Conclusions

The results of our study show the possibility of latent existence and progression of periaortic/periarterial lesions, the efficacy of corticosteroid therapy in preventing new aneurysm formation in patients without luminal dilatation of periaortic/periarterial lesions, and the possibility that a small proportion of patients may actually experience luminal dilatation of periaortic/periarterial lesions in IgG4-related PAo/PA. To confirm the efficacy and safety of corticosteroid therapy in patients with versus without luminal dilatation, and to devise a more useful and safe treatment strategy, including administration of other immunosuppressants, a larger-scale prospective study is required.

Abbreviations

AIP: Autoimmune pancreatitis; CDC: Comprehensive diagnostic criteria; CRP: C-reactive protein; CT: Computed tomography; EVAR: Endovascular aortic repair; FDG-PET/CT: 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography; IgG4: Immunoglobulin G4; IgG4-RD: Immunoglobulin G4 (IgG4)–related disease; IgG4-related PAo/PA: IgG4-related aortitis/periaortitis and periarteritis; PSL: Prednisolone.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IM and MK were responsible for study conception and design, data collection, data analysis and manuscript writing. DI, MoY, KY, TS, YU, SM, YM and TW were responsible for data collection, data analysis and critical revision of the manuscript SK, KH, KN and YN were responsible for study conception and design and critical revision of the manuscript. HT and HU were responsible for data collection, data analysis and critical revision of the manuscript. MaY was responsible for study conception and design, data collection, data analysis and critical revision of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ORIGINAL ARTICLE

Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes

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Abstract

Background The number of patients suffering from diabetic nephropathy resulting in end-stage kidney disease is increasing worldwide. In clinical settings, there are limited data regarding the impact of the urinary albumin-to-creatinine ratio (UACR) and reduced estimated glomerular filtration rate (eGFR) on renal and cardiovascular outcomes and all-cause mortality.

Methods We performed a historical cohort study of 4328 Japanese participants with type 2 diabetes from 10 centers. Risks for renal events (requirement for dialysis or transplantation, or half reduction in eGFR), cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), and all-cause mortality were assessed according to UACR and eGFR levels.

Results During follow-up (median 7.0 years, interquartile range 3.0–8.0 years), 419 renal events, 605 cardiovascular events and 236 deaths occurred. The UACR levels increased the risk and the adjusted hazard ratios for these three events. In addition to the effects of UACR levels, eGFR stages significantly increased the adjusted hazard ratios for renal events and all-cause mortality, especially in

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patients with macroalbuminuria. Diabetic nephropathy score, based on the prognostic factors, well predicted incidence rates per 1000 patient/year for each event.
Conclusions Increased UACR levels were closely related to the increase in risks for renal, cardiovascular events and all-cause mortality in Japanese patients with type 2 diabetes, whereas the association between high levels of UACR and reduced eGFR was a strong predictor for renal events.

Keywords Diabetic nephropathy · Chronic kidney disease · Albuminuria · Cardiovascular disease · Mortality · Glomerular filtration rate

Introduction

Diabetic nephropathy is a leading cause of end-stage kidney (renal) disease (ESKD or ESRD) worldwide [1]. In addition, cardiovascular diseases and deaths increase in patients with diabetic nephropathy before and after dialysis [2–4]. Therefore, to determine and manage risk factors for progression of renal and cardiovascular outcomes and mortality is of importance to prolong the life expectancy of diabetic patients.

A high urinary albumin-to-creatinine ratio (UACR) and low estimated glomerular filtration rate (eGFR) have been believed to be predictors for diabetic ESKD and death [5–7]. Kidney Disease Improving Global Outcomes (KDIGO) provided a new classification for chronic kidney disease (CKD) by adding stages that stratified urinary albumin excretion as well as eGFR and emphasizing clinical diagnosis [8]. This new classification, mainly based on the collaborative meta-analysis of general population cohorts [8], has shed light on prognosis assigned by clinical diagnosis, stage, and other key factors relevant to renal and cardiovascular outcomes. However, the clinical impact of UACR levels in combination with eGFR on outcomes in Japanese patients with diabetic nephropathy needs to be confirmed. Therefore, deeper clinical insights of UACR along with GFR are required to provide a key for the pathogenesis and outcomes of progressive renal complications, and associated cardiovascular events in type 2 diabetic patients.

Here we examined the prognostic value of UACR and eGFR for renal events, cardiovascular events and all-cause mortality in Japanese patients with type 2 diabetes. Furthermore, we proposed a diabetic nephropathy score for predicting prognosis in diabetic patients.

Subjects and methods

Subjects

This study was a historical cohort consisting of 4814 Japanese patients with type 2 diabetes who were treated by trained physicians at 10 centers between 1985 and 2010. Four hundred and fifty-nine patients were excluded because of age <18 ($n = 6$), follow-up <1 year ($n = 151$) and no measurement of urinary albumin or HbA1c or blood pressure (BP) ($n = 329$), leaving 4328 Japanese patients to be enrolled in this study. Patients with secondary diabetes, renal transplantation or dialysis were also excluded.

This study was conducted according to the ethical guidelines for epidemiological research designed by the Japanese Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour, and Welfare (http://www.lifescience.mext.go.jp/files/pdf/n796_01.pdf).

The study design was included in a comprehensive protocol of retrospective study at the Division of Nephrology, Kanazawa University Hospital approved by Kanazawa University ethical committee (approval number 815).

Follow-up and assessments

Type 2 diabetes was defined according to the Japan Diabetes Society (JDS) criteria [9]. In this historical cohort study, UACR and eGFR were also determined. Measurement of UACR, by a turbidimetric immunoassay at each laboratory, was performed on spot urine samples at baseline. Serum creatinine was measured at baseline, at subsequent yearly intervals, and at the end of follow-up. Serum and urinary concentrations of creatinine were measured by an enzymatic method, and eGFR was estimated using the equation proposed by the Japanese Society of Nephrology [10]. Both UACR and serum creatinine were measured at local laboratories. At each study visit, blood pressure (BP) was measured in the sitting position. Hypertension was defined as BP $\geq$ 140/90 mmHg or

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current use of antihypertensive drugs. Non-fasting blood samples were obtained for measurements of HbA1c and lipid levels at local laboratories. HbA1c was measured and standardized by the JDS (normal range 4.3–5.8 %) and certified by the US National Glycohemoglobin Standardization Program (National Glycohemoglobin Standardization Program, NGSP; NGSP = JDS + 0.4) [9].

UACR and GFR categories

Based on the new classification of CKD [8], the albuminuria category was classified at baseline as normoalbuminuria (<30 mg/g), microalbuminuria (≥30 and <300 mg/g), and macroalbuminuria (≥300 mg/g). In addition, baseline eGFR levels were divided into six categories: ≥90, 60–89, 45–59, 30–44, 15–29 and <15 ml/min per 1.73 m^2. Patients examined in this study were categorized and assessed based on the above classifications.

Outcomes

The main outcomes of this study were renal events (requirement for dialysis or transplantation, or half reduction in eGFR), cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), and all-cause mortality death. These conditions corresponded to the International Classification of Diseases, 11th version (http://www.who.int/classification/icd/en/). Definitions for nonfatal myocardial infarction and nonfatal stroke are given elsewhere [11]. Patients were referred to cardiologists, neurosurgeons, neurologists or else to confirm diagnoses. Only the first event of the relevant outcome type was included in each analysis and the last day of the observation period was also noted if there were no incidences.

