Non-Proteinuric Diabetic Kidney Disease (NP-DKD)

Jaafari nia Dr
Nephrologist
Shahid Sadoughy University,Yazd

Diabetology **2024**,
Published: 2 September 2024

- This review examines the potential differences in clinical presentation, outcomes, and management between individuals with proteinuric DKD (P-DKD) and non-proteinuric DKD (NP-DKD).
- We analyzed articles published globally from 2000 and 2024.

- Non-proteinuric DKD (NP-DKD) is defined by an eGFR of less than 60 mL/min/1.73 m^2 and a urinary albumin–creatinine ratio (UACR) below 300 mg/g, or more recently below 30 mg/g

- Recent reports suggest that the prevalence of NP-DKD ranges from 20% to 40%, with a prevalence of 20% among patients with type 1 diabetes (T1DM) and approximately 40% among those with type 2 diabetes mellitus (T2DM)
- However, some studies have reported an even higher prevalence of NP-DKD among diabetic patients, with estimates reaching 50–60%

Results:

- Individuals with NP-DKD generally have lower blood pressure levels and a more favorable lipid profile
- histological studies show that P-DKD is associated with more severe glomerulosclerosis, mesangial expansion, arteriolar hyalinosis, interstitial-fibrosis/tubular atrophy, and immune complex deposits.

- those with P-DKD are more likely to develop diabetic retinopathy and have a higher risk of all-cause mortality and progression to ESKD.
- risk of progression to ESKD is relatively lower in NP-DKD when compared to P-DKD

- Strategies to slow DKD progression, applicable to both NP-DKD and P-DKD, include non-pharmacologic and pharmacologic interventions such as renin–angiotensin system blockers, sodium-glucose co-transporter-2 inhibitors, finerenone, and glucagon-like protein receptor agonists.

- Albuminuria is a well-established risk factor for the progression of DKD
- In addition to being a marker of kidney disease severity, albuminuria has a direct toxic effect on the kidneys.
- It contributes to cellular apoptosis, senescence, overproduction of reactive oxygen species, endoplasmic reticulum stress, and epithelial-mesenchymal transition in proximal renal tubular epithelial cells

- excessive albumin levels increase the expression of cell cycle arrest inducers p21 and p16, reduce the level of the cellular proliferation marker Ki-67, and raise the level of the cellular senescence marker β-galactosidase .

- The factors contributing to this DKD phenotype are not fully understood but may include an increase in the number of elderly patients, as well as those with DM, hypertension, dyslipidemia, obesity, hyperuricemia, microangiopathy, or more intensive treatment regimens, including the use of renoprotective agents .

- Research shows that clinical factors associated with NP-DKD include female sex, hypertension, smoking, poor glycemic control, absence of diabetic retinopathy, and use of the RAAS inhibitors

- The NEFRON study found diabetic patients with an eGFR < 60 mL/min/1.73 m^2 and albuminuria were more likely to have a history of hypertension, retinopathy, macrovascular disease, or a first-degree relative with CKD compared to those with an eGFR ≥ 60 mL/min/1.73 m^2. This association was not seen in T2DM patients with normoalbuminuric renal impairment.

- the prevalence of diabetic retinopathy was significantly higher in patients with P-DKD compared to those with NP-DKD (66.4% vs. 38.9%, respectively). NP-DKD patients had better renal outcomes and maintained significantly higher serum albumin levels compared to those with P-DKD (41.11 ± 3.61 g/L vs. 32.65 ± 5.81 g/L, respectively) .NP-DKD patients also had lower levels of LDL and HDL cholesterol compared to P-DKD patients .

- These findings emphasize the association of proteinuria as a key indicator of worse renal outcomes and mortality in patients with CKD.

