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

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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 m²) 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.3 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-
Participants aged 19-72 years who had been followed for at least 3 years from 1 April 2008 to 31 March 2014 and have health examination data were included and followed to 30 November 2017.

Excluded
Did not have diabetes mellitus (n=336,712)
Previous TRDED events (n=512)

n = 22,981
Excluded
Did not have full health examination data (n = 14,464)

n = 8,517
Excluded
eGFR <30, eGFR >100 (mL/min/1.73m²) (n=808)

Study participants
n = 7,709

Figure. Flow chart for the extraction of study participants.
Table 1. Characteristics of Study Participants According to Presence or Absence of TRDED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 7709)</th>
<th>TRDED (−) (n = 7541)</th>
<th>TRDED (+) (n = 168)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, %</td>
<td>6293 (82)</td>
<td>6152 (82)</td>
<td>141 (84)</td>
<td>0.437</td>
</tr>
<tr>
<td>Age, y</td>
<td>51 ± 9</td>
<td>51 ± 9</td>
<td>53 ± 8</td>
<td>0.012</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5 ± 4.4</td>
<td>25.5 ± 4.4</td>
<td>25.9 ± 4.1</td>
<td>0.238</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130 ± 17</td>
<td>130 ± 17</td>
<td>134 ± 17</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 ± 11</td>
<td>80 ± 11</td>
<td>81 ± 12</td>
<td>0.081</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.8 ± 1.3</td>
<td>6.8 ± 1.2</td>
<td>8.4 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>51 ± 14</td>
<td>50 ± 13</td>
<td>69 ± 23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mM</td>
<td>7.6 ± 2.1</td>
<td>7.5 ± 2.0</td>
<td>10.2 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mM</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>0.471</td>
</tr>
<tr>
<td>LDLC, mM</td>
<td>3.3 ± 0.8</td>
<td>3.3 ± 0.8</td>
<td>3.3 ± 0.8</td>
<td>0.546</td>
</tr>
<tr>
<td>Triglycerides, mM</td>
<td>1.4 (0.9–2.0)</td>
<td>1.4 (0.9–2.0)</td>
<td>1.4 (0.9–2.1)</td>
<td>0.164</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>2.700 (35)</td>
<td>2.651 (35)</td>
<td>49 (29)</td>
<td>0.108</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>75.4 ± 12.3</td>
<td>75.4 ± 12.3</td>
<td>76.4 ± 14.4</td>
<td>0.396</td>
</tr>
<tr>
<td>OP, %</td>
<td>539 (7)</td>
<td>505 (7)</td>
<td>34 (20)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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 (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 pattern with decreased eGFR without proteinuria have been organized public health insurance system that equally covers management-based outcomes in Japan is that the well-organized public health insurance system that equally covers

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 colleagues1 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 colleagues2 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 m² 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 or did they separate severe eGFR reduction (eGFR<30 ml/min/1.73 m²) from their analysis.3

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,8 hyperglycemia, 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...
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 had already developed 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.

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References