Statistical analysis

Data are expressed as mean ± SD or median (interquartile range). Incidence rates of renal events, cardiovascular events, and all-cause death for different categories were calculated. Cox proportional hazards analysis was used to compute hazard ratios and 95 % confidence intervals (CI) to assess the impact of albuminuria and eGFR on the outcomes by using the group with eGFR ≥60 ml/min per 1.73 m^2 and/or the group with normoalbuminuria (<30 mg/g) as the reference [8]. In multivariate analysis, adjustment for risk factors for renal events, cardiovascular events, or all-cause mortality included age, gender, HbA1c, and systolic BP. A p value <5 % was considered significant. p values for trend tests examined whether UACR and eGFR levels were associated with increased hazard ratios. Trend tests across increasing risks for renal, cardiovascular events and all-cause mortality are stratified by factors for diabetic nephropathy score.

All analyses were performed with the statistical software package SPSS (SPSS Japan, Tokyo, Japan).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of patients examined in this study. The 4328 patients were distributed according to CKD stage and were followed until the onset of the first event or the end of the observation period (Table 1).

Incidence of numbers of patients of each event

During a median follow-up of 7.0 years (interquartile range 3.0–8.0 years), 419 renal events, 605 cardiovascular events and 236 deaths occurred, which were stratified by stages of renal function and levels of UACR with each event (Table 2). The incidence rates of each outcome per 1000 person-years were 19.8 for renal events, 23.3 for cardiovascular events and 8.4 for all-cause mortality. The incidence of each event increased with worsening of UACR levels and eGFR stages. Of importance, high incidence rates were noted in patients with macroalbuminuria plus reduced eGFR, especially for renal events (Table 2).

Risk for renal events, cardiovascular events, and all-cause mortality stratified by albuminuria and eGFR

Risks for renal events, cardiovascular events and all-cause mortality were evaluated by Cox proportional hazards analysis. The estimates were adjusted for age, gender, HbA1c, and systolic BP. The adjusted hazard ratios for renal events were 3.21 (95 % CI 2.31–4.47) for microalbuminuric patients and 21.86 (95 % CI 16.15–29.59) for macroalbuminuric patients as compared to normoalbuminuric patients as reference. Similarly, the adjusted hazard ratios for cardiovascular events and all-cause mortality were 1.38 (95 % CI 1.14–1.67) and 1.37 (95 % CI 0.99–1.89) for microalbuminuric patients and 2.05 (95 % CI 1.61–2.58) and 3.60 (95 % CI 2.53–5.20) for macroalbuminuric patients as compared to reference, respectively. Interestingly, UACR levels had the most significant impact on renal events. In addition to the effects of UACR levels, eGFR stages significantly increased the adjusted hazard ratios for renal events in patients with macroalbuminuria (Table 3). In Table 3, hazard ratios for cardiovascular events increased in patients with a higher UACR. In

Table 1 Baseline characteristics of participants ($n = 4328$)

Variable	All	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	p For trend
N	4328	2679	1115	534	
Age (years; mean [SD])	60.2 (11.6)	59.5 (11.4)	61.9 (11.5)	59.8 (12.0)	<0.001
Male (*n* [%])	2546 (58.8)	1531 (57.1)	656 (58.8)	359 (67.2)	<0.001
Kidney factors					
UACR (mg/g; median [IQR])	18.2 (8.6–66.6)	10.2 (6.5–16.4)	66.6 (42.6–121.3)	994.8 (518.5–2272.5)	<0.001
eGFR (ml/min/1.73 m^2; mean [SD])	77.0 (25.9)	81.3 (23.8)	76.4 (25.3)	56.9 (28.0)	<0.001
eGFR ≥90 (*n* [%])	1201 (27.7)	839	297	65	
eGFR 60–89 (*n* [%])	2051 (47.4)	1371	530	150	
eGFR 45–59 (*n* [%])	642 (14.8)	345	174	123	
eGFR 30–44 (*n* [%])	311 (7.2)	109	100	102	
eGFR 15–29 (*n* [%])	117 (2.7)	15	14	88	
eGFR <15 (*n* [%])	6 (0.1)	0	0	6	
BP (mmHg)					
Systolic BP (mean [SD])	131.0 (18.6)	127.2 (16.6)	134.2 (18.4)	143.0 (22.0)	<0.001
Diastolic BP (mean [SD])	74.3 (18.0)	73.3 (20.7)	74.8 (11.8)	78.1 (13.1)	<0.001
Other major risk factors					
HbA1c (%; mean [SD])	7.6 (1.7)	7.5 (1.7)	7.8 (1.7)	7.9 (1.8)	<0.001
Total cholesterol (mg/dL; mean [SD])	205.2 (35.9)	205.3 (34.1)	202.2 (33.9)	214.2 (50.2)	0.925
Body mass index (kg/m^2; mean [SD])	25.3 (4.2)	25.1 (4.2)	25.5 (4.2)	25.4 (4.8)	0.098

Table 2 Number of patients and incidence rates of each outcome stratified by stages of eGFR and albuminuria

UACR	eGFR (ml/min/1.73 m^2)					
	>90	60–89	45–59	30–44	15–29	<15
Renal events (RRT or halving reduced eGFR)						
Normoalbuminuria	58 (4.2)		4 (2.3)	3 (6.9)	1 (21.3)	0
Microalbuminuria	31 (17.2)	41 (13.1)	15 (18.0)	10 (21.0)	1 (25.6)	0
Macroalbuminuria	20 (59.5)	62 (87.7)	56 (126.7)	54 (193.5)	61 (309.6)	2 (250.0)
Cardiovascular events						
Normoalbuminuria	229 (16.2)		40 (23.1)	14 (33.0)	1 (18.9)	0
Microalbuminuria	31 (16.1)	95 (28.7)	33 (32.6)	28 (56.1)	2 (43.5)	0
Macroalbuminuria	7 (17.2)	41 (44.6)	30 (44.3)	30 (64.2)	23 (57.9)	1 (100.0)
All-cause mortality						
Normoalbuminuria	70 (4.7)		26 (13.8)	4 (8.2)	4 (67.8)	0
Microalbuminuria	11 (5.4)	32 (8.9)	13 (11.9)	5 (8.5)	6 (117.6)	0
Macroalbuminuria	6 (14.4)	13 (12.3)	19 (24.6)	13 (23.6)	12 (26.8)	2 (142.9)

Number of patients (incidence rates per 1000 person-years)

RRT renal replacement therapy

addition, our results showed that there was a slight increase in the hazard ratios of cardiovascular events based on UACR levels plus co-existing reduced eGFR, especially in patients with microalbuminuria based on p for trend. In contrast, all-cause mortality was strongly associated with reduced eGFR <30 ml/min per 1.73 m^2, and the presence of macroalbuminuria even with preserved eGFR. The present study also revealed that normoalbuminuric renal insufficient diabetic patients did not have relatively poor outcomes for renal events. Table 4 highlights the impact of low GFR and/or UACR on three distinct outcomes.

