Concept of Diabetic Kidney Disease

– Paradigm Shift from Albuminuria-Based to GFR-Based Kidney Disease –

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Diabetic nephropathy is one of the most frequent complications in type 1 and type 2 diabetes and the leading cause of chronic kidney disease (CKD) in patients starting renal replacement therapy in developed countries. Early detection along with multifactorial treatments, such as blood glucose control with sodium glucose cotransporter 2 inhibitors and blood pressure control with renin-angiotensin system blockers, are of particular importance to prevent disease progression and reduce mortality. In clinical settings, diabetic nephropathy is typically diagnosed by detecting microalbuminuria, the earliest indicator of this disease, in patients with diabetes for whom other causes of albuminuria are absent. However, recent renal biopsy based studies have demonstrated that albuminuria is neither a specific nor a sensitive biomarker for the development of diabetic nephropathy.

The classical diabetic nephropathy is characterized by the progressive increase of albuminuria from normoalbuminuria to microalbuminuria and macroalbuminuria, declining glomerular filtration rate (GFR), and eventual end-stage renal disease. However, the clinical course of diabetic nephropathy has changed profoundly in recent years, due to the diversification of diabetes, therapeutic successes, as well as an aging population. Indeed, CKD attributable to diabetes which runs an atypical clinical course (*i.e.*, so-called non-albuminuric renal function decline) has increased over the past decades.

The paradigm shift from albuminuria-based to GFR-based kidney disease results in a new concept of diabetic kidney disease (DKD). This review article describes the concept of DKD, and differences between classical diabetic nephropathy and DKD.

Key words: diabetic nephropathy, diabetic kidney disease (DKD), natural history, chronic kidney disease (CKD), early decliner

Introduction

According to the International Diabetes Federation, the proportion of the population suffering from diabetes is projected to grow from 425 million people in 2017, to 629 million people by 2045. One of

the most devastating complications of this disease is chronic kidney disease (CKD).

Moderately increased albuminuria is widely accepted as the earliest clinical sign of diabetic nephropathy. In developed countries, diabetic nephropathy is the leading cause of CKD and

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Figure-1 The number of patients who underwent hemodialysis and primary cause of ESRD in Japan. The number of patients who underwent hemodialysis has been increasing year after year. Since 1998, the leading cause of ESRD has become diabetic nephropathy instead of chronic glomerular nephritis, although the incidence rates for ESRD attributable to diabetes have stabilized over the past few years. The data reported here have been provided by the Japanese Society for Dialysis Therapy (JSDT). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the JSDT.

end-stage renal disease (ESRD), and is associated with increased mortality due to cardiovascular disease. Approximately 30%–40% of patients with type 2 diabetes develop diabetic nephropathy. Since 1998, in Japan, diabetic nephropathy has replaced chronic glomerular nephritis as leading cause of ESRD, although the incidence rates of ESRD that are attributable to diabetes have stabilized over the past few years (Figure-1).

Albuminuria is not only a hallmark of diabetic nephropathy but also an independent risk factor of cardiovascular disease. It is noteworthy that patients with diabetic nephropathy are more likely to die than to progress to ESRD¹⁾. The natural history of diabetic nephropathy is characterized by a progressive albuminuria, followed by a decline in the GFR, eventually leading to ESRD. However, accumulating evidence indicates that the natural history of diabetic nephropathy has changed profoundly during last few decades because of the diversification of diabetes, therapeutic successes, and aging of the overall population. This review article deals with the transition of the natural course of the disease from diabetic nephropathy to diabetic kidney disease (DKD), and describes the differences and similarities between these two diseases.

Diagnosis of diabetic nephropathy

Diabetic nephropathy is one of the microvascular complications of diabetes, which is characterized by renal tissue damage attributable to chronic hyperglycemia and hemodynamic change. Increased albuminuria is widely accepted as the first clinical sign of diabetic nephropathy. The measurement of albuminuria is useful not only for predicting the progression of diabetic nephropathy, but also for monitoring patient response to treatment. However, the interpretation of albuminuria can be complicated by a number of factors. This is because albuminuria may be increased by other types of progressive kidney disease, episodic hyperglycemia, high blood pressure, high protein diet, exercise, urinary tract infection, fever, and congestive heart failure, and therefore the presence of albuminuria is not always specific to identifying patients with diabetic nephropathy²⁾.

