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REVIEW ARTICLE

Clinical impact of albuminuria in diabetic nephropathy

Takashi Wada · Miho Shimizu · Tadashi Toyama · Akinori Hara · Shuichi Kaneko · Kengo Furuichi

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Abstract Patients suffering from diabetic nephropathy, resulting in end-stage renal failure, are increasing in number. The pathophysiology of diabetic nephropathy remains to be fully investigated. In the clinical setting, the presence of albuminuria/overt proteinuria and a low glomerular filtration rate may predict poor renal prognosis, but the prognosis of the normoalbuminuric renally insufficient diabetic patient remains controversial. In addition to the measurement of urinary albumin excretion, biomarker studies to detect diabetic nephropathy more specifically at the early stage have been performed worldwide. There is a growing body of evidence for remission and/or regression of diabetic nephropathy, which may be an indicator for cardiovascular and renal risk reduction. Deeper insights into the pathological characteristics as well as the clinical impact of albuminuria on renal and cardiovascular outcome are required.

Keywords Diabetic nephropathy · Albuminuria · Proteinuria · Glomerular filtration rate · Cardiovascular disease · Renal outcome

T. Wada (✉)
Division of Nephrology, Department of Laboratory Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan
e-mail: twada@m-kanazawa.jp

M. Shimizu · T. Toyama · A. Hara
Division of Nephrology, Department of Disease Control and Homeostasis, Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

S. Kaneko
Department of Disease Control and Homeostasis, Institute of Medical, Pharmaceutical and Health Sciences, Faculty of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan

K. Furuichi
Division of Blood purification, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa 920-8641, Japan

K. Furuichi
Division of Nephrology, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa 920-8641, Japan

Introduction

Based on the annual report of the Japanese Society for Dialysis Therapy (JSDT), diabetic nephropathy is a leading cause of end-stage renal failure in Japan [1]. The number of dialysis patients had increased to 297,126 by the end of 2010. According to the annual report of the JSDT, diabetic nephropathy has been a leading primary disease of new patients who have been started on dialysis since 1998 [1]: the number of such patients with diabetic nephropathy has increased to 43.5%. In addition, cardiovascular diseases and deaths in patients with diabetes and underlying renal disease before and after dialysis has increased [2, 3]. Therefore, preventing and halting the progression of diabetic nephropathy is important if we are to prolong the survival of such patients.

Characteristic pathologic changes associated with diabetic nephropathy are accumulation of extracellular matrix (ECM) and the infiltration of inflammatory cells into glomeruli and tubulointerstitial regions [4, 5]. These pathologic abnormalities are induced by alterations in ECM production or degradation [6]. Generally speaking, the occurrence of albuminuria is a reflection of increased matrix deposition, leading to glomerular and tubulointerstitial lesions. Diabetic nephropathy is a clinical entity in

which the presence of persistent albuminuria and declines in renal function and glomerular filtration rate (GFR) are the major characteristic findings, which are closely associated with end-stage renal diseases, enhanced cardiovascular morbidity and eventual mortality [7]. The incidence of albuminuria, which currently contributes to the diagnosis of diabetic nephropathy, is well correlated with a decrease in GFR and the incidence of cardiovascular diseases.

Here, we focus on the clinical impact of albuminuria along with GFR levels on the progression of diabetic nephropathy and the incidence of cardiovascular diseases, which is closely related to the mortality of patients with diabetic nephropathy in this manuscript.