The clinical significance of diabetic nephropathy score in predicting the prognoses of renal events, cardiovascular events, and all-cause mortality

Considering the results of univariable and multivariable analyses, weighted arbitrary scores were allocated to each

Table 3 Hazard ratios based on CKD stages for each outcome

UACR	eGFR (ml/min/1.73 m^2)						*p* for trend (eGFR)
	>90	60–89	45–59	30–44	15–29	<15	
Renal events (RRT or halving reduced eGFR)							
Normoalbuminuria	1.00 (Reference)	1.00 (Reference)	0.69 (0.24–1.98)	1.83 (0.53–6.31)	11.59 (1.43–93.78)	NA	0.85
Microalbuminuria	3.31 (2.07–5.28)	3.04 (1.98–4.68)	3.36 (1.63–6.93)	3.10 (1.41–6.83)	3.60 (0.42–31.28)	NA	0.60
Macroalbuminuria	11.14 (5.87–21.17)	15.64 (10.30–23.74)	33.37 (20.58–50.91)	41.36 (25.09–68.16)	71.58 (40.41–126.80)	NA	<0.01
p for trend (albuminuria)	<0.01	<0.01	<0.01	<0.01	0.06	NA	
Cardiovascular events							
Normoalbuminuria	1.00 (Reference)	1.00 (Reference)	1.05 (0.73–1.49)	1.30 (0.74–2.28)	0.42 (0.06–3.06)	NA	0.46
Microalbuminuria	1.01 (0.69–1.49)	1.48 (1.15–1.90)	1.33 (0.89–2.00)	1.85 (1.20–2.85)	0.47 (0.11–1.97)	NA	0.04
Macroalbuminuria	1.28 (0.56–2.94)	2.10 (1.46–3.02)	1.85 (1.23–2.78)	2.37 (1.55–3.63)	2.09 (1.26–3.45)	12.76 (0.95–171.19)	0.20
p for trend (albuminuria)	0.81	<0.01	0.09	0.45	0.17	NA	
All-cause mortality							
Normoalbuminuria	1.00 (Reference)	1.00 (Reference)	1.67 (1.02–2.74)	1.22 (0.43–3.46)	8.19 (2.65–25.34)	NA	<0.01
Microalbuminuria	1.51 (0.78–2.95)	1.44 (0.92–2.24)	1.22 (0.63–2.35)	0.84 (0.31–2.26)	8.36 (2.81–24.90)	NA	0.04
Macroalbuminuria	4.37 (1.70–11.24)	1.92 (0.97–3.79)	4.84 (2.72–8.62)	4.09 (2.00–8.34)	6.16 (2.80–13.56)	70.57 (3.65–1363.68)	0.06
p for trend (albuminuria)	0.01	0.01	0.01	0.02	0.80	NA	

The estimates are adjusted for age, gender, HbA1c, systolic BP

RRT renal replacement therapy, *NA* not available

Table 4 Hazard ratios based on levels of UACR and eGFR for each outcome

UACR	eGFR (ml/min/1.73 m^2)		
	>60	30–59	<30
Renal events (RRT or halving reduced eGFR)			
Normoalbuminuria	1.00 (Reference)		49.82 (29.9–83.0)
Microalbuminuria	3.26 (2.34–4.55)		
Macroalbuminuria	13.6 (9.3–20.0)	33.0 (22.7–48.2)	
Cardiovascular events			
Normoalbuminuria	1.00 (Reference)		1.54 (1.00–2.39)
Microalbuminuria	1.40 (1.16–1.69)		
Macroalbuminuria	1.90 (1.36–2.65)	2.09 (1.54–2.84)	
All-cause mortality			
Normoalbuminuria	1.00 (Reference)		7.08 (4.16–12.05)
Microalbuminuria	1.30 (0.93–1.81)		
Macroalbuminuria	2.34 (1.35–4.04)	4.59 (2.90–7.25)	

The estimates are adjusted for age, gender, HbA1c, systolic BP

selected variable on the basis of each odds ratio (OR), and we defined a summation of scores as a new risk scoring system as the diabetic nephropathy score. We evaluated the diabetic nephropathy score for predicting the prognoses of renal events, cardiovascular events, and all-cause mortality. Each prognostic factor has a score and the maximum score is 6—microalbuminuria = 1, macroalbuminuria = 2, eGFR <45 ml/min per 1.73 m^2 = 1, age ≥60 years = 1, systolic BP >130 mmHg = 1, and HbA1c (NGSP) ≥6.9 % = 1. This score put stress on amounts of UACR. Importantly, this simple score well predicted the incidence rates per 1000 patient/year for each event (Table 5).

Discussion

In this study we examined the clinical impact of UACR as well as the evaluation of GFR on outcomes in diabetic patients. We now report that increased urinary albumin excretion was strongly associated with risks for renal

Table 5 Diabetic nephropathy score reflects diabetic outcomes

	Renal events (RRT or halving reduced eGFR)				Cardiovascular events				All-cause mortality			
Score	Number of patients	Number of incidents	Rate per 1000 patient-years	95 % CI	Number of patients	Number of incidents	Rate per 1000 patient-years	95 % CI	Number of patients	Number of incidents	Rate per 1000 patient-years	95 % CI
0	204	0	0.0		204	2	1.4	0.2–5.1	204	0	0.0	
1	902	18	3.1	1.9–5.0	954	58	9.7	7.4–12.6	954	13	2.1	1.1–3.6
2	1228	54	6.9	5.2–9.0	1,310	174	21.4	18.4–24.9	1310	71	8.1	6.3–10.3
3	952	96	16.6	13.4–20.0	1,017	161	26.2	22.3–30.6	1017	62	9.4	7.2–12.0
4	471	118	46.6	38.5–56.0	532	116	39.0	32.2–46.8	532	45	13.4	9.8–18.0
5	213	93	103.8	83.8–127.0	238	71	60.5	47.3–76.3	238	35	25.5	17.7–35.4
6	61	40	216.2	154.5–294.0	73	23	80.4	51.0–120.7	73	10	28.1	13.5–51.7
p for trend			<0.001				<0.001				<0.001	

events, cardiovascular events and deaths in Japanese patients with type 2 diabetes. Of note, eGFR stages significantly increased the adjusted hazard ratios for renal events, especially when co-existing with macroalbuminuria, while patients with normoalbuminuria had relatively low risks for renal events. All-cause mortality was strongly associated with reduced eGFR <30 ml/min per 1.73 m^2 and the presence of macroalbuminuria even with preserved eGFR. However, the association between normoalbuminuria and reduced eGFR showed relatively low risks for cardiovascular events in the cohort of the Japanese population with type 2 diabetes. These findings suggested that diabetic patients with macroalbuminuira and low GFR had risks for adverse outcomes, even though UACR levels and eGFR had distinct clinical impacts on each event, respectively. Finally, the diabetic nephropathy score based on our present study may be useful for predicting the prognoses of outcomes in diabetic patients.

The present study has clearly shown that renal insufficiency plus the presence of macroalbuminuria accelerated risks for adverse outcomes, especially renal events. Recently, KDIGO reported the definition, classification and prognosis of CKD based both on estimated GFR and urinary levels of albumin excretion, emphasizing that a decrease in GFR as well as macroalbuminuria is important for renal outcomes of CKD [8]. In addition, the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study reported that reduced eGFR with macroalbuminuria was associated with a higher risk for renal events [6]. Interestingly, the Casale Monferrato study revealed that macroalbuminuira was the main predictor of mortality, independently of both eGFR and cardiovascular risk factors [12]. In contrast, reduced eGFR did not increase the adjusted hazard ratio for renal events even in patients with microalbuminuria. This may be partly because the number of microalbuminuric patients with reduced GFR having renal events was relatively small as shown in Table 2. Collectively, these findings suggest that the assessment of macroalbuminuria as well as levels of eGFR may enable us to predict high risk for renal events.

The association between UACR and reduced eGFR showed relatively low risks for cardiovascular events, even though the incidence rate of cardiovascular events was 23.3, which was almost comparable to that observed in the Japan Diabetes Complications Study (JDCS) [13]. Our results also demonstrated that UACR was closely associated with cardiovascular events in patients with eGFR 60–89 ml/min per 1.73 m^2 and that reduced eGFR was important in microalbuminuric patients based on *p* values for trend. Of note, Yokoyama et al. recently reported that the risk for cardiovascular events was associated with progression of UACR stage in type 2 Japanese diabetic

patients [14]. In contrast, reduced eGFR was a high risk for developing cardiovascular endpoints (cardiovascular death, new admissions due to to angina, myocardial infarction, stroke, revascularization or heart failure) and all-cause mortality independent of UACR [15]. Interestingly, the Second Nord-Trøndelag Health (HUNT II) study [16] reported that reduced eGFR with higher UACR was associated with a higher risk for cardiovascular events. This discrepancy compared to our present study may be partly because the number of patients with cardiovascular events in the present study was relatively small as shown in Table 2. Further studies will be required to examine this discrepancy.

