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# CLINICAL CRITERIA AND LONG-TERM COMPLICATIONS OF DIABETIC RENAL DISEASE

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**Abstract:**

*Renal disease in diabetic patients is mediated by a set of complicated hemodynamic, metabolic, and inflammatory factors. Diabetic kidney disease (DKD) increases the risk of requiring replacement therapy and renal transplantation as well as all-cause mortality. DKD is characterized by albuminuria, a low glomerular filtration rate (GFR, lower than <60 mL/min/1.73 $m^2$), or both of them and it develops over a period between 10 and 20 years. Such a condition is preventable through strict blood pressure and glycemic control yet early diagnosis is necessary to improve the outcome. It is necessary to consider DKD detection in diabetic patients with a low GFR even in normoalbuminuric cases. However, patients with type I diabetes and microalbuminuria are more likely to develop overt nephropathy although both types of diabetes with established nephropathy would progress to renal failure at the same rate. Long-term complications, including renal failure and cardiovascular events (stroke and nonfatal myocardial infarction), could be minimized via conducting future research studies that possibly reveal potent biomarkers for early detection and enhance the therapeutic approaches based on an adequate understanding of disease pathogenesis.*

**Keywords**: *Diabetic nephropathy, diabetic kidney disease, cardiovascular complications, microalbuminuria, glomerular filtration rate.*

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## INTRODUCTION:

Diabetes has long been identified as one of the most significant public health issues worldwide. According to the recent estimates of the International Diabetes Federation in 2017, approximately 425 million people had diabetes, and this figure is expected to rise to 552 million by 2030 [1]. The increasing incidence of diabetes would have not only deleterious manifestations but also the subsequent complications might augment the established burden. A range of complications has been identified, including acute life-threatening consequences, such as ketoacidosis or severe hypoglycemia to chronic complications that involve multiple organs, such as diabetes-related retinopathy, neuropathy, nephropathy, or cardiovascular disease (CVD).

The prevalence of such complications is hardly estimated on the global level, possibly because of the variations in diagnostic standards utilized in each country. Nonetheless, a considerable number of diabetic patients would develop one or more complications during their life. For example, evidence from the UK Prospective Study [2] revealed that albuminuria had been developed in about 38% of patients with newly diagnosed type II diabetes mellitus (DM), while renal impairment (as indicated by a creatinine clearance less than 60 mL/min) was reported in 29% of them. Furthermore, the risk of these complications increased with prolonged diabetes durations with a relative male propensity [2]. Among the United Stated populations, the demographically-adjusted prevalence of diabetic kidney disease (DKD) has been increased from 18% to 34% during the period from 1988 to 2008 ($P$=0.003 for trend) [3].

DKD is classically referred to as a kidney disease attributable to DM although the different types of kidney disease and DM are both deemed as common chronic conditions. Therefore, individuals with DM may have interrelated etiologies of their impaired kidneys. Interestingly, both types of diabetes are frequently complicated with DKD, which might ultimately develop to end-stage renal disease (ESRD). Indeed, diabetic nephropathy contributes to 50% of the total ESRD cases in the developing countries [4]. DKD is also associated with extraordinarily higher costs for medical care, possibly due to the strong correlation with the development of ESRD and CVD [5].

In the light of increased disease burden and the subsequent unfavorable consequences, DKD should be outlined correctly. Despite the significant improvements in the managemental procedures, the increasingly reported numbers of DKD patients emphasizes the that the management is still not adequate. It is imperative for each clinician to be aware of the diagnostic approaches to manage the diabetic patients accordingly and prevent ESRD. As the first step in diagnosis, we reviewed the pathophysiological aspects of DKD and focused on the clinical characteristics of DKD along with providing an insight into the potential long-term complications to be considered during management.

## METHODS:

This review was based on a systematic search process in October 2018, including the following scientific databases: Pubmed, Embase, and Google Scholar. We used multiple combinations of these keywords or their equivalents: “diagnosis of diabetic kidney disease”, “diabetes complications”, “clinical criteria of diabetic kidney disease”, “microscopical changes”, “diabetes complications”, “diabetic nephropathy”, “end-stage renal disease”. Articles published in peer-reviewed journals and those written in English were eligible as long as their full-text version was available. Data from review articles, retrospective cohort studies, clinical trials, and systematic reviews were considered. However, conference proceedings and non-English manuscripts were excluded.

