Overt Proteinuria, Moderately Reduced eGFR and Their Combination Are Predictive of Severe Diabetic Retinopathy or Diabetic Macular Edema in Diabetes

Masahiko Yamamoto,[1] Kazuya Fujihara,[1] Masahiro Ishizawa,[1] Taeko Osawa,[1] Masanori Kaneko,[1] Hajime Ishiguro,[1] Yasuhiro Matsubayashi,[1] Hiroyasu Seida,[2] Nauta Yamanaka,[2] Shiro Tanaka,[3] Satoru Kodama,[1] Hiruma Hasebe,[4] and Hirohito Sone[1]

[1]Department of Hematology, Endocrinology and Metabolism, Niigata University Faculty of Medicine, Niigata, Japan
[2]Japan Medical Data Center Co., Ltd., Tokyo, Japan
[3]Department of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[4]Department of Ophthalmology, Niigata University Faculty of Medicine, Niigata, Japan

Correspondence: Kazuya Fujihara, Niigata University Faculty of Medicine, Department of Hematology, Endocrinology and Metabolism, 1-757 Asahimachi, Niigata, Niigata 951-8510, Japan; kafujihara-dm@umin.ac.jp.

Submitted: January 27, 2019
Accepted: May 27, 2019

Citation: Yamamoto M, Fujihara K, Ishizawa M, et al. Overt proteinuria, moderately reduced eGFR and their combination are predictive of severe diabetic retinopathy or diabetic macular edema in diabetes. *Invest Ophthalmol Vis Sci*. 2019;60:2685–2689. https://doi.org/10.1167/iovs.19-26749

Purpose. Since the combined effects of proteinuria and a moderately decreased eGFR on incident severe eye complications in patients with diabetes are still largely unknown, these associations were determined in a large historical cohort of Japanese patients with diabetes mellitus.

Methods. We evaluated the effects of overt proteinuria (OP) (dipstick 1+ and over) and/or moderately reduced estimated glomerular filtration rate (eGFR) (MG) (baseline eGFR 30.0–54.9 mL/min/1.73 m^2) on the incidence of treatment-required diabetic eye diseases (TRDED). We divided 7709 patients into four groups according to the presence or absence of OP and MG: no OP without MG (NP[MG−]), OP without MG (OP[MG−]), no OP with MG (NP[MG+]), and OP with MG (OP[MG+]). Multivariate Cox analyses were performed to calculate hazard ratios (HRs) with 95% confidence intervals for combinations of the presence and/or absence of OP and MG on the risk of developing TRDED.

Results. During the median follow-up period of 5.6 years, 168 patients developed TRDED. HRs for OP and MG for incident TRDED were 1.91 (95% confidence interval, 1.27–2.87) and 1.90 (1.11–3.23), respectively. HRs for incident TRDED were 1.73 (1.11–2.69) and 5.57 (2.40–12.94) for OP(MG−) and OP(MG+), respectively, in comparison with NP(MG−).

Conclusions. In Japanese patients with diabetes, OP and MG were separately as well as additionally associated with higher risks of TRDED. Results indicate the necessity of the simultaneous assessment of proteinuria and eGFR for appropriate evaluation of risks of severe eye complications in patients with diabetes.

Keywords: overt proteinuria, moderately reduced eGFR, vision-threatening treatment-required diabetic eye diseases

Diabetic retinopathy (DR) is a leading cause of impaired vision and quality of life. Urinary protein, including albuminuria as well as a lower estimated glomerular filtration rate (eGFR), are known as independent predictors of the development and progression of DR and/or diabetic macular edema (DME). However, the combined effects of urinary protein and moderately reduced eGFR as predictors of these conditions have been scarcely investigated,[1,2] although diabetic kidney disease (DKD) are considered due to a combination of these elements. Recently, much focus has been placed on not only traditional diabetic nephropathy (normal eGFR and proteinuria) but also DKD with decreased eGFR without proteinuria. Diabetic nephropathy, also known as DKD, results in decreases in kidney function in patients with diabetes mellitus. Kidney damage may cause proteinuria and/or decreased eGFR, which are used to monitor the status of diabetic nephropathy. In a very early stage of diabetic nephropathy the eGFR increases, but with progression of the diabetic nephropathy, the eGFR gradually decreases. Furthermore, there are few data to address the issue of whether urinary protein, including microalbuminuria or a moderate decline of eGFR, is a competing risk factor for the development and progression of DR.[1] Therefore, using a current large nationwide database of Japanese diabetic patients, we analyzed the impact of urinary protein, moderately reduced eGFR, and their combination on severe DR or severe DME, defined as vision-threatening treatment-required diabetic eye diseases (TRDED), which without treatment present the danger of blindness in Japanese patients with diabetes. The risk of TRDED according to these parameters was assessed in this study.

