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ARTICLE

Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS)

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Abstract
Aims/hypothesis The aim of this study was to determine the incidence and progression rates of diabetic retinopathy and their associations in Japanese individuals with type 2 diabetes.
Methods This is a part of the Japan Diabetic Complications Study (JDCS), a multi-centred randomised trial of type 2 diabetes patients aged 40–70 years with an 8 year follow-up. There were 1,221 patients without diabetic retinopathy at baseline; incidence of diabetic retinopathy was defined as the development of any diabetic retinopathy. There were 410 patients with mild non-proliferative diabetic retinopathy at baseline; progression of diabetic retinopathy was defined as the development of severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy. We used multivariate proportional Cox hazard models, and generalised additive models were also applied to identify potential threshold effect.
Results The incidence and progression rate of diabetic retinopathy was 38.3/1,000 person-years and 21.1/1,000 person-years, respectively. Higher HbA_{1c} (adjusted HR [aHR] per 1% [10.9 mmol/mol] 1.36 [95% CI 1.28–1.45]), longer duration of diabetes (aHR per 5 year period 1.26 [95% CI 1.17–1.35]), higher systolic blood pressure (aHR per +10 mmHg 1.01 [95% CI 1.00–1.02]) and higher body mass index (aHR per 1 kg/m^2 1.05 [95% CI 1.00–1.09]) were associated with incident diabetic retinopathy. The association between HbA_{1c} and incident diabetic retinopathy was linear; the association with duration of diabetes increased rapidly between 5 and 10 years. Higher HbA_{1c}

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was also associated with progression of diabetic retinopathy (aHR per 1% [10.9 mmol/mol] 1.66 [95% CI 1.41–1.96]).
Conclusions Observed incidence and progression rates of diabetic retinopathy seemed lower than that in western populations. HbA_{1c} was the only factor associated with both incidence and progression of diabetic retinopathy. The strength of the association between duration of diabetes and incidence of diabetic retinopathy increased rapidly during a period of 5 to 10 years duration of diabetes.
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Keywords Diabetic retinopathy · HbA_{1c} · Incidence · Japan Diabetes Complications Study (JDCS) · Type 2 diabetes

Abbreviations
JDCS Japan Diabetes Complications Study

Introduction

Diabetic retinopathy is one of the leading causes of blindness in the working-age population [1]. Although improved management of risk factors and advances in treatment modalities for diabetic retinopathy have contributed to reducing the risk of blindness from this pathology [2–4], type 2 diabetes per se has been continuously increasing in Asian populations [5, 6]. The report from the International Diabetes Federation estimated that people with diabetes in the Asian Pacific region will increase from 137 million in 2010 to 214 million by 2030 [7]. Because diabetic retinopathy is one of the common microvascular complications in diabetes, the number of people with diabetic retinopathy is also estimated to increase. Therefore, specific incidence and progression rates of diabetic retinopathy in Asian diabetic patients are necessary to estimate the burden and thus to develop strategic preventive interventions for the management of diabetic retinopathy.

While long-term incidence of diabetic retinopathy is well documented in western populations, such as in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [8], the Fyn Study [9] or in a Hispanic population in the US [10], there has been insufficient information from Asian populations. Those studies reported from Asian countries are either based on relatively small sample sizes or single hospital-based samples [11–14].

With regard to the risk associations for diabetic retinopathy, duration of diabetes and HbA_{1c} are two key risk predictors of diabetic retinopathy; diabetic retinopathy develops in nearly 80% of those with type 2 diabetes with duration of diabetes of 15 years [15]. However, detailed association between duration of diabetes or HbA_{1c} and incidence or progression of diabetic retinopathy in Asian samples is also not well documented. Okudaira et al. [16] has reported association between duration of diabetes or HbA_{1c} and progression of diabetic retinopathy in Japanese patients with early-onset type 2 diabetes. Shiraiwa et al. has reported that postprandial hyperglycaemia was more influential than fasting glycaemia or HbA_{1c} in the risk of incidence or progression of diabetic retinopathy in Japanese patients with diabetes who were admitted to their hospital [17, 18].

Recently, the American Diabetes Association recommended using HbA_{1c} levels to diagnose diabetes based on the observation that the prevalence of diabetic retinopathy increases rapidly in individuals with $HbA_{1c} \geq 6.5\%$ (47.5 mmol/mol) [19]. However, whether there is a clear cut-off value in HbA_{1c} associated with rapid increased incidence or progression of diabetic retinopathy is uncertain.

