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Clinical impact of albuminuria in diabetic nephropathy

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Abstract

Patients suffering from diabetic nephropathy, resulting in end-stage renal failure, are increasing in number. Pathophysiology of diabetic nephropathy remains to be fully investigated. In clinical settings, the presence of albuminuria/overt proteinuria and low glomerular filtration rate may predict poor renal prognosis, however, the prognosis of normoalbuminuric renal insufficient diabetic patients remains contravertial. In addition to the measurement of urinary albumin excretion, biomarker studies to detect diabetic nephropathy in the earlier stage more specifically have been investigated worldwide. A growing body of evidence reveals that remission and/or regression of diabetic nephropathy has been noted, which may be an indicator for cardiovascular and renal risk reduction. Deeper insights into pathological characteristics as well as clinical impacts of albuminuria on renal and cardiovascular outcome would be required.

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 increased to 290, 675 at the end of 2009. According to the annual report of JSDT, diabetic nephropathy has been a leading primary disease of new patients started on dialysis since 1998 (1). The number of patients with diabetic nephropathy increased to 44.5% of new patients started on dialysis. In addition, cardiovascular diseases and death in patients with diabetes as underling renal disease before and after dialysis increase (2-3). Therefore, the prevention and halting the progression of diabetic nephropathy is of importance to prolong the life survival.

Characteristic pathologic changes of diabetic nephropathy are accumulation of extracellular matrix (ECM) and the infiltration of inflammatory cells in glomeruli and tubulointerstitial regions (4-5). These pathologic abnormalities are implicated to be induced by the alterations of ECM production or degradation (6). Generally speaking, the occurrence of albuminuria is a reflection of the increase in matrix deposition, leading to the glomerular and tubulointerstitial lesions. Diabetic nephropathy is a clinical entity in which the presence of persistent albuminuria and decline in renal function as glomerular filtration rate (GFR) are the major characteristic findings, closely associated with end-stage renal diseases, enhanced cardiovascular morbidity and eventual mortality (7). The incidence of albuminuria, contributing to the diagnosis of the presence of diabetic nephropathy at present, is well correlated with decrease in GFR and the incidence of cardiovascular diseases as well.

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, closely related to the mortality in patients with diabetic nephropathy in this manuscript.

Albuminuria as the diagnosis of diabetic nephropathy

The definite diagnosis of diabetic nephropathy is based on the pathological findings, such as the presence of diffuse mesangial lesions and nodular lesions. However, renal biopsy is not performed to all patients with diabetic nephropathy. In clinical settings, the presence of persistent proteinuria as well as other complications, such as diabetic retinopathy, and renal dysfunction are of importance for the diagnosis of diabetic nephropathy. However, the earlier detection of the presence of diabetic nephropathy is clinically required for the better prognosis. To detect earlier diabetic nephropathy, the measurement of urinary excretion of albumin is essential at present. The increased excretion of albumin (albuminuria) is implicated to be an early diagnostic tool for diabetic nephropathy. In this aspect, Mogensen et al. proposed a classification of diabetic nephropathy in patients with type 1 diabetes based on increased urinary albumin excretion, once diabetic nephropathy was diagnosed (8). Diabetic nephropathy is also staged in Japan (9, 10) and described by Yokoyama et al. as follows (11): Stage I: urinary albumin-to-creatinine ratio (ACR) <30mg/g creatinine; stage II: ACR≧30 and <300mg/g creatinine (i.e., albuminuria); stage III: ACR ≧ 300mg/g creatinine and/or persistent proteinuria with serum concentration of creatinine <2mg/dl; stage IV: serum concentration of creatinine ≧2mg/dl with protenuria; and stage V: being treated with dialysis. The Japan Diabetes Clinical Data Management Study Group (JDDM)