Albuminuria in the diagnosis of diabetic nephropathy

The definitive diagnosis of diabetic nephropathy is based on pathological findings such as the presence of diffuse mesangial lesions and nodular lesions. However, renal biopsy is not performed for all patients with diabetic nephropathy. In the clinical setting, the presence of persistent proteinuria as well as other complications such as diabetic retinopathy and renal dysfunction is important in the diagnosis of diabetic nephropathy. However, early detection of the presence of diabetic nephropathy is clinically required for the best prognosis. The measurement of urinary albumin excretion is currently crucial to the detection of early diabetic nephropathy. The increased excretion of albumin (albuminuria) is an early diagnostic indicator of diabetic nephropathy. Thus, Mogensen et al. [8] proposed a classification of diabetic nephropathy in patients with type 1 diabetes based on increased urinary albumin excretion once diabetic nephropathy was diagnosed. Diabetic nephropathy is also staged in Japan [9, 10], and the staging was described by Yokoyama et al. [11] as follows: stage I: urinary albumin-to-creatinine ratio (ACR) <30 mg/g creatinine; stage II: ACR $\geq$ 30 and <300 mg/g creatinine (i.e., albuminuria); stage III: ACR $\geq$ 300 mg/g creatinine and/or persistent proteinuria with serum concentration of creatinine <2 mg/dl; stage IV: serum concentration of creatinine $\geq$2 mg/dl with proteinuria; and stage V: being treated with dialysis. The Japan Diabetes Clinical Data Management Study Group (JDDM) reported that the prevalence of albuminuria (stage II) in Japanese type 2 diabetic patients was 32%, which is very similar to the 39% observed in the DEMAND study [12]. These results suggest that albuminuria is common, and that 76% of patients with diabetic nephropathy are categorized as stage II, as evidenced by the presence of albuminuria. Further, 58% of the patients enrolled were at stage I, 7% were at stage III, 2.6% were at stage IV, and 0.4% were at stage V [11]. A very recent study from the Japan Diabetes Complications Study (JDCS) revealed that the annual transition rate to proteinuria (ACR $\geq$ 300 mg/g creatinine) was 0.67%, and that this was substantially higher for the low-albuminuric group (defined as a urinary ACR of 30–150 mg/g creatinine) than for the normoalbuminuric group (defined as a urinary ACR of <30 mg/g creatinine) [13]. In this sense, UKPDS 64 reported that the progression to albuminuria occurred at 2.0% per year, and from albuminuria to macroalbuminuria at 2.8% per year [14]. However, about 40% of the diabetic patients had no urinary albumin excretion measurements, regardless of the recommendation for the JDDM cohort [11]. Therefore, the measurement of urinary albumin excretion is required for the early detection of diabetic nephropathy in Japan.

Biomarkers for diabetic nephropathy and disease progression

Further studies to detect diabetic nephropathy more specifically at the early stage in addition to urinary albumin excretion are needed. In this sense, biomarker studies to identify the presence and predict the progression of diabetic nephropathy have been performed worldwide [15]. Recently, Kamijo-Ikemori et al. [16] reported that urinary levels of liver-type fatty acid-binding protein (L-FABP) accurately reflected the severity of diabetic nephropathy in type 2 diabetes. Importantly, urinary L-FABP levels were high in patients with normoalbuminuria, suggesting its usefulness for detecting early nephropathy in these patients. Further, an increase in urinary Smad1—a key transcriptional factor for mesangial matrix expansion in diabetic nephropathy—at the early stage was correlated with subsequent development of glomerulosclerosis in experimental rodent models [17]. Regarding renal function, serum cystatin C was reported to be a good marker for nephropathy [18]. Notably, cases of early renal dysfunction, defined by a loss of cystatin C GFR exceeding −3.3%/year, occurred in 9% of the normoalbuminuria group and 31% of the albuminuria group [19].

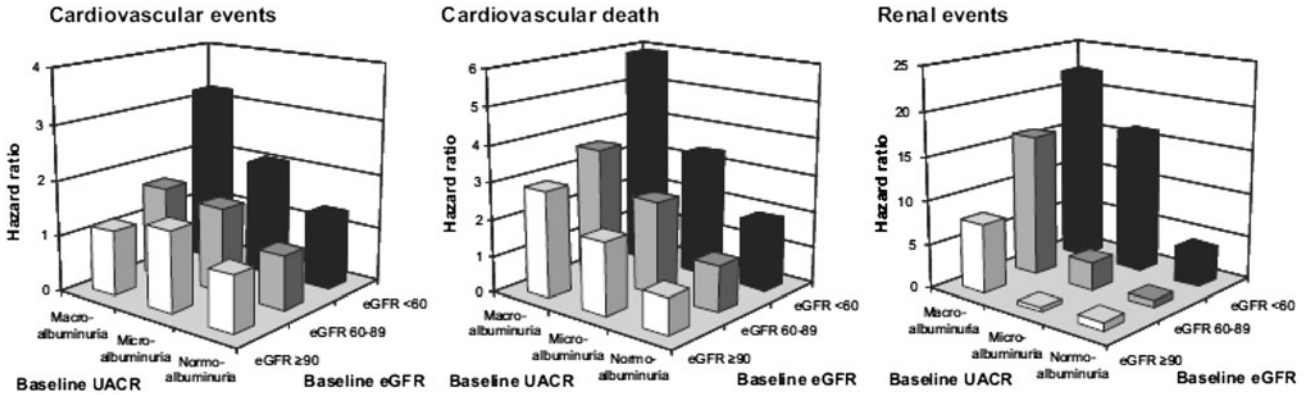
Prevalence of albuminuria and low GFR in type 2 diabetic patients in Japan