This study aims to determine the incidence and progression rate of diabetic retinopathy in adult Japanese patients with type 2 diabetes, together with their risk associations, with a focus in the duration of diabetes and HbA_{1c}. We used a multi-centred cohort of the Japan Diabetes Complications Study (JDCS) with 8 years of follow up.

Methods

This study is a part of the JDCS, a Japanese nationwide multi-centred randomised trial of 2,033 adults (1,087 men and 946 women) with type 2 diabetes aged between 40 and 70 years. Details of study design have been described elsewhere [20, 21]. Baseline characteristics of the study participants are shown in Table 1. In brief, study participants were invited to participate if they had an HbA_{1c} level of more than 6.5% (47.5 mmol/mol) and were aged 40–70 years; patients with impaired glucose tolerance were excluded. As a result, the HbA_{1c} level of study patients ranged between 6.0% (42.1 mmol/mol) and 15.8% (149.2 mmol/mol). Those who have major ocular disease (e.g. glaucoma, dense cataract or history of cataract surgery) were excluded from the current analysis. Participants were randomly assigned to a lifestyle intervention or conventional treatment and followed up annually from March 1996 until March 2003. We analysed follow-up data until March 2003. The study was approved by the committee of the Ministry of Health, Labour and Welfare, Japan. We obtained written informed consent from all patients. As we reported in our previous paper, there was no significant difference in incidence or progression of diabetic retinopathy between the control group and the intervention group (aHR for incidence or progression of

Table 1 Baseline clinical characteristics of type 2 diabetes patients in the Japan Diabetes Complications Study

Characteristic	Incidence of diabetic retinopathy (n=1,221)	Progression of diabetic retinopathy (n=410)
Sex (female %)	45.0	49.5
Age (years)	58.2±6.9	59.1±6.9
Diabetes duration (years)	9.8±6.8	12.8±7.1
<5 years (%)	26.2	11.5
5–10 years (%)	33.6	27.6
≥10 years (%)	40.2	60.9
BMI (kg/m^2)	23.1±3.1	23.1±3.0
Systolic blood pressure (mmHg)	130.9±16.1	132.8±16.3
Diastolic blood pressure (mmHg)	77.2±10.0	76.3±9.4
Fasting plasma glucose[a] (mmol/l)	8.4 (7.3–9.9)	8.5 (7.3–9.9)
HbA_{1c} at baseline (%)	7.8±1.3	8.0±1.2
HbA_{1c} at baseline (mmol/mol)	61.7±14.2	63.9±13.1
<7.0% (<53.0 mmol/mol) (%)	27.2	21.5
7.0 to <9.0% (53.0 to <74.9 mmol/mol) (%)	59.4	57.8
≥9.0% (≥74.9 mmol/mol) (%)	13.4	20.7
Total cholesterol (mmol/l)	5.2±0.9	5.1±0.8
LDL-cholesterol (mmol/l)	3.2±0.8	3.1±0.8
Triacylglycerol[a] (mmol/l)	1.2 (0.6–1.7)	1.1 (0.6–1.7)
HDL-cholesterol (mmol/l)	1.4±0.5	1.5±0.4
Exercise (kJ/day)[a]	602.1 (129.3–1,243.1)	498.3 (96.2–1,259.0)
Therapy components		
Diabetes		
Diet only (%)	24.2	10.0
Insulin (%)	14.0	27.1
Sulfonylureas (%)	56.1	64.3
α-Glucosidase inhibitors (%)	16.8	22.0
Biguanides (%)	4.7	6.5
Insulin sensitisers (%)	1.8	1.5
Antihypertensive agents (%)	25.0	26.8
Agents for hyperlipidaemia (%)	24.4	26.1
Smoking status		
Current smoker (%)	29.7	23.9
Past smoker (%)	24.4	22.9
Never smoked (%)	46.0	53.2
Alcohol intake		
0 g/day (%)	61.3	63.3
1–37 g/day (%)	30.9	31.2
≥38 g/day (%)	7.8	5.4

Data are percentages or mean± SD except for: [a] median (IQR)

diabetic retinopathy compared with the control arm: 0.82 [95% CI 0.65–1.02] and 0.76 [95% CI 0.45-1.22], respectively) [21].

