SPECIAL ARTICLE

A new classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy

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Abstract The Joint Committee on Diabetic Nephropathy has revised its Classification of Diabetic Nephropathy (Classification of Diabetic Nephropathy 2014) in line with the widespread use of key concepts such as the estimated glomerular filtration rate (eGFR) and chronic kidney disease. In revising the Classification, the Committee carefully evaluated, as relevant to current revision, the report of a study conducted by the Research Group of Diabetic Nephropathy, Ministry of Health, Labour and Welfare of Japan. Major revisions to the Classification are summarized as follows: (1) eGFR is substituted for GFR in the Classification; (2) the subdivisions A and B in stage 3 (overt nephropathy) have been reintegrated; (3) stage 4 (kidney failure) has been redefined as a GFR less than 30 mL/min/ 1.73 m^2, regardless of the extent of albuminuria; and (4) stress has been placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy.

Keywords Diabetic nephropathy · Chronic kidney disease (CKD) · Albuminuria · Proteinuria · Glomerular filtration rate (GFR)

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Introduction

Diabetic nephropathy became the leading cause of chronic dialysis in 1998. Since then, the incidence of this condition has increased with only a recent plateau. However, diabetic nephropathy continues to account for a large proportion of all cases of chronic kidney disease (CKD) and remains by far the most common underlying cause of chronic dialysis among all kidney diseases [5], consequently leading to the escalation of healthcare costs, thus representing a compelling medico-social issue of interest.

The Classification of Diabetic Nephropathy (hereafter "Classification") developed earlier by the Research Group

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of Diabetic Nephropathy at the Ministry of Health, Labour and Welfare (MHLW) [6] and later revised by the Joint Committee on Diabetic Nephropathy (hereafter "Committee") [7] is widely used in Japan. However, as the concept of CKD was proposed, followed by the classification of CKD stages [8], it became clear that there exists a sub-population of patients with discrepant classifications of diabetic nephropathy and CKD. This is thought to be due to the fact that diabetic nephropathy is primarily classified according to the extent of albuminuria in addition to the glomerular filtration rate (GFR) (i.e., creatinine clearance [CCr]), whereas CKD is primarily classified based on the estimated GFR [estimated GFR (eGFR)]. Meanwhile, eGFR has become increasingly used to assess GFR, and a new classification of CKD was developed in 2012 [9]. Against this background, the Committee therefore discussed issues of interest in depth and sought to develop a revision of the Classification.

Development of the 2014 Classification (Revised Classification) (see Table 1)

Prior to revising the Classification, as part of a MHLW-subsidized project on kidney disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan", a "historical cohort study" was conducted by the Research Group of Diabetic Nephropathy, MHLW, involving a total of 4,355 subjects with type 2 diabetes from 10 participating healthcare facilities with the aim of evaluating renal events (i.e., a decrease in eGFR to half the baseline level and/or the need for dialysis), cardiovascular events and all-cause mortality [10, 11]. Summarized below are the major findings of this study (for detailed information, please access the MHLW website http://www.mhlw.go.jp/ or refer to the literature cited above).

1. Renal and cardiovascular events and all-cause mortality were significantly increased in the subjects with micro- or macroalbuminuria compared to that observed in the subjects with normoalbuminuria.

2. In those with renal impairment (defined as a GFR less than 60 mL/min/1.73 m^2):

   a. The risk of renal events increased in association with the onset of microalbuminuria and further increased with the onset of macroalbuminuria in the subjects;

   b. The risk of cardiovascular events was increased in those with micro-/macroalbuminuria; and

   c. All-cause mortality was increased in the subjects with macroalbuminuria as well as those with normoalbuminuria and microalbuminuria who exhibited a GFR of less than 30 mL/min/1.73 m^2.

While that study was not a true prospective study and involved only a limited number of facilities and patients from a population known to be less prone to cardiovascular

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events than those in Western countries, the findings provide important insight into the prognosis of diabetic nephropathy in Japanese patients. Therefore, in seeking to revise the Classification, the Committee gave due consideration to the above findings. At the same time, the following considerations were also taken into account.

1. The bulk of evidence for the classification of diabetic nephropathy comes from randomized controlled studies enrolling patients with diabetic nephropathy as defined based on the extent of albuminuria, and very little evidence is available for diabetic nephropathy as defined based on GFR.
2. The current "Medical Service Fee Schedule for Guidance on Preventing Diabetes-Associated Dialysis" was developed with the Classification in mind.
3. The "Guidelines for Clinical Efficacy Evaluation of Pharmacological Agents for Diabetic Nephropathy (Draft)" currently in use were developed with the Classification in mind.

Therefore, after giving due consideration to all of these issues during the course of several sessions, the Committee decided to leave the Classification essentially unchanged for now (Table 1), while showing how it may be aligned with the widespread CKD classification based on GFR (eGFR) ("see Appendix"). The former is not, however, presented as a heat map, due to the limitations of the study referred to above, which involved a small number of patients with diabetic nephropathy and included no dialysis patients, providing the basis for this revision. Again, as all kidney diseases affecting patients with diabetes are covered in the Classification, the Committee called for attention with notes included which were required, in order to highlight the importance of the differential diagnosis

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Table 1 Classification of Diabetic Nephropathy 2014

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/ 1.73 m²)
Stage 1 (pre-nephropathy)	Normoalbuminuria (< 30)	≥30[a]
Stage 2 (incipient nephropathy)	Microalbuminuria (30–299)[b]	≥30
Stage 3 (overt nephropathy)	Macroalbuminuria (≥ 300) or Persistent proteinuria (≥ 0.5)	≥30[c]
Stage 4 (kidney failure)	Any albuminuria/proteinuria status[d]	<30
Stage 5 (dialysis therapy)	Any status on continued dialysis therapy	