Methods

This study reviewed data provided from a national health insurance claim-based database in Japan consisting of participants insured by a health insurance provider for company employees.[3] We described details of the claims data previous-

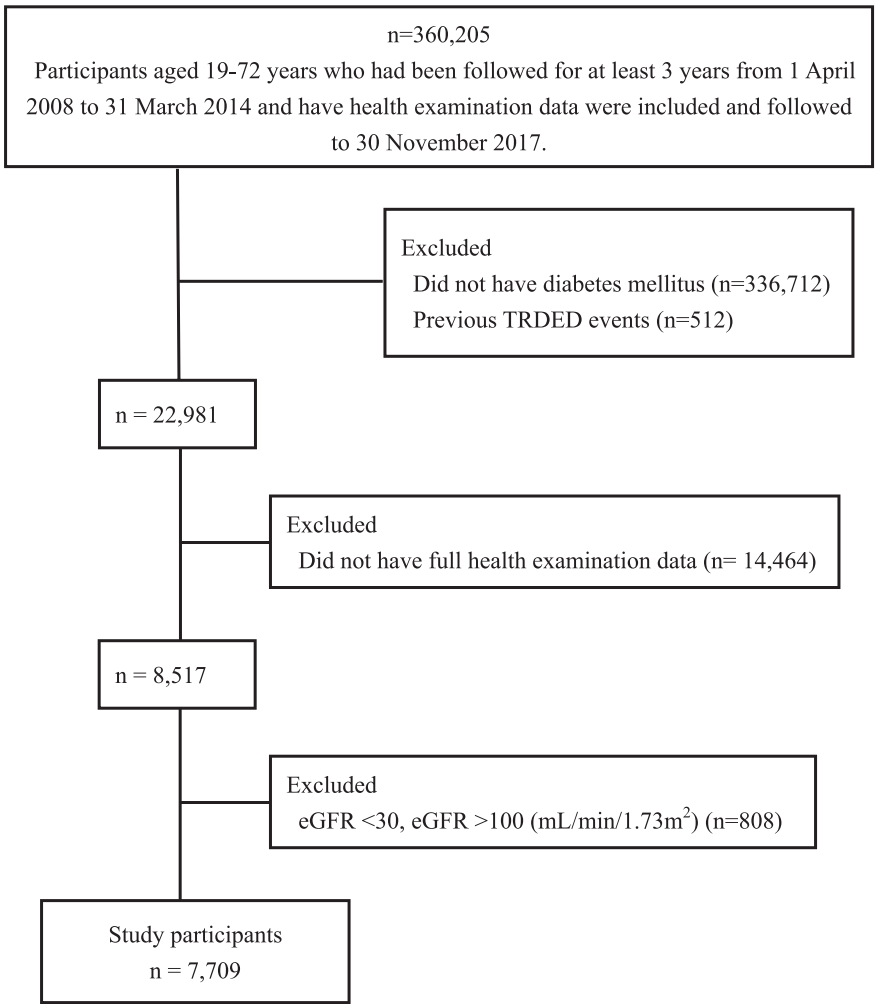

Figure. Flow chart for the extraction of study participants.

ly.[3,4] We included participants in this dataset who had at least a 1-year TRDED-free period before baseline and had been followed for at least 3 years between April 1, 2008, and March 31, 2014, and followed until November 30, 2017.