This study also revealed that normoalbuminuric renal insufficient diabetic patients did not have relatively poor renal outcomes. In fact, the percentage of diabetic patients with normoalbuminuria and low eGFR is supposed to be relatively common in clinical settings. In this aspect, Yokoyama et al. [17] described that the proportion of subjects with low eGFR (<60 ml/min per 1.73 m^2) and normoalbuminuria was 11.4 % of type 2 diabetic patients examined (262/2,298). Supporting our notion, Rigalleau et al. [18] reported that risk for renal progression in such patients with type 1 or type 2 diabetes is lower. On the contrary, all-cause mortality, not cardiovascular events, was strongly associated with reduced eGFR <30 ml/min per 1.73 m^2 in normoalbuminuric diabetic patients in this present study. Supporting this notion, hazard ratios for all-cause mortality as well as cardiovascular mortality increased in normoalbuminuric diabetic patients with low GFR [19]. The FIELD study also revealed that normoalbuminuric patients with eGFR 30–59 ml/min per 1.73 m^2 had a higher risk of 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 [7]. Interestingly, in the ADVANCE study, patients with normoalbuminuria and eGFR <60 ml/min/1.73 m^2 had a 3.95-fold higher risk for renal events, a 1.33-fold higher risk for cardiovascular events and a 1.85-fold higher risk for cardiovascular death [6]. In contrast, Vlek et al. [20] reported that eGFR <60 ml/min per 1.73 m^2 without UACR mainly influenced the risk of vascular events (hazard ratio 1.50; 1.05–2.15), but did not affect all-cause mortality. Furthermore, in type 2 diabetic patients, eGFR provided no further information for all-cause mortality and cardiovascular mortality in normoalbuminuric patients [14]. Therefore, further studies are needed to determine renal outcomes as well as all-cause mortality in normoalbuminuric diabetic patients with low eGFR.

We proposed a novel diabetic nephropathy score to predict incidence rates per 1000 patient/year for each event. To date, few studies have addressed individual prognostic factors/scores to predict outcomes of diabetic complications in clinical settings. Couchoud et al. [21] reported development and validation of a prognostic score for 6-month mortality in elderly patients starting dialysis for ESKD. Nine risk factors were selected and points assigned for the score were body mass index <18.5 kg/m^2 (2 points), diabetes (1 point), congestive heart failure stages III to IV (2 points), peripheral vascular disease stages III to IV (2 points), dysrhythmia (1 point), active malignancy (1 point), severe behavioral disorder (2 points), total dependency for transfers (3 points) and unplanned dialysis (2 points). These scores effectively predict short-term prognosis among elderly patients, in which approximately 20 % of the patients had diabetic nephropathy. In contrast to this previous study, our simple prognostic scoring system may clearly predict cardiovascular events and all-cause mortality as well as renal events for patients of any age. Even though validation of this score system will be required for other cohorts, this system seems simple and useful for predicting clinical aspects.

To date, UACR levels and reduced eGFR have independently been reported to predict cardiovascular and real outcomes in diabetes [6]. Previously, diabetic patients with microalbuminuria/macroalbuminuira had a risk for adverse outcomes, including cardiovascular events, cardiovascular death, and renal events as reported by the ADVANCE study [6]. Importantly, the present study, consisting of 4328 Japanese patients with type 2 diabetes, was critically different from the ADVANCE study in terms of (1) being a historical cohort study consisting of 10 centers, (2) longer observation period (median 7.0 years), (3) including the assessment of all-cause mortality, (4) including assessment of each event based on the new classification CKD stages, and (5) providing a diabetic nephropathy score to predict the prognoses of renal events, cardiovascular events, and all-cause mortality. Therefore, our present study further revealed the clinical significance of UACR and eGFR on adverse outcomes in diabetic patients.

There are several limitations to this study. First, the lack of histologically proven diabetic nephropathy should be discussed, even though diabetic nephropathy is clinically diagnosed by the presence of microalbuminuria. Second, the low incidence of cardiovascular events may result in a relatively weak statistical power. Furthermore, the lack of data regarding whether enrolled patients have predisposing cardiovascular diseases must be considered. However, this multicenter observational study of 4328 diabetic patients over 7 years may strengthen the present results and increase the accuracy of risk estimation and establishment of a prognostic diabetic nephropathy score.

In conclusion, these results conclude that the presence of microalbuminuria/macroalbuminuria is closely related to the increase in risks for adverse outcomes in Japanese diabetic patients, whereas the association between

macroalbuminuria and reduced eGFR was a strong predictor for renal events. Further studies will be required to validate the prognostic factors and related diabetic nephropathy score by using other cohorts together with future perspectives.

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REVIEW ARTICLE

Kidney lesions in diabetic patients with normoalbuminuric renal insufficiency

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Abstract Diabetic nephropathy is a leading cause of end-stage renal disease in Japan. Microalbuminuria has been considered as the first clinical sign of diabetic nephropathy. However, recent studies demonstrated that normoalbuminuric renal insufficiency is not uncommon for diabetic patients, especially in type 2 diabetes. Although the pathogenesis of normoalbuminuric renal insufficiency in diabetic nephropathy remains to be fully elucidated, distinct clinical and pathological features of diabetic patients with this finding have been reported as compared to those in diabetic patients with a typical clinical course. In type 1 diabetes, more advanced glomerular lesions were found in patients with normoalbuminuric renal insufficiency than in patients with normoalbuminuric preserved renal function. In contrast, disproportionately advanced tubulointerstitial and vascular lesions, despite minor diabetic glomerular lesions, which denote the presence of diabetic kidney lesions as well as nephrosclerosis, were likely to be related to the development of normoalbuminuric renal insufficiency in some type 2 diabetic patients. In addition, long-term outcomes of diabetic patients with normoalbuminuric renal insufficiency remain controversial. Further studies to gain a better understanding of the structural–functional relationships and natural history of diabetic patients with normoalbuminuric renal insufficiency may improve the benefits of therapeutic interventions for diabetic nephropathy.

Keywords Diabetic nephropathy · Normoalbuminuric renal insufficiency · Kidney lesions · Nephrosclerosis · Comprehensive medicine · Humans

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Introduction

Diabetic nephropathy is a leading cause of end-stage renal disease in Japan [1]. The percentage of patients with diabetic nephropathy was 44.1 % among new dialysis patients, and 37.1 % among all dialysis patients at the end of 2012 based on the latest annual report of the Japanese Society for Dialysis Therapy.

Albuminuria and glomerular filtration rate (GFR) are recommended for use as clinical markers of diabetic nephropathy, and microalbuminuria has been considered as the first clinical sign of diabetic nephropathy [2–5]. However, recent studies demonstrated that reduction in GFR may precede the development of microalbuminuria in some diabetic patients [6–14].

