Diabetic retinopathy is a prognostic factor for progression of chronic kidney disease in the patients with type 2 diabetes mellitus

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Abstract

Since both retinopathy and nephropathy are major diabetic microvascular complications, we investigated whether severity of diabetic retinopathy (DR) has adverse effects on renal function and albuminuria in the patients with type 2 diabetes mellitus (DM). We screened 2,197 adult patients with type 2 DM who had undergone fundus exam between August 2006 and February 2014. Among them, 1,592 subjects with available serial renal function and albuminuria measurement were included in the analysis. DR status was classified as no DR, non-proliferative DR (NPDR), and proliferative DR (PDR). The risk of CKD progression was assessed according to DR severity. A total of 384 (24.1%) had NPDR and 202 (12.7%) had PDR at either eye. The mean follow-up period was 5.6±2.1 years. DR was associated with lower body mass index, lower plasma hemoglobin, lower serum albumin level, longer duration of DM, poorer control of blood sugar, lower estimated glomerular filtration rate (eGFR), and greater amount of albuminuria. Interestingly, baseline DR severity was associated with faster renal function decline and greater albuminuria progression. In multivariate analysis, NPDR had 2.9 times and PDR had 16.6 times higher risk for CKD progression. Our findings showed that baseline DR severity is a prognostic factor for future CKD progression in type 2 DM patients. Therefore, clinicians must evaluate DR severity at the first visit and closely monitor renal function and albuminuria in the subjects with severe DR.

Introduction

Both diabetic retinopathy (DR) and nephropathy are typical microvascular complications of diabetes mellitus (DM). It is well known that the prevalence of chronic kidney disease (CKD) and DR increases proportionally to the disease duration in type 2 DM [1, 2]. CKD and DR also share common risk factors such as smoking, poor glycemic control, systolic hypertension, or dyslipidemia [1, 3, 4]. Since both CKD and DR reflect similar pathogenesis and microvascular lesions, it is reasonable to assume that development of DR may predict development and progression of CKD.
However, the association between DR and CKD has not been well established in type 2 DM, and a few studies found that their association in type 2 DM patients is much weaker than that in type 1 DM patients [5, 6]. In addition, the role of DR as a predictor for development and progression of CKD is still controversial. The Microalbuminuric Collaborative Study Group found that DR was not an independent predictor of albuminuria [7], but other researchers found that the presence and severity of DR are still indicators for the risk of developing proteinuria [2, 8].

Recently, a few prospective cohort studies suggested that the presence of retinopathy is related to the development and progression of renal diseases in both diabetic and non-diabetic CKD patients [9–13]. However, there was no study evaluating the effect of DR severity upon CKD progression in type 2 DM patients. Therefore, we aimed to assess the value of DR severity to predict renal dysfunction and albuminuria progression in type 2 DM patients.

Materials and methods

Medical records from a total of 2,197 adult patients with type 2 DM who visited ophthalmology clinic in Kangnam Sacred Heart Hospital from August 2006 to February 2014 were screened for enrollment. Type 2 DM was diagnosed when the patient is older than 20 years old and presents with one of the followings according to World Health Organization diabetes diagnostic criteria: 1) fasting blood glucose \( \geq 6.99 \text{ mmol/L} \), 2) 2-hour plasma glucose level after 75 g oral glucose tolerance test \( \geq 11.1 \text{ mmol/L} \), 3) random plasma glucose level \( \geq 11.1 \text{ mmol/L} \) with diabetic symptoms, 4) glycated hemoglobin (HbA1c) \( \geq 48 \text{ mmol/mol (6.5%)} \) [14]. Among 2,197 patients, 547 patients were excluded from the analysis due to following reasons: 400 with no serial follow-up data over 1 year (272 with single eGFR measurement, 128 with eGFR follow-up measurement within a year (mean follow-up duration 199.4±103.3 days), 118 with advanced CKD (CKD stage 4 and 5), 17 type 1 DM, 49 without retinal exams, 8 hypertensive retinopathy, 6 loss of vision, 6 artificial eyes, and 1 retinal vein occlusion (Fig 1).