- The incidence of arteriolar hyalinosis was significantly lower in the NP-DKD group compared to the P-DKD group (66.7% vs. 88.9%) .Additionally, NP_DKD patients had lower deposition of IgM and C1q deposition on direct immunofluorescence compared to P-DKD patients (11.1% vs. 77.8% for IgM, and 0.0% vs. 58.3% for C1q)

- Although proteinuric patients had significantly higher C3 deposition overall, C3 and C4 levels serum levels were similar between P-DKD and NP-DKD groups.
- Complement deposition in the kidney, particularly C1q and C3, correlates with more severe renal damage in DKD, including functional impairment (lower eGFR and higher proteinuria) and structural damage (interstitial fibrosis and tubular atrophy [IFTA], interstitial inflammation, vascular lesions, and global sclerosis)

Springernature

Volume 24, pages 573–581, (2020)

- It has become clear that a substantial proportion of patients either with type 1 diabetes or type 2 diabetes have renal function loss without proteinuria, known as nonproteinuric diabetic kidney disease.
- This phenotype of diabetic kidney disease suggests that there is a dissociation between renal function and level of albuminuria in patients with diabetes .

- this phenotype of diabetic kidney disease is due to an increase of elderly diabetic patients, or an increase of multidisciplinary treatment including renoprotective agents in general use.

- Despite increasing recognition of the prevalence of nonproteinuric diabetic kidney disease, clinical pictures, pathological characteristics, renal prognosis, and mortality among nonproteinuric diabetic kidney disease have not fully investigated.
- These inconsistent findings may be due to a small number of study population.

- They may also arise from the timing of the biopsy; for example, clinical characteristics in patients with eGFR 50 mL/min/1.73 m^2 may be different from those in patients with the same backgrounds but with eGFR 25 mL/min/1.73 m^2;
- or age and duration of diabetes may affect pathological findings.

- We have shown that patients with nonproteinuric diabetic kidney disease have fewer of typical morphological features, not only in glomerulus but also in interstitium and arterioles, associated with diabetic nephropathy (diabetic glomerulopathy) .
- For example, the prevalence of glomerular nodular lesions was 22% in nonproteinuric diabetic kidney disease and 54% in proteinuric diabetic kidney disease.

- our study has shown that patients with nonproteinuric diabetic kidney disease carry a lower risk of progression of renal function loss, compared to those with proteinuric diabetic kidney disease, around 20% of those with nonproteinuric diabetic kidney disease experienced progression to advanced CKD or ESKD in 10 years

Table : Pathological characteristics among nonproteinuric and proteinuric diabetic kidney disease

Pathological characteristics at biopsy	Propensity matched cohort		
	Nonproteinurics (*n* = 82)	Proteinurics (*n* = 164)	*p* value
Fioretto classification (%)			< 0.001
CI	62	17	
CII	20	66	
CIII	18	17	
Tervaert (RPS) classification (%)			< 0.001
I	31	4	
IIa	22	14	
IIb	10	20	
III	25	52	
IV	2	10	

Fioretto Classification; CI, normal or near normal renal structure; CII, typical diabetic kidney disease; CIII, A typical patterns of renal injury; Tervaert (RPS) classification, Renal Pathology Society diabetic kidney disease classification; I; Mild or nonspecific light microscopy changes and electron microscopy-proven glomerular membrane thickening; IIa; Mild mesangial expansion; IIb, Severe mesangial expansion; III; Nodular sclerosis (Kimmelstiel-Wilson lesion); IV, Advanced diabetic glomerulosclerosis

Springer

2020 Mar 31;24(7):573–581

- the primary pathological findings in nonproteinuric diabetic kidney disease are similar findings to hypertensive nephrosclerosis, characterized by glomerular sclerosis, interstitial fibrosis and tubular atrophy, and arteriosclerosis .

- Another possibility is that patients with nonproteinuric diabetic kidney disease is mostly comprised of those who responded well to renin-angiotensin system blockades that results in nonproteinuria via protecting glomerulus.

- A couple of studies report that the prevalence of diabetic retinopathy is lower in those with nonproteinuric diabetic kidney disease than those with proteinuric diabetic kidney disease, suggesting microangiopathy may not be the main pathogenic factor, rather past history of macrovascular disease such as cardiovascular disease may be a potential pathogenic factor in nonproteinuric diabetic kidney disease

- However, this mechanism seems doubtful from our results showing that there were no differences in prevalence of retinopathy and CVD events among nonproteinuric and proteinuric diabetic kidney disease

Biomolecules

6 April 2023 / Revised: 25 April 2023 / Accepted: 25 April 2023 / Published: 26 April 2023

- non-albuminuric DKD (eGFR < 60 mL/min/1.73 m^2, absence of albuminuria), whose pathogenesis is still unknown. However, various hypotheses have been formulated, the most likely of which is the acute kidney injury-to-chronic kidney disease (CKD) transition, with prevalent tubular, rather than glomerular, damage (typically described in albuminuric DKD).