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On the other hand, pathological markers of diabetic nephropathy are complicated because a variety of renal lesions can be found in diabetic nephropathy. In addition, factors such as obesity, hypertension, dyslipidemia, and aging, which are frequent complications in type 2 diabetes, cause a wide variety of pathological changes [15–17]. Currently, renal biopsy is not always applicable for diabetic patients with a typical clinical course. The latest committee report by the Japan Renal Biopsy Registry (J-RBR) and the Japan Kidney Disease Registry (J-KDR) indicated that the percentage of diabetic nephropathy was 5.1 % (376/7442) in the pathological diagnoses as classified by pathogenesis in J-RBR 2009 and 2010 [18]. Therefore, the structural–functional relationships of diabetic nephropathy remain to be fully investigated.

Previously, Takazakura et al. [19] reported the clinical factors related to the development and progression of renal lesions in diabetic nephropathy by evaluation of serial renal biopsies or autopsy. In this study, significant relationships were found between progression of diabetic glomerulosclerosis and clinical factors such as the control of blood glucose, type of diabetes, age at onset, type of treatment, and degree of obesity. Subsequently, we conducted a long-term retrospective study to evaluate the structural–functional relationships and prognostic impacts of clinicopathological parameters for renal events, cardiovascular events, and all-cause mortality among 260 Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy [20]. Our study suggested that the characteristic pathological lesions and macroalbuminuria (severe proteinuria) were closely related to the long-term outcomes of diabetic nephropathy in type 2 diabetes. Based on our results, it is reasonable to predict renal prognosis of diabetic nephropathy by a combination of clinical and pathological parameters. Furthermore, we speculate that the evaluation of renal pathology provides a key note to have deeper insights for 'Comprehensive Medicine in Humans' including renal events and cardiovascular events in patients with diabetic nephropathy.

Here, we focus on the clinical characteristics, renal lesions, and outcomes of diabetic nephropathy with normoalbuminuric renal insufficiency, and describe future perspectives for clinical research on diabetic nephropathy.

Prevalence of normoalbuminuric renal insufficiency in diabetes

The prevalence of normoalbuminuria among type 1 diabetic patients with low GFR (<60 ml/min/1.73 m^2) was 23.6 % (21/89) in the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study conducted in 1982–2006 [6].

In contrast, the prevalence of normoalbuminuria among type 2 diabetic patients with low GFR (<60 ml/min/1.73 m^2) was 32 % in the Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes (DEMAND) study conducted in 2002–2005 [7], 35.1 % (60/171) in the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988–1994 [8], 50.8 % (575/1132) in the United Kingdom Prospective Diabetes Study (UKPDS)-74 study conducted in 1977–1991 [9], 51.8 % (262/506) in the Japan Diabetes Clinical Data Management (JDDM) study conducted in 2004–2005 [10], 55.0 % (506/920) in the National Evaluation of the Frequency of Renal Impairment cO-existing with Non-insulin-dependent diabetes (NEFRON) study conducted in 2005 [11], 56.5 % (1673/2959) in the Renal Insufficiency And Cardiovascular Events (RIACE) study conducted in 2007–2008 [12], 61.6 % (1252/2033) in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study conducted in 2001–2003 [13], and 71.3 % (290/407) in the Swedish National Diabetes Register conducted in 2002–2007 [14]. These results suggest that normoalbuminuric renal insufficiency is not uncommon among diabetic patients, especially in type 2 diabetes.

Pathogenesis of normoalbuminuric renal insufficiency in diabetes

There are several possible pathogenic mechanisms that may account for the development of normoalbuminuric renal insufficiency in diabetes. One possibility is that renal ischemia due to intrarenal arteriosclerosis may be related to the development of normoalbuminuric renal insufficiency. A negative correlation between GFR and the intrarenal arterial resistance index was found in type 2 diabetes, regardless of albuminuria stage [21, 22]. In addition, carotid intimal medial thickness, carotid stiffness, and silent cerebral infarction were also reported to be associated with impaired kidney function in type 2 diabetes, independent of microalbuminuria [21, 23].

The other possibility is that genetic susceptibility may contribute to the development of normoalbuminuric renal insufficiency. Polymorphisms of the protein kinase C-β gene were reported to be associated with accelerated decline of estimated GFR (eGFR) in type 2 diabetes without overt proteinuria [24].

Although the increasing use of renin–angiotensin system (RAS) blockade may be related to the increasing prevalence of normoalbuminuric renal insufficiency, the RIACE study showed that the use of RAS blockade was

more common in patients with albuminuric renal insufficiency than in those with normoalbuminuric renal insufficiency [12].

Clinical characteristics associated with normoalbuminuric renal insufficiency in diabetes

The reported clinical characteristics of diabetic patients with normoalbuminuric renal insufficiency include a higher proportion of females, a shorter duration of diabetes, lower prevalence of hypertension, smoking, retinopathy, neuropathy, previous cardiovascular disease, and antihypertensive agents including RAS blockade, lower levels of hemoglobin A1c and triglycerides, and higher levels of hemoglobin and high-density lipoprotein cholesterol, as compared to patients with albuminuric renal insufficiency [10, 12, 25]. In addition, compared to patients with normoalbuminuric preserved renal function, those with normoalbuminuric renal insufficiency are older, more frequently females and non-smokers, and have a higher prevalence of hypertension, dyslipidemia, metabolic syndrome, and previous cardiovascular disease, and higher levels of homeostasis model assessment of insulin resistance [10, 26].

Although our study of 260 type 2 diabetic patients with biopsy-proven diabetic nephropathy (96 females, 106 males; age 58.2 ± 11.4 years) included negative proteinuria as well as trace proteinuria in the normoalbuminuria (normal proteinuria) category based on the new classification of chronic kidney disease [3, 4], 154 (59.2 %) of the 260 patients showed low eGFR (<60 ml/min/1.73 m^2), and 15 (9.7 %) of the 154 patients with low eGFR were not associated with albuminuria (proteinuria) [20]. Table 1 presents the baseline clinical and pathological findings of fifteen patients with normoalbuminuria (normal proteinuria) and low eGFR [7 males, 8 females; an average age 62.5 years (range 49–72 years)] at the time of renal biopsy.

The mean eGFR was 46.0 ml/min/1.73 m^2 (range 25.6–57.2 ml/min/1.73 m^2), the mean duration of diabetes was 7.5 years (range 0–21 years), and the mean hemoglobin A1c level (NGSP) was 7.8 % (range 4.5–11.9 %). The prevalence of diabetic retinopathy, hypertension, dyslipidemia, and history of cardiovascular disease were 50.0 % (6/12), 35.7 % (5/14), 27.3 % (3/11), and 14.3 % (2/14), respectively. Our study demonstrated lower prevalence of hematuria and retinopathy, shorter duration of diabetes, lower systolic blood pressure, and higher hemoglobin level in patients with normoalbuminuria (normal proteinuria) and low eGFR as compared to patients with micro/macroalbuminuria (mild/severe proteinuria) and low eGFR. In addition, when compared to patients with normoalbuminuria (normal proteinuria) and preserved eGFR, those with normoalbuminuria (normal proteinuria) and low eGFR were older. Our findings were consistent with previous reports, and provided additional information on the prevalence of hematuria. Furthermore, our study showed that aging was associated with low eGFR regardless of albuminuria (proteinuria) category, and that hematuria, diabetic retinopathy, and low hemoglobin were associated with the progression of albuminuria (proteinuria) regardless of eGFR category [20].