Diabetic nephropathy does not always progress from one stage to the next. The revised classification takes into account findings on the prognosis of type 2 diabetic patients from a "historical cohort study" conducted as part of the MHLW-subsidized Project on Kidney Disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan" [10, 11]

[a] While a GFR of less than 60 mL/min/1.73 m² is consistent with the diagnosis of CKD, underlying causes other than diabetic nephropathy may be involved in patients with a GFR below 60 mL/min/1.73 m² thus calling for the differential diagnosis between diabetic nephropathy and any other potential non-diabetic kidney diseases

[b] Patients with microalbuminuria are to be diagnosed as incipient nephropathy after the differential diagnosis based on the criteria for an early diagnosis of diabetic nephropathy

[c] Precautions are required in patients with macroalbuminuria, in whom renal events (e.g., a decrease in eGFR to half its baseline value, the need for dialysis) have been shown to increase as the GFR decreases below 60 mL/min/1.73 m²

[d] All patients with a GFR of less than 30 mL/min/1.73 m² are classified as exhibiting kidney failure, regardless of their urinary albumin/protein values. However, in those with normoalbuminuria and microalbuminuria, the differential diagnosis is required between diabetic nephropathy and any other potential non-diabetic kidney diseases

Key Precautions in View of Drug Use: This table is intended, first and foremost, as a classification of diabetic nephropathy and not as a guide to drug use. All drugs, including anti-diabetic drugs, particularly renally metabolized agents, are to be used in accordance with their prescribing information, with due consideration to relevant factors such as GFR in each patient

between diabetic nephropathy and non-diabetic kidney disease in all stages. The differential diagnosis calls for collaboration with nephrologists; such collaboration is not limited to cases requiring a renal biopsy. Furthermore, given that the disease may not always progress in some patients, numerous notes were included in the table in order to call attention to these cases. Additionally, in view of the potential need to use multiple anti-diabetic drugs over time, "Key Precautions in View of Drug Use" are included below the table. The major revisions to the Classification are summarized below:

1. eGFR is now substituted for GFR in the Classification.

2. The stages used in the Classification have been simplified to include normoalbuminuria, microalbuminuria, macroalbuminuria and kidney failure.

3. The division between A and B (early versus late macroalbuminuria) in stage 3 has been abandoned and A and B have been reintegrated, due to the paucity of evidence for proteinuria of 1 g/day as the threshold for dividing the stage.

4. Kidney failure has been redefined in all cases as a GFR less than 30 mL/min/1.73 m^2, which represents the threshold value for kidney failure obtained by quantifying the existing definition of kidney failure in the Classification based on the Classification of the Japanese Society of Nephrology (JSN) [12] with all other pre-kidney failure conditions redefined as a GFR of 30 mL/min/1.73 m^2 or greater.

5. Qualifying or illustrating phases in parentheses, such as "e.g., incipient nephropathy", have been retained throughout the Classification, as they have become common currency in the field, although their removal from the Classification was suggested during the process of revision.

6. Stress is now placed on the differential diagnosis of diabetic nephropathy versus non-diabetic kidney disease as being crucial in all stages of diabetic nephropathy.

Of note, the American Diabetes Association (ADA) proposed in its Clinical Practice Recommendations 2013 that all cases of albuminuria of 30 μg/mg Cr (=mg/g Cr) be defined as "increased urinary albumin excretion", thus abandoning the division between micro- and macroalbuminuria [13]. Again, while this concept was retained in the Clinical Practice Recommendations 2014, the ADA further proposed that microalbuminuria and macroalbuminuria be redefined as persistent albuminuria of 30–299 mg/24 h and ≥300 mg/24 h, respectively [14]. While this change may result in the terms micro- and macroalbuminuria ceasing to be common currency in the clinical setting in the US, to avoid confusion, the Committee has chosen not to follow suit and rather err on the side of caution, thereby retaining these terms in the Classification, given that they are less likely to no longer be used in scientific publications and are expected to remain common currency in Japan.

Last but not least, with a number of multicenter prospective studies currently underway, including the Japan Diabetes Complication and Prevention prospective (JDCP) study, JSN registries, Japan Diabetes Clinical Data Management (JDDM) studies and Japan Diabetes Optimal Integrated Treatment for 3 Major Risk Factors of Cardiovascular Diseases (J-DOIT3) randomized study, the Committee also plans to further revise the Classification in a timely fashion as required, as relevant evidence becomes available from these and other studies.

Conclusions

In order to resolve the discrepancy between the existing Classification of Diabetic Nephropathy and the current Classification of CKD stages, the Joint Committee on Diabetic Nephropathy revised its Classification of Diabetic Nephropathy. The new classification has already been uploaded onto the website of each member society represented on the Joint Committee as of January 10, 2014. Again, in view of further revisions in the years to come, the Joint Committee has termed the revised classification as the "Classification of Diabetic Nephropathy 2014."

Appendix

Relationship between the 2014 categories for diabetic nephropathy stages and the CKD severity categories

	Albuminuria category	A1	A2	A3
	Quantitative urinary albumin estimation Urinary albumin/Cr ratio (mg/g Cr) (quantitative urinary protein estimation) (urinary protein/Cr ratio (g/g Cr))	Normoalbuminuria < 30	Microalbuminuria 30-299	Macroalbuminuria ≥300 (or increased proteinuria) (≥0.50)
GFR category (mL/min/1.73 m^2)	≥90 60-89 45-59 30-44	Stage 1 (pre-nephropathy)	Stage 2 (incipient nephropathy)	Stage 3 (overt nephropathy)
	15-29 < 15	Stage 4 (kidney failure)		
	(dialysis therapy)	Stage 5 (dialysis therapy)		

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