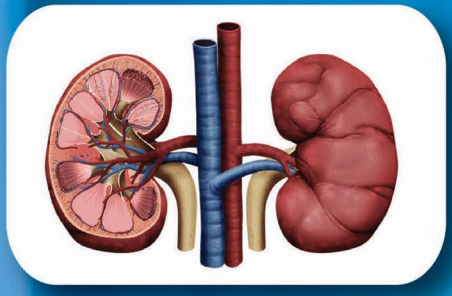
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Complications in Diabetes Mellitus

Bench to Bedside

with a focus on Diabetic Kidney Disease



Manoj Chadha

Foreword
Marc Evans

JAYPEE

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Pathophysiology of Diabetic Kidney Disease

2

Preethi S, Bidisha Das, Himadri Das, Vanita Goyal

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CHAPTER OVERVIEW

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- ❑ Introduction
- ❑ Risk factors
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- ❑ Natural history of DKD
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- ❑ Screening of DKD
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SUMMARY

Diabetic kidney disease (DKD) is the most important and common reason for end-stage renal disease (ESRD). Various risk factors—susceptibility factors, initiation factors, and progression factors—contribute to the pathology of DKD. Eventually, there is interstitial fibrosis and glomerulosclerosis resulting in diabetic nephropathy. Various pathological changes include an increase in the size of the kidney, thickening of the basement membrane of glomerulus, nodular changes, diffuse glomerular lesions, and development of arteriolar lesions; the vessel walls are occupied by hyaline material. The natural history of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) is different. DKD also increases the risk of cardiovascular disease. Diabetic nephropathy accounts for 30% of chronic kidney disease (CKD) which progresses to ESRD, but only 3% require renal replacement therapy.

INTRODUCTION

Diabetic kidney disease is the prominent cause of the ESRD worldwide. About 30% of adults with T1DM and 40% with T2DM eventually develop DKD. The prevalence of the DKD runs in parallel to the increasing worldwide prevalence of diabetes mellitus (DM).[1]

Long-term inadequate glycemic control, along with several other factors, contributes to the development of DKD. As a result, there is an alteration in

the kidney function and impact on the kidney structure. In the diabetic kidney, several pathological changes, such as glomerular and tubular basement membrane thickening, mesangial expansion, and glomerular sclerosis, result in the development of DKD.[2] This chapter details the pathology of DKD.

RISK FACTORS

The risk factors of DKD can be classified as follows (**Table 1**):[1]

- Susceptibility factors
- Initiation factors
- Progression factors

Hyperglycemia and hypertension (HTN) are the most important risk factors of DKD.[1]

Hyperglycemia

Diabetic kidney disease is again multifactorial.

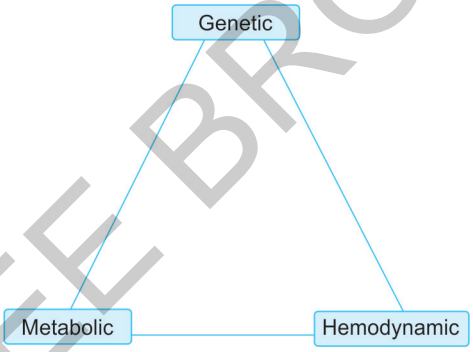


TABLE 1: Risk factors of diabetic kidney disease.

Susceptibility factors	Initiation factors	Progression factors
• Older age • Sex (men) • Race/Ethnicity (black, American Indian, Hispanic, Asian/Pacific Islanders) • Family history of diabetic kidney disease • Hyperglycemia • Obesity • Hypertension • Smoking • High protein intake	• Genetic kidney disease • Hyperglycemia • Obesity • Acute kidney injury • Toxins • Hypertension	• Race/Ethnicity (black, American Indian, Hispanic, Asian/Pacific Islanders) • Hyperglycemia • Obesity • Hypertension • Acute kidney injury • Toxins • Smoking • (Very) High protein intake

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Poor glycemic control and the duration of hyperglycemia are independent risk factors for the progression of a diabetic to proteinuria and ESRD. According to the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies, intensive glycemic control, that is target glycated hemoglobin (HbA1c) should be <7%, reduces the risk of microalbuminuria by 34% and macroalbuminuria by 56% over 9 years. At 22 years, intensive glycemic control reduced the risk of low estimated glomerular filtration rate (eGFR; <60 mL/min/1.73 m^2) by 50%. The beneficial effect of intensive glycemic control extended beyond the study period, which is called the "metabolic memory" or the "legacy effect." Early intensive glucose control can help prevent irreversible damage to the kidneys like epigenetic changes.[3-5]

The factors that contribute to DKD in the presence of chronic hyperglycemia are:[6]