Pathological characteristics associated with normoalbuminuric renal insufficiency in diabetes

There have been few studies regarding the pathological characteristics of diabetic nephropathy with normoalbuminuric renal insufficiency. A study of 8 long-standing type 1 diabetic women with normoalbuminuria and low GFR (75 ± 10 ml/min/1.73 m^2), as measured by creatinine clearance, found that these patients had more advanced glomerular lesions, such as higher volume fraction of mesangium, greater index of arteriolar hyalinosis, and higher percentage of global glomerular sclerosis than 19 normoalbuminuric women with preserved GFR (115 ± 15 ml/min/1.73 m^2) [27]. Similarly, another study indicated that 23 long-standing type 1 diabetic patients with normoalbuminuria and low GFR (<90 ml/min/1.73 m^2), as measured by either iothalamate clearance or creatinine clearance, had more advanced glomerular lesions, such as more increased glomerular basement membrane width and greater fractional volume of glomerulus occupied by mesangium, when compared with 82 normoalbuminuric patients with preserved GFR (≥90 ml/min/1.73 m^2) [28]. In addition, the Cohen diabetic rat, an animal model of type 2 diabetes which shows progressive depression of renal function without proteinuria or hypertension, was reported to show classical diabetic glomerulosclerosis, including mesangial matrix expansion, thickened basement membranes, and increased deposition of type IV collagen [29].

Our study of 260 type 2 diabetic patients also demonstrated that diffuse lesions, nodular lesions, tubulointerstitial lesions, and vascular lesions in patients with normoalbuminuria (normal proteinuria) and low eGFR (<60 ml/min/1.73 m^2) were more advanced compared to those in patients with normoalbuminuria (normal proteinuria) and preserved eGFR (≥60 ml/min/1.73 m^2) in type 2 diabetes [20].

Fioretto et al. [15, 16] proposed a classification system including three major categories based on renal biopsy lesions in type 2 diabetic patients with microalbuminuria and proteinuria—category I with normal or near-normal renal structure (35 % of patients with microalbuminuria

Table 1 Clinicopathological findings at the time of renal biopsy and outcomes in type 2 diabetic patients with normoalbuminuria (normal proteinuria) and low eGFR <60 ml/min/1.73 m^2

Case		Clinical and pathological findings at the time of renal biopsy									Outcomes			
no.	Gender	Age (years)	eGFR (ml/min/1.73 m^2)	Diabetes duration (years)	Hemoglobin A1c (%) (NGSP)	Diabetic retinopathy	Hypertension	Dyslipidemia	History of CVD	Category of renal lesions	Follow-up (years)	Renal events	CVD events	All-cause mortality
1	Male	69	25.6	2	n.d.[a]	n.d.	n.d.	n.d.	n.d.	III	n.d.	n.d.	n.d.	n.d.
2	Female	71	31.7	4	4.5	(−)	(−)	(−)	(−)	II	4.6	(−)	(−)	(−)
3	Male	56	32.1	15	7.1	n.d.	(−)	(−)	(−)	II	16.4	(−)	(−)	(−)
4	Female	61	36.1	1	6.5	(−)	(+)	(−)	(−)	III	5.1	(−)	(−)	(−)
5	Female	64	39.2	21	8.0	(−)	(+)	n.d.	(−)	II	14.5	(+)	(−)	(−)
6	Female	53	41.3	6	7.5	(+)	(+)	(−)	(+)	III	7.0	(−)	(−)	(−)
7	Female	61	49.4	10	6.5	(−)	(−)	(+)	(+)	III	21.8	(−)	(+)	(−)
8	Male	72	51.2	17	11.9	(+)	(−)	(−)	(−)	III	3.6	(−)	(−)	(−)
9	Male	65	52.7	5	5.9	(−)	(−)	(−)	(−)	III	5.3	(−)	(−)	(+)
10	Male	64	53.0	2	7.0	(−)	(−)	(−)	(−)	III	5.6	(−)	(−)	(−)
11	Male	61	53.7	0[b]	6.0	(−)	(−)	n.d.	(−)	III	13.7	(−)	(−)	(−)
12	Female	64	55.5	10	11.8	(+)	(+)	(−)	(−)	III	2.7	(−)	(+)	(−)
13	Female	63	55.7	10	9.9	(+)	(−)	(+)	(−)	II	5.3	(−)	(−)	(−)
14	Female	65	56.0	1	8.0	(+)	(+)	(+)	(−)	II	2.1	(−)	(−)	(−)
15	Male	49	57.2	8	8.3	(+)	(−)	n.d.	(−)	II	13.4	(−)	(+)	(−)

Presence of diabetic retinopathy, hypertension, dyslipidemia, and history of CVD are indicated by (+). Category of renal lesions was evaluated according to the classification proposed by Fioretto et al. [15, 16]

eGFR estimated glomerular filtration rate, *CVD* cardiovascular disease, *n.d.* no data, *NGSP* National Glycohemoglobin Standardization Program

[a] This patient had poorly controlled type 2 diabetes, which was followed at another hospital

[b] This patient was diagnosed for the first time with type 2 diabetes by a random blood glucose test and an oral glucose tolerance test at the time of renal biopsy

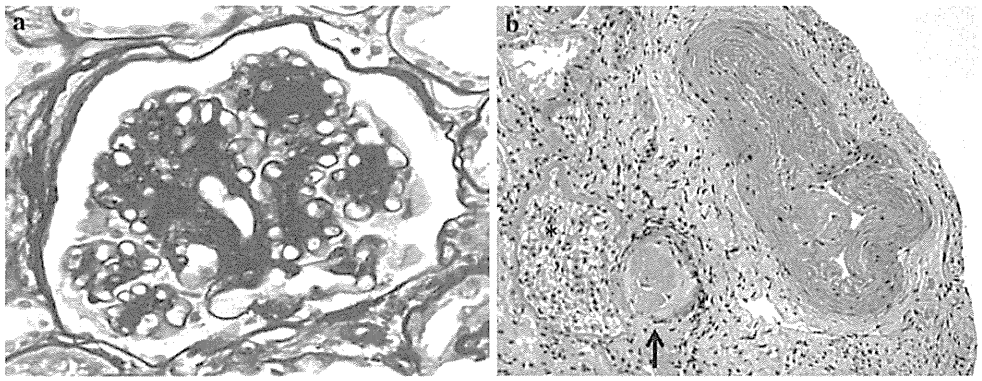

Fig. 1 Representative microscopic findings in type 2 diabetic patients with normoalbuminuria (normal proteinuria) and low eGFR (<60 ml/min/1.73 m^2). **a** Severe diffuse lesions in a patient classified as typical lesions of diabetic nephropathy (category II) (Case no. 3, Table 1; periodic acid-Schiff (PAS) stain ×200). **b** Mild diffuse lesions (*asterisk*) associated with global glomerular sclerosis (*arrow*) and disproportionately advanced arteriosclerosis, which denotes the presence of diabetic kidney lesions as well as nephrosclerosis, in a patient classified as atypical patterns (category III) (Case no.12, Table 1; PAS stain ×100)

and 10 % of patients with proteinuria); category II with typical diabetic lesions with an approximately balanced severity of glomerular, tubulointerstitial, and arteriolar changes similar to type 1 diabetes (30 % of patients with microalbuminuria and 55 % of patients with proteinuria); and category III with disproportionately advanced tubulointerstitial lesions, vascular lesions, and global glomerulosclerosis, despite minor diabetic glomerulopathy (35 % of patients with microalbuminuria and 35 % of patients with proteinuria). We categorized the renal lesions of 15 patients with normoalbuminuria (normal proteinuria) and low eGFR according to this classification (Table 1). As a result, no patients were classified as having almost normal biopsies (category I), 6 patients (40 %) were classified as having typical lesions of diabetic nephropathy (category II), and 9 patients (60 %) were classified as having atypical patterns (category III). Representative microscopic findings of renal biopsies from type 2 diabetic patients with normoalbuminuria (normal proteinuria) and low eGFR are shown in Fig. 1. Figure 1a shows severe diffuse lesions in a patient classified as category II (Case no. 3, Table 1). Figure 1b shows mild diffuse lesions associated with global glomerular sclerosis and disproportionately advanced arteriosclerosis, which denotes the presence of diabetic kidney lesions as well as nephrosclerosis, in a patient classified as category III (Case no. 12, Table 1). Another study of type 2 diabetic patients with low eGFR (<60ml/min/1.73 m^2) by research biopsy also indicated that the typical glomerular changes of diabetic nephropathy were less common in normoalbuminuric (3/8) patients than in microalbuminuric (5/6) or macroalbuminuric (17/17) patients [30].