As previously described, diabetic nephropathy is diagnosed through the detection of albuminuria. Recently, Kidney Disease: Improving Global Outcomes (KDIGO) reported the definition, classification and prognosis of chronic kidney disease based on both estimated GFR and urinary levels of albumin excretion [20]. In this sense, there are diabetic patients with decreases in GFR and normoalbuminuria. Is diabetic nephropathy observed in such patients? In fact, the percentage of diabetic patients with normoalbuminuria and low estimated GFR is believed to be relatively high. Importantly, Yokoyama et al. [21] described

that the proportion of subjects with low estimated GFR (<60 ml/min/1.73 m^2) and normoalbuminuria was 11.4% of the type 2 diabetic patients examined (262/2298). In this manuscript, 63.4% of the 262 patients studied had neither diabetic retinopathy nor neuropathy. On the other hand, these patients were older and included a higher proportion of women and patients with hypertension, hyperlipidemia and cardiovascular disease, as well as fewer smokers compared with those with normoalbuminuria and preserved GFR. In contrast, the proportion of type 2 diabetic patients with preserved GFR but albuminuria or overt proteinuria was 27% (755/2791). Most importantly, the lack of histologically proven diabetic nephropathy should be discussed. In type 1 diabetes patients with normoalbuminuria and low GFR, renal biopsy specimens revealed more advanced diabetic glomerular lesions. It is worth noting that a reduced GFR was found much more often among female patients, particularly if retinopathy and/or hypertension were also present [22]. Deep insight into the prevalence and prognoses of these patients with proven pathological characteristics and grading is required to understand the pathophysiology of diabetic nephropathy in greater depth, together with future perspectives.

Clinical impacts of albuminuria and GFR on the prognoses of diabetic patients

Obviously, diabetic patients who had both albuminuria/overt proteinuria and low GFR were at risk of adverse outcomes, including cardiovascular events, cardiovascular death, and renal events, as reported by the Action in Diabetes and Vascular Disease: Preterax and DiamicroN MR Controlled Evaluation (ADVANCE) study [23] (Fig. 1). Do normoalbuminuric renally insufficient diabetic patients have a poor prognosis? Rigalleau et al. [24] reported that the risks of renal progression and death in these patients with type 1 or type 2 diabetes are lower. Concomitantly, in type 2 diabetic patients, the Casale Monferrato study revealed that macroalbuminuira was the main predictor of mortality, independently of both estimated GFR and cardiovascular risk factors, whereas the estimated GFR provided no further information on all-cause mortality and cardiovascular mortality in normoalbuminuric patients [25]. Supporting this notion, regarding renal end-points, there was also a progressive increase in risk associated with declined renal function, which was mainly observed in the albuminuric group in Chinese type 2 diabetic patients [26]. Interestingly, those with a reduced estimated GFR were at high risk of developing cardiovascular end-points (cardiovascular death, new admissions due to angina, myocardial infarction, stroke, revascularization or heart failure) and all-cause mortality, independent of albuminuria [26]. In contrast, as previously described, in the ADVANCE study, patients with normoalbuminuria and estimated GFR <60 ml/min per 1.73 m^2 had a 3.95-fold higher risk of renal events, a 1.33-fold higher risk of cardiovascular events, and a 1.85-fold higher risk of cardiovascular death [23] (Fig. 1). Moreover, Vlek et al. reported that an estimated GFR <60 ml/min/1.73 m^2 without albuminuria was



Baseline UACR	Baseline eGFR (ml/min/1.73 m^2) GFR ≥90	GFR 60-89	GFR <60
Normoalbuminuria	1.00 (Reference)	0.98 (0.78-1.22)	1.33 (1.02-1.75)
Microalbuminuria	1.48 (1.09-2.01)	1.54 (1.20-1.98)	2.04 (1.54-2.69)
Macroalbuminuria	1.18 (0.52-2.69)	1.67 (1.09-2.57)	3.23 (2.20-4.73)