## RESULTS AND DISCUSSION:

The search process yielded a total of 2394 records, of which 153 records were screened for their titles and abstracts. Ultimately, data from 31 articles were collected and organized in the relevant sections in this review.

### Pathophysiology

The progression of nephropathy involves a highly complicated process given the variable types and roles of renal cells. The pathogenic changes of DKD are mediated by several pathways. The hemodynamic pathway includes activation of the renin–angiotensin–aldosterone system (RAAS) which results in the elevation of angiotensin II levels and subsequent vasoconstriction of the efferent arterioles. Such phenotype has been associated with albuminuria and nephropathy in human [6]. Endothelin-1 is also an important mediator of vasoconstriction that mimics RAAS actions [7].

Another inflammatory pathway contributes to the incidence of DKD parallel with the chronic activation of the innate immune system as well as some low-grade inflammatory reactions [8]. Hyperglycemia can cause increased expression of the nuclear factor NF-κB (which has been associated with proteinuria) [9], activation of the Janus Kinase 2 (which is negatively

correlated with estimated glomerular filtration rate [GFR]) [10], and increased expression of tumor necrosis factor (TNF)-$\alpha$ and interleukin (IL)-6 (contribute to glomerular basement membrane thickening and albuminuria) [11, 12]. Collectively, the renal injury may be viewed as an increased in thickness of the glomerular membrane, mesangial nodule formation (Kimmelsteil-Wilson bodies), development of microaneurysms, and other pathological changes.

Finally, A metabolic pathway of DKD has been well-described in 2001, where the hyperglycemic state has been found to increase glycolysis [13]. These changes would ultimately promote glomerular hyperfiltration. The latter is mediated by hypertension and obesity via multiple mechanisms, including glomerular enlargement and increased transmitted systemic blood pressure [14]. It is worthy to note that glomerular hyperventilation occurs in 40% of patients with T1DM and up to 75% in T2DM [15]. This pathological process plays a significant role in the damage of renal glomeruli, the main filtration component, and the preglomerular vessels [16].

**Clinical Criteria**

DKD is characterized by albuminuria (albumin to creatinine ratio is $\geq$ 30 mg/g), a GFR lower than <60 mL/min/1.73 $m^2$, or both of them [17]. Although DKD is commonly known as diabetic nephropathy, it also includes ischemic nephropathy, atheroembolic disease, and interstitial fibrosis. Traditionally, the existence of overt proteinuria was the main diagnostic feature of DKD. In addition, it was thought that if a kidney disease has developed in a patient with longstanding diabetes, then the renal disease would not be caused by DM. Later, a more comprehensive perspective has shown a progressive development of microalbuminuria, glomerular hyperfiltration, overt proteinuria, and decreased GFR, giving rise to ultimate dialysis [18]. However, a more heterogeneous picture of DKD has been revealed by additional investigations [19].

The onset of DKD starts with the development of proteinuria and a gradual decline in GFR over a period between 10 and 20 years. Diabetes-induced proteinuria is referred to as elevated protein concentration greater than 500mg/24 hours, which might be preceded by a state of microalbuminuria (30-299 mg/24 hours) [20]. In T1DM, microalbuminuria will be considered confirmatory if it persists within 7-10 years of diagnosis [21]. The majority of patients with such persistent form usually develop a 10-20% annual increase of urinary albumin secretion to overt proteinuria within the following 10-15 years, and this might reach up to 32 years in rare cases [22]. Subsequently, the GFR declines significantly at a rate of 2-20 mL/min/year. Eventually, after 20 years, 75% of patients will develop renal failure and fatal uremic complications [23]. The significance of monitoring GFR and proteinuria in T1DM has been emphasized by Caramori et al. [24] who observed that low GFR was associated with microscopically-detected advanced glomerulopathy despite normal albumin excretion in the urine.

