REVIEW ARTICLE

Decoding Diabetic Kidney Disease: In-Depth Analysis of Prevalence, Risk Factors, Biomarkers, and Management Strategies

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ABSTRACT

End-stage kidney disease (ESKD) is primarily caused by diabetic kidney disease (DKD), a common ailment that affects people all over the world and results from diabetes mellitus. Hemodynamic, metabolic, and inflammatory factors interact to influence its development. However, these changes are not unique to DKD, necessitating the development of novel biomarkers to support diagnosis, tracking, evaluation of treatment efficacy, and outcome prediction. High blood sugar levels trigger the disease by increasing the production of reactive oxygen species. Despite its significance as a global medical condition, people often ignore it. DKD causes major challenges for the community, finances, and individuals. Symptoms often remain unnoticed until they become evident, resulting in significant consequences. The absence of detailed data and infrequent screening protocols impede the early identification of diabetic kidney disease (DKD). The right medications and a precise diagnosis could help regulate the illness, prolong life, and lessen the psychological and financial burden on those affected. DKD frequently emerges right after the condition becomes severe. This research aims to identify global cases, factors that heighten the risk of developing DKD, and potential indicators for early diagnosis of DKD.

KEY WORDS: Diabetes mellitus (DM), Diabetic kidney disease (DKD), Epidemiology, Prevalence, Biomarkers, Diagnosis, Management.

Introduction

This article examines the inflammatory aspect of diabetic kidney disease (DKD) and the potential use of new biomarkers in DKD treatment[1]. It highlights the importance of early identification of inflammatory biomarkers for minimizing consequences and maximizing treatment choices[2].

Diabetic nephropathy, also known as diabetic kidney disease (DKD), is a unique condition-affecting individuals with both diabetes and chronic kidney disease[3], altering the kidney's function and altering the body's waste and fluid elimination. The symptoms of this condition are albuminuria, edema, polyuria, nausea, anemia, and hypertension[4].

The condition escalates the chance of death by 31.1% in individuals who have diabetes, and this risk amplifies as the seriousness of the disease progresses[5]. Timely identification of DKD is essential in order to mitigate the impact on both individuals and the economy. Nevertheless, it often goes unnoticed until significant issues arise.

Implementing early detection methods is a financially efficient strategy to lessen the overall impact. This research focuses on the worldwide incidence, risk factors, and potential early indications of DKD.[6]

Epidemiology and Perspectives in DKD

Diabetes mellitus affects 10.5% of people aged 20-79 globally, with 537 million cases reported in 2021 and projected to reach 643 million by 2030[7]. The disease often takes 4-7 years to diagnose, and clinical damage often does not manifest until later[8].

Access this article online

Quick Response Code:

Website: www.jmsh.ac.in

Doi: 10.46347/jmsh.v10.i2.24.182

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The development and advancement of this illness include several factors, including hemodynamic, metabolic, and inflammatory processes. The inflammatory axis is becoming a crucial target for therapeutic intervention[9].

In China, 38.8% of individuals diagnosed with diabetes had DKD, while 2.9% had it in rural dwellers[10]. In India, 34.4% had DKD, and 62.3% had it in a multicenter study[11]. The older population in the eastern Mediterranean has the highest rates of diabetes mellitus and CKD-DM. In Japan, 15.3% of patients with type 2 diabetes had a poor estimated glomerular filtration rate[12]. In the UK, 28% of patients had renal impairment after a 15-year follow-up period. In the United States, 2.2% of the population has DKD, and the prevalence is rising in direct correlation with diabetes occurrence[13]. The research emphasizes that in order to overcome DKD, there is a need for more awareness and preventative efforts.

Diabetic Kidney Disease (DKD) is a prevalent global health issue, with an estimated incidence of 1.75 in people with diabetes[14]. Research conducted in China, India, and the United Arab Emirates reveals varying incidences of DKD.

Pathophysiology of DKD

The etiology of diabetic kidney disease (DKD) involves a multifactorial interaction of inflammatory, hemodynamic, and metabolic variables[15]. Hyperglycemia sets off a series of metabolic reactions that result in endothelial dysfunction, oxidative stress, and damage to the tubules and glomerulus[16]. Tubular dysfunction affects the processes of reabsorption and secretion, whereas renal hyperfiltration and elevated intraglomerular pressure lead to glomerular damage[17]. Renal injury is further aggravated by chronic inflammation and fibrosis, which leads to a steady loss in kidney function[12]. Comprehending these pathophysiological pathways is essential for creating tailored treatments meant to maintain renal function and enhance DKD outcomes.