Baseline UACR	Baseline eGFR (ml/min/1.73 m^2) GFR ≥90	GFR 60-89	GFR <60
Normoalbuminuria	1.00 (Reference)	1.22 (0.81-1.84)	1.85 (1.17-2.92)
Microalbuminuria	1.96 (1.16-3.32)	2.52 (1.65-3.84)	3.37 (2.15-5.30)
Macroalbuminuria	2.87 (1.01-8.18)	3.61 (2.02-6.43)	5.93 (3.45-10.20)

Baseline UACR	Baseline eGFR (ml/min/1.73 m^2) GFR ≥90	GFR 60-89	GFR <60
Normoalbuminuria	1.00 (Reference)	0.89 (0.31-2.58)	3.95 (1.38-11.34)
Microalbuminuria	0.45 (0.05-3.83)	3.17 (1.15-8.74)	16.19 (6.16-42.54)
Macroalbuminuria	7.82 (1.51-40.53)	16.13 (5.49-47.42)	22.20 (7.62-64.72)

Fig. 1 Combined effects of albuminuria and eGFR levels at baseline on the risk of an adverse outcome. The estimates are adjusted for baseline covariates, including age, gender, duration of diabetes, SBP, history of currently treated hypertension, history of macrovascular disease, HbA1c, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, BMI, electrocardiogram abnormalities, current smoking, and current drinking. (From Ref. [23] reproduced with permission from the American Society of Nephrology)

the strongest risk factor in the occurrence of vascular events (hazard ratio 1.50; 1.05–2.15) [27]. Recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study revealed that normoalbuminuric patients with eGFR 30–59 ml/min per 1.73 m^2 were at higher risk of a cardiovascular event, cardiovascular death, noncoronary heart disease death, and death from any cause than normoalbuminuric patients with eGFR ≥60 ml/min per 1.73 m^2 [28]. Interestingly, high normal levels of albuminuria (≥5 μg/min) predicted the development of micro- and macroalbuminuria and increased mortality in Brazilian type 2 diabetic patients [29]. Furthermore, in Japanese patients with type 1 and type 2 diabetes, even within the normal range (≤30 mg/g), ACR ≥10 mg/g in women and ≥5 mg/g in men was associated with a significantly greater rate of decline in eGFR relative to subjects with ACR ≤5 mg/g [30]. It is of interest that the risk of cardiovascular events in individuals with diabetes increases with the ACR, starting well below the microalbumin cutoff [31]. Taken together, an evaluation of the clinical impact of albuminuria along with an evaluation of the effect of GFR on the prognoses of diabetic patients is required.

Remission/regression of albuminuria in patients with diabetic nephropathy

Fioretto et al. [32] reported that pancreas transplantation reversed the lesions of diabetic nephropathy in patients with type 1 diabetes mellitus, but that reversal required more than 5 years of normoglycemia. A growing body of evidence since then has pointed to the possibility of remission and/or regression of diabetic nephropathy, especially in patients treated with renin-angiotensin system blockade drugs. However, there is a lack of data on pathological findings in these patients. In the clinical setting, Perkins et al. [33] stated that regression of albuminuria was frequent in patients with type 1 diabetes mellitus, with a 6-year cumulative incidence of 58%. In this context, the definition of regression of microalbuminuria is a 50% reduction in albumin excretion from one 2-year period to the next. In addition, Hovind et al. [34] at the Steno Diabetes Center reported that the total number of patients who obtained remission was 92 (31%), with a duration of remission of 3.4 years, and regression occurred in 67 (22%) of 301 consecutive type 1 diabetic patients with diabetic nephropathy. Remission was defined as albuminuria <200 μg/min sustained for at least 1 year and a decrease of at least 30% from pre-remission levels, and regression as a rate of decline in GFR equal to the natural aging process: ≤1 ml/min/year during the investigation period in this report. Moreover, remission of nephrotic-range albuminuria in type 1 diabetic patients was also reported at the Steno Diabetes Center [35]. In this report, remission was induced in 28 of 126 (22%) patients; 21 were predominantly treated with angiotensin-converting enzyme (ACE) inhibitors, and 7 with non-ACE inhibitor medications. Remission lasted 3.6 years. In particular, more women (37%) than men (16%) obtained remission. In addition to type 1 diabetic patients, recent studies have revealed that remission is induced in type 2 diabetic patients. Araki et al. [36] reported that a reduction in urinary albumin excretion rate was frequent, with a 6-year cumulative incidence of 51% for remission, defined as a shift to normoalbuminuria, and 54% for regression, defined as a 50% reduction in the urinary albumin excretion rate. Interestingly, in this particular study, the frequency of progression to overt proteinuria was 28%, and albuminuria of short duration, the use of renin-angiotensin system-blocking drugs, and lower titers for HbA1c and systolic blood pressure were independently associated with remission or regression. More recently, JDCS revealed that a return from low microalbuminuria to normoalbuminuria was observed in 137 out of 452 patients (30.3%) [13].