Conversely, DKD in T2DM patients is less sensitive to albuminuria. The overt disease could be apparent only in 20-40% of diabetic patients with microalbuminuria and, of them, only 20% will develop renal failure at the same decline rates of GFR as compared to T1DM [23]. According to the U.K. Prospective Diabetes Study (UKPDS), microalbuminuria has been developed in only 2% of T2DM patients each year, while approximately one-third of the participants had a low GFR (<60 ml/min/1.73 $m^2$) within 15 years of diagnosis [2]. Notably, albuminuria may be regarded as a dynamic, nonstabilized parameter rather than increasing in a consistent linear pattern. As a consequence, a recent paradigm of normoalbuminuric diabetic kidney disease (NADKD) has emerged, and the epidemiological studies have demonstrated that this condition is common. In general, the prevalence of NADKD is non-negligible since the normoalbuminuric T2DM patients with chronic kidney disease constituted a range between 14.29% and 63% in different epidemiological studies [2, 25, 26]. Chen et al. [27] have proposed a set of diagnostic criteria for NADKD, including a decrease in estimated GFR below 60 mL/min/1.73 $m^2$ with normal urinary protein levels along with the exclusion of other secondary renal diseases, such as obstructive and hypertensive nephropathy. For GFR estimation, a specific equation relying on serum cystatin c has been found to better predict long-term renal outcomes in diabetic patients when compared to a serum creatinine-based equation [28].

**The prominent risk factors**

The overt nephropathic disease in diabetic patients may be related to hypertension. For example, in an early UKPDS [29], a group of diabetic patients with a poor blood pressure control had a significantly higher proportion of patients with albuminuria (greater than 50 mg/L) compared to another group with tightly-controlled blood pressure. This was confirmed by Ravid et al. [30] who found a significant delay in the onset of deteriorated renal functions in patients with

T2DM and microalbuminuria (mean 143 mg/24 h) when their blood pressure was controlled by enalapril as compared to placebo ($P < 0.005$). Notably, prior to the onset of renal failure, early epidemiological studies have revealed an association between albuminuria and hypertension in T2DM [31, 32]. Indeed, such evidence indicates a robust association of developing DKD in diabetic patients with poor blood pressure control. Once the nephropathic changes have been developed, blood pressure may be elevated yet a transient improvement of the glycemic control may be seen due to the reduced renal insulin secretion [33].

In addition, although a subset of patients with a good glycemic control developed DKD in an early study [34], subsequent investigations have revealed that poor glycemic control may contribute to the development of diabetes-related microvascular complications, including DKD [35]. A community-based study[36] has shown a positive association between uncontrolled glycated hemoglobin (HbA1c) levels and the risk of chronic kidney disease even in the absence of microvascular pathology as indicated by albuminuria. As such, the role of urinary albumin screening may be interpreted cautiously in some instances for the detection of DKD.

**The microscopical changes**

In T1DM, thickening of the glomerular basement membrane is usually detected within 1.5-2 years of diagnosis, which may be associated with a typical thickening of the tubular basement membrane [37]. Subsequently, mesangial volume expansion takes place in the following 5-7 years [38] along with segmental mesangiolysis (leading to the development of the aforementioned microaneurysms and nodules) [39]. Interestingly, both mesangial expansion and increased glomerular basement membrane thickness have been associated with albuminuria, hypertension, and GFR in T1DM patients [40].