reported that the prevalence of albuminuria as Stage II in Japanese type 2 diabetic patients was 32%, which is almost similar to 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 patients enrolled were staged as Stage I, 7% as Stage III, 2.6% as Stage IV and 0.4% as Stage V (11). A very recent study from the Japan Diabetes Complications Study (JDCS) revealed that the annual transition rate to proteinuria (ACR $\geqq$ 300mg/g creatinine) was 0.67% and that this was substantially higher for the low-albuminuric group defined as a urinary ACR of 30 to 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, from albuminuria to macroalbuminuria at 2.8% per year (14).** However, about 40% of diabetic patients had no urinary albumin excretion measurements regardless of recommendation in JDDM cohort (11). Therefore, the measurement of urinary albumin excretion is required for the earlier detection of diabetic nephropathy in Japan.

Biomarkers for diabetic nephropathy and disease progression

Further studies to detect diabetic nephropathy in the earlier stage more specifically 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 investigated worldwide (15). Recently, Kamijo-Ikemori et al. reported that urinary levels of liver-type fatty acid-binding protein (L-FABP) accurately reflected the

severity of diabetic nephropathy in type 2 diabetes (16). Importantly, urinary L-FABP levels were high in the patients with normoalbuminuria, suggesting its usefulness to detect earlier nephropathy in these patients. Further, the increase in urinary Smad1, a key transcriptional factor for mesangial matrix expansion in diabetic nephropathy, in early stage was correlated with later development of glomerulosclerosis in experimental rodent models (17). Regarding renal function, serum cystatin C was reported to be a good marker for detecting nephropathy (18). Notably, cases of early renal dysfunction, defined by loss in 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 by the detection of albuminuria. Recently, Kidney Disease Improving Global Outcomes (KDIGO) reported the definition, classification and prognosis of chronic kidney disease based both on estimated GFR and urinary levels of albumin excretion (20). In this sense, there are diabetic patients with decrease 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 supposed to be relatively common. Importantly, Yokoyama et al. described that the proportion of subjects with low estimated GFR (<60ml/min/1.73m^2) and normoalbuminuria was 11.4% of type 2 diabetic patients examined (262/2298) (21). In this manuscript, 63.4% of these 262 patients had neither diabetic retinopathy nor neuropathy. Of note, these patients were older and included a higher proportion of women and patients with hypertension, hyperlipidemia and cardiovascular disease, and fewer smokers compared with those

with normoalbuminuria and preserved GFR. In contrast, the proportion of type 2 diabetic patients with preserved GFR, having albuminuria or overt proteinuria was 27% (755/2791). Most importantly, the lack of histological 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. Of note, the finding of reduced GFR was much more common among female patients, particularly if retinopathy and/or hypertension were also present (22). Deep insight into prevalence and prognosis of these patients with proven pathological characteristics and grading would be required to understand the pathophysiology of diabetic nephropathy more in depth together with future perspectives.

Clinical impacts of albuminuria and GFR on the prognosis in diabetic patients

Obviously, the diabetic patients together with albuminuria/overt proteinuria and low GFR had the risk for 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) (Figure 1). Do normoalbuminuric renal insufficient diabetic patients have poor prognosis? Rigalleau et al. reported that risk for renal progression and death in these patients with type 1 or type 2 diabetes is lower (24). 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 estimated GFR provided no further information for 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 associations with declined renal function, which was mainly observed in the albuminuric group in Chinese type 2 diabetic patients (26). Interestingly, reduced estimated GFR were at high risk of developing cardiovascular end points (cardiovascular death, new admissions due to angina, myocardial infarction, stroke, revasculization or heart failure) and all-cause mortality independent of albuminuria (26). On the contrary, as previously described, in ADVANCE study, patients with normoalbuminuria and estimated GFR<60ml/min per 1.73 m^2 had a 3.95-fold higher risk for renal event, a 1.33-fold higher risk for cardiovascular events and a 1.85-fold higher risk for cardiovascular death (23) (Figure 1). Moreover, Vlek et al. reported that estimated GFR<60 ml/min/1.73 m^2 without albuminuria mainly influenced the risk 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 had a higher risk of a cardiovascular events, cardiovascular death, non-coronary heart disease deaths, death from any cause than normoalbuminuric patients with eGFR ≧60 ml/min per 1.73 m^2 (28). Interestingly, high normal levels of albuminuria (>5μg/min) predict 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), albumin-to-creatinine ratio ≧10mg/g in women and ≧5mg/g in men was associated with a significantly greater rate of decline in eGFR relative to subjects with albumin-to-creatinine ratio <5 mg/g (30). It is of interest that the risk of cardiovascular events in**