Because of this, definitive diagnosis of diabetic nephropathy requires performing renal biopsy to identify characteristic pathological findings, such as diffuse mesangial expansion, nodular sclerosis, double contour of the basement membrane, exudative lesions, mesangiolysis, and polar vasculosis

Table-1 Pathological findings of diabetic nephropathy

Glomerular lesion	Diffuse lesion (Mesangial expansion, Increased extracellular matrix)
	Nodular lesion (Nodular sclerosis)
	Double contour of basement membrane, Subendothelial space widening
	Exudative lesion
	Mesangiolysis
	Peri-hilar neo-vascularization (Polar vasculosis)
	Global glomerulosclerosis, Collapsing glomerulopathy, Ischemic nephropathy
	Segmental glomerulosclerosis
	Glomerulomegaly
Interstitial lesion	Interstitial fibrosis and tubular atrophy (IFTA)
	Interstitial cell infiltration, Interstitial inflammation
Vascular lesion	Arteriolar hyalinosis
	Intimal thickening

Red: specific findings for diabetic nephropathy.

Blue: common findings for diabetic nephropathy and nephrosclerosis.

Cited by the pathological diagnostic manual for diabetic nephropathy and nephrosclerosis in Japan published in 2014.

Table-2 Clinical features of diabetic nephropathy

1. History of diabetes: > 5 years
2. Presence of diabetic retinopathy and/or neuropathy
3. Persistent and gradual increase in albuminuria, followed by declining GFR
4. No severe hematuria and/or cellular casts

(Table-1)³⁾. The earliest finding typically observed is the thickening of the glomerular basement membrane. However, data regarding the effectiveness of renal biopsy in diagnosis is relatively limited, because it is not usually performed in patients with diabetes if the typical clinical course of diabetic nephropathy is already suspected. It is likely not feasible to perform renal biopsies in all patients with diabetes and micro- or macro-albuminuria, especially considering the dramatically increasing numbers of diabetes cases. It also appears there are few merits of performing invasive renal biopsies in patients who have typical diabetic clinical characteristics, because there are no specific treatments available at present beyond diet restriction and the optical control of diabetes, hypertension, and dyslipidemia. Because of this, the diagnosis of diabetic nephropathy is usually made based solely on clinical findings without pathological supportive evidence (Table-2). It is of importance to rule out concomitant glomerulonephritis by performing

renal biopsies if albuminuria appears within 5 years of the onset of diabetes, or if patients with diabetes exhibit acute kidney injury, acute onset of nephrotic syndrome, or severe hematuria and/or cellular casts. Therefore, the clinical diagnosis of diabetic nephropathy is often highly subjective.

Little is known about the severity and frequency of renal structural changes before the onset of clinical findings. Recently, Klessens *et al.*⁴⁾ demonstrated that approximately 60% (106/168) of patients with diabetes exhibited the histopathologic changes of diabetic nephropathy using autopsy samples, and remarkably, approximately 20% (20/106) of these never exhibited albuminuria. This indicates that the prevalence of histologically-diagnosed diabetic nephropathy is higher than expected, and that the lack of albuminuria may not always rule out the presence of structural alteration in patients with diabetes. Furthermore, the presence of histological findings did not correlate with albuminuria, and therefore, the histopathologic changes of diabetic nephropathy may develop at least in part before the onset of albuminuria⁴⁾.

