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DKD Pathogenesis, Treatment

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DM

Leading cause of CKD & ESKD in worldwide.

A complex & heterogeneous diease

Etiologic pathways including

-Changes in glomerular hemodynamics,

-Oxidative stress (OS) & inflammation, &

-IFTA.

PATHOGENESIS

-Hyperglycemia

-Production of AGE (advanced glycation end-products) & ROS (reactive oxygen species) that activate intercellular signaling for proinflammatory & profibrotic gene expression with production of mediators for cellular injury [2,3].

Hyperglycemia plays a central role, & Hyperinsulinemia & insulin resistance also may incite pathogenic mechanisms.

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-Alterations in glomerular hemodynamics,

-Inflammation, &

-Fibrosis

are primary mediators of kidney tissue damage.

Glomerular hemodynamics

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Glomerular hyperfiltration

The diabetic milieu activates

-RAAS & downstream mediators,

-Kidney hypertrophy,

-Increased RPF, & FF, & an abnormally elevated GFR [4].

In the early stages of DM, "whole kidney GFR" & "single nephron GFR (SNGFR)" are increased [5,6].

Glomerular hyperfiltration

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Increased vasodilators (ANP, NO, & prostanoids), & a relative deficiency or resistance to insulin have a preferential impact on reducing afferent arteriole resistance [5,6,7].

By contrast, an increase in vasoconstrictors, (AT II, thromboxane & endothelin 1), have a greater effect to increase efferent arteriole resistance that increases intraglomerular pressure & triggers a sclerotic response in DKD [4].

Tubular function impact on glomerular hemodynamics Via tubuloglomerular feedback.

DM decreases Na delivery to the macula densa due to proximal tubule hypertrophies & then SGLT1 & SGLT2 (sodium-glucose cotransporters) upregulates. [1]

This effect underscored by findings that SGLT2is causes short-term decline in eGFR but a long-term delay in kidney disease progression [8-12].

Glomerular hyperfiltratio

Occurs in DM due to impaired autoregulatory responses of afferent arterioles to fluctuations in BP[16] that transmitted to glomerular capillaries, hyperfiltration & increased intraglomerular pressure, SNGFR, physical stress to capillary walls, podocytes, mesangium & ultimately triggering a profibrotic response.

When whole kidney GFR decreases, RPF is shunted to the remaining viable glomeruli, causing further increases in SNGFR of the less damaged glomeruli.

Studies in DM have demonstrated association between elevated eGFR & worsening albuminuria [5].

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Lower prevalence of hyperfiltration in type 2 versus type 1 DM may Due to **older age** & **glomerulosclerosis** from **HTN** &/or **age-related** senescence of the kidney.

A meta-analysis of 10 studies of patients with type1 DM & measured GFR found that hyperfiltration was associated with a higher risk of moderately or severely increased albuminuria at 11 years (OR: 2.7, 95% CI 1.2-6.1) [23].

Normalization of whole kidney hyperfiltration slow the rate of CKD progression. One of the primary mechanisms by which ACEis & ARBs mitigate kidney disease, as they preferentially decrease arteriolar resistance in the efferent compared with afferent arteriole, thereby lowering glomerular pressure [25].

Innate immunity, OS, & inflammation

Innate immunity is an increasingly recognized contributor to the pathogenesis of DKD via OS & & inflammation.

Hyperglycemia, insulin resistance & dyslipidemia cause increased formation of AGE, which, upon binding to AGE receptors (RAGE) located on multiple cell types in the kidney, induces production of numerous cytokines TNF, IL-6, IL-1beta via activation of nuclear transcription factors, such as NF-kappaB [27,28].

A similar signaling pathway occurs via stimulation of TLRs by exposure to hyperglycemia & damaged cellular components (as occurs with OS). OS & inflammation are tightly intertwined, creating a vicious cycle wherein one process begets the other [3,29].

Macrophage infiltration is a hallmark of DKD, correlates with worsening disease [30,31]. Macrophages recruited & activated by hyperglycemic stress, angiotensin II, oxidized LDL, AGE, & KIM1 [32]. The result is increased OS & production of injurious cytokines including TGF-beta & platelet derived growth factor.