CKD was defined by Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline based on estimated glomerular filtration rate (eGFR) and albuminuria [15]. The eGFR was calculated by CKD-EPI creatinine equation [16]. Serum creatinine was measured by IDMS-traceable method [17]. Annual eGFR decline rate was calculated from the difference of eGFR between recent follow-up and the initial visit divided by follow-up years. The degree of albuminuria was measured by random urine albumin-to-creatinine ratio (UACR). The CKD progression was defined based on one or more of the following: 1) decline in GFR category \(( \geq 90 \text{ mL/min/1.73m}^2 \) to \(60–89 \text{ mL/min/1.73m}^2 \), 45–59 \( \text{G3a} \), 30–44 \( \text{G3b} \), 15–29 \( \text{G4} \), <15 \( \text{G5} \) \text{ mL/min/1.73m}^2 \) accompanied by a 25% or greater drop in eGFR from baseline, 2) sustained declined in eGFR of more than 5 mL/min/1.73m^2/year [18]. Albuminuria progression was defined by one or more step progression in albuminuria (normo-albuminuria (UACR < 30mg/g) to micro-albuminuria (30mg/g \leq UACR < 300 mg/g) or macro-albuminuria (UACR \geq 300 mg/g), micro-albuminuria to macro-albuminuria) during follow-up.

The status of DR was evaluated by slit-lamp examination, indirect ophthalmoscopy and/or fluorescein angiography by ophthalmologists. To evaluate the effect of DR severity upon CKD progression, retinopathy was classified into following categories; no DR, non-proliferative DR (NPDR), and proliferative DR (PDR) [19]. Each eye was given a DR grade and the final DR severity was determined by the result of more severe eye. The progression of DR was defined by more than 1 step progression in DR grade of either eye or the development of PDR requiring photocoagulation or vitrectomy [20].

The following data were obtained from each patient: age, gender, duration of DM, use of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) at initial visit, body mass index (BMI) at initial visit, serial measurements of serum creatinine,
**Results**

**Baseline characteristics of the subjects according to the status of diabetic retinopathy**

A total of 1,592 patients were included in the analysis (Table 1). Mean age was 57.9 ± 11.2 years old, and female was slightly predominant (n = 841, 52.8%). The mean follow-up period was 5.6 years.
### Table 1. Baseline characteristics of the subjects classified by diabetic retinopathy.

| Variables                  | No DR (n = 1,006) | NPDR (n = 384) | PDR (n = 202) | p-value |
|----------------------------|------------------|---------------|---------------|---------|
| Age (years)               | 57.5±11.2        | 59.3±10.9     | 57.3±11.2     | 0.016   |
| Male (%)                  | 470 (46.7)       | 175 (45.6)    | 106 (52.5)    | 0.252   |
| Hypertension (%)          | 485 (50.2)       | 201 (54.6)    | 87 (43.5)     | 0.04    |
| BMI (kg/m²)               | 25.4±3.6         | 24.6±3.5      | 23.5±3.4      | <0.001  |
| DM duration (years)       | 6.7±6.3          | 11.9±8.0      | 12.0±8.2      | <0.001  |
| ACEi or ARB (%)           | 471 (46.8)       | 202 (52.6)    | 97 (48.0)     | 0.154   |
| Total cholesterol (mg/dL) | 167.1            | 166.9         | 168.4±4.19    | 0.892   |
| Albumin (g/dL)            | 4.4±0.4          | 4.3±0.5       | 4.2±0.6       | <0.001  |

- **DR**: diabetic retinopathy; **NPDR**: non-proliferative diabetic retinopathy; **PDR**: proliferative diabetic retinopathy; **BMI**: body mass index; **DM**: diabetes mellitus; **ACEi**: angiotensin converting enzyme inhibitor; **ARB**: angiotensin receptor blocker; **sBP**: systolic blood pressure; **dBP**: diastolic blood pressure; **HbA1c**: hemoglobin A1c; **FPG**: fasting plasma glucose; **eGFR**: estimated glomerular filtration rate; **UACR**: urinary albumin-to-creatinine ratio

| Albumin (mg/dL) | 12.6 [7.0, 24.5] | 23.1 [10.6, 98.9] | 37.0 [16.5, 235.5] | <0.001 |
| Hemoglobin (g/dL) | 13.5±1.6 | 13.0±1.8 | 12.3±1.8 | <0.001 |
| Total cholesterol (mg/dL) | 167.1±35.8 | 166.9±41.2 | 168.4±41.9 | 0.892 |
| UACR (mg/g)  | 81.5±18.5       | 76.1±19.6     | 72.4±22.3     | <0.001  |

DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio

Diabetic retinopathy and CKD progression

±2.1 years. A total of 586 (36.8%) patients had DR at the initial visit. Among them, 384 (24.1%) had NPDR and 202 (12.7%) had PDR at either eye. Compared to the patients without DR, the patients with NPDR and PDR had lower BMI (24.6±3.5 and 23.5±3.4 vs. 25.4±3.6 kg/m², p<0.001), longer duration of DM (11.9±8.0 and 12.0±8.2 vs. 6.7±6.3 years, p<0.001), higher level of HbA1c (8.3±1.8 and 8.5±2.1 vs. 7.5±1.7%, p<0.001), lower hemoglobin level (13.0±1.8 and 12.3±1.8 vs. 13.5±1.6 g/dL, p<0.001) and lower serum albumin level (4.3±0.5 and 4.2±0.6 vs. 4.4±0.4 g/dL, p<0.001). In addition, patients with NPDR and PDR showed decreased eGFR (76.1±19.6 and 72.4±22.3 vs. 81.5±18.5 mL/min/1.73m², p<0.001) and increased amount of albuminuria (median 12.6 and 23.1 vs. 37.0 mg/g, p<0.001) compared to those without DR.

### Severity of diabetic retinopathy affects the rate of renal function decline

To assess whether DR severity affects subsequent renal function decline rate, we compared annual decline rate of eGFR among subjects with different DR severity. Since baseline renal function is a strong predictor of future eGFR decline, we divided subjects into groups based on baseline CKD stages according to GFR categories (Fig 2). Among the subjects with baseline CKD stage 1 (n = 517), patients with NPDR (n = 102) and PDR (n = 51) showed faster eGFR decline rate (-3.2±6.44 and -4.16±5.43 mL/min/1.73m² per year) compared to those without DR (n = 364, -0.83±3.48 mL/min/1.73m² per year, p<0.001). The subjects in CKD stage 2 (n = 797) at baseline showed preserved renal function among no DR subjects (0.47±3.22 mL/min/1.73m² per year) while rapid progression in NPDR and PDR (-1.91±5.71 and -3.97±6.08 mL/min/1.73m² per year) patients (p<0.001). The results were similar for those in CKD stage 3a (n = 188) and 3b (n = 90) showing preserved renal function in no DR subjects (1.24±3.91 and 0.5±4.34 mL/min/1.73m² per year) while rapid progression in NPDR (-0.53±4.25 and -2.3±3.34 mL/min/1.73m² per year) and PDR (-2.58±5.71 and -2.89±9.19 mL/min/1.73m² per year) patients (p<0.001).
Diabetic retinopathy is a risk factor for CKD progression

To evaluate the effect of DR severity upon CKD progression, 1,592 subjects were further divided into group of CKD progression (n = 311) and non-progression (n = 1,281, Table 2). The subjects with CKD progression showed lower BMI (24.4 ± 3.7 vs. 25.2 ± 3.6 kg/m², p = 0.014), longer duration of DM (11.2±8.2 vs. 8.0±7.1 years, p<0.001), more frequent use of ACEi or ARB (55% vs. 46.8%, p = 0.009) and higher HbA1c (8.6±2.2 vs. 7.6±1.7%, p<0.001). They also showed lower baseline eGFR (73.0±22.6 vs. 80.5±18.5 mL/min/1.73m², p<0.001), greater amount of albuminuria (median 13.5 vs. 36.7 mg/g, p = 0.001), lower plasma hemoglobin (12.5±2.0 vs. 13.4±1.6 g/dL, p<0.001), and lower serum albumin level (4.1±0.6 vs. 4.5±0.4 g/dL, p<0.001). The subjects with CKD progression also showed larger proportion of albuminuria (median 13.5 vs. 36.7 mg/g, p = 0.001), lower plasma hemoglobin (12.5±2.0 vs. 13.4±1.6 g/dL, p<0.001), and lower serum albumin level (4.1±0.6 vs. 4.5±0.4 g/dL, p<0.001). The subjects with CKD progression also showed higher proportion of DR progression (25.5% vs. 16.2%, p = 0.003).