A nation-wide biopsy based study in Japan demonstrated that specific pathological findings for diabetic nephropathy are observed even in patients with normoalbuminuria (the early stage of nephropathy)^{5) 6)}. In early-stage diabetic nephropathy, diffuse lesions are a very common finding

Clinical feature	Classical diabetic nephropathy	Nephrosclerosis-based DKD
Proteinuria	Large	Small
Retinopathy	Common	Rare
Duration of diabetes	Long	Short
Renal atrophy	Rare	Common

Figure-2 Clinical features distinguishing classical diabetic nephropathy from nephrosclerosis-based DKD

If patients with diabetes had no diabetic retinopathy after a long period of diabetes, relatively small amount of protein, or exhibit severe renal atrophy, we may suspect nephrosclerosis-based DKD rather than classical diabetic nephropathy.

whereas nodular lesions and mesangiolysis are unusual (<20%); however, patients exhibiting these demonstrated a particularly poor kidney disease prognosis. Because pathological findings cannot always be predicted from clinical findings, the value of renal biopsy in patients with diabetes is being recently reassessed to be of higher importance.

Patients are often encountered where it is difficult to distinguish classical diabetic nephropathy from nephrosclerosis-based DKD (CKD attributable to hypertension rather than diabetes) in a clinical setting. It is important to distinguish between these two diseases, as GFR decline generally appears to be steeper in patients with classical diabetic nephropathy (proteinuric DKD) compared to those with nephrosclerosis-based DKD (nonproteinuric DKD)⁷⁾. Yamanouchi *et al.*⁷⁾ demonstrated that the pathological findings in patients with proteinuric DKD were more severe than those with nonproteinuric DKD, where pathology is less severe even in regards to interstitial and vascular lesions. It may be possible however to diagnose nephrosclerosis-based DKD with several clinical features alone (Figure-2). If patients with diabetes had no diabetic retinopathy after a long period of the onset of diabetes, relatively small amounts of protein, or exhibit severe renal atrophy, nephrosclerosis-based DKD may be suspected though this clinical diagnosis is therefore also highly subjective as is the case for diabetic nephropathy.

Circulating tumor necrosis factor receptors as an alternative to albuminuria

Given the limitation of performing renal biopsies for all patients with diabetes, specific biomarkers for the development and/or progression of kidney disease other than albuminuria are urgently needed. Recently, micro-inflammation has been thought to be involved in the pathogenesis of diabetic nephropathy⁸⁾. Among inflammatory biomarkers, circulating Tumor necrosis factor receptors (TNFRs: TNFR1 and TNFR2) seem to be the most promising biomarker to predict future GFR decline in patients who are in a wide variety of disease stages across both types of diabetes^{9) 10)}. One striking feature is that the performance of this biomarker appears to be independent of albuminuria and GFR, and also predicts mortality in patients who underwent hemodialysis¹¹⁾. Moreover, several recent studies indicate that levels of circulating TNFRs are associated with histopathological findings of IgA nephropathy, and circulating TNFR2 levels were significantly decreased after tonsillectomy with steroid pulse therapy^{12) 13)}. Therefore, circulating TNFRs might be useful for predicting the progression of various types of kidney diseases other than diabetic nephropathy.

Diversified natural history of patients with diabetes and chronic kidney disease

The clinical course of classical diabetic nephropathy is characterized by progressive albuminuria, followed by a decline in the GFR, eventually leading to ESRD. In this clinical disease course, progression

was considered to be one-way, as once patients with diabetes and microalbuminuria progress to macroalbuminuria over a decade, macroalbuminuria was believed to never regress to microalbuminuria and is followed by GFR decline¹⁴⁾. However, recent studies have shown that remission &

regression of microalbuminuria is a common feature that far outweighs progression to proteinuria (Figure-3)¹⁵⁾⁻¹⁷⁾.

Regarding GFR decline, some studies demonstrate that it may precede the onset of microalbuminuria^{18) 19)}. A study by Joslin revealed that GFR decline begins with an earlier stage of diabetic nephropathy than initially suspected, and approximately one-third patients with type 1 diabetes and microalbuminuria already exhibited GFR decline²⁰⁾. Early GFR decline was recognized less often (approximately 10%), even in patients with type 1 diabetes and normoalbuminuria²⁰⁾. In the UK Prospective Diabetes Study, comprised of patients with recent-onset type 2 diabetes, almost half of those who develop an estimated creatinine clearance of <60 ml/min/1.73 m² did not have increased albuminuria during the median follow up of 15 years²¹⁾. Thus, some patients with diabetes progress to GFR decline without increased albuminuria, known as non-albuminuric renal function decline. Indeed, clinical findings of kidney disease among US adults with diabetes have profoundly changed as follows; the prevalence of albuminuria decreased by 24%, while the prevalence GFR decline increased by 61% (according to National Health and Nutrition Examination Survey data)²²⁾.

