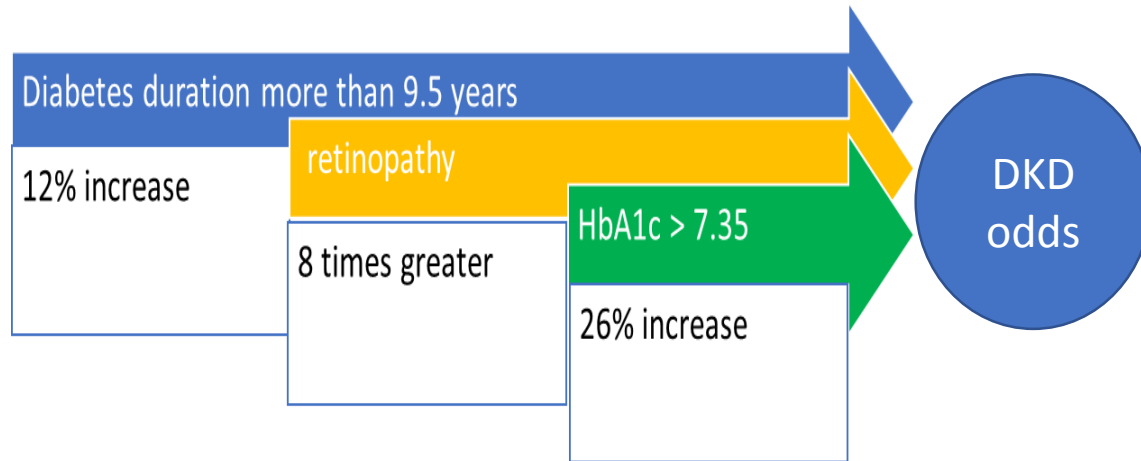
- A meta-analysis of 48 studies (2017)
NDKD prevalence: 3%- 82.9%
- A meta-analysis of 40 studies (2020)
NDKD prevalence: 40.6%
NDKD+DKD prevalence: 18.1%

- Although some other studies demonstrated that NDKD was common in diabetic patients with massive proteinuria, the patients number were limited.
- Turkish study (2021):
serum creatinine level and microscopic hematuria were not found to be associated with NDKD.

Serra Artan.turkjnephrol (2021). Tung X. Diabetes Ther (2020). Fiorentino M. Nephrol Dial Transplant (2017)

Discussion. (continued)

- In Our study:



DKD patients had lower GFR compare to those with NDKD

- Other series:

- China study (2019):
absence of DRP, non-nephrotic-range proteinuria, and a GFR > 90 mL/min significantly indicated NDKD.
- Almost all studies conclusive that the presence of Diabetic retinopathy and longer duration of DM more than 5-10 years is associated with an increased risk for DKD.

Yung Z. Diabetes Metab Syndr Obes. 2019. Artan AS.turkjnephrol.2021

Discussion. (continued)

The most common histopathologic diagnosis of NDKD

Our study:

Membranous glomerulonephritis(MGN): 13.9%

Focal-segmental glomerulosclerosis: 9.7%

IgA nephropathy: 5.7%

Tubulointerstitial nephritis: 6.6%

- Meta-analysis of 40 studies (2020):

MGN: Asia (21.4%), Africa (5.15%), Europe (22.6%)

FSGS: North America (22%), Oceania (63.9%)

AIN: 9.3% (overall)

- Meta-analysis of 48 studies (2017):

Overall, IgA nephropathy was the most common

IgAN: in 16 studies, mostly from Asia (21.3%)

MGN: in 9 studies,

FSGS: in 6 studies, mostly seen in America (22%) and Europe (19%)

AIN: in 4 studies

MPGN : more common in Asia (17.6%)

Tung X. Diabetes Ther (2020). Fiorentino M. Nephrol Dial Transplant (2017)

Table 1 Renal biopsy results and pathological types of renal disease in patients with type 2 diabetes mellitus

Country	Study population (n)	Number of cases diagnosed by pathology (%)			NDKD characteristics (%)	Mixed characteristics (%)	
		DN	NDKD	Mixed			
Asia							
China [15]	207	51 (24.6)	142 (68.6)	14 (6.8)	MN (34.5), IgAN (19.7)	MN (35.7), TIL (28.6), IgAN (21.4)	
China [16]	505	302	174	29 (5.7)	MN (32.2), IgAN (21.8), MCD	IgAN (37.9), MN (34.5), MCD/	
Turkey [37]				71		34 (47.9) 37 (52.1) 0 (0.0)	
China [17]	244					FSGS (18.9), CTIN (16.2), MN (13.5), ATN (10.8)	
China [18]	220				Turkey [38]	48	20 (41.7) 24 (50.0) 4 (8.3)
China [19]	273					MN (29.2), TIN (20.8), IgAN/FSGS/MCD (12.5)	
					Iran [39]	46	16 (34.8) 20 (43.5) 10 (21.7)
Taiwan [20]	50					MN (45.0), FSGS (30.0)	
Hong Kong [21]	68	24 (32.3)	31 (45.6)	13 (19.1)	IgAN (32.3), HRD (22.6), MN (16.1)	IgAN (23.1), MN (23.1), HRD (15.4)	
Korea [22]	110	41 (37.3)	59 (53.6)	10 (9.1)	IgAN (43.5), MN (14.5), RPGN (7.2), TIL (4.3)	IgAN (60.0), MCD/RPGN (10.0)	
Korea [23]	220	114 (51.8)	86 (39.1)	20 (9.1)	Mild-to-moderate proteinuria: IgAN (27.3), AIN (12.7), RPGN (10.9), ATN (9.0); Heavy proteinuria: MN (35.5), IgAN/MCD (12.9), MPGN (9.7)	Mild-to-moderate proteinuria: MN/ATN (33.3) Heavy proteinuria: MN (52.9), IgAN (17.6)	
Korea [24]	119	43 (36.1)	64 (53.8)	12 (10.1)	MN (29.7), MCD (18.8), FSGS/IgAN (12.5)	MN (50.0), FSGS/IgAN (8.3), AIN/MPGN (8.3)	
Korea [25]	126	50 (39.7)	65 (51.6)	11 (8.7)	MN (20), IgAN (13.8), FSGS (12.3)	IgAN (63.6), FSGS/MN (18.2)	

Diabetes Ther (2020) 11:1983-1999



Tung X. Diabetes Ther (2020).



Conclusion

- NDKD has been reported at different rates in many regions, since our study was conducted in a nephrology referral center, it seems that its results can be generalized to Iran.
- The frequency of NDKD varies widely depending on selection criteria for kidney biopsy between different centers, so it seems that we need to define new criteria for decision on kidney biopsy in diabetic patients.





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Thank you all