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Diabetic retinopathy is a risk factor for albuminuria progression

To evaluate the effect of DR severity upon albuminuria progression, a total of 948 subjects with serial albuminuria data over 1 year were included in the analysis (Table 3). A total of 644 subjects were excluded from the analysis for the following reasons: 546 without initial albuminuria data, 61 with initial macroalbuminuria (UACR ≥ 300 mg/g), and 37 without serial albuminuria data. Among 948 subjects, 180 patients showed albuminuria progression while 768 patients showed stable amount of albuminuria. The group with albuminuria progression showed longer duration of DM (9.2 ± 7.4 vs. 7.7 ± 6.9 years, p = 0.008), more frequent use of ACEi or ARB (67.8% vs. 50.9%, p < 0.001), higher HbA1c (8.2 ± 2.2 vs. 7.5 ± 1.7%, p < 0.001) and lower baseline eGFR (median 13.6 vs. 18.5 mg/g, p = 0.014). As same as those with CKD progression, the group with albuminuria progression showed larger proportion of NPDR and PDR compared to those without progression (30.0% and 15.0% vs. 18.8% and 4.5%, p < 0.001). The proportion of the subjects with albuminuria progression increased as DR severity increased (14.4% vs. 27.1% vs. 43.5%, p < 0.001, Fig 4). However, proportion of DR progression during follow-up was not different between two groups (18.8% vs. 13.9%, p = 0.148).

Diabetic retinopathy is a prognostic factor for progression of chronic kidney disease

To assess whether DR severity is a prognostic factor for CKD progression, we performed binary logistic regression analysis. In the univariate analysis, low BMI, longer DM duration, use of ACEi or ARB at the initial visit, higher HbA1c, lower baseline eGFR, higher baseline
UACR, lower plasma hemoglobin, lower serum albumin, presence of DR, and presence of DR progression were all related to the CKD progression (Table 4, p < 0.05).

When we performed multiple logistic analysis after adjusting for DM duration, use of ACEi or ARB, HbA1c, baseline eGFR, baseline UACR, plasma hemoglobin and serum albumin levels, baseline DR severity and DR progression status, DR severity was independently associated with CKD progression showing that NPDR has 2.9 times and PDR has 16.6 times higher risk for CKD progression compared to no DR group (Table 5, p for trend < 0.001). However, DR progression during follow-up period was not an independent risk factor for CKD progression (p = 0.563).

Discussion

The current study was performed to show the importance of baseline DR severity upon prospective renal function decline and albuminuria progression. Our study showed that DR was associated with longer duration of DM, poorer control of blood sugar, lower eGFR, greater amount of albuminuria, and poorer nutritional indices (serum albumin, BMI, and plasma hemoglobin). Interestingly, baseline DR severity was associated with progressive renal function decline and albuminuria progression. Even after adjusting for other risk factors, NPDR had 2.9 times and PDR had 16.6 times higher risk for CKD progression in type2 DM subjects. On the other hand, DR progression during follow-up period did not affect future CKD progression.

It is well known that the association between DR and CKD is strong and the presence of CKD almost always accompany DR [21]. However, this association is known to be weaker in
A large amount of cross-sectional studies demonstrated that the presence of DR is associated with concurrent renal dysfunction [9, 12, 13, 22]. However, only a few studies have evaluated causal relationship between DR and CKD. Trevisan et al. demonstrated that the rate of renal function decline was larger with those who have retinopathy and proteinuria compared to those without retinopathy [23]. Another study evaluated the effect of retinopathy upon renal outcome in elderly group and showed that retinopathy even affects faster renal function decline in non-DM subjects [8]. There was also the study evaluating the effect of DR upon renal outcome compared to the non-diabetic hypertensive retinopathy [11]. However, there was no study to evaluate the renal outcome according to DR severity. Our study is the first large-scale study to evaluate the effect of DR severity upon renal outcome. Previous association studies only described the association of the ‘presence of DR’ with either eGFR decline or proteinuria progression. However, our study is the first study to evaluate the effect of ‘degree of DR’ but not the presence of DR upon CKD progression.