Figure-3 Progression pattern of diabetic nephropathy from standpoint of albuminuria-based model

A. Classical model of diabetic nephropathy. Once albuminuria increases and reaches macroalbuminuria, disease progression is considered to be one-way.

B. New model of diabetic nephropathy. Even in patients with macroalbuminuria, some patients regress to micro- or normoalbuminuria.

Figure-4 Diversified natural history of diabetic nephropathy

Clinical course of diabetic nephropathy is diversified into various types. (1) GFR decline starts after the onset of macroalbuminuria [classical diabetic nephropathy (Albuminuria-based model)]. (2) GFR decline precedes the onset of macroalbuminuria [Early progressive renal function decline (GFR-based model)]. (3) GFR declines without increasing albuminuria [Non-albuminuric renal function decline (Nephrosclerosis-based model)]. (4) GFR maintains even in increase of albuminuria.

(Adapted from Gohda T, *et al*: Juntendo Medical Journal, 2018; 64 (3): 227-234²³⁾)

Figure-5 Conceptual diagram of diabetic kidney disease (DKD)

Type 2 diabetes often occurs late in life and is diagnosed after onset of other related comorbidities such as hypertension and dyslipidemia. Therefore, it would be difficult to know how much diabetes affect the primary or secondary kidney disease. Thus, kidney disease attributable at least in part to diabetes is referred to DKD. DKD is the concept which includes diabetic nephropathy, and may have other etiologies of CKD. The term of “CKD with diabetes” is defined if patients with diabetes also have IgA nephropathy. Because differences among diabetic nephropathy, DKD, and CKD with diabetes are unspecific in some case, they are shown by dashed lines.

Several factors are considered to be associated with this observation. Firstly, the increase of nephrosclerosis-based DKD with aging may be deeply involved in this observation, though as previously discussed, it is very difficult to distinguish between classical diabetic nephropathy and nephrosclerosis-based DKD. Second, the wide use of renin-angiotensin system blockers, such as angiotensin receptor blockers and angiotensin converting enzyme inhibitor, delayed the onset of microalbuminuria in patients with diabetes beyond their blood pressure-lowering effects. Third, intensive blood glucose control is also suspected to delay the onset of microalbuminuria.

Taken together, renal impairments attributable to diabetes are diverse, classified into various types as shown in Figure-4²³⁾. Therefore, if CKD is in part caused by diabetes, it defines DKD²⁴⁾ -i.e., DKD is the concept which includes diabetic nephropathy (Figure-5). Furthermore, if patients with diabetes occur with chronic glomerular nephritis which is not directly associated with diabetes, this defines CKD with diabetes as a larger disease concept.

Conclusion

Kidney disease which is at least partially attributable to diabetes is referred to as DKD. Thus, DKD is

the concept which includes diabetic nephropathy, and may have other etiologies of CKD. Many patients with progressive DKD follow a classical albuminuria-based pathway, whereas several patients follow a non-albuminuria-based (GFR-based pathway). Although there may be difficulty in distinguishing classical diabetic nephropathy from nephrosclerosis-based DKD using clinical and biochemical characteristics without pathological findings, it is imperative to consider the probable cause of renal impairment in the treatment and prognosis of such patients.

In conclusion, albuminuria is not always sensitive and specific for early detection of renal tissue damage and predicting renal function decline. Therefore, this warrants the development of biomarkers as an alternative to albuminuria in order to identify patients at risk of diabetic nephropathy, perform early diagnosis (renal tissue damage) of disease, and early detection of disease progression.

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