individuals with diabetes increases with the albumin-to-creatinine ratio, starting well below the microalbumin cutoff (31). Taken together, evaluation of clinical impacts of albuminuria along with the evaluation of GFR on the prognosis in diabetic patients is required.

Remission/regression of albuminuria in patients with diabetic nephropathy

Of note, Fioretto et al. reported that pancreas transplantation reversed the lesions of diabetic nephropathy in patients with type 1 diabetes mellitus, but that reversal required more than five years of normoglycemia (32). Thereafter, a growing body of evidence reveals that remission and/or regression of diabetic nephropathy has been noted these days, especially in patients treated with renin-angiotensin system blockade drugs. The issues are lack of data on pathological findings in these patients. In clinical settings in patients with type 1 diabetes mellitus, Perkins et al. described that regression of albuminuria was frequent, with a six-year cumulative incidence of 58% (33). In this context, definition of regression of microalbuminuria is a 50 percent reduction in albumin excretion from one two-year period to the next. In addition, Hovind et al. at 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 67 (22%) in 301 consecutive type 1 diabetic patients with diabetic nephropathy (34). Remission was defined as albuminuria <200 microg/min sustained for at least one year and a decrease of at least 30% from preremission levels, and regression as rate of decline in GFR equal to the natural aging process: < or =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 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, 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 reveal that remission is induced in type 2 diabetic patients. Araki et al. reported that reduction of urinary albumin excretion rate was frequent, with a 6-year cumulative incidence of 51% for remission, defined as shift to normoalbuminuria, and 54% for regression, defined as a 50% reduction in urinary albumin excretion rate (36). 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 return from low-microalbuminuria to normoalbuminuria was observed in 137 out of 452 patients (30.3%) (13).

Further, clinical impact of remission/regression on renal outcome and cardiovascular events remains fully investigated. Importantly, Araki et al. have reported that a reduction of albuminuria in patients with type 2 diabetes is an indicator for cardiovascular and renal risk reduction (37). In this study, the cumulative incidence of death 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 insights into pathological characteristics as well as clinical impacts on renal and cardiovascular outcomes when remission/regression is induced would be needed.

Hematuria in diabetic nephropathy

Incidence of hematuria, other major characteristics finding than albuminuria/overt proteinuria, was reported in 14 out of 34 Japanese patients with biopsy-proven diabetic nephropathy (38). Patients having hematuria had a significantly lower renal function and the prevalence of nephrotic syndrome and retinopathy was significantly higher than that in the patients without hematuria. Interestingly, based on a logistic regression analysis, the presence of nephrotic syndrome and known duration of diabetes were identified to be significant predictors for hematuria with diabetic nephropathy.

Concluding remarks and future directions

A deep insight of the onset and progression of albuminuria along with GFR may provide a key for the pathogenesis of progressive kidney complications and associated cardiovascular diseases. Further studies for clinical characteristics and pathological findings of kidney involvement in patients with diabetes would be required for a better understanding and the therapeutic benefit for diabetic nephropathy.

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Figure legend

Figure 1

Combined effects of albuminuria and eGFR levels at baseline on the risk for adverse outcomes. 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. Copyright 2009 American Society of Nephrology. From J Am Soc Nephrol, vol 20, 1813-1821. Reproduced with permission from American Society of Nephrology.

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