- In more recent years, the National Evaluation of the Frequency of Renal Impairment Coexisting with NIDDM (NEFRON) survey of primary care patients with type 2 diabetes found that 55% of those with low eGFR were persistently non-albuminuric .

- In the Renal Insufficiency And Cardiovascular Events (RIACE) cohort ,non-albuminuric DKD patients were more frequently female and nonsmokers, and had lower levels of glycated hemoglobin (HbA1c), but did not have longer diabetes duration compared with those patients with albuminuria.

- Multiple regression analysis confirmed that the non-albuminuric phenotype is associated with women, but not with HbA1c.

- In a cohort of 562 Korean patients with type 2 diabetes ,the normoalbuminuric DKD phenotype was associated with women, a shorter duration of diabetes, a lower prevalence of diabetic retinopathy, and a lower prevalence of antihypertensive medications use when compared with micro- and macro-albuminuric kidney disease.

- Therefore, non-albuminuric DKD decreased progressively with an increase in the duration of diabetes and an increase in the severity of retinopathy.

Non-albuminuric DKD phenotype: a breakthrough in DKD classic conception

Albuminuric DKD		Non-albuminuric DKD
UACR > 30 mg/g	 	eGFR < 60 ml/min/1.73m^2 and UACR < 30 mg/g
Microangiopathy	 	Macroangiopathy
Correlation with retinopathy	 	No correlation with retinopathy
Glomerulosclerosis	 	Tubular and vascolar damage
Male sex		Female sex
Correlation with Hb1Ac	 	No correlation with Hb1Ac

Table 1.

Histological manifestations of diabetic kidney disease.

Class	Description
I	Mild or nonspecific light microscopy changes and electron microscopy-proven GBM thickening [24]
IIa	Mild mesangial expansion (in >25% of the observed mesangium) [25]
IIb	Severe mesangial expansion (in >25% of the observed mesangium)
III	Nodular sclerosis (Kimmelstiel-Wilson lesion) [26,27]
IV	Advanced diabetic glomerulosclerosis (<50% of glomeruli) [28]

- In 2019, Yamanouchi et al. retrospectively assessed 526 patients with DKD, showing that normal or almost normal renal structure was most common (62%) in the patients with non-albuminuric DKD, while the typical DKD pattern was most prevalent (66%) in the albuminuric DKD group
- This showed multifactorial pathophysiology for the renal disease in these patients, with potential contributions from aging, hypertension, and vascular disease.

- mesangial expansion and GBM thickness are correlated with lower eGFR in individuals with albuminuric DKD . By contrast, in the non-albuminuric phenotype, these histological changes were seen less frequently, with major tubulointerstitial and vascular (with varying degrees of arteriosclerosis) rather than glomerular involvement, suggesting a different pathogenetic process in this phenotype.

Pathogenesis

- The pathogenesis of non-albuminuric DKD is still unknown, and in recent years, various hypotheses have been formulated to explain the pathogenesis of this phenotype.
- There is growing evidence linking the development of the non-albuminuric phenotype in patients with diabetes to acute kidney injury (AKI) to CKD transition.
- The most likely hypothesis is the development of small and repeated episodes of AKI, sometimes even subclinical, of any nature, ischemic, infectious, toxic, or obstructive. This determines the development of CKD due to tubular damage.

- Diabetic subjects are more exposed to this type of damage for the following reasons: the greater tendency to tubular hypoxia ,being in therapy with RAAS blockers that increase the susceptibility of the tubule to renal hypoxia ,and a lower capacity for tubular regeneration.
- Patients with diabetes often suffer multiple episodes of AKI due to vascular changes, endothelial cell injury, toxicity associated with medications, and multiple surgeries, while some episodes of mild AKI may go undetected.