Table 1 provides a comprehensive overview of the various factors that contribute to the development and progression of DKD, emphasizing the need for comprehensive management strategies.[18]

The metabolic route encompasses the use of polyol, hexosamine, advanced glycation end products, and protein kinase C[19]. Hyperglycemia leads to kidney injury by forming glycosylated end products, activating protein kinase C, and synthesizing diacylglycerol[20].

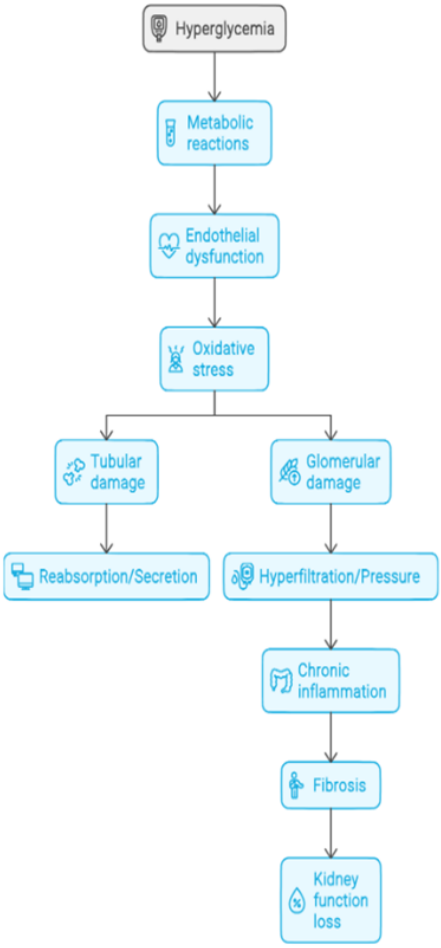

Figure 1: [1,2] The Pathophysiology of Diabetic Kidney Disease

Limitations of Conventional Biomarkers

Albuminuria and a decrease in the estimated glomerular filtration rate (eGFR), which is determined by blood creatinine levels, are diagnostic indications of diabetic kidney disease (DKD).[21] Albuminuria is a reliable biomarker for predicting future progression and evaluating treatment efficacy. Urinary albumin excretion (UAE) is used for risk stratification and measures the extent of albuminuria, making it a crucial tool in diagnosing and managing DKD[22].

Table 1: Comprehensive overview of the various factors that contribute to the development and progression of DKD

Sr.No	Contributors	Description
1	Hyperglycemia	Elevated blood glucose levels leading to metabolic changes and kidney damage
2	Hypertension	High blood pressure contributing to renal microvascular damage
3	Dyslipidemia	Abnormal lipid metabolism leading to endothelial dysfunction and renal injury
4	Genetic Predisposition	Inherited susceptibility to kidney disease in individuals with diabetes
5	Inflammation	Chronic low-grade inflammation exacerbating renal damage
6	Oxidative Stress	Imbalance between reactive oxygen species (ROS) and antioxidant defenses
7	Renin-Angiotensin System Activation	Over-activation of the renin-angiotensin system leading to vasoconstriction and fibrosis
8	Protein Kinase C Activation	Dysregulation of protein kinase C signaling pathways contributing to renal injury
9	Advanced Glycation End Products (AGEs)	Accumulation of AGEs leading to endothelial dysfunction and inflammation
10	Renal Hyperfiltration	Increased glomerular filtration rate resulting in glomerular damage
11	Endothelial Dysfunction	Impaired endothelial function contributing to vascular pathology
12	Podocyte Injury	Damage to podocytes disrupting glomerular filtration barrier
13	Tubulointerstitial Fibrosis	Accumulation of extracellular matrix proteins leading to renal fibrosis
14	Autoimmunity	Immune-mediated injury to renal tissue in susceptible individuals
15	Environmental Factors	Lifestyle, diet, and other environmental factors influencing disease progression

Glomerular filtration rate (GFR) is the primary clinical biomarker used to evaluate the prognosis of diabetic kidney disease (DKD) during follow-up. When glomerular filtration rate falls, there is a clear correlation between structural damage and kidney function, but this association is less apparent with mild albuminuria or a slight decline in eGFR[23].