Among the 360,205 individuals who met these criteria, 22,981 persons with diabetes were included (Figure). Of these 22,981 persons, 14,464 patients who did not have full health examination data were excluded.

Among the remaining eligible 8517 participants, 808 patients with eGFR <30 mL/min/1.73 m^2 or eGFR >100 mL/min/1.73 m^2 were excluded. We included individuals with eGFR 30 to 100 mL/min/1.73 m^2 in this analysis. This study finally included 7709 participants.

We classified participants as having diabetes mellitus (DM) depending on their HbA1c, fasting plasma glucose, and claims database data. Criteria for DM was HbA1c ≥48 mmol/mol (6.5%) or fasting plasma glucose ≥7.0 mM or both without prescribed antidiabetic drugs or with a prescribed antidiabetic drug irrespective of fasting plasma glucose or HbA1c values.[4]

We identified TRDED according to claims using the *International Classification of Diseases, 10th Revision* codes for DR, diabetic maculopathy, or DME in E 103, 113, or 143 and medical procedures. Occurrence of TRDED was determined as a composite of the diagnosis of DR and/or diabetic maculopathy and/or DME and the administration of medical procedures, such as retinal photocoagulation treatment and/or pars plana vitrectomy and/or intraocular injection with steroids and anti-VEGF agents for 1 month or more beginning at the observational period.

The eGFR was calculated using the following equation by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female).[5] Urinary protein was assessed by test strip and a baseline result of ≥1+ indicated overt proteinuria (OP), which reportedly corresponds to a urinary protein concentration of ≥30 mg/dL. Although the dipsticks used depended on the respective facilities, dipsticks manufactured by Eiken Chemical Co., Ltd. (Tokyo, Japan), Siemens Healthcare K.K. (Tokyo, Japan), and ARKRAY, Inc. (Kyoto, Japan) had a 40.6%, 22.6%, and 23.4% share, respectively, in Japan.

Results of urinary protein were primarily determined by machine (84.0% of facilities). Moderately reduced eGFR (MG) was defined as baseline eGFR 30.0 to 54.9 mL/min/1.73m^2.

Participants were categorized into four groups: no OP (NP) without MG (NP[MG–]), OP without MG (OP[MG–]), NP with MG(NP[MG+]), and OP with MG (OP[MG+]).

Categorical variables were expressed as numerals and percentages and compared with χ^2 tests. Continuous variables were expressed as mean ± SD or median and interquartile range. Continuous variables were compared using the unpaired Student's *t*-test or the Mann-Whitney *U* test for two-group comparisons based on distributions.

The Cox proportional-hazards regression model identified variables related to the incidence of TRDED. In Cox analysis,

Table 1. Characteristics of Study Participants According to Presence or Absence of TRDED

		TRDED		
	Total (n = 7709)	**(−) (n = 7541)**	**(+) (n = 168)**	***P* Value**
Sex, male, %	6293 (82)	6152 (82)	141 (84)	0.437
Age, y	**51 ± 9**	**51 ± 9**	**53 ± 8**	**0.012**
Body mass index, kg/m^2	25.5 ± 4.4	25.5 ± 4.4	25.9 ± 4.1	0.218
Systolic blood pressure, mm Hg	**130 ± 17**	**130 ± 17**	**134 ± 17**	**0.001**
Diastolic blood pressure, mm Hg	80 ± 11	80 ± 11	81 ± 12	0.081
HbA1c, %	**6.8 ± 1.3**	**6.8 ± 1.2**	**8.4 ± 2.1**	**<0.001**
HbA1c, mmol/mol	**51 ± 14**	**50 ± 13**	**69 ± 23**	**<0.001**
Fasting plasma glucose, mM	**7.6 ± 2.1**	**7.5 ± 2.0**	**10.2 ± 4.6**	**<0.001**
HDL-C, mM	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	0.471
LDL-C, mM	3.3 ± 0.8	3.3 ± 0.8	3.3 ± 0.9	0.546
Triglycerides, mM	1.4 (0.9–2.0)	1.4 (0.9–2.0)	1.4 (0.9–2.1)	0.164
Current smoking, %	2,700 (35)	2,651 (35)	49 (29)	0.108
eGFR, mL/min/1.73 m^2	75.4 ± 12.3	75.4 ± 12.3	76.4 ± 14.4	0.396
OP, %	**539 (7)**	**505 (7)**	**34 (20)**	**0.003**

Data are presented as numbers, means ± SDs, median and interquartile range, or percentages. Bolded values indicate statistical significance.

