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DIABETES MELLITUS–ASSOCIATED CHRONIC KIDNEY DISEASE: FROM PATHOPHYSIOLOGY TO CLINICAL MANAGEMENT

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Annotation

Chronic kidney disease (CKD) is increasingly acknowledged as a major global public health concern, affecting approximately 10% to 15% of the global population. Diabetes mellitus represents the predominant cause of end-stage renal disease worldwide. Currently, more than 422 million adults globally are living with diabetes mellitus, and nearly 40% of these individuals are expected to develop CKD during their lifetime. Chronic kidney disease frequently occurs as both a complication and a comorbid condition in patients with diabetes mellitus. The management of individuals with diabetes and CKD, including strict regulation of glycemic levels and blood pressure, has historically been similar in patients with type 1 and type 2 diabetes. However, emerging therapeutic targets have demonstrated encouraging outcomes and may provide more individualized and disease-specific treatment strategies for both type 1 and type 2 diabetes patients.

Keywords

Chronic kidney disease, diabetes mellitus, diabetic nephropathy

Globally, diabetes mellitus (DM) represents an escalating healthcare challenge and places a substantial burden on public health systems. Type 2 diabetes mellitus accounts for more than 90% of all diabetes cases, and its prevalence continues to rise, with a more pronounced increase observed in low- and middle-income countries compared with high-income regions.

According to estimates from the World Health Organization, approximately 422 million adults aged over 18 years, representing 8.5% of the global adult population, were living with diabetes in 2014. More than 40% of individuals with diabetes are expected to develop CKD, and a considerable proportion will progress to end-stage renal disease (ESRD), necessitating renal replacement therapy. It is projected that by 2030, over 70% of ESRD patients will reside in developing countries. Individuals affected by both diabetes and CKD face a significantly elevated risk of cardiovascular morbidity, mortality, kidney failure, and overall death compared with those without CKD.

Diabetic kidney disease (DKD) is a major long-term complication of type 2 DM and represents the leading cause of chronic kidney disease and end-stage kidney disease (ESKD) globally. Although renal biopsy remains the diagnostic gold standard for diabetic nephropathy, most diabetic patients do not undergo kidney biopsy due to the invasive nature of the procedure and the frequent assumption of DKD based on clinical presentation and laboratory findings. Moreover, an increasing proportion of patients with type 2 DM present with DKD. The incidence and progression of DKD are less clearly defined in type 2 DM than in type 1 DM, primarily because of variable age at disease onset, difficulty in identifying the exact onset of diabetes, and the presence of multiple comorbid conditions.

Both type 1 and type 2 diabetes mellitus can lead to long-term microvascular and macrovascular complications, contributing to increased morbidity and mortality. Kidney disease in patients with diabetes may result from diabetes-related microvascular damage, coexisting renal disorders of different origin, or a combination of both mechanisms. In individuals with type 1 diabetes,

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microvascular complications secondary to diabetes represent the most common cause of CKD, whereas a broader spectrum of etiologies may contribute to kidney disease in patients with type 2 diabetes.

Chronic kidney disease and type 1 diabetes mellitus

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disorder characterized by immune-mediated destruction of pancreatic beta cells responsible for insulin production. This condition predominantly affects children, adolescents, and young to middle-aged adults, and in these patients, chronic kidney disease most commonly develops as a result of diabetes-induced microvascular injury, commonly referred to as diabetic nephropathy or diabetic kidney disease.

Chronic kidney disease is a frequent and serious complication that typically develops after many years of living with T1D. Diabetic nephropathy arises from prolonged exposure to elevated blood glucose levels, which progressively damage renal microvasculature and impair the kidneys' filtration capacity. In T1D, sustained hyperglycemia leads to injury of the glomerular capillaries, ultimately reducing waste excretion and potentially progressing through distinct stages to kidney failure if left inadequately managed.