There can be some possible explanation about why DR severity affects renal function deterioration. Firstly, DR and diabetic CKD are both microvascular complication which lead to extravasation and inflammation. Previous study by Matsuyama et al. suggested that pigment epithelium-derived factor, an inhibitor for angiogenesis, is significantly elevated in the type 2 DM patients with DR and CKD, which may indicate microvascular damage [24]. Another study by Yang et al. also suggested that retinal damage marker found in urine proteome reflect renal progression in type 2 DM patients [25]. However, other recent study by McKay et al. showed that mere retinal microvascular parameters including vascular caliber, tortuosity, and fractal dimension cannot predict renal outcome in type 2 DM patients [26]. Moriya et al. suggested that microalbuminuria together with DR result in glomerulosclerosis and renal

| Parameters                  | Albuminuria progression | P-value |
|-----------------------------|-------------------------|---------|
|                            | (-) (n = 768)           | (+) (n = 180) |         |
| Age (years)                 | 56.5±10.6               | 57.4±12.0 | 0.328   |
| Male (%)                    | 47.4%                   | 40.0%    | 0.081   |
| Hypertension (%)            | 46.9%                   | 52.3%    | 0.206   |
| BMI (kg/m²)                 | 25.1±3.5                | 25.2±3.6 | 0.75    |
| DM duration (years)         | 7.7±6.9                 | 9.2±7.4  | 0.008   |
| ACEi or ARB (%)             | 391 (50.9)              | 122 (67.8) | <0.001 |
| HbA1c (%)                   | 7.5±1.7                 | 8.2±2.2  | <0.001  |
| Cr at baseline (mg/dL)      | 0.92±0.21               | 0.98±0.26 | 0.006   |
| eGFR at baseline (mL/min/1.73m²) | 82.3±17.5             | 76.7±20.1 | 0.001   |
| UACR at baseline (mg/g)     | 13.6 [7.4, 27.4]        | 18.5 [10.1, 28.5] | 0.014 |
| Hemoglobin (g/dL)           | 13.5±1.7                | 13.3±1.5 | 0.127   |
| Total cholesterol (mg/dL)   | 163.8±34.0              | 164.0±35.2 | 0.941  |
| Albumin (g/dL)              | 4.5±0.4                 | 4.4±0.4  | 0.198   |
| DR at baseline (%)          |                        |         | <0.001  |
| No DR                       | 76.6%                   | 55.0%    |         |
| NPDR                        | 18.9%                   | 30.0%    |         |
| PDR                         | 4.6%                    | 15.0%    |         |
| DR progression (%)          | 13.9%                   | 18.8%    | 0.148   |

BMI, body mass index; DM, diabetes mellitus; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy

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Fig 4. Proportion of the subjects with albuminuria progression according to initial diabetic retinopathy status. Albuminuria progression was defined by one or more step progression in albuminuria (normo-albuminuria (UACR < 30mg/g) to micro-albuminuria (30mg/g ≤ UACR < 300 mg/g) or macro-albuminuria (UACR ≥ 300 mg/g), micro-albuminuria to macro-albuminuria) during follow-up. The proportion of the subjects with albuminuria progression increased as DR severity increased (14.4% vs. 27.1% vs. 43.5%, p < 0.001). DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 4. Binary logistic regression analysis for CKD progression.