TRDED comparisons were made with a reference group having NP(MG−). Covariates included traditional risk factors for DR (age, sex, body mass index, systolic blood pressure, HbA1c, fasting plasma glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and smoking status) in each model. Statistical tests used a significance level of 0.05, using SPSS, version 21.0, for Windows (SPSS, Chicago, IL, USA). The study design was consistent with the guidelines of the Declaration of Helsinki, and this study was approved by the Ethics Committee of Niigata University.

Results

Among 7709 patients (19–72 years old), 168 TRDED events occurred during the observational period (median 5.6 years). Cumulative incidence rate of TRDED was 3.9 per 1000 person-years. Table 1 shows baseline characteristics of the total study participants as well as those who did or did not develop TRDED.

Multivariate Cox analysis showed hazard ratios (HRs) for OP, MG, and HbA1c for incident TRDED of 1.91 (95% confidence interval, 1.27–2.87), 1.90 (1.11–3.23), and 1.50 (1.35–1.66), respectively. Compared with participants having NP(MG−), those with OP(MG−) and OP(MG+) had HRs of 1.73 (1.11–2.69) and 5.57 (2.40–12.94), respectively, for TRDED (Table 2). Interaction between MG and OP was not statistically significant (P = 0.186). The association between MG and OP was not synergistic but additive. When we reanalyzed our database excluding the past history of dialysis at baseline (2/7709), this relation was unchanged.

Discussion

To our knowledge, this is the first longitudinal study of a large population to find that OP in combination with moderately decreased eGFR was useful to assess the risk of developing advanced retinopathy. Recently, not only classical diabetic nephropathy (normal eGFR and proteinuria) but also a DKD pattern with decreased eGFR without proteinuria have been receiving much attention. Thus, we thought that an evaluation of the risk of future occurrence of DR and/or DME that was stratified according to DKD patterns would be useful for formulating future preventive and treatment strategies for DR and/or DME.

Most previous studies regarding DR and/or DME risk have used only eGFR, albuminuria, or proteinuria as a single variable for renal function. The longitudinal impact of combined renal function indicators on DR has not been thoroughly investigated; in fact, there have been only two small-scale studies.[1,2]

Chen and colleagues[1] analyzed the development of DR of various severities that included only 487 older type 2 diabetes patients. They found that overall microalbuminuria and a higher eGFR presented a significantly greater risk for development and progression of DR than moderate renal impairment and normoalbuminuria. However, no significance was found when those with advanced DR were separately analyzed.

Although Romero-Aroca and colleagues[2] aimed to determine the incidence of any DR and their risk factors in 366 patients with type 1 diabetes, details were lacking with regard to the study population. However, it was concluded that the incidence rate of any DR was greater in those with type 1 diabetes than in those with type 2 diabetes. Although they very recently also reported that the combination of eGFR <60 mL/min/1.73 m^2 and microalbuminuria was an important risk factor for DME and sight-threatening DR development, they did not address the combined effects of both markers in detail nor did they separate severe eGFR reduction (eGFR<30 mL/min/1.73 m^2) from their analysis.[6]

Although this study cannot reveal potential mechanisms for the increase in the progression of DR and/or DME in accordance with renal function, some underlying mechanisms may be suggested. Many systemic factors, including oxidative stress,[7] advanced glycation end products, abnormality of protein kinase C or renin-angiotensin system,[7] hyperglycemia,[8] inflammation, and vascular endothelial dysfunction,[9] were associated with microvasculature damage both in the retina and kidney.

