

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

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Keywords

Albuminuria, Diabetic nephropathy, Glomerular filtration rate

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J Diabetes Invest 2015; 6: 242–246

doi: 10.1111/jdi.12319

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 (CKD). 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, Labor and Welfare of Japan. Major revisions to the Classification are summarized as follows: (i) eGFR is substituted for GFR in the Classification; (ii) the subdivisions A and B in stage 3 (overt nephropathy) have been reintegrated; (iii) stage 4 (kidney failure) has been redefined as a GFR <30 mL/min/1.73 m², regardless of the extent of albuminuria; and (iv) 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.

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 diseases⁵, 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 of Dia-

betic Nephropathy at the Ministry of Health, Labor 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 stages⁸, it became clear that there exists a subpopulation of patients with discrepant classifications of diabetic nephropathy and CKD. This is thought to be because of 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 2012⁹. Against this background, the Committee therefore discussed issues of interest in depth, and sought to develop a revision of the Classification.

†Joint Committee on Diabetic Nephropathy members are in Appendix 2.
Received 12 November 2014; revised 17 November 2014; accepted 17 November 2014

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**DEVELOPMENT OF THE 2014 CLASSIFICATION
(REVISED CLASSIFICATION)**

Prior to revising the Classification, as part of a MHLW-subsidized project on kidney disease, entitled 'Diabetic Nephropathy Research, from the Ministry of Health, Labor 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 health-care 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 that 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 <60 mL/min/1.73 m²):
 - 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 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 <30 mL/min/1.73 m².

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 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 might be aligned with the widespread CKD classification based on GFR (eGFR; Appendix 1). 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 where required, in order to highlight the importance of the differential diagnosis 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 antidiabetic drugs over time, 'Key Precautions in View of Drug Use' are included below the table. The major revisions to the Classification are summarized as 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 m², 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 m² 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 macroalbuminuria¹³. 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, respectively¹⁴. While this

Table 1 | Classification of Diabetic Nephropathy 2014jdi†

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/1.73 m ²)
Stage 1 (pre-nephropathy)	Normoalbuminuria (<30)	≥30‡
Stage 2 (incipient nephropathy)	Microalbuminuria (30–299)§	≥30
Stage 3 (overt nephropathy)	Macroalbuminuria (≥300) or persistent proteinuria (≥0.5)	≥30¶
Stage 4 (kidney failure)	Any albuminuria/proteinuria status††	<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' carried out as part of the Ministry of Health, Labor and Welfare-subsidized Project on Kidney Disease, entitled 'Diabetic Nephropathy Research, from the Ministry of Health, Labor and Welfare of Japan'10,11. ‡Although a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² is consistent with the diagnosis of chronic kidney disease, underlying causes other than diabetic nephropathy might 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. §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. ¶Precautions are required in patients with macroalbuminuria, in whom renal events (e.g., a decrease in estimated GFR [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. ††All patients with a GFR of less than 30 mL/min/1.73 m² are classified as showing 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 renal 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 antidiabetic 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.

change may result in the terms micro- and macroalbuminuria ceasing to be common currency in the clinical setting in the USA, 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 three 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.'

ACKNOWLEDGMENTS

The Joint Committee on Diabetic Nephropathy would like to extend its heartfelt thanks to all investigators in the Research Group of Diabetic Nephropathy, Ministry of Health, Labor and Welfare of Japan for their contributions, which provided the basis for the current revision. Masakazu Haneda has received speaker honoraria from pharmaceutical companies Boehringer Ingelheim GmbH, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Daiichi-Sankyo Co., Ltd., Taisho Pharmaceutical Co., Ltd., Sanofi K.K., Merck Sharp & Dohme, Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd., Kowa Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Novartis Pharma K.K.; and scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., Merck Sharp & Dohme, Boehringer Ingelheim GmbH, and Eli Lilly and Company. Daisuke Koya has received speaker honoraria from pharmaceutical companies Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, and Eli Lilly and Company; and research grants from Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, Japan Tobacco Inc., Eli Lilly and Company, and Ono Pharmaceutical Co., Ltd. Tetsuya Babazono has received speaker honoraria from pharmaceutical company Merck Sharp & Dohme. Tatsumi Moriya has received travel expenses from pharmaceutical companies Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd. and Daiichi-