| Parameter                  | Odds ratio | Confidence interval | p-value |
|----------------------------|------------|---------------------|---------|
| Age, yr                    | 1.007      | 0.996–1.019         | 0.204   |
| Male                       | 1.198      | 0.935–1.535         | 0.153   |
| HTN                        | 1.157      | 0.899–1.489         | 0.258   |
| BMI, kg/m²                 | 0.943      | 0.899–0.988         | 0.014   |
| DM duration, yr            | 1.055      | 1.039–1.072         | <0.001  |
| Use of ACEi or ARB         | 1.391      | 1.084–1.784         | 0.009   |
| HbA1c, %                   | 1.308      | 1.227–1.395         | <0.001  |
| Baseline eGFR, mL/min/1.73m² | 0.981    | 0.974–0.987         | <0.001  |
| Baseline UACR, mg/g        | 1.002      | 1.001–1.003         | <0.001  |
| Plasma hemoglobin, g/dL    | 0.743      | 0.689–0.801         | <0.001  |
| Total cholesterol, mg/dL   | 1.003      | 1.000–1.006         | 0.057   |
| Serum albumin, g/dL        | 0.186      | 0.14–0.247          | <0.001  |
| NPDR (vs. no DR)           | 4.052      | 2.993–5.488         | <0.001  |
| PDR (vs. no DR)            | 9.293      | 6.569–13.146        | <0.001  |
| DR progression             | 1.769      | 1.230–2.545         | 0.002   |

CKD, chronic kidney disease; HTN, hypertension; BMI, body mass index; DM, diabetes mellitus; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DR, diabetic retinopathy.
However, our study suggested that DR severity independently affect renal function deterioration after adjustment for albuminuria status. Meanwhile, DR progression was not an independent risk factor for further progression of CKD. This may be a part due to missing data. Only 1,422 patients had available follow-up retinal exam more than a year apart and another 170 patients with both PDR at the baseline were excluded from the data analysis. In addition, some subjects were excluded from the analysis due to advanced CKD at baseline (n = 108), macro-albuminuria at baseline (n = 61), and no available albuminuria data (n = 546). Therefore, whether DR progression may reflect the renal outcome should be assessed in the future in a large prospective cohort study.

This study has several limitations. The data in this study was collected retrospectively from a single center. Secondly, we did not collect 24-hour urine samples to quantify the amount of albuminuria. We used albumin-to-creatinine ratio in random urine to quantify the amount of albuminuria. In addition, there were some missing data regarding serial follow up of albuminuria. Thirdly, we neither perform kidney biopsy to see the severity of diabetic nephropathy nor unravel the possible mechanism underlying relationship between DR and CKD. Lastly, this study design limits inferences on causality. These subjects were from the Korean population and were visited in the hospital and the results cannot be generalized to general population and other ethnic groups. Therefore, prospective, cohort-based study should be warranted to reproduce and confirm our study finding.

In conclusion, DR was a prognostic factor for CKD progression in type2 DM patients. Therefore, clinicians must evaluate DR severity at the first visit and closely monitor renal function and albuminuria in the subjects with severe DR.

Author Contributions

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Table 5. Multiple logistic regression analysis for prediction of CKD progression.

| Parameter                  | Odds ratio | Confidence interval | p-value |
|---------------------------|------------|---------------------|---------|
| Baseline eGFR <60 mL/min/1.73m² | 2.068      | 1.062–4.027         | 0.033   |
| Baseline UACR ≥30 mg/g   | 3.314      | 1.847–5.947         | <0.001  |
| Albumin <4.0 g/dL        | 2.840      | 1.495–5.394         | 0.001   |
| NPDR (vs. no DR)         | 2.910      | 1.602–5.285         | <0.001  |
| PDR (vs. no DR)          | 16.582     | 2.431–113.123       | 0.004   |
| DR progression           | 1.213      | 0.631–2.330         | 0.563   |
| Hemoglobin <10 g/dL      | 1.849      | 0.619–5.520         | 0.271   |
| HbA1c ≥7.0%              | 1.703      | 0.901–3.218         | 0.101   |
| BMI <25 kg/m²            | 1.642      | 0.942–2.860         | 0.08    |
| DM duration ≥10 years    | 0.978      | 0.537–1.780         | 0.942   |
| Use of ACEi or ARB       | 1.121      | 0.625–2.009         | 0.702   |

CKD, chronic kidney disease; HbA1c, hemoglobin A1c; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DR, diabetic retinopathy; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio

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