Further, the clinical impact of remission/regression on renal outcome and cardiovascular events is still to be fully investigated. Importantly, Araki et al. [37] have reported that a reduction in albuminuria in patients with type 2 diabetes is an indicator of cardiovascular and renal risk reduction. In this study, the cumulative incidence of mortality from and hospitalization for renal and cardiovascular events was significantly lower in patients with a 50% reduction. Collectively, remission/regression in patients with diabetic nephropathy is relatively frequent, and insight into the pathological characteristics as well as the clinical impact on renal and cardiovascular outcomes when remission/regression is induced is needed.

Hematuria in diabetic nephropathy

Hematuria, the other major characteristic finding aside from albuminuria/overt proteinuria, was reported in 14 out of 34 Japanese patients with biopsy-proven diabetic nephropathy [38]. Patients with hematuria had significantly lower renal function, and the prevalences of nephrotic syndrome and retinopathy were significantly higher than in patients without hematuria. Interestingly, based on a logistic regression analysis, the presence of nephrotic syndrome and a known duration of diabetes were identified as significant predictors for hematuria with diabetic nephropathy.

Concluding remarks and future directions

Deep insights into the onset and progression of albuminuria along with GFR may elucidate the pathogenesis of

progressive kidney complications and associated cardiovascular diseases. Further studies of the clinical characteristics and the pathological findings of kidney involvement in patients with diabetes are required for a better understanding of diabetic nephropathy and the benefits of therapy for it.