Changes in the present and prior estimated GFRs (eGFRs) are important indicators of how the illness is likely to proceed. The glomerular filtration rate (GFR) is often estimated using the CKD-EPI and MDRD equations.[24] However, it is important to note that these equations have the potential to either underestimate or overestimate the actual GFR. This discrepancy may occur because of compensatory adjustments in the functioning of the remaining nephrons[25]. Particularly for those with the common normoalbuminuric phenotype who lack particular therapy options, the diagnostic and follow-up techniques already in use have drawbacks.[26]

The research highlights the need for novel biomarkers to improve diagnostic and monitoring methods for diabetic kidney disease, focusing on their effectiveness in diagnosing, monitoring progression, assessing treatment response, and predicting prognosis.[27] The study will investigate the practical application of new biomarkers, as illustrated in Figure 2.

Figure 2 shows tables that provide comprehensive list of overview of conventional biomarkers[28,29] vs novel biomarkers[30–32] commonly used in clinical practice to diagnose, monitor, and manage Diabetic Kidney Disease, focusing on kidney function, damage, and overall metabolic control.

Novel Biomarkers in Diabetic Kidney Disease

Early detection is crucial for managing diabetes-related kidney disease, but traditional diagnostic techniques often lead to delayed diagnosis[33]. The study of DKD pathophysiology and mechanisms has heightened the importance of discovering novel biomarkers in urine and serum through proteomics and metabolomics.

Advancements in kidney damage knowledge have led to the development of biomarkers that can aid in diagnosing diabetic kidney disease (DKD). These biomarkers, unlike conventional ones like

Table A: Comprehensive list of overview of Conventional Biomarkers

Sr. no	Conventional Biomarkers	Type	Description	Clinical Relevance
1	Albuminuria	Urinary	Presence of albumin in urine, indicative of kidney damage	Gold standard for DKD diagnosis and monitoring
2	Estimated Glomerular Filtration Rate (eGFR)	Blood/ Calculation	Calculation of kidney function based on serum creatinine levels using equations such as MDRD or CKD-EPI.	Assesses the degree of kidney function and stages of CKD.
3	Neutrophil Gelatinase-Associated Lipocalin (NGAL)	Urinary	Marker of tubular injury and inflammation	Early detection of AKI and DKD progression
4	Kidney Injury Molecule-1 (KIM-1)	Urinary	Tubular injury marker associated with inflammation and fibrosis	Prognostic marker for DKD progression and renal function decline
5	Serum Cystatin C	Blood	Protein used to estimate GFR. independent of muscle mass.	More accurate in detecting early declines in kidney function than creatinine.
6	Urinary Biomarkers (e.g., MCP-1, TGF-β1, IL-6)	Urinary	Inflammatory and fibrotic markers reflecting renal damage	Potential for early detection and risk stratification
7	High-Sensitivity C-Reactive Protein (hs-CRP)	Blood	Marker of systemic inflammation associated with DKD	Predictive of cardiovascular risk in DKD patients
8	FGF-23	Blood	Phosphate-regulating hormone associated with mineral metabolism and cardiovascular disease	Predictor of CKD progression and adverse outcomes in DKD
9	Urinary Exosomal microRNAs	Urinary	Small non-coding RNAs implicated in gene expression regulation	Potential for early detection and therapeutic monitoring
10	Urinary Albumin Excretion	Urinary	Measurement of albumin-to-creatinine ratio (UACR) in a spot urine sample.	Early markers of kidney damage Persistent albuminuria indicates DKD.
11	Serum Creatinine	Blood	Measurement of creatinine levels in the blood to estimate GFR.	Elevated levels indicate reduced kidney function.
12	Blood Urea Nitrogen (BUN)	Blood	Measurement of nitrogen in the blood that comes from the waste product urea.	Elevated levels indicate impaired kidney function.
13	Urinary Total Protein	Urinary	Measurement of total protein in the urine.	Indicates the presence and extent of proteinuria.
14	Hemoglobin A1c (HbA1c)	Blood	Measurement of average blood glucose levels over the past 2-3 months.	Indicates glycemic control, a crucial factor in managing DKD.