Assessment of diabetic retinopathy Presence and severity of diabetic retinopathy was determined annually by local ophthalmologists at each study site and history of ocular surgery was also surveyed. Following the international diabetic retinopathy and diabetic macular oedema disease scales [22], severity of diabetic retinopathy was categorised into five stages of 'no retinopathy', 'mild non-proliferative diabetic retinopathy', 'moderate non-proliferative diabetic retinopathy', 'severe non-proliferative diabetic retinopathy', and 'proliferative diabetic retinopathy'. To validate the consistency of grading between study sites, we cross-examined fundus images and evaluated the agreement in grading between local ophthalmologists and retinal specialists (RK and HY). The estimate of kappa statistics for the

agreement was 0.56 (95% CI 0.52–0.59) and was considered to be above moderate.

Definition of incidence and progression of diabetic retinopathy 'Incidence of diabetic retinopathy' was defined as having no diabetic retinopathy signs in either eye at baseline and having mild to severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy in either of the eyes at two consecutive follow-up years. 'Progression of diabetic retinopathy' was defined as having mild non-proliferative diabetic retinopathy at baseline, and having severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, or laser photocoagulation treatment for diabetic retinopathy at follow-up at two consecutive follow-up years.

Statistical analysis The primary endpoint was 'time-to-incidence' or 'time-to-progression' of diabetic retinopathy. The time from baseline registration was calculated for each participant from the starting point to the date of incidence of diabetic retinopathy, or progression of diabetic retinopathy. In addition to the events of incidence or progression of diabetic retinopathy, cataract surgery and death were considered as censoring. We used the Kaplan–Meier method to plot the cumulative proportion of incidence or progression of diabetic retinopathy. We reported crude and multivariate-adjusted hazards ratios (aHRs) using the Cox proportional hazard models. In the multivariate model, covariates were selected by the backward selection method at $p>0.1$ from the following variables: age, sex, duration of diabetes, age at diagnosis of diabetes, life style intervention, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, HbA_{1c} at baseline, HDL-cholesterol, LDL-cholesterol, triacylglycerol, smoking (current vs non-current smoker), alcohol consumption (≥38 g/day vs 1–37 g/day vs 0 g/day) and intervention (vs control). We also examined associations between diabetic retinopathy and HbA_{1c} using time-dependent Cox regression analysis, which incorporates all measurements of HbA_{1c} during follow up as one time-dependent covariate. To explore whether there is any dynamic change in risk associations, such as a rapid increase in risk of incident diabetic retinopathy, we used multivariate-adjusted generalised additive models with a spline function of three degrees of freedom including diabetes duration, BMI, systolic blood pressure and HbA_{1c} as covariates. All p values are two-sided and $p<0.05$ was considered statistically significant. Statistical analyses were carried out using the SAS software package (version 9.2; SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of people at risk of incidence or progression of diabetic retinopathy are shown in Table 1. The baseline HbA_{1c} level for the entire study sample was 7.8±1.3% (61.7±14.2 mmol/mol) (range 6.0–15.8% [42.1–149.2 mmol/mol]). There were 1,221 patients who had no diabetic retinopathy at baseline and were at risk of incident diabetic retinopathy; there were 325 cumulative incident cases of diabetic retinopathy (risk in 8 year period 26.6%; annual risk 3.3%), and the incidence rate was 38.3/1,000 person-years. There were 410 patients who had mild non-proliferative diabetic retinopathy at baseline and were at risk of progression of diabetic retinopathy; there were 65 cumulative cases with a progression of diabetic retinopathy (risk in 8 year period 15.9%; annual risk 2.0%), and the progression rate was 21.1/1,000 person-years.

Using the stepwise backward variable selection method, duration of diabetes (aHR 1.26 [95% CI 1.17–1.35] per +5 years, $p<0.0001$), higher BMI (aHR 1.05 [95% CI 1.00–1.09] per +1 kg/m^2, $p=0.019$), higher systolic blood pressure (aHR 1.09 [95% CI 1.02–1.17] per +10 mmHg, $p=0.014$) and higher HbA_{1c} (aHR 1.36 [95% CI 1.28–1.45] per +1% [10.9 mmol/mol], $p<0.0001$), were selected as significant characteristics associated with incidence of diabetic retinopathy (Table 2). In contrast, higher HbA_{1c} was the only characteristic selected as significantly associated with progression of diabetic retinopathy (aHR per +1% [10.9 mmol/mol] 1.66 [95% CI 1.41–1.95], $p<0.0001$) (Table 2).