In T2DM, it has been shown that only one-third of patients with T2DM and associated microalbuminuria had a typical picture of diabetic glomerulopathy [41]. The remaining samples showed variable findings, ranging between a relatively normal renal tissue to severe tubulointerstitial lesions. Further challenging findings have reported DKD, as evidenced by thickening of the glomerular basement membrane, in prediabetics, including those with metabolic syndrome and proteinuria, even up to two years prior to the overt incidence of DM [42]. The histopathological changes are less prominent, and their association with clinical presentation is less apparent [43]. Furthermore, the prevalence of nondiabetic renal disease in T2DM patients is debatable. Pham et al. [44] conducted a retrospective analysis of biopsy reports of diabetic patients during a ten-year period and showed a high prevalence of nondiabetic renal disease (53.2%), particularly in young-aged patients, and this was frequently associated with focal segmental glomerulosclerosis. However, it seems that the outcomes of such study were affected by selection bias, probably because patients undergoing kidney biopsies are expected to have an atypical form of kidney disease. This is because another analytic investigation of a former randomized clinical trial has shown a remarkably less prevalence rate (<10%) of nondiabetic kidney disease in T2DM concomitant with albuminuria [45]. These different aspects of presentation of the pathological changes in T2DM may be attributable to several factors: (1) prediagnostic exposure to hyperglycemia for long times, (2) older-aged patients, (3) the high probability to atherosclerotic changes, and (4) prediagnostic treatment with RAAS inhibitors. Therefore, Tervaert et al. [46] have introduced a classification system of the pathologic changes implied in DKD, considering a separate assessment of the interstitial and vascular alterations independent of other DKD criteria related to albuminuria, GFR, or type of diabetes (Table 1).

Table 1: The pathologic classification of DKD. Adapted from Karl and Sharma [47]

| DKD class | The pathologic criteria |
|---|---|
| 1 | Thickness of the glomerular basement membrane (isolated) |
| 2 | • Mesangial expansion (mild in the "2a" class and severe in the "2b" class).<br>• No nodular sclerosis<br>• Global glomerulosclerosis in less than 50% of glomeruli |
| 3 | • With nodular sclerosis<br>• Multiple glomeruli with a nodular increase in mesangial matrix |
| 4 | Advanced global glomerulosclerosis (in more than 50% of glomeruli) |

**Long-term complications**

DKD constitutes significant health and financial burdens for the patient and healthcare systems. For example, Shimizu et al. [48] investigated the long-term events that occurred in T2DM patients (n=260) with biopsy-confirmed nephropathic changes over a mean follow-up period of eight years. They found

that renal events represented the most frequent complications (n=118), including a 50% reduction in the estimated GFR as compared to baseline or undergoing dialysis, followed by cardiovascular complications in 62 cases (stroke, coronary interventions, or myocardial infarction) and all-cause mortality (n=45). Importantly, the major determinants of long-term renal complications were severe proteinuria (macroalbuminuria), low estimated GFR (< 60 ml/min/1.73 $m^2$), interstitial fibrosis and tubular atrophy, glomerular lesions, and arteriosclerosis. The latter was the sole determinant of cardiovascular events [48].

Focusing on renal complications, diabetes remains the leading cause of progression to ESRD in the United States and multiple countries in the world [49]. For instance, in a study involving a non-European ethnic group [49], the number of patients with T1DM and T2DM who underwent ESRD treatment due to diabetes had an 18-fold increase from 1980 to 2008. Likewise, the number of patients who required renal replacement therapy attributable to DKD has evidenced a remarkable increase from 16% to 31% during the period from 1997 to 2006 in Iran [50]. Prevalence estimates in Saudi Arabia indicate that 26.6% of ESRD cases were complicated diabetic patients and diabetes was the most prevalent co-morbidity in patients on dialysis (59%) [51]. However, a more recent epidemiological study has shown that diabetic nephropathy was reported only in 18% of ESRD patients in Tabuk area [52] although another single-center-based study reported a higher prevalence rate (30.4%) in the same region [53].

DM is primarily a metabolic disorder that causes renal failure, which in turn could be associated with an increase in need of insulin [54, 55]. Uremic toxins are accumulated, and the increase in parathyroid hormone in chronic complicated cases would lead to the development of insulin resistance [56], especially in the skeletal muscles. Such resistance is caused mainly by impaired insulin binding to its specific receptors and subsequent disruption of glycogen production and glucose metabolism [57]. Seemingly, in anemic patients with chronic renal failure (CRF), the corrective erythropoietin production would eventually deteriorate insulin resistance [58]. Other CRF-related factors include metabolic acidosis and low vitamin D levels that contribute to insulin resistance [59]. Paradoxically, although non-diabetic CRF patients usually have impaired insulin sensitivity, they will not be hyperglycemic unless they have a genetic predisposition [60, 61].