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References

1. Nakai S, Suzuki K, Masakane I, Wada A, Itami N, Ogata S, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2008). Ther Apher Dial. 2010;14:505–40.
2. Nakayama M, Sato T, Sato H, Yamaguchi Y, Obara K, Kurihara I, et al. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study. Clin Exp Nephrol. 2010;14:333–9.
3. Foley RN, Culleton BF, Parfrey PS, Harnett JD, Kent GM, Murray DC, et al. Cardiac diseases in diabetic end-stage renal disease. Diabetologia. 1997;40:1307–12.
4. Saito Y, Kida H, Takeda S, Yoshimura M, Yokoyama H, Koshino Y, et al. Mesangiolysis in diabetic glomeruli: its role in the formation of nodular lesions. Kidney Int. 1988;34:389–96.
5. Wada T, Furuichi K, Sakai N, Iwata Y, Yoshimoto K, Shimizu M, et al. Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions in human diabetic nephropathy. Kidney Int. 2000;58:1492–9.
6. Furuichi K, Hisada Y, Shimizu M, Okumura T, Kitagawa K, Yoshimoto K et al. Matrix metalloproteinase-2 (MMP-2) and membrane-type 1 MMP (MT1-MMP) affect the remodeling of glomerulosclerosis in diabetic OLETF rat. Nephrol Dial Transplant 2011 (Epub ahead of print).
7. Parving HH. Diabetic nephropathy: prevention and treatment. Kidney Int. 2001;60:2041–55.
8. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. Diabetes. 1983;32(Suppl 2):64–78.
9. Shigeta Y, Kikkawa R. Diabetic nephropathy in Japan. Diabetes Res Clin Pract. 1994;24(Suppl):S191–7.
10. Guideline Committee of the Japan Diabetes Society. Japan Diabetes Society guideline for the management of diabetes based on scientific evidence. Tokyo: Japan Diabetes Society; 2004.
11. Yokoyama H, Kawai K, Kobayashi M, Japan Diabetes Clinical Data Management Study Group. Microalbuminuria is common in Japanese type 2 diabetic patients: a nationwide survey from the Japan Diabetes Clinical Data Management Study Group (JDDM 10). Diabetes Care. 2007;30:989–92.
12. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG, DEMAND investigators. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. Kidney Int. 2006;69:2057–63.
13. Katayama S, Moriya T, Tanaka S, Tanaka Y, Yajima H, Sone S, et al. Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS). Diabetologia. 2011;54:1025–31.
14. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, UKPDS GROUP. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63:225–32.
15. Valk EJ, Bruijn JA, Bajema IM. Diabetic nephropathy in humans: pathologic diversity. Curr Opin Nephrol Hypertens. 2011;20:285–9.
16. Kamijo-Ikemori A, Sugaya T, Yasuda T, Kawata T, Ota A, Tatsunami S, et al. Clinical significance of urinary liver-type fatty acid-binding protein in diabetic nephropathy of type 2 diabetic patients. Diabetes Care. 2011;34:691–6.
17. Mima A, Arai H, Matsubara T, Abe H, Nagai K, Tamura Y, et al. Urinary Smad1 is a novel marker to predict later onset of mesangial matrix expansion in diabetic nephropathy. Diabetes. 2008;57:1712–22.
18. Kimura T, Ikeda H, Fujikawa J, Nomura K, Aoyama T, Wada Y, et al. Usefulness of serum cystatin C in Japanese patients with type 2 diabetes mellitus and nephropathy. Diabetes Res Clin Pract. 2009;83:e58–61.
19. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, et al. Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol. 2007;18:1353–61.
20. Levey AS, de Jong PE, Coresh J, Nahas ME, Astor BC, Matsushita K, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80:17–28.
21. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y, Kobayashi M, Japan Diabetes Clinical Data Management Study Group. Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). Nephrol Dial Transplant. 2009;24:1212–9.
22. Caramori ML, Floretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes. 2003;52:1036–40.
23. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol. 2009;20:1813–21.
24. Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, et al. Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care. 2007;30:2034–9.
25. Bruno G, Merletti F, Bargero G, Novelli G, Melis D, Soddu A, et al. Estimated glomerular filtration rate, albuminuria and mortality in type 2 diabetes: the Casale Monferrato study. Diabetologia. 2007;50:941–8.
26. So WY, Kong AP, Ma RC, Ozaki R, Szeto CC, Chan NN, et al. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. Diabetes Care. 2006;29:2046–52.
27. Vlek AL, van der Graaf Y, Spiering W, Algra A, Visseren FL, SMART study group. Cardiovascular events and all-cause mortality by albuminuria and decreased glomerular filtration rate in patients with vascular disease. J Intern Med. 2008;264:351–60.
28. Drury PL, Zannino TD, Ehnholm C, Flack J, Whiting M, Fassett R, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2011;54:32–43.
29. Murussi M, Campagnolo N, Beck MO, Gross JL, Silveiro SP. High-normal levels of albuminuria predict the development of micro- and macroalbuminuria and increased mortality in Brazilian type 2 diabetic patients: an 8-year follow-up study. Diabetes Med. 2007;24:1136–42.
30. Babazono T, Nyumura I, Toya K, Hayashi T, Ohta M, Suzuki K, et al. Higher levels of urinary albumin excretion within the normal range predict faster decline in glomerular filtration rate in diabetic patients. Diabetes Care. 2009;32:1518–20.

31. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–6.
32. Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions diabetic nephropathy after pancreas transplantation. N Engl J Med. 1998;339:69–75.
33. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003;348:2285–93.
34. Hovind P, Rossing P, Tarnow L, Smidt UM, Parving HH. Remission and regression in the nephropathy of type 1 diabetes when blood pressure is controlled aggressively. Kidney Int. 2001;60:277–83.
35. Hovind P, Rossing P, Tarnow L, Toft H, Parving J, Parving HH. Remission of nephrotic-range albuminuria in type 1 diabetic patients. Diabetes Care. 2001;24:1972–7.
36. Araki S, Haneda M, Sugimoto T, Isono M, Isshiki K, Kashiwagi A, et al. Factors associated with frequent remission of microalbuminuria I patients with type 2 diabetes. Diabetes. 2005;54:2983–7.
37. Araki S, Haneda M, Koya D, Hidaka H, Sugimoto T, Isono M, et al. Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. Diabetes. 2007;56:1727–30.
38. Akimoto T, Ito C, Saito O, Takahashi H, Takeda S, Ando Y, et al. Microscopic hematuria and diabetic glomerulosclerosis—clinicopathological analysis of type 2 diabetic patients associated with overt proteinuria. Nephron Clin Pract. 2008;109:c119–26.