Sankyo Co., Ltd. Hirofumi Makino has received speaker honoraria from pharmaceutical companies AbbVie GK, Astellas Pharma Inc., Boehringer Ingelheim GmbH, Daiichi-Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Merck Sharp & Dohme, Novartis Pharma K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co. and Mitsubishi Tanabe Pharma Corporation; research grants from Project for accelerating Practice and Research on Community Medicine in Okayama Prefecture; scholarship grants from Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Merck Sharp & Dohme, Takeda Pharmaceutical Co., Ltd. and Mitsubishi Tanabe Pharma Corporation. Kenjiro Kimura has received research grants from pharmaceutical companies Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Limited., Boehringer Ingelheim GmbH, Baxter International Inc. and Sekisui Medical Co., Ltd. Takashi Wada has received speaker honoraria from pharmaceutical company Daiichi-Sankyo Co., Ltd. and scholarship grants from Chugai pharmaceutical Co., Ltd. Susumu Ogawa has received speaker honoraria from pharmaceutical companies Daiichi-Sankyo Co., Ltd., Eli Lilly and Company, and Novo Nordisk Pharma Ltd.; and research grants from Daiichi-Sankyo Co., Ltd. Masaaki Inaba has received speaker honoraria from pharmaceutical companies Bayer Yakuhin, Ltd., Takeda Pharmaceutical Co., Ltd., Merck Sharp & Dohme, Kyowa Hakko Kirin Co., Ltd. and Asahi Kasei Pharma Corporation; and research grants from Bayer Yakuhin, Ltd., Kyowa Hakko Kirin Co., Ltd., and Eli Lilly and Company. Yoshihiko Kanno has received scholarship grants from pharmaceutical company Chugai Pharmaceutical Co., Ltd., and travel expenses from Abbott Japan Co., Ltd. Takashi Shigemats has received research grants from the pharmaceutical company Bayer Yakuhin, Ltd. Kazunori Utsunomiya, Yoshiki Suzuki, Ikuto Masakane, Ken Tsuchiya, Keiko Honda, Kazuko Ichikawa, Kenichiro Shide have no conflict of interest.

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APPENDIX 1

Relationship between the 2014 categories for diabetic nephropathy stages and the chronic kidney disease 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 15–29 <15 (Dialysis therapy)	Stage 1 (pre-nephropathy) Stage 4 (kidney failure) Stage 5 (dialysis therapy)	Stage 2 (incipient nephropathy)	Stage 3 (overt nephropathy)

APPENDIX 2

The Joint Committee on Diabetic Nephropathy has been established by the Japan Diabetes Society, Japanese Society of Nephrology, Japanese Society for Dialysis Therapy, and Japan Society of Metabolism and Clinical Nutrition, which published the revised edition of 'Classification of Diabetic Nephropathy 2014' in *J Jpn Diabetes Soc* 2014; **57**: 529–534 (in Japanese)¹, *Jpn J Nephrol* 2014; **56**: 547–552 (in Japanese)², *J Jpn Soc Dial Ther* 2014; **47**: 415–419 (in Japanese)³ and *Clinical Nutrition* 2014; **17**: 325–330 (in Japanese)⁴. This is the English version of that revision. This article has been jointly published in *Diabetology International* (doi: 10.1007/s13340-014-0197-4) by the Japan Diabetes Society, *Journal of Diabetes Investigation*, by the Asian Association for the Study of Diabetes and *Clinical and Experimental Nephrology* (doi: 10.1007/s10157-014-1057-z), by the Japanese Society of Nephrology.

Joint Committee on Diabetic Nephropathy: Japan Diabetes Society – Masakazu Haneda, Kazunori Utsunomiya, Daisuke Koya, Tetsuya Babazono, Tatsumi Moriya; Japanese Society of Nephrology – Hirofumi Makino, Kenjiro Kimura, Yoshiki Suzuki, Takashi Wada, Susumu Ogawa; Japanese Society for Dialysis Therapy – Masaaki Inaba, Yoshihiko Kanno, Takashi Shigematsu, Ikuto Masakane, Ken Tsuchiya; Japan Society of Metabolism and Clinical Nutrition – Keiko Honda, Kazuko Ichikawa, Kenichiro Shide.