We examined only cases with imminent vision impairment requiring an ophthalmological intervention. There are enormous differences in urgency, the impact on quality of life, and the medical cost between severity stages of DR, indicating the need for an ophthalmological intervention even though there has been remarkable progress in the management of DR in the past few decades, including the use of anti-VEGF agents.[10,11]

Strengths of this analysis are the long observational period, very low rate of participants lost to follow-up, and veracious TRDED detection based on practical medical treatment. Another advantage of using the claim-based database or management-based outcomes in Japan is that the well-organized public health insurance system that equally covers

Table 2. HRs With 95% Confidence Interval of Baseline Values for Each Variable for TRDED Risk According to Categories of eGFR and Dipstick Urinalysis for OP Analyzed by Cox Models

	Model 1			Model 2		
	Cases/Total *n*	HR (95% CI)	*P* Value	Cases/Total *n*	HR (95% CI)	*P* Value
Age, y		**1.04 (1.02–1.06)**	**<0.001**		**1.04 (1.02–1.06)**	**<0.001**
Sex, male		1.23 (0.79–1.92)	0.357		1.24 (0.80–1.93)	0.345
Body mass index per 5 kg/m^2		1.04 (0.86–1.26)	0.707		1.04 (0.86–1.26)	0.709
Systolic blood pressure per 10 mm Hg		1.08 (0.99–1.19)	0.091		1.08 (0.99–1.19)	0.101
HbA1c per 1%, 11 mmol/mol		**1.50 (1.35–1.66)**	**<0.001**		**1.50 (1.36–1.66)**	**<0.001**
Fasting plasma glucose per 1 mM		**1.11 (1.05–1.17)**	**<0.001**		**1.11 (1.05–1.18)**	**<0.001**
HDL-C per 1 mM		0.99 (0.61–1.61)	0.975		0.99 (0.61–1.61)	0.966
LDL-C per 1 mM		0.85 (0.70–1.02)	0.076		0.85 (0.71–1.02)	0.087
Log-triglycerides per 1		0.80 (0.58–1.10)	0.161		0.80 (0.58–1.10)	0.163
Current smoker		**0.69 (0.49–0.99)**	**0.042**		**0.69 (0.49–0.98)**	**0.040**
Overt proteinuria	**34/539**	**1.91 (1.27–2.87)**	**0.002**		NA	
Moderately reduced eGFR	**16/361**	**1.90 (1.11–3.23)**	**0.019**		NA	
NP, MG−		NA		124/6864	1.00 (reference)	
NP, MG+		NA		10/306	1.52 (0.78–2.95)	0.217
OP, MG−		NA		**28/484**	**1.73 (1.11–2.69)**	**0.015**
OP, MG+		NA		**6/55**	**5.57 (2.40–12.94)**	**<0.001**

A total of 168 patients developed TRDED. Model 1: adjusted for age, sex, body mass index, systolic blood pressure, HbA1c, fasting plasma glucose, LDL-C, HDL-C, triglycerides, smoking status, and separately for OP and moderately reduced eGFR, respectively. Model 2: adjusted for age, sex, body mass index, systolic blood pressure, HbA1c, fasting plasma glucose, LDL-C, HDL-C, triglycerides, smoking status, and for the combination of moderately reduced eGFR and OP. Bolded values indicate statistical significance. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable.

all people in Japan enabled ophthalmologists to select the best treatment regardless of a patient's economic status.

However, this study has several limitations. First, we had no information on the duration of diabetes and fundus examinations. Second, urine protein was evaluated with the dipstick semiquantitative method, which could have over- or underestimated the presence of proteinuria. Although there was no information on types of diabetes and duration of diabetes, most patients were considered to have type 2 DM because the prevalence of type 1 DM is extremely low in East Asia. Third, we evaluated only baseline values of the parameters in this study; therefore, the results could have been influenced by therapeutic management. Also, we could not evaluate changes in the parameters such as in eGFR, proteinuria, or HbA1c. Fourth, although we attempted to exclude patients who already had TRDED at baseline using claims data, we could not exclude all such cases that had TRDED before baseline. Fifth, although we adopted TRDED as an outcome in this study because it is based on the judgment of ophthalmologists on the necessity for treatment in real-world clinical settings instead of using outcomes predominantly based on criteria for results of fundus examinations, conventional criteria based on fundus examinations or fluorescein angiography would be more important and superior to definitions based on claims data. Sixth, not all cases in this analysis were included as having TRDED because some did not go to the hospital and remained untreated and undetected. Seventh, it is possible that missing clinical examination data such as retinal information to verify the diagnosis of DR and/or DME would lead to a biased effect from misclassification of information. Eighth, we made every effort to select procedure codes specific to DR or DME in order to avoid mistakenly including procedures that required treatment caused by conditions other than severe DR or DME. Also, we excluded specific procedures for other eye diseases, such as cataract. However, there would remain a possibility of inaccuracy in diagnosis. Last, there is also the possibility of inaccuracy of data induced by missing data, miscoding, or incomplete data for the reasons not related to medicine, such as losses to follow-up or an alteration in insurance.