These associations between HbA_{1c} and incidence or progression of diabetic retinopathy remained consistent

Table 2 Associations between incidence or progression of diabetic retinopathy and risk factors selected by the stepwise backward procedure in multivariate Cox regression models

Variable	Incidence of diabetic retinopathy (n=1,221)			Progression of diabetic retinopathy (n=410)		
	aHR	95% CI	p value	aHR	95% CI	p value
Diabetes duration (per 5 year period)	1.26	(1.17–1.35)	<0.0001	–	–	–
BMI (per 1 kg/m^2)	1.05	(1.00–1.09)	0.019	–	–	–
Systolic blood pressure (per 10 mmHg)	1.09	(1.02–1.17)	0.014	–	–	–
HbA_{1c} (per 1% [10.9 mmol/mol])	1.36	(1.28–1.45)	<0.0001	1.66	(1.41–1.95)	<0.0001

when we used HbA_{1c} level as a time-dependent covariate accounting for change in HbA_{1c} during the follow-up period (aHRs for incidence or progression of diabetic retinopathy per +1% [10.9 mmol/mol] change in HbA_{1c}: 1.36 [95% CI 1.27–1.47], $p<0.0001$ and 1.33 [95% CI 1.11–1.60], $p=0.001$, respectively).

When we replaced duration of diabetes with age at diagnosis of diabetes (≥50 years old vs <50 years old) in the multivariate model, individuals who were diagnosed with diabetes at ≥50 years old were significantly less likely to develop diabetic retinopathy compared with individuals who were diagnosed at <50 years old (aHR 0.72 [95% CI 0.57–0.90], $p=0.004$).

Figure 1a,b show the Kaplan–Meier plot for the incidence and progression of diabetic retinopathy by three levels of HbA_{1c}. Compared with patients with HbA_{1c} <7.0% (53.0 mmol/mol), individuals with 7.0% (53.0 mmol/mol)≤HbA_{1c}<9.0% (74.9 mmol/mol) and individuals with HbA_{1c} ≥9.0% (74.9 mmol/mol) had significantly higher risk of incident diabetic retinopathy (HR 1.98 [95% CI 1.44–2.70], $p<0.0001$, and 4.04 [95% CI 2.83–5.78], $p<0.0001$, respectively). Patients with HbA_{1c} ≥9.0% (74.9 mmol/mol) had an eightfold higher risk of progression of diabetic retinopathy compared with that in the patients with HbA_{1c} <7.0% (53.0 mmol/mol) (HR7.92, 95% CI 3.08–20.36, $p<0.0001$).

Association between risk over an 8 year period of the incidence of diabetic retinopathy and HbA_{1c} (Fig. 2a) or diabetes duration (Fig. 2b) were estimated using generalised additive models. As shown, there was no indication of the presence of a threshold in associations between HbA_{1c} and risk of incidence of diabetic retinopathy. In contrast, as shown in Fig. 2b, there was a dynamic increase in the risk of developing diabetic retinopathy between 5 years and 10 years of duration of diabetes. In general, the risk of incidence of diabetic retinopathy increases with longer duration of diabetes; it increases more rapidly between 5 years (0.185, 95% CI 0.149–0.227) and 10 years (0.313, 95% CI 0.263–0.368). The risk of incidence of diabetic retinopathy is more stable with <5 years or ≥10 years of duration of diabetes.