- It is also likely that the AKI-to-CKD transition is responsible for the decline of eGFR in patients with non-albuminuric DKD, which is characterized mostly by tubulointerstitial injury and fibrosis.
- Moreover, it has been suggested that non-albuminuric DKD probably underlies macroangiopathy instead of microangiopathy as the prevailing pathology; the weak association of the non-albuminuric phenotype with diabetic retinopathy seems to confirm this statement .

- Conversely, a recent study in patients with type 2 diabetes, reduced eGFR, and various degrees of albuminuria showed that, while typical glomerulopathy was observed in virtually all subjects with micro- or macro-albuminuria, only half of the normoalbuminuric patients had typical lesions and almost all of them had varying degrees of arteriosclerosis .

- Few patients with diabetes and decreased eGFR in the absence of proteinuria have been biopsied and the results reported. Any number of other renal lesions could be present in these patients, including atheroembolism, renovascular disease, or tubulointerstitial disease from the many medications used to treat comorbidities.
- patients with diabetes have a high risk for cardiovascular events and many comorbidities that confer risk for AKI. It is possible that unresolved episodes of AKI account for the decreased eGFR seen in many non-proteinuric patients with diabetes.
- Lastly, non-proteinuric diabetic kidney disease may represent a genetically different form of DKD.

- The Chronic Renal Insufficiency Cohort (CRIC) study was conducted in patients with diabetes and CKD and demonstrated that those with non-albuminuric DKD have a much lower risk for ESRD, CKD progression, or rapid decline in eGFR compared with those in whom albuminuria or proteinuria is present.

Table 2.

Studies on DKD phenotypes and cardiovascular risk

ADVANCE Post-Hoc Analysis (Ninomiya et al., 2009) [38] *			
Cardiovascular events			
	eGFR ≥ 90	***eGFR 60–89***	***eGFR < 60***
Normoalbuminuria	1.00 (reference)	0.98 (0.78–1.22)	1.33 (1.02–1.75)
Microalbuminuria	1.48 (1.09–2.01)	1.54 (1.20–1.98)	2.04 (1.54–2.69)
Macroalbuminuria	1.18 (0.52–2.69)	1.67 (1.09–2.57)	3.23 (2.20–4.73)
Cardiovascular death			
	eGFR ≥ 90	***eGFR 60–89***	***eGFR < 60***
Normoalbuminura	1.00 (reference)	1.22 (0.81–1.84)	1.85 (1.17–2.92)
Microalbuminuria	1.96 (1.16–3.32)	2.52 (1.65–3.84)	3.37 (2.15–5.30)
Macroalbuminuria	2.87 (1.01–8.18)	3.61 (2.02–6.43)	5.93 (3.45–10.20)

FIELD posthoc Analysis (Drury et al., 2011) [43] #			
Cardiovascular events			
	eGFR ≥ 90	***eGFR 60–89***	***eGFR < 60***
Normoalbuminura	1.00 (reference)	1.11 (0.95–1.29)	1.63 (1.20–2.20)
Microalbuminuria	1.25 (1.01–1.54)	1.43 (1.18–1.72)	1.94 (1.37–2.73)
Macroalbuminuria	1.19 (0.76–1.85)	1.77 (1.33–2.36)	2.30 (1.48–3.55)
Cardiovascular death			
	eGFR ≥ 90	***eGFR 60–89***	***eGFR < 60***
Normoalbuminura	1.00 (reference)	1.17 (0.80–1.72)	2.36 (1.29–4.31)
Microalbuminuria	1.73 (1.08–2.77)	1.38 (0.88–2.15)	2.96 (1.59–5.51)
Macroalbuminuria	1.89 (0.83–4.27)	2.59 (1.49–4.50)	5.26 (2.73–10.15)

