Prevalence of retinopathy and its risk factors in a Japanese population

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ABSTRACT

Aims/Introduction: To determine the prevalence and risk factors of retinopathy and validity of the current diagnostic cut-offs for diabetes by using data of health check-up examinees.

Materials and Methods: The study comprises 1,864 Japanese who participated in the general health check-up program and did not have a previous history of cardiovascular disease. Non-mydriatic 45° digital fundus photographs were taken twice annually. Multivariate logistic regression model was used to identify risk factors for retinopathy in participants without previously diagnosed diabetes.

Results: The overall prevalence of retinopathy in participants with and without previously diagnosed diabetes were 23.3% (28/120) and 4.2% (74/1,744), respectively. Univariate logistic regression analysis identified age, systolic blood pressure (SBP), fasting plasma glucose (FPG) and hemoglobin A1c (HbA_{1c}) as risk factors for retinopathy. Multivariate logistic regression analysis showed that FPG or both HbA_{1c} and SBP were significant, positive and independent risk factors for retinopathy. The prevalence of retinopathy increased with deterioration of glucose categories ($P < 0.001$ for FPG or HbA_{1c}). However, a statistically significant increased risk of retinopathy remained only in participants with FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5% compared with those with the lowest quartile of glucose in the participants without previously diagnosed diabetes after adjusting for age and SBP.

Conclusions: The prevalence of retinopathy was 4.2%, and FPG or both HbA_{1c} and SBP were positive and independent risk factors for retinopathy in health check-up examinees without previously diagnosed diabetes. The FPG 7.0 mmol/L or HbA_{1c} 6.5% seems to be appropriate to diagnose diabetes in view of its association with retinopathy. (J Diabetes Invest, doi: 10.1111/jdi.12044, 2013)

KEY WORDS: Fasting plasma glucose, Hemoglobin A1c, Retinopathy

INTRODUCTION

The International Expert Committee of the American Diabetes Association (ADA), the European Association for the Study of Diabetes and the World Health Organization (WHO) have recommended that hemoglobin A1c (HbA_{1c}), fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG) on a 75-g oral glucose tolerance test (OGTT) be included in the diagnosis of diabetes[1–3]. The Japan Diabetes Society (JDS) has tackled the issue of HbA_{1c} from its own standpoint and reviewed existing OGTT data from 6,658 Japanese subjects[4]. In the JDS report, a very high correlation between FPG and HbA_{1c} was seen, with a FPG of 7.0 mmol/L corresponding to a HbA_{1c} of 6.5%. In the same manner, a correlation was identified between OGTT 2-h PG value and HbA_{1c}, with an OGTT 2-h PG value of 11.1 mmol/L corresponding to a HbA_{1c} of 6.4%. Furthermore, the prevalence of diabetic retinopathy has substantially increased at a HbA_{1c} level of 6.5%[5]. Then, since spring 2010, a HbA_{1c} of 6.5% has been included as a component of the diagnosis of diabetes and solely used for epidemiological purposes in Japan[4].

Retinal signs, such as isolated microaneurysms, retinal hemorrhages, hard exudates and cotton wool spots, are occasionally observed in subjects without clinically diagnosed diabetes[6–16]. The prevalence of retinopathy has been reported to be 4.8–15.5% in subjects without diabetes. However, these reports used different definitions of diabetes, such as FPG alone, a combination of FPG and 2-h PG, non-fasting glucose, current use of diabetes medications or a self-reported history of diabetes. None of the aforementioned studies applied HbA_{1c} to diagnose diabetes. Furthermore, almost all of the reports examined white populations; only a few were from Asia[6–8]. Thus, the aim of the present study was to determine the prevalence of retinopathy and its risk factors in the Japanese health check-up examinees not previously diagnosed with diabetes. Furthermore, the validity of current diagnostic cut-offs on FPG and HbA_{1c} was evaluated, with respect to the prevalence of retinopathy.

Participants

From February 2006 to January 2007, a total of 3,804 men and 2,208 women participated in a general health check-up program at Saitama-ken Saiseikai Kurihashi (SSK) Hospital in

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Saitama, Japan, and have been followed up in the Kurihashi Lifestyle Cohort Study to clarify the relationship between risk factors and lifestyle-related diseases and mortality. Of those, 1,387 men and 588 women aged 21–85 years had glucose measurements (FPG and HbA_{1c}) and retinal photographs taken twice a year. Participants were excluded if they had anemia (hemoglobin <13.0 g/dL for men or <12.0 g/dL for women; $n = 164$) or a previous history of cardiovascular events ($n = 34$) and if retinal grading did not meet between two independent ophthalmologists (CS and AH; $n = 42$). The remaining 1,351 men and 513 women were used for data analysis.