These results suggest that multifactorial pathogenesis in addition to diabetic conditions may contribute to the kidney lesions in type 2 diabetic patients with normoalbuminuric renal insufficiency.

Outcomes of diabetic patients with normoalbuminuric renal insufficiency

Although the outcome of diabetic patients with normoalbuminuric renal insufficiency remains controversial, it is likely to be better than that of diabetic patients with albuminuria, even with preserved renal function. In a study of 89 diabetic patients with eGFR <60 ml/min/1.73 m^2 (22 type 1 diabetes, 67 type 2 diabetes), 15 (17 %), 36 (40 %), and 38 (43 %), were found to be normoalbuminuric, microalbuminuric, and macroalbuminuric at baseline, respectively. During the 38-month follow-up, none of the normoalbuminuric patients started dialysis (microalbuminuric patients 2/36, macroalbuminuric patients 10/38), and their albumin excretion rates and serum creatinine levels were stable. Furthermore, none of the normoalbuminuric patients died (microalbuminuric patients 3/36, macroalbuminuric patients 7/38) during the follow-up period [25]. In a population-based study of 1,538 people with type 2 diabetes, 51, 32, and 17 %, were found to be normoalbuminuric, microalbuminuric, and macroalbuminuric at baseline, respectively. During the 11-year follow-up, increasing trends of hazard rate ratios for all-cause mortality and cardiovascular mortality by decreasing eGFR values were observed in macroalbuminuric people only [31]. In addition, our study also showed similar results [20]. In our study, the outcomes were defined as the first occurrence of renal events (requirement of dialysis, or a 50 % decline in eGFR from baseline), cardiovascular events (cardiovascular death, nonfatal myocardial infarction, coronary interventions, or nonfatal stroke), and all-cause mortality. The mean follow-up period was 8.1 years (range 5–9,739 days), and there were 118 renal events, 62 cardiovascular events, and 45 deaths during the follow-up period. The hazard ratios for renal events, cardiovascular events, and all-cause mortality were increased by

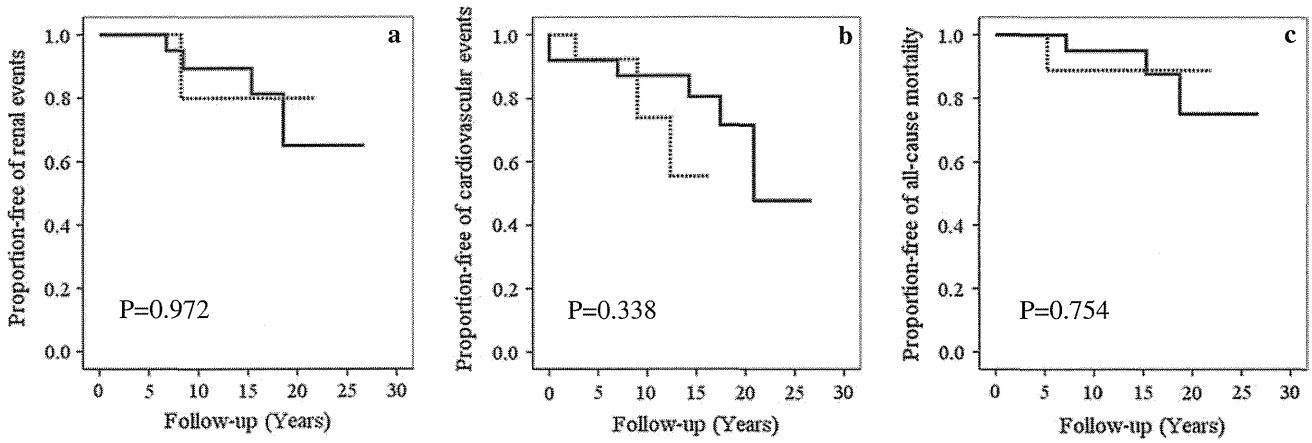

Fig. 2 Event-free rates of **a** renal events, **b** cardiovascular events, and **c** all-cause mortality in type 2 diabetic patients with normoalbuminuria (normal proteinuria) stratified by eGFR categories according to Kaplan–Meier method. Differences between groups were compared by the log-rank test. *Solid line* normoalbuminuria (normal proteinuria) and eGFR ≥60 ml/min/1.73 m^2 group, *dotted line* normoalbuminuria (normal proteinuria) and eGFR <60 ml/min/1.73 m^2 group

decreasing eGFR levels in patients with macroalbuminuria (severe proteinuria) only, and macroalbuminuria (severe proteinuria) was a major clinical determinant of renal events and all-cause mortality. Fifteen patients with normoalbuminuria (normal proteinuria) and low eGFR had 1 renal event, 3 cardiovascular events, and 1 death during the follow-up period (Table 1). One patient who developed end-stage renal disease was positive for anti-hepatitis C virus (HCV) antibody, although renal biopsy showed typical diabetic glomerular lesions, such as diffuse and exudative lesions, without HCV-related glomerulonephritis (Case no. 5, Table 1). Event-free rates of renal events, cardiovascular events, and all-cause mortality in patients with normoalbuminuria (normal proteinuria) were not significantly different between eGFR categories (Fig. 2).

In contrast to the previous results outlined above, including our report, several studies showed that higher levels of urinary albumin excretion within the normal range predict faster decline in GFR and higher incidence of cardiovascular disease in diabetic patients [32, 33]. Furthermore, some studies demonstrated that albuminuria and renal function independently or respectively predict renal events, cardiovascular events, and death in diabetic patients [13, 34–36]. Therefore, further studies on clinical impacts of low GFR without albuminuria and new biomarkers for early and definitive diagnosis of diabetic nephropathy are required in clinical settings.

In this sense, the newly established prospective registry system, the Japan Diabetic Nephropathy Cohort Study (JDNCS), may provide key insights for future perspectives [37]. The Japanese Society of Nephrology established a nationwide, web-based, and prospective registry system including two basic registries— the J-RBR and the J-KDR [18, 38]. In addition to the two basic registries, the JDNCS enrolled Japanese diabetic patients with broad-ranging albuminuria (proteinuria) stage and GFR levels. The aims of the JDNCS are to obtain clinical data and urine samples for revising the clinical staging of diabetic nephropathy, and to develop new diagnostic biomarkers for early detection or prediction of diabetic nephropathy. The prevalence of normoalbuminuria in patients with low eGFR (<60 ml/min/1.73 m^2) at baseline was 19.8 % in the JDNCS. Interestingly, the JDNCS is now prospectively collecting clinical data annually. Moreover, participants with diabetes are also enrolled in the J-RBR and the J-KDR [37]. Therefore, the combined data of the three registries will allow evaluation of the natural course and long-term outcomes of diabetic nephropathy, including patients with normoalbuminuric renal insufficiency, in the near future.