RIACE (Penno et al., 2018) [44] @						
All-cause death						
	eGFR ≥90	***eGFR 75–89***	***eGFR 60–74***	***eGFR 45–59***	***eGFR 30–44***	***eGFR <30***
UACR <10	1.00 (ref.)	0.80 (0.67–0.96)	1.10 (0.83–1.12)	1.32 (1.97–1.62)	1.85 (1.40–2.44)	1.61 (0.88–2.97)
UACR 10–29	0.94 (0.78–1.12)	1.05 (0.89–1.25)	1.06 (0.88–1.27)	1.39 (1.14–1.69)	2.25 (1.79–2.82)	2.25 (1.49–3.37)
UACR 30–299	1.31 (1.08–1.60)	1.31 (1.09–1.58)	1.39 (1.15–1.68)	1.48 (1.22–1.80)	2.09 (1.69–2.59)	2.79 (2.09–3.70)
UACR ≥300	2.19 (1.55–3.11)	2.48 (1.82–3.38)	1.71 (1.23–2.36)	2.26 (1.71–3.00)	2.78 (2.14–3.63)	4.66 (3.59–6.05)

JDDM 54 (Yokoyama et al., 2020) [45] $				
	Alb− eGFR−	*Alb+ eGFR−*	*Alb− eGFR+*	*Alb+ eGFR+*
CVD	1.00 (reference)	1.75 (1.32–2.34)	1.06 (0.63–1.79)	2.30 (1.57–3.39)
Death or CVD	1.00 (reference)	1.73 (1.35–2.21)	1.02 (0.66–1.60)	2.32 (1.67–3.24)

Analysis from Hong Kong Diabetes Biobank (Jin et al., 2022) [46] °				
	Alb− GFR−	*Alb+ GFR−*	*Alb− GFR+*	*Alb+ GFR+*
All-cause mortality	1.00 (reference)	2.00 (1.52–2.63)	1.59 (1.04–2.44)	3.26 (2.43–4.38)
CVD	1.00 (reference)	1.19 (1.02–1.40)	1.14 (0.88–1.48)	1.47 (1.23–1.76)
Hospitalization for HF	1.00 (reference)	3.14 (2.09–4.73)	3.08 (1.82–5.21)	5.50 (3.63–8.34)

- In the Jin et al. trial ,renal outcomes were also investigated. It was found that the risk of CKD progression was higher in patients with albuminuria with or without decreased eGFR compared with those with decreased eGFR without albuminuria.

- Similarly, Yokohama et al. showed that the annual decline rate in eGFR was slower in non-albuminuric DKD than in albuminuric DKD.

Non-Albuminuric DKD Therapy

- Currently, there are no specific therapies for non-albuminuric DKD.
- It is generally assumed that management of several risk factors such as high glucose levels, high blood pressure, hypercholesterolemia, and other factors, can protect renal function and delay the progression to chronic renal failure.

- whether this approach may be effective in patients with non-albuminuric DKD remains to be shown.
- Whether RAS blockers can be used for non-albuminuric DKD treatment is currently unclear.
- Recent randomized controlled trials (RCTs) demonstrated that both SGLT-2i and GLP1-RAs reduce cardiovascular and renal events in type 2 diabetes patients .
- Based on growing clinical evidence, the American Diabetes Association recommends SGLT2i or GLP1-RAs in patients with ASCVD or DKD.

- However, no head-to-head RCT has directly compared the risk-reduction effects of SGLT2i and GLP1-RAs on cardiovascular and renal events in diabetic patients according to the presence or absence of albuminuria as the primary outcome.

- These classes of drugs have extensively demonstrated their protective effect on kidney disease in diabetic patients, as previously reported.
- However, data concerning therapy in the non-albuminuric phenotype are still inadequate and no studies have been carried out investigating this subgroup of patients with DKD.

- However, none of these studies specifically analyzes the distinction of the effect of SGLT2i on the various phenotypes of DKD.
- . Unfortunately, subgroup analysis evaluated patients only on the basis of preserved/reduced eGFR and presence/absence of albuminuria, without considering both factors simultaneously for defining the phenotypes, albuminuric and non-albuminuric.
- This prevented them from drawing any conclusion on the possible therapeutic effect of these drugs in non-albuminuric DKD.

- For this reason, there are still no specific guidelines on the use of these drugs in one phenotype rather than the other, generically referring to diabetic patients with CKD.