Macrophages are also a rich source of TNF-alpha, a pleiotropic cytokine resulting in renal hypertrophy, podocyte & tubular epithelial cell injury, & the triggering of a cascade of other cytokines [31,33].

Hyperglycemia

also results in increased shunting of glucose through non-glycolytic pathways such as the polyol pathway, which increases OS.

Protein kinase C (PKC) activated by a hyperglycemia, decreased eNOS & increased endothelin 1 & VEGF, which promotes endothelial instability & NF-kappaB stimulated cytokine production.

Mesangial cell hypertrophy & matrix accumulation, hallmarks of diabetic glomerulosclerosis, are mediated by the TGF-beta system [34,35]. TGF-beta production by the mesangial cell is activated by a hyperglycemia & angiotensin II & has been found to not only trigger glomerular extracellular mesangial matrix production but also to decrease the production of matrix metalloproteinases, which are responsible for keeping extracellular matrix in check through degradation [34].

A primary mediator of TGF-beta on mesangial expansion is connective tissue growth factor (CTGF); however, CTGF can also be directly stimulated by hyperglycemia, mechanical strain, & AGE [36].

VEGF

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proliferation & endothelial permeability are increased in DKD mediated by VEGF [37], particularly when accompanied by diabetes-induced downregulation of endothelial NO production [38]. Angiopoietins (ANGPT) are also important regulators of endothelial function, necessitating a balance between ANGPT1, which stabilizes the endothelium, & ANGPT2, which promotes endothelial proliferation [39].

The ratio of ANGPT2 to ANGPT1 is elevated in both experimental models of DKD as well as from tissue specimens from human diabetic glomerulopathy.

IFTA

Hyperglycemia results in shunting of glucose through the hexosamine pathway & subsequently increased production of TGF-beta & plasminogen activator inhibitor 1 (PAI-1) [41].
Damage to the proximal tubular cell from AGE, angiotensin II, & albuminuria also results in increased TGF-beta with consequent conversion of pericytes into myofibroblasts (epithelial to mesenchymal transformation), infiltration of macrophages, & an excess of collagen & fibronectin deposition [1,42].

EPIDEMIOLOGY & RISK FACTORS

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Incidence & prevalence

The true incidence & prevalence of CKD & kidney failure from diabetes is **impossible** to know, because **kidney biopsies** (the gold standard for diagnosis of **DKD** are infrequently performed in patients with **diabetes & CKD**.

The burden of DKD is high

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Decreased QOL &

Increased rates of disability & premature death [45].

Globally, the age-standardized incidence of DKD decreased by approximately 10% from 1990 to 2017; however, DALY & mortality increased over this period (by approximately 20% & 10%, respectively) [46].

Health care costs are also significantly increased in people with DKD [47].

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Although the prevalence of **diabetes** in the **US** has **risen** over the last 20 years from 6 to 10%, the proportion of people with diabetes who also have **CKD has remained relatively stable** (approximately 25 to 30%) [48]. \

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The prevalence of albuminuria (ie, a urine alb/Cr≥30 mg/g) in diabetics decreased from approximately 20% during the period from 1988 to 1994 to approximately 15% during the period from 2009 to 2014.

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Prevalence of decreased eGFR, defined as an eGFR <60 mL/min/1.73 m2, increased from approximately 10 to 15%.

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CKD awareness in Diabetics is extremely poor even in the US.

Only 10% of stage 3 CKD

This proportion is higher among stage 4 CKDs [43,49,50].

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Risk factors for DKD

There is a strong genetic basis for DKD, both modifiable & nonmodifiable environmental risk factors play an important role via direct tissue damage & indirect or epigenetic modification.

Age

Increasing age is directly related to the prevalence of **DKD** with decreased eGFR, rising from

- 8% in the 5th decade to
- 19% in the 6th decade &
- 35% in the 7th decade of life [66].