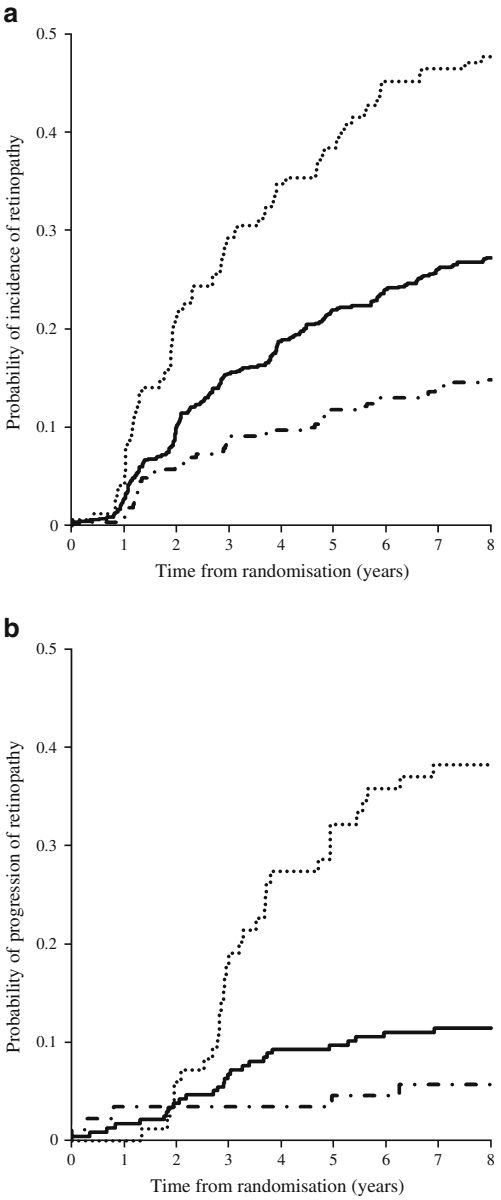

Fig. 1 **a** Kaplan–Meier plot for the incidence of retinopathy by HbA_{1c} level (dotted line, HbA_{1c} ≥9.0%; black line, 9.0%>HbA_{1c}≥ 7.0%; dashed line, HbA_{1c} <7.0%). **b** Kaplan–Meier plot for the progression of retinopathy by HbA_{1c} level (dotted line, HbA_{1c} ≥9.0%; black line, 9.0%>HbA_{1c} ≥7.0%; dashed line, HbA_{1c}<7.0%) (HbA_{1c} 7% is equivalent to 53.0 mmol/mol; 9% is equivalent to 74.9 mmol/mol)

Discussion

Using the JDCS cohort, we reported the incidence rate of diabetic retinopathy in Japanese adult type 2 diabetes patients with a long-term follow up of 8 years. The observed incident rate (38.3/1,000 person-years) was close to the previous reports of incident rate of diabetic retinopathy from Asian populations [13, 14].

Strengths of our study are that it involved a multi-centred study design covering a large geographical area in Japan, and a large sample size of >1,000. Limitations might include the accuracy of diabetic retinopathy grading based on clinical diagnosis, when compared with grading based on seven-field stereo fundus photography. Although we validated the consistency of grading as moderate compared with photographic grading in a sub-sample, subtle diabetic retinopathy change can be overlooked and the outcomes of incidence or progression of diabetic retinopathy can be underestimated. Selection bias by

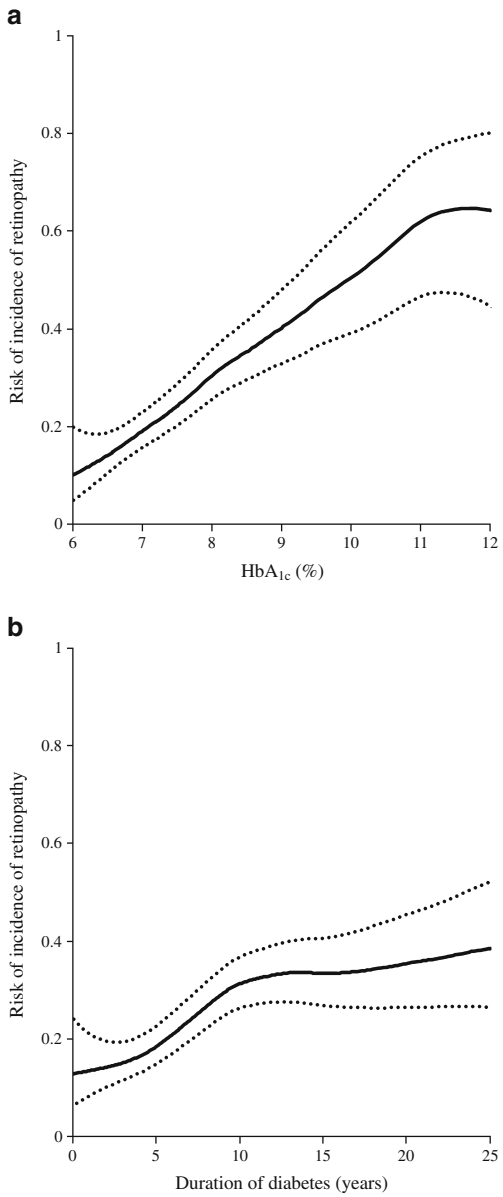

Fig. 2 **a** Risk (black line) and 95% CI (dotted lines) of the incidence of retinopathy in relation to HbA_{1c} estimated by generalised additive models. **b** Risk (black line) and 95% CI (dotted lines) of the incidence of retinopathy in relation to diabetes duration estimated by generalised additive models

including patients for lifestyle intervention might overestimate the incidence and progression of diabetic retinopathy than in the diabetic population in general.