Table B: Comprehensive list of overview of Novel Biomarkers

Sr. no	Novel Biomarkers	Type	Description	Clinical Relevance
1	Urinary Retinol-Binding Protein (RBP)	Urinary	Marker of tubular proteinuria.	Indicates proximal tubular damage and early renal dysfunction.
2	Kidney Injury Molecule-1 (KIM-1)	Urinary	Tubular injury marker associated with inflammation and fibrosis	Prognostic marker for DKD progression and renal function decline
3	Serum soluble urokinase plasminogen activator receptor (suPAR)	Blood	Marker of systemic inflammation and immune activation	Associated with DKD development and progression
4	Urinary Liver-Type Fatty Acid-Binding Protein (L-FABP)	Urinary	Marker of proximal tubular injury and oxidative stress	Predictive of early DKD progression and adverse outcomes
5	Urinary Netrin-1	Urinary	Axonal guidance cue protein involved in tubular integrity and repair	Elevated levels associated with DKD progression and renal fibrosis
6	Plasma Soluble Endothelial Protein C Receptor (sEPCR)	Blood	Endothelial cell marker reflecting endothelial dysfunction	Predictive of renal and cardiovascular outcomes in DKD
7	Urinary Aquaporin-2 (AQP2)	Urinary	Water channel protein reflecting tubular function and urine concentration	Potential marker for DKD progression and response to therapy
8	Plasma Angiopoietin-like 4 (ANGPTL4)	Blood	Lipid metabolism regulator associated with inflammation and endothelial dysfunction	Elevated levels predictive of DKD progression and cardiovascular events
9	Plasma Pentraxin-3 (PTX3)	Blood	Acute phase protein involved in innate immunity and inflammation	Associated with DKD severity and cardiovascular risk
10	Plasma Betatrophin	Blood	Hormone implicated in pancreatic beta-cell proliferation and insulin resistance	Elevated levels correlate with DKD severity and decline in renal function
11	Transforming Growth Factor-Beta 1 (TGF-β1)	Urinary/Blood	Marker associated with renal fibrosis and inflammation.	Correlates with the severity of renal damage and progression of DKD.
12	N-Acetyl-β-D-Glucosaminidase (NAG)	Urinary	Enzyme marker of tubular damage.	Elevated levels indicate early tubular injury.
13	Plasma Beta-2 Microglobulin	Blood	Marker of tubular reabsorption efficiency.	Elevated levels are associated with tubular dysfunction and early kidney damage.
14	Urinary Angiotensinogen	Urinary	Marker associated with intrarenal RAAS activation.	Indicates early intrarenal angiotensin II activity and kidney injury.

Figure 2: [1,2]This table provides acomprehensive list of overview of Conventional biomarkers[28,29]vs novelbiomarkers[30–32]commonly used in clinical practice to diagnose, monitor, and manage DiabeticKidney Disease, focusing on kidney function, damage, and overall metabolic control.

serum creatinine, can enhance the accuracy of DKD assessments, making them more precise tools for evaluating kidney function[34].

The AKI agreement asserts that biomarkers should not replace conventional testing and clinical evaluations but rather serve as supplementary examinations to identify individuals who can benefit from cardiovascular risk prevention and management strategies[35].

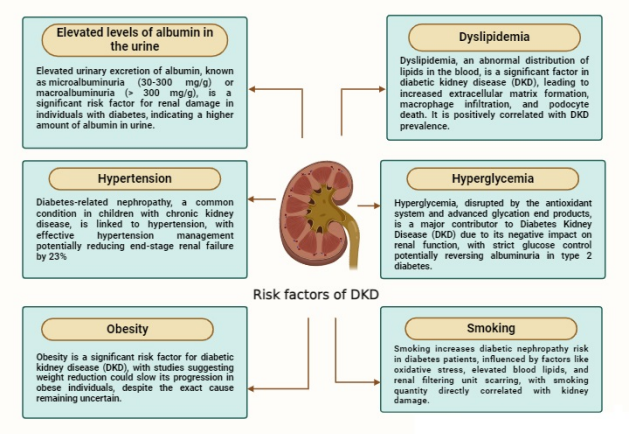

Figure 3: [1,2] Potential Risk factors of DKD[36,37]

Biomarkers for the early diagnosis of DKD

Biomarkers like urine albumin excretion rate, UAER, UACR, and eGFR help detect renal damage before clinical signs of diabetic kidney disease (DKD)[6]. New biomarkers like L-FABP, NGAL, and KIM-1 show promise in early detection of renal damage. Integrating these indicators into clinical practice can help mitigate DKD development and related consequences through early intervention and individualized care techniques.