The incidence rate of diabetic ESKD is

- 142, 274, 368, & 329 cases/100,000 among diabetic persons aged
- <45, 45 to 64, 65 to 74, & ≥75 years, respectively [67].

Ancestry/ethnicity

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Compared with White populations, African American, Hispanic American, & American Indian populations have higher rates of albuminuria, decreased eGFR, & ESKD [43,70,71].

The highest rates of ESKD were historically among American Indians; however, with public health interventions, rates have declined significantly in this population [72]. Incidence rates of diabetic ESKD among African Americans, Hispanic Americans, and White Americans are estimated at 409, 307, & 266 cases/100,000 diabetic persons; although these rates appear to be declining among White patients, this does not appear to be the case in underrepresented populations & may actually be rising among the Mexican-American population [48,67].

Sex

Both CKD in general & DKD in particular are more common in females [43]. However, compared with females, males have a significantly higher risk of progression from late-stage CKD to ESKD HR 1.37, 95% CI 1.17-1.62) [73].

Low socioeconomic status

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The disparity in DKD among underrepresented populations is explained in large part by socioeconomic status, which is tightly intertwined with educational attainment. Albuminuria & decreased eGFR (<60mL/min/1.72 m2) is more common among individuals with lower education level, even after controlling for sociodemographic & clinical factors [74]. After controlling for self-reported race, the incidence rate of ESKD in one study was 4.5-fold higher among populations in which >25% lived below the poverty level as compared with populations in which <5% lived below the poverty level [75]. Socioeconomic status in people with type 1 diabetes is also associated with pathogenic factors involved in DKD, including glomerular hyperfiltration & levels of certain cytokines [76].

Obesity

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Even in the absence of diabetes, obesity leads to a form of secondary FSGS, termed "obesity-related glomerulopathy (ORG)" [79]. Notably, approximately 40% of these patients have features of DKD (mesangial expansion, GBM thickening, & nodular glomerulosclerosis), even in the absence of diabetes [80].

Obesity is a significant risk factor for DM2 & can often accompany DM1 due to the rising prevalence of obesity in the general population [81]. As a result, ORG & DKD often coexist & share many clinical & pathogenic features such as glomerular hyperfiltration, progressive albuminuria, podocyte injury, & FSGS [82]. Obesity results in activation of the RAAS, causing increased Na retention, activation of the sympathetic nervous system, & increased intraglomerular capillary pressure, exacerbating the same processes caused by diabetes & also resulting in glomerulosclerosis [4].

Visceral obesity

has a greater association with incident & progressive DKD than general obesity [83], possibly due to increased adipocyte cytokine production. On the other hand, adiponectin production from adipocytes is reduced, resulting in reduced AMP-activated protein kinase (AMPK) activation & ultimately increased OS & podocyte injury [84]. There is also increased production of TNFalpha, IL-6, & leptin in obese individuals, which results in greater TGFbeta production [85,86].

Smoking

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-Can result in nodular sclerosis of the kidney that is similar to diabetic glomerulosclerosis. -

-Triggers many of the same pathogenic pathways that are active in DKD, such as endothelial dysfunction, OS, & inflammation [87].

HTN

is important to the pathogenesis & progression of DKD. There is a linear relationship between BP the risk for adverse kidney outcomes [104,105]. A systolic BP>140 mmHg has consistently been found to increase the risk for the development of severely increased albuminuria & stage 3 CKD [104].

Genetic factors

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Environmental factors may explain some of the disparities in DKD among **African American, Hispanic American, & American Indian populations** [106]. **Familial clustering of DKD & diabetic ESKD** has long been recognized [107], with **heritability** estimates ranging from **0.30 to 0.75 depending** upon the population (eg, ancestry, ethnicity, diabetes type) & trait under study (eg, albuminuria, eGFR, ESKD) [108].

APOL1 gene

has been found to explain much of the disparity in nondiabetic ESKD among Black individuals but has not born out as a causative factor for DKD [114]. However, APOL1 variants are associated with an increased risk for progression of DKD in Black patients.


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