- Triggering of oxidative stress
- Inflammation mediated by altered metabolic pathways
- Promotion of progression of cell injury

Hypertension

Hypertension is a significant risk factor as well. Controlling blood pressure (BP) is found beneficial in the prevention of CKD in DM. The prevalence of HTN in India will be around 214 million by 2025. It is increasing in both the rural and the urban populations and in males and females equally. The target BP should be <140/90 mm Hg for all diabetic patients and for patients with proteinuria >1 g, BP should be <125/75 mm Hg. Maintaining target BP levels for over a median duration of 15 years is found to reduce the risk of micro- and macrovascular complications by 37% when compared to BP > 180/105 mm Hg. There is a 15% increase in the risk of micro- and macroalbuminuria for every 10 mm Hg increase in mean systolic BP.[1]

The factors that contribute to DKD in the presence of HTN are:[7]

- Excess sodium retention
- Sympathetic nervous system (SNS) activation
- Renin–angiotensin–aldosterone system (RAAS) activation
- Endothelial cell dysfunction (ECD)
- Increased oxidative stress

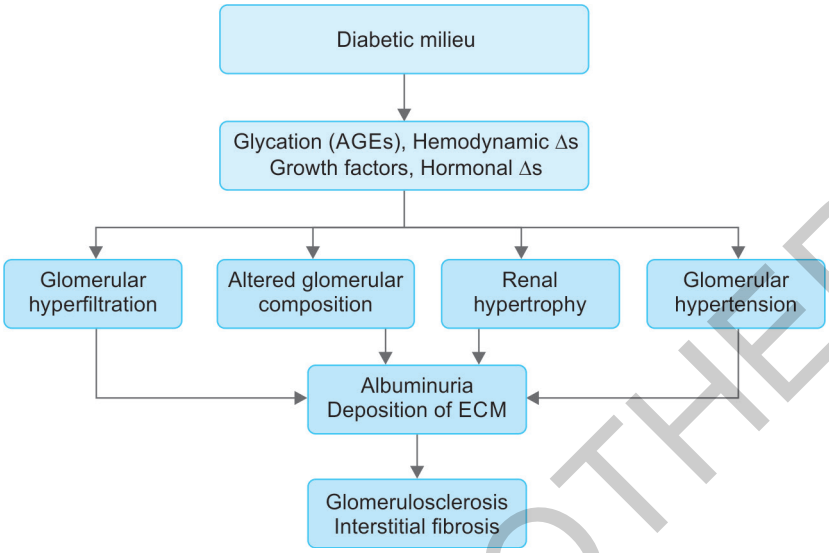
OVERVIEW TO PATHOLOGY

Initiation

Diabetes mellitus and the factors associated with DM lead to the following:[8]

- Mesangial expansion and injury are induced.
- Advanced glycation end products (AGEs) are produced and circulated.
- Growth factors get elaborated.
- There are hemodynamic changes.
- There are hormonal changes.

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(AGEs: advanced glycation end products; ECM: extracellular matrix)

FLOWCHART 1: Overview to the pathology of diabetic kidney disease.

Potentiation

There is production of reactive oxygen species and inflammatory mediators. These factors then contribute to the development of DKD, resulting in the development of the following (**Flowchart 1**):[8]

- Glomerular hyperfiltration
- Glomerular hypertension
- Renal hypertrophy
- Altered glomerular composition

Pathological Changes

The renal changes begin to happen, eventually causing interstitial fibrosis and glomerulosclerosis. The factors are as follows:[8]

- Deposition of extracellular matrix (ECM)
- Thickening of glomerular basement membrane
- Proliferative changes
- Tubular atrophy

RENAL CHANGES

There is an increase in the size of the kidney by 15% with the onset of DM. Hyperfiltration of glomerulus occurs in the early stage of both T1DM and T2DM. This hyperfiltration is due to the hypertrophy and hyperplasia of the cortical tubules, and concomitant renal enlargement occurs. As age increases, the eGFR

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decreases by 1 mL/min/1.73 m^2. This reduction in eGFR leads to masking of renal hyperfiltration in the elderly patients.[8]

The earliest changes include:

- Glomerular basement membrane thickening
- Mesangium expansion

Later on:

- Afferent arteriolar hyalinization
- Fibrin cap and capsular drop
- Glomerular sclerosis, diffuse and nodular
- Interstitial fibrosis

Diffuse glomerular lesions are much more common. The glomerular lesions are characterized by diffuse mesangial matrix expansion. Afferent and efferent vessels of the kidney develop arteriolar lesions. The arteriolar lesions are common and predominant. With the chronicity, the vessel walls are occupied by hyaline material entirely.[8] In nodular glomerulosclerosis, the nodules are acellular, spherical, eosinophilic, and are reactive to periodic acid-Schiff stain. These nodules are called Kimmelstiel–Wilson nodules. Nodules are found in 10–50% of the CKD patients.[8] However, it is essential to note that nodular and diffuse varieties are not specific to DKD but also are found in several other conditions.[8]

NATURAL HISTORY OF DIABETIC KIDNEY DISEASE

Type 1 Diabetes Mellitus

- Following 11–23 years of diagnosis of T1DM, proteinuria appears.
- There is an increase in serum creatinine concentration after 13–25 years.
- It takes about 18–30 years for the development of ESRD.