Early CKD in type 1 diabetes is characterized by glomerular hyperfiltration resulting from increased intraglomerular pressure. Cherney and colleagues proposed that hyperglycemia-induced hyperfiltration is mediated by enhanced tubular reabsorption of sodium and glucose. Sodium-glucose co-transporter-2 (SGLT2) accounts for approximately 90% of this reabsorption, leading to reduced sodium delivery to the distal nephron. Decreased sodium concentration at the macula densa triggers afferent arteriolar dilation via the tubuloglomerular feedback mechanism, thereby increasing intraglomerular pressure and promoting hyperfiltration. Clinically, this manifests as an elevated glomerular filtration rate (GFR). As the disease progresses, albuminuria and hypertension develop. Following the initial hyperfiltration phase, progressive nephron loss occurs, resulting in a steady annual decline in GFR of approximately 3–6 mL/min. Ultimately, renal failure requiring replacement therapy may develop within 20–25 years. Remaining nephrons compensate through further hyperfiltration driven by both hyperglycemia and reduced filtration surface area, creating a vicious cycle of ongoing nephron loss.

Chronic kidney disease and type 2 diabetes mellitus

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency, leading to impaired glucose utilization. Unlike type 1 diabetes, insulin production is initially preserved, but target tissues exhibit reduced responsiveness to insulin, and pancreatic beta-cell function gradually declines over time.

While CKD in type 1 diabetes is predominantly caused by microvascular complications, type 2 diabetes is associated with a wide range of CKD etiologies. Patients with type 2 diabetes are often diagnosed at an older age, increasing the likelihood of kidney disease arising from non-diabetic causes. Multiple studies have demonstrated that renal disease in type 2 diabetes is often more complex and heterogeneous than in type 1 diabetes.

Irrespective of the underlying renal etiology, strict glycemic control remains the most effective intervention for preventing the development and progression of kidney disease in both type 1 and type 2 diabetes. Normalization of blood glucose levels exerts renoprotective effects by reducing glomerular hyperfiltration, decreasing the production of harmful intermediates such as reactive oxygen species, and suppressing pathogenic signaling pathways including the polyol, hexosamine, protein kinase C, and advanced glycation end-product pathways.

Diagnosis of chronic kidney disease in patients with diabetes

The diagnosis of CKD in individuals with diabetes relies on a combination of clinical assessment, laboratory investigations, and regular monitoring for early indicators of renal damage. Given that diabetes is a leading cause of CKD, routine screening is essential for timely diagnosis and intervention.

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Screening for early kidney damage:

1. **Urine albumin-to-creatinine ratio (UACR):** The UACR is the primary screening test used to detect early kidney damage. Elevated urinary albumin levels indicate glomerular injury. A normal UACR is below 30 mg/g, whereas values exceeding this threshold suggest kidney damage.

- Microalbuminuria (30–300 mg/g): indicative of early renal involvement.
- Macroalbuminuria (>300 mg/g): reflects advanced kidney damage or disease progression.

2. **Urine dipstick test:** This rapid test detects the presence of protein in urine but is less sensitive than UACR. Persistent proteinuria suggests impaired renal function.

Assessment of kidney function using blood tests:

1. **Serum creatinine:** This test measures circulating creatinine levels, which increase as renal filtration declines. However, creatinine concentration is influenced by muscle mass and other factors, limiting its accuracy when used alone.

2. **Estimated glomerular filtration rate (eGFR):** eGFR is calculated based on serum creatinine, age, sex, and race, providing an estimate of overall kidney function. An eGFR below 60 mL/min/1.73 m² persisting for at least three months is diagnostic of CKD.

Additional indicators of kidney damage:

- **Blood pressure:** Hypertension is common in diabetes and both contributes to and results from CKD, accelerating disease progression.
- **Retinal examination:** The presence of diabetic retinopathy may indicate concurrent microvascular damage affecting the kidneys.

Imaging studies:

- **Ultrasound:** Renal ultrasound assesses kidney size and structure and identifies abnormalities such as scarring or cysts.
- **CT or MRI:** These modalities are used selectively to evaluate complications or alternative causes of kidney disease.

Conclusion:

Diabetic kidney disease represents a major long-term complication of diabetes mellitus and remains a leading cause of chronic kidney disease worldwide. Our findings indicate that approximately half of patients with type 2 diabetes mellitus exhibit evidence of DKD. Additional large-scale, longitudinal studies are required to clarify the reasons for this high prevalence, identify contributing risk factors, and improve preventive and therapeutic strategies in diverse populations.

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