Conclusion

We focused on the structural–functional relationships and outcomes of diabetic nephropathy with normoalbuminuric renal insufficiency. Although the pathogenesis of normoalbuminuric renal insufficiency in diabetic nephropathy remains to be fully elucidated, disproportionately advanced tubulointerstitial lesions, vascular lesions, and global glomerulosclerosis, despite minor diabetic glomerular lesions, which denote the presence of diabetic kidney lesions as well as nephrosclerosis, are likely to be related to the development of normoalbuminuric renal insufficiency in some type 2 diabetic patients. However, other processes may contribute to the development of normoalbuminuric renal insufficiency with advanced diabetic glomerular lesions. Furthermore, long-term outcomes of diabetic patients with normoalbuminuric renal insufficiency remain

controversial. Further studies to gain a better understanding of the structural–functional relationships and natural history of diabetic patients with normoalbuminuric renal insufficiency may provide insights for the development of therapeutic strategies for diabetic nephropathy.

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Conflict of interest No potential conflicts of interest relevant to this article were reported.

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REVIEW ARTICLE

WCN 2013 Satellite Symposium "Kidney and Lipids"

Treatment and impact of dyslipidemia in diabetic nephropathy

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Abstract Recent epidemiological research revealed that dyslipidemia is a risk factor for development and progression of diabetic nephropathy. Results from interventional studies revealed the possibility that antihyperlipidemic agents have a better effect on diabetic nephropathy through improvement of albuminuria and loss of renal function. In addition, dyslipidemia may be a consequence of albuminuria and renal dysfunction, thereby perpetuating kidney damage. Today, the proportion of diabetic patients receiving statins is increasing due to their beneficial effect on cardiovascular mortality. However, treatment for patients should be determined based on consideration of the risk and benefit of the treatment. More insight into the pathogenesis of diabetic nephropathy and the effects of life-style changes is required.

Keywords Diabetic nephropathy · Dyslipidemia · Cardiovascular disease · End-stage renal disease

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Introduction

In the past, epidemiological research in diabetes has found that albuminuria and renal dysfunction are dominant risk factors for the progression of diabetic nephropathy. Some interventional studies have revealed that strict glycemic control reduces the risk of development and progression of albuminuria [1, 2].

It is a crucial fact that diabetic patients are at high risk of cardiovascular events. To prevent these events, dyslipidemia should be carefully controlled because it is one of the well-known risk factors. Statins and fibrates are representative drugs for dyslipidemia. Besides reducing plasma cholesterol levels they are thought to have many pleiotropic effects including improvement of endothelial function and inflammation [3, 4]. However, treatment of patients with dyslipidemia is complicated because it is not a simple metabolic disorder but closely related to the patient's lifestyle. For this reason, lowering the level of cholesterol will not always result in a reduction of the risks.

Here, we focus on the treatment and impact of dyslipidemia on the progression of diabetic nephropathy.

Dyslipidemia as a complication of diabetic nephropathy

One cross-sectional study implied that patients with diabetic nephropathy had significant increases in triglycerides and total cholesterol levels, reduced levels of apolipoprotein A (ApoA)-I and ApoA-II, and increased levels of ApoC-II and ApoC-III [5]. Other cross-sectional studies of patients from the Diabetic Control and Complications Trial/Epidemiology of Diabetic Interventions and Complications study group revealed that high levels of triglycerides, low-density lipoprotein (LDL) cholesterol, total

cholesterol, and ApoB are associated with albuminuria [6]. ApoB is thought to be related to cardiovascular events in some studies [7, 8]. In this way, the studies revealed the relationships between lipid profiles and diabetic nephropathy.

Cardiovascular events are also important complications in diabetic patients [9]. A meta-analysis reported the relationship between dyslipidemia and cardiovascular risk [10]; however, risks for diabetic patients are not well known.

Dyslipidemia and loss of renal function

The 'lipid nephrotoxicity' hypothesis was advocated by Moorhead et al. in 1982 as a description of the effect of dyslipidemia on renal dysfunction [11]. Under this hypothesis, mesangial proliferation caused by accumulation of lipoprotein into mesangial cells induces glomerulosclerosis. This theory has been updated recently including the concept of inflammation stress modifying lipid homeostasis and tissue lipid accumulation [12]. With regard to diabetes and lipids, Hartroft [13] discovered in 1954 that intraluminal fat was found in both preglomerular and postglomerular vessels of diabetics patients with Kimmelstiel–Wilson lesions. In addition to this study, a lot of basic research has discovered the mechanisms between dyslipidemia and diabetic nephropathy [14]. Studies revealed that transforming growth factor-β signaling [15], renin–angiotensin system [16], S100A8/TLR4 signaling [17], and oxidative stress [18] may play an important role in the progression of diabetic nephropathies. Concerning the development of albuminuria, the importance of the deterioration of glycocalyx, which is on the surface of endothelium, was highlighted [19]. These factors orchestrated each other, thereby perpetuating the progression of diabetic nephropathy. Further studies will be required for a better understanding of diabetic nephropathy.

Some epidemiological studies of general cohorts have elucidated the relationships between dyslipidemia and loss of renal function. The Framingham Offspring Study which consists of 1,916 general population subjects with a follow-up of 9.5 years, revealed that low high-density lipoprotein (HDL) cholesterol levels are one of the risk factors for incident albuminuria [20]. An analysis of 1,440 general Japanese cohorts that participated in the Hisayama study revealed that metabolic syndrome defined as the presence of components including high triglyceride levels and low HDL cholesterol levels are associated with a risk of developing chronic kidney disease (CKD) [21]. A study of 4,483 healthy males revealed that dyslipidemia including high total cholesterol levels, high non-HDL cholesterol levels, and low HDL cholesterol levels are associated with a risk of renal dysfunction [22].

According to these facts, dyslipidemia may be one of the potential risk factors for loss of renal functions in a healthy subject.

Relationships between dyslipidemia and progression or regression of diabetic nephropathy

The stages in diabetic renal disease were reported by Mogensen et al. [23] in 1983. According to their theory, elevated urinary albumin excretion and following persistent proteinuria are important manifestations of diabetic nephropathy, and many studies defined them as surrogate markers for end-stage renal disease.

Some cohort studies of diabetic patients have proven the risk factors associated with the progression or regression of the staging. Regarding the development of micro- and macroalbuminuria, a cohort study of 27,805 patients with type 1 diabetes followed up for 2.5 years revealed that, besides diabetes duration and glycosylated hemoglobin, dyslipidemia is a risk factor for developing albuminuria [24]. A cohort study of 574 patients with type 2 diabetes followed up for 7.8 years also revealed that, as well as high mean blood pressure and hyperglycemia, high plasma cholesterol levels are the main risk factors for development of dyslipidemia [25]. In this study, the participants with a combination of these three risk factors are a high-risk group for progression to diabetic nephropathy.

Associations between reduction of urinary albumin and dyslipidemia were reported in a cohort study of 386 patients with type 1 diabetes [26]. In this study, along with low levels of glycosylated hemoglobin and low systolic blood pressure, low levels of both cholesterol and triglycerides were independently associated with regression of microalbuminuria. Moreover, these factors had additive effects on regression of microalbuminuria.

A small number of studies reported an association between dyslipidemia and loss of renal functions. Regarding the rate of decline in glomerular filtration rate (GFR), a prospective study of 30 patients with type 1 diabetes revealed that high serum cholesterol, triglycerides and apolipoprotein B were correlated to a rapid decline in glomerular filtration rate [27].

As described above, evidence has been accumulated to suggest that dyslipidemia is one of the risk factors for progression and regression of diabetic nephropathy. However, as far as we knew, there have been few studies reporting the association with end-stage renal disease, or renal replacement therapy. A report of a scientific workshop sponsored by the National Kidney Foundation (NKF) and the US Food and Drug Administration (FDA) indicated that evidence was insufficient to use a change of albuminuria as a surrogate marker as a clinical endpoint [28].