Timely identification and suitable therapies are vital for effectively treating kidney disease (DKD), as they may effectively slow down the course of the illness, enhance life expectancy, and alleviate the physical, emotional, and financial strain associated with it[38]. The absence of diagnostic indicators, such as albuminuria and serum creatinine, poses a hindrance to the timely detection of a condition[39]. Research has shown that albuminuria is an unreliable and insensitive indicator, while serum creatinine does not possess strong predictive capability[40]. Hence, new biomarkers are needed for early diagnosis and treatment of DKD due to their sensitivity and predictability, as existing biomarkers are not very sensitive.

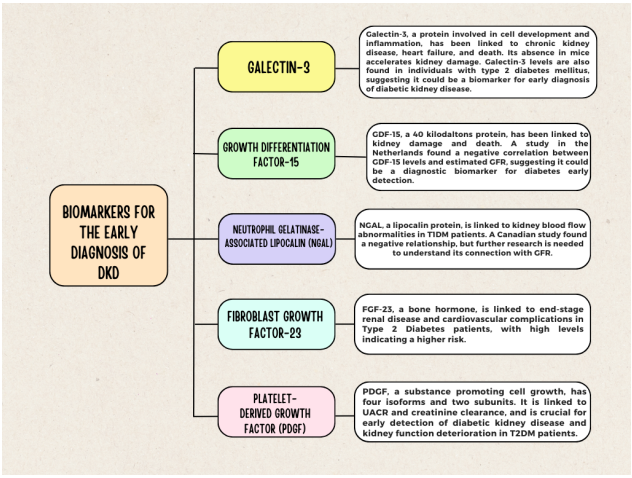

Figure 4: [1,2] Potential Biomarkers for the early diagnosis of DKD [41–43]

Diagnosis of DKD

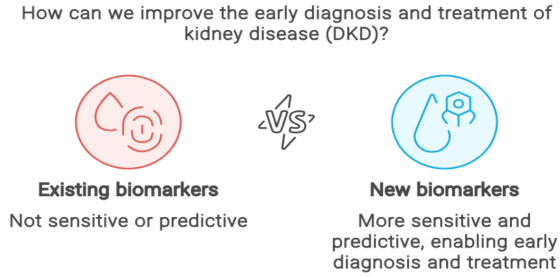

Figure 5: Type of biomarker are more important for disease diagnosis and treatment

Diagnosis of diabetic kidney disease involves assessing urine albumin excretion and glomerular filtration rate (GFR)[44]. Early renal impairment is detected through albuminuria screening, while chronic albuminuria and GFR measurement aid in staging DKD severity[45]. Further diagnostic procedures include serum biomarkers, kidney biopsy, and renal imaging. Early identification and monitoring are crucial for prompt intervention and therapy to prevent DKD from progressing to end-stage renal disease.

Table 2 shows various diagnostic assessments used in the diagnosis of DKD, focusing on indicators of kidney function, damage, and overall metabolic control. These steps help in early detection, monitoring disease progression, and guiding treatment decisions.[46]