In the advanced stages, when the GFR is <15-20 cc/min, insulin excretion and renal degradation are reduced; both are considered of an important clinical significance. Despite the apparent increase in insulin requirements due to insulin resistance, the need for insulin administration is decreased in the light of decreased insulin degradation, which may even resolve in T2DM and progress to hypoglycemia. At this stage, insulin requirements are affected by several factors, such as undergoing hemodialysis, peritoneal dialysis, renal replacement therapy (taking into account the subsequent clinical improvement and increased food intake) which may alleviate uremic toxicity [61]. The efficacy of such therapies were apparent in a study conducted during the period between 1980 and 2007, where the survival of T1DM patients who underwent renal replacement therapy has evidenced a significant improvement despite the concomitant increase in the age of patients, probably due to the achieved progress in therapeutic approaches for both diabetes and dialysis [62].

However, referring to mortality outcomes, a population cohort study in Australia and New Zealand performed on kidney transplant recipients with diabetes showed significantly higher mortality rates (25.3/100 recipients) in the first 10 years post-transplantation when compared to non-diabetics (11.5/100 recipients) [63]. The same study demonstrated a two-fold increase in the risk of all-cause mortality in diabetic patients, particularly those aged <40 years.

The mortality pattern in T2DM may have a relatively different paradigm since the increased rates of mortality among T2DM patients due to cardiovascular etiologies may change the ultimate number that might progress to renal complications and need renal replacement therapy [64]. Given the increased risk of CVD in diabetic patients, the nephropathic complications might augment the unfavorable cardiovascular consequences [18]. Additionally, kidney disease is associated with an increased risk of diabetic macrovascular complications, such as stroke and heart attacks [65]. More specifically, T2DM and comorbid albuminuria are independent risk factors for CVD, and the burden may be even higher in CVD associated with NADKD [26]. The increased risk of CVD in diabetic patients with chronic renal disease led to the recommendations of establishing the preventive measures of CDV in those populations as if these events have been experienced [66]. Some cohort-based studies demonstrated that the risk of CVD and

mortality is increased remarkably in patients with T1DM and T2DM, whether associated with evidence of DKD or normal GFR levels when compared to those with healthy nondiabetic individuals [67-69]. In T1DM, among 4,201 Finnish patients, the risk of mortality was 3.6-fold higher as compared to sex- and age-matched healthy individuals during a median follow-up period of 7 years [67]. Similar outcomes have been obtained in another population-based study on 658 American T1DM patients over 20 years [70]. Therefore, reducing the risk of CVD complications seems to be imperative in patients with diabetic nephropathy to improve the general diabetic outcomes.

Finally, the financial outcomes of DKD are also significant. Kumpatla et al. [71] have demonstrated a four-fold increase in the of the average cost of treating DKD and a higher expenditure for hospital admissions when compared to those without complications. In the United States, it has been found that the annual cost of diabetic nephropathy incurred by all players in the healthcare industry is 13 times greater than in the UK [72]. Evidently, successful DKD interventions would save substantial costs incurred by healthcare systems.

## CONCLUSION:

The clinical importance of DKD is apparent in both types of diabetes although the prevalence of progressive renal impairment is generally underestimated in T2DM. However, the risk of developing ESRD seems to be equivalent. ESRD yields a poor survival outcome in diabetic patients when compared to nondiabetic individuals despite the advanced progress in dialysis and renal replacement therapies. Furthermore, the high prevalence of CVD in diabetic nephropathy highlights the necessity of early and aggressive interventions to control the upcoming consequences. Early DKD diagnosis should not be based solely on albuminuria, but rather the normoalbuminuric paradigm should be considered in diabetic patients with low estimated GFR.

Therefore, clinicians should be aware of the evident biomarkers of DKD diagnosis, including urinary albumin excretion, GFR, and other markers of endothelial dysfunction and arterial stiffness given the associated microvascular complications. Employing non-invasive, convenient, and easy to use urinary or serum markers is crucial to detect renal lesions at early stages. Conducting further research is indispensable to identify early predictors of DKD for proactive interventions and to preclude or minimize the incidence of irreversible long-term complications. This would eventually help reduce the significant health burden related to the cardiovascular and renal systems.

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