FPG ≥7.0 mmol/L or HbA_{1c} ≥6.5% was used to diagnose newly diagnosed diabetes according to the JDS, ADA and WHO criteria[2–4].

MATERIALS AND METHODS

Participants were classified into six groups according to glucose concentration based on quartiles in the non-diabetic glucose range, newly diagnosed diabetes for FPG or for HbA_{1c} and previous diagnosed diabetes (FPG categories: <4.9, 4.9–5.1, 5.2–5.4, 5.5–6.9, ≥7.0 mmol/L and previously diagnosed diabetes; HbA_{1c} category: <5.4, 5.4–5.5, 5.6–5.7, 5.8–6.4, ≥6.5% and previously diagnosed diabetes).

Measurement of Variables

The health check-up procedures at SSK Hospital included biochemical laboratory tests and a self-administered questionnaire regarding smoking status and medical history. Smoking status was classified into three categories (never, past and current smoker). The height, weight, blood pressure and waist circumference of all participants were measured. Body height was measured to the nearest 0.1 cm with the participant standing without shoes. The participants were requested to wear light indoor clothes before their bodyweight was measured to the nearest 0.1 kg. Blood pressure was measured in a sitting position after 5 min of rest using an automatic sphygmomanometer (Medical Electronics Sphygmomanometer TM-2655P; A&D Co. Ltd, Tokyo, Japan). Body mass index (BMI) was calculated as the bodyweight (in kg) divided by the body height squared (in meters).

Blood samples were obtained in the morning after a 10-h fast. FPG (glucose oxidase method), HbA_{1c} (high-performance liquid chromatographic method), total cholesterol (TC; oxidase method), triglyceride (TG; enzymatic method), high-density lipoprotein (HDL) cholesterol (direct method), uric acid (UA; uricase peroxidase method) and white blood cell (WBC) count (multi-angle polarized scatter separation method) were measured in the hospital laboratory. Fasting immunoreactive insulin (F-IRI), concentrations were measured by immune-radiometric assay at a commercial laboratory. The mean coefficient of variation of HbA_{1c} was 1.16%. HbA_{1c} values were estimated as National Glycohemoglobin Standardization Program equivalent values calculated from the formula HbA_{1c} (%) = 1.02 × HbA_{1c} (JDS) (%) + 0.25%[17]. Anthropometric and laboratory data at the first examination were used for data analysis.

Fundus Examination

On two occasions per year, a retinal photograph centered at the optic disc and macula was taken of one eye of each participant, using a 45° 6.3-megapixel digital non-mydriatic camera with a 10D single-lens reflex back. Two retinal photographs per one participant were used for retinal grading by two independent masked ophthalmologists (CS and AH). The presence of retinopathy was defined by the following conditions: microaneurysms, any retinal hemorrhage, and soft and hard exudates.

Statistical Analysis

The χ^2-test was used to compare proportions, and Student's *t*-test was used to compare means between two groups.

The univariate logistic regression analysis was carried out to test the association between an independent variable and the presence of retinopathy in participants without previously diagnosed diabetes. The independent variables tested in the model were FPG (1 mmol/L), HbA_{1c} (1%), age (10 years), sex, systolic blood pressure (SBP; 10 mmHg), TC (1 mmol/L), TG (1 mmol/L), HDL2 cholesterol (1 mmol/L), BMI (1 kg/m^2), UA (1 μmol/L), WBC count (1000/μL), F-IRI (1 μU/mL) and smoking status. Subsequently, multivariate logistic regression analysis was carried out to test whether variables identified as significant in the aforementioned univariate model were independently associated with the presence of retinopathy.

The proportions of the participants with retinopathy were calculated in the six glucose categories described earlier, and a logistic regression model was used to test the effect of glucose category on retinopathy. In this model, FPG and HbA_{1c} were treated as categorical variables, and six glucose categories were coded as 1–6 for each of FPG and HbA_{1c}. Thus, the category with the lowest value was coded as one followed by the next lowest value coded as two, and so on. The category of 'previously diagnosed diabetes' was coded as six. To examine the appropriate cut-off for the prediction of retinopathy, each of the categories 2–5 was compared with category one, the lowest quartile of the non-diabetic glucose range; that is, FPG category '<4.9' or HbA_{1c} category '<5.4'.

The Statistical Package for Social Sciences for Windows (version 17.0; SPSS, Chicago, IL, USA) was used for all statistical analyses. All reported *P*-values are two-tailed, and $P < 0.05$ was considered statistically significant.

The study was approved by the Institutional Review Board of SSK Hospital and Tokyo Women's Medical University, and informed consent was obtained from the study participants.