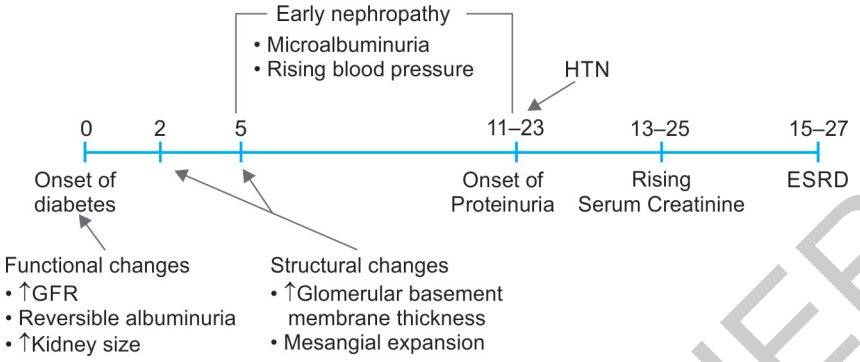
Type 2 Diabetes Mellitus

- Proteinuria and biopsy changes suggesting diabetic nephropathy could be present even before the diagnosis of T2DM.
- In T2DM, the major macrovascular changes and their complications may occur at any point in the history of DM.
- The eGFR reduces at a rate of about –0.9 ± 2.9 mL/min/1.73 m^2 per year in T2DM.
- Even in the presence of biopsy-proven diabetic nephropathy, up to 25% of patients have little or no proteinuria (**Flowchart 2**).

DIABETES IN CHILDREN

Microalbuminuria often develops during puberty, whilst its prevalence during the prepubertal period is generally low . The increasing prevalence of microalbuminuria during puberty is due to the influence of hormonal and metabolic changes, as well as poor compliance with treatment.[9] During adolescence,

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(ESRD: end-stage renal disease; GFR: glomerular filtration rate; HTN: hypertension)

FLOWCHART 2: Diabetic nephropathy—natural course.

several factors, both genetic and environmental, can influence the development of microalbuminuria and other vascular complications of diabetes. The characteristic hormonal and metabolic milieu of puberty makes this population particularly vulnerable to the effect of the metabolic derangement of diabetes. Puberty is characterized by rapid renal growth and glomerular hyperfiltration,[10] and these two factors can affect microalbuminuria risk, independently of glycemic control.[10,11] Recent studies have reported that many cases of microalbuminuria can regress to normoalbuminuria during follow-up. In particular, among adults with T1DM, the percentage of regression to normoalbuminuria may be 40–50%.[12] In particular, microalbuminuria is persistent in only 50% of adolescents whereas in the other 40–50%, urinary albumin excretion returns to the normal range 3–10 years following the onset of microalbuminuria.[12,13]

SCREENING OF DIABETIC KIDNEY DISEASE

- Measurement of BP
- Dipstick proteinuria
- Serum creatinine for assessment of eGFR
- Manifestation of diabetic nephropathy, often develops during adolescence. Adolescents with T1DM should undergo annual screening for microalbuminuria from the age of 9–11 years

CONCLUSION

- Diabetic kidney disease is among the most common causes of CKD and accounts for about 30%.
- Proteinuria is the harbinger of diabetic nephropathy.
- Proteinuria is a marker of endothelial dysfunction and an independent determinant of cardiovascular morbidity and mortality.
- Hyperglycemia and HTN are the most important risk factors of DKD.

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- Structurally, there is an increase in the size of the kidney due to hypertrophy of tubules.
- Pathological changes include the following:
  - The basement membrane of the glomerulus thickens.
  - Nodular and diffuse glomerulosclerosis
  - Arteriolar hyalinization occurs.
- Screening:
  - Type 1 diabetes mellitus after 5 years
  - Type 2 diabetes mellitus at the onset of disease
  - Children with DM at the onset of puberty

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Complications in

Diabetes Mellitus

Bench to Bedside
with a focus on Diabetic Kidney Disease

A handbook to sensitize the physicians to think about DKD while managing hyperglycemia and to make an early diagnosis and refer to a nephrologist at the right time instead of a wait-and-watch approach.

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