The incidence rate of diabetic retinopathy in this study was comparable to previous studies from Asian populations. Kim et al. [13] reported the incidence rate of diabetic retinopathy in Korean type 2 diabetic patients as 44.4/1,000 person-years over a follow-up of 5.3 years; Sasaki et al. [14] reported the incidence rate of diabetic retinopathy as 39.8/1,000 person-years in Japanese type 2 diabetes patients (n=976; follow-up of 8.3 years). The observed incident rate in this study was slightly lower than that reported in white or Hispanic populations in western countries (3.3% in this study vs 4.4–8.6%) [10, 23, 24].

With regard to risk associations, HbA_{1c} (either at baseline or change over time) was the most relevant risk factor for both incidence and progression of diabetic retinopathy. Risk of incidence and progression of diabetic retinopathy increased linearly by 36% and 66% for every 1% [10.9 mmol/mol] increase in HbA_{1c} at baseline, respectively. This association was consistently found when we treat HbA_{1c} level as a time-dependent variable accounting for change in HbA_{1c} over follow-up time. We also found that here were no suggestions of a threshold effect in HbA_{1c} level, which would rapidly increase the risk of incidence or progression of diabetic retinopathy; the association between HbA_{1c} level and incidence or progression of diabetic retinopathy seems to be linear (Fig. 2a). One limitation of our study is that individuals involved in this study have an HbA_{1c} range of 6.0% (42.1 mmol/mol) to 15.8% (149.2 mmol/mol), and we cannot confirm whether there is a threshold effect outside this range. This warrants further study to determine the therapeutic target with a cut-off HbA_{1c} value for reducing risk of incidence or progression of diabetic retinopathy. We have also observed that individuals who were diagnosed at ≥50 years old were significantly less likely to develop diabetic retinopathy compared with individuals who were diagnosed at <50 years old; association of HbA_{1c} and incidence or progression of diabetic retinopathy did not change significantly even adjusting for age at onset.

An association between longer duration of diabetes and incidence of diabetic retinopathy was also confirmed in this study. With regard to the duration of diabetes, the risk of incidence of diabetic retinopathy increases rapidly from 5 years to 10 years duration while the change in risk was stable at <5 years or ≥10 years of duration (Fig. 2b). Although the duration of diabetes is not a modifiable risk characteristic, our findings might contribute to better management strategies by suggesting that patients with 5–10 years of duration of diabetes may have greater risk of developing diabetic retinopathy and thus need more intensive follow up compared with those with ≥10 years of duration of diabetes.

We found an association between higher BMI and incidence of diabetic retinopathy. While it is still controversial, obesity has been shown to be associated with increased risk of incident diabetic retinopathy [1]. In our earlier analysis, we have reported a significant difference in BMI in persons with type 2 diabetes between western and Japanese populations [25]; BMI in Japanese patients with type 2 diabetes was significantly lower than that in western populations [25]. In this study, we found that higher BMI is significantly associated with the incidence of diabetic

retinopathy even within the relatively lower BMI range (23.1 ± 3.0 kg/m^2). This finding warrants further research to assess whether Asian individuals who are overweight are also at risk of developing diabetic retinopathy.

In conclusion, we have reported the incidence rate and progression rate of diabetic retinopathy in adult Japanese patients with type 2 diabetes over 8 years. We found that higher HbA_{1c} level was significantly and linearly associated with both incidence and progression of diabetic retinopathy. Higher BMI and higher systolic blood pressure were also associated with higher risk of developing diabetic retinopathy. Duration of diabetes was also associated with increasing risk of incidence of diabetic retinopathy; the risk of incidence of diabetic retinopathy increases rapidly between 5 and 10 years. This study emphasises the importance of glycaemic control in the management of diabetic retinopathy in Asian patients with type 2 diabetes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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