In conclusion, our findings implied that the combination of OP and moderately decreased eGFR had an additive association for the incidence of vision-threatening severe DR requiring ophthalmological intervention, suggesting the necessity of considering moderately decreased eGFR in addition to proteinuria in strategies for preventing the future occurrence of severe retinopathy.

Acknowledgments

Presented in part at the 61st Annual Meeting of the Japan Diabetes Society, Tokyo, Japan, May 24–26, 2018, and the 78th American Diabetes Association scientific sessions, Orlando, Florida, June 22–26, 2018.

The authors thank Mami Haga and Natsuko Tada, Niigata University Faculty of Medicine, for their excellent secretarial assistance.

Supported by the Japan Society for the Promotion of Science (JSPS).

Disclosure: **M. Yamamoto**, None; **K. Fujihara**, None; **M. Ishizawa**, None; **T. Osawa**, None; **M. Kaneko**, None; **H. Ishiguro**, None; **Y. Matsubayashi**, None; **H. Seida**, None; **N. Yamanaka**, None; **S. Tanaka**, None; **S. Kodama**, None; **H. Hasebe**, None; **H. Sone**, None

References

1. Chen YH, Chen HS, Tarng DC. More impact of microalbuminuria on retinopathy than moderately reduced GFR among type 2 diabetic patients. *Diabetes Care*. 2012;35:803–808.
2. Romero-Aroca P, Navarro-Gil R, Valls-Mateu A, Sagarra-Alamo R, Moreno-Ribas A, Soler N. Differences in incidence of diabetic retinopathy between type 1 and 2 diabetes mellitus: a nine-year follow-up study. *Br J Ophthalmol*. 2017;101:1346–1351.
3. Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of

disease classifications and anonymous record linkage. *J Epidemiol*. 2010;20:413–419.

4. Fujihara K, Igarashi R, Yamamoto M, et al. Impact of glucose tolerance status on the development of coronary artery disease among working-age men. *Diabetes Metab*. 2017;43:261–264.
5. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992.
6. Romero-Aroca P, Baget-Bernaldiz M, Navarro-Gil R, et al. Glomerular filtration rate and/or ratio of urine albumin to creatinine as markers for diabetic retinopathy: a ten-year follow-up study. *J Diabetes Res*. 2018;2018:5637130.
7. Sabanayagam C, Foo VH, Ikram MK, et al. Is chronic kidney disease associated with diabetic retinopathy in Asian adults? *J Diabetes*. 2014;6:556–563.
8. Man REK, Sasongko MB, Wang JJ, et al. The association of estimated glomerular filtration rate with diabetic retinopathy and macular edema. *Invest Ophthalmol Vis Sci*. 2015;56:4810–4816.
9. Moriya T, Tanaka S, Kawasaki R, et al. Diabetic retinopathy and microalbuminuria can predict macroalbuminuria and renal function decline in Japanese type 2 diabetic patients: Japan Diabetes Complications Study. *Diabetes Care*. 2013;36:2803–2809.
10. Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology*. 2006;113:1695.e1691–e1615.
11. Chen E, Park CH. Use of intravitreal bevacizumab as a preoperative adjunct for tractional retinal detachment repair in severe proliferative diabetic retinopathy. *Retina*. 2006;26:699–700.

Investigative Ophthalmology & Visual Science