Table 2: Various diagnostic assessments used in the diagnosis of DKD

Sr. no	Diagnostic Step	Description
A	**Screening**	
1	Annual Screening	All patients with diabetes should undergo annual screening for kidney disease
2	Urinary Albumin Excretion	Measurement of urinary albumin-to-creatinine ratio (UACR) in a spot urine sample. Persistent albuminuria (>30 mg/g) indicates kidney damage[7]
3	Glomerular Filtration Rate (GFR)	Calculation of estimated GFR (eGFR) using equations such as MDRD or CKD-EPI. Decreased eGFR (<60 mL/min/1.73m ^ 2) indicates kidney damage
B	**Diagnostic Confirmation**	
1	Confirmation of Albuminuria	Confirmatory testing with at least two out of three urine samples collected over 3-6 months
2	Measurement of Serum Creatinine	Measurement of serum creatinine levels to estimate GFR and assess kidney function
C	**Additional Tests**	
1	Renal Imaging	Imaging studies such as ultrasound to assess kidney structure and identify anatomical abnormalities
2	Serum Biomarkers	Measurement of serum cystatin C or urinary biomarkers (e.g., KIM-1, NGAL) for additional information about kidney injury and prognosis
3	Renal Biopsy	In select cases, renal biopsy may be indicated to confirm diagnosis and guide treatment decisions
D	**Evaluation of Complications**	
1	Cardiovascular Assessment	Assessment of cardiovascular risk factors (hypertension, dyslipidemia) given the high risk of cardiovascular disease in DKD
2	Screening for Other Complications	Regular screening for other diabetes-related complications such as retinopathy and neuropathy
E	**Monitoring and Follow-up**	
1	Regular Monitoring	Regular monitoring of kidney function (eGFR, UACR), blood pressure, glycemic control, and other relevant parameters to guide treatment and assess disease progression
2	Multidisciplinary Care	Collaborative care involving primary care providers, endocrinologists, nephrologists, and other specialists for comprehensive management of DKD and associated comorbidities

Diagnosing diabetic kidney disease (DKD) involves UACR measurement and GFR assessment, which should be less than 60 ml/min per 1.73 m^2. Even in cases of type 1 and type 2 diabetes, GFR decreases even when the ratio is within permissible limits. It is crucial for diabetics to check their creatinine levels annually. GFR can be calculated using formulas like the MDRD formula and the CKD-EPI equation. The American Diabetes Association recommends screening for nephropathy in all patients with type 2 diabetes and those with type 1 diabetes for more than five years.

Conclusion

In recent years, new treatments for DKD have emerged due to ongoing research into potential targets for prediction, follow-up, and prevention. Nevertheless, the integration of these indicators into clinical practice is currently undergoing development. Advancements in the development of new molecules and therapeutic approaches show promise for expanding the options available to doctors for more effective and individualised therapies in the future.

DKD is a medical disaster with high occurrence rates, inadequate detection methods, and a lack of new indicators for early diagnosis. Multinational and multicenter epidemiological investigations are necessary to validate the potential and suitability of novel plasma and urine biomarkers, which are proving effective for timely detection.

Table 3: Tabular representation of the management and treatment of Diabetic Kidney Disease (DKD)[47,48]

Sr. no	Treatment	Description	Examples
1	Glycemic Control	Tight glycemic control to delay DKD progression	Metformin, Insulin, SGLT2 inhibitors
2	Blood Pressure Management	Use of RAAS blockers to reduce proteinuria and slow DKD progression	ACE Inhibitors (e.g., Lisinopril), ARBs (e.g., Losartan)
3	Lipid Management	Statin therapy to reduce cardiovascular risk in DKD	Atorvastatin, Rosuvastatin
4	Protein Restriction	Moderate protein restriction to reduce proteinuria	Dietary counseling
5	Sodium Restriction	Limiting sodium intake to manage hypertension and fluid retention	Dietary counseling
6	RAAS Blockade	Use of ACE inhibitors or ARBs to preserve renal function	Enalapril, Irbesartan
7	Anticoagulation Therapy	Consideration of anticoagulation to reduce thromboembolic risk	Enoxaparin, Apixaban
8	Antiplatelet Therapy	Use of antiplatelet agents to reduce cardiovascular risk	Aspirin, Clopidogrel
9	Lifestyle Modifications	Promotion of healthy lifestyle behaviors.	Diet, Exercise, Smoking cessation
10	Regular Monitoring	Monitoring kidney function, blood pressure, and glycemic control.	eGFR, UACR, Blood pressure
11	Referral to Nephrology	Consultation with nephrologist for comprehensive management.	Nephrologist appointment

Acknowledgment

We thank **Krescent Medical Research Pvt Ltd**., for overall technical guidance during the preparation of this manuscript.

Financial support and sponsorship: Nil.

Conflicts of Interest: The authors declare no conflict of interest.

Software used: The figures were created using BioRender[1] and Canva[2].

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How to cite this article: Upadhye KS, Patidar H. Decoding Diabetic Kidney Disease: In-Depth Analysis of Prevalence, Risk Factors, Biomarkers, and Management Strategies. J Med Sci Health 2024; 10(2):204-212

Date of submission: 10.06.2024
Date of review: 13.06.2024
Date of acceptance: 16.07.2024
Date of publication: 29.07.2024