RESULTS

The overall prevalence of retinopathy in participants with and without previously diagnosed diabetes was 23.3% (28/120) and 4.2% (74/1,744), respectively.

Participant Characteristics According to Retinal Condition in Participants Without Previously Diagnosed Diabetes

In the data analysis of 1,744 participants without previously diagnosed diabetes, participants with retinopathy were more likely to be women than men, older and had higher blood pressure, FPG and HbA_{1c} than those without retinopathy (Table 1). No difference was found in lipid profiles, smoking status, WBC counts or F-IRI between participants with retinopathy and those without.

Risk Factors for Retinopathy in Participants Without Previously Diagnosed Diabetes

Table 2 shows risk factors identified for retinopathy in the univariate logistic regression analysis. Age, SBP, HbA_{1c} and FPG were revealed as positive risk factors for retinopathy.

In the multivariate model (table 3), either FPG (model 1) or HbA_{1c} (model 2), but not both, was used as a variable as they are tightly associated with each other: Thus, in model 1, FPG was used; while in model 2, HbA_{1c} was used in place of FPG, in addition to age and SBP, which were associated with retinopathy in the univariate analysis. The multivariate logistic regression model showed that FPG ($P = 0.003$; model 1) or both SBP ($P = 0.03$; model 2) and HbA_{1c} ($P = 0.011$; model 2) were significant, positive and independent risk factors for retinopathy (Table 3).

Table 1 | Clinical characteristics by presence or absence of retinopathy in 1,744 participants without previously diagnosed diabetes

	Retinopathy absent	Retinopathy present	*P*-value
n	1,670	74	–
Men (%)	72.2	62.2	0.044
Age (years)	51 ± 8	53 ± 7	0.016
Body mass index (kg/m^2)	23.4 ± 3.0	23.8 ± 2.7	0.319
Current smokers (%)	50.7	50.0	0.499
Systolic blood pressure (mm Hg)	126 ± 17	131 ± 17	0.006
Diastolic blood pressure (mm Hg)	77 ± 12	81 ± 13	0.011
Fasting plasma glucose (mmol/L)	5.3 ± 0.7	5.7 ± 1.5	<0.001
HbA_{1c} (%)	5.2 ± 0.5	5.4 ± 0.8	0.001
Total cholesterol (mmol/L)	5.36 ± 0.88	5.42 ± 0.89	0.579
Triglyceride (mmol/L)	1.24 ± 0.73	1.28 ± 0.71	0.680
HDL cholesterol (mmol/L)	1.46 ± 0.39	1.47 ± 0.38	0.738
Fasting immunoreactive insulin (IU/mL)	6.9 ± 4.1	7.1 ± 4.1	0.785
Uric acid (μmol/L)	326 ± 83	318 ± 76	0.414
White blood cell count (/μL)	5,470 ± 1,560	5,410 ± 1,520	0.747

The $\chi 2$-test was used to compare proportions and Student's *t*-test was used to compare means between two groups. Data are means (standard deviations) or proportions. HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein.

Table 2 | Univariate logistic regression analysis to predict the presence of retinopathy in 1,744 participants without previously diagnosed diabetes

Independent variables	Beta-coefficients	Standard errors	*P*-values
Age (10 years)	0.358	0.148	0.016
Sex (women vs men)	0.456	0.246	0.064
Systolic blood pressure (10 mmHg)	0.178	0.065	0.006
HbA_{1c} (1%)	0.479	0.155	0.002
Fasting plasma glucose (1 mmol/L)	0.337	0.960	<0.001
Body mass index (1 kg/m^2)	0.037	0.037	0.318
Total cholesterol (1 mmol/L)	0.074	0.133	0.579
HDL cholesterol (1 mmol/L)	0.102	0.305	0.737
Triglyceride (1 mmol/L)	0.062	0.151	0.680
Smoking status (current or past vs never)	−0.029	0.238	0.904
Uric acid (1 μmol/L)	−0.001	0.001	0.414
Fasting immunoreactive insulin (1 μU/mL)	0.013	0.047	0.785
White blood cell count (1/μL)	−0.003	0.008	0.747

HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein.

Table 3 | Multivariate logistic regression analysis to predict the presence of retinopathy in 1,744 participants without previously diagnosed diabetes

Independent variables	Beta-coefficients	Standard errors	*P*-values
Model 1			
Age (10 years)	0.287	0.154	0.062
Systolic blood pressure (10 mmHg)	0.130	0.068	0.055
Fasting plasma glucose (1 mmol/L)	0.295	0.099	0.003
Model 2			
Age (10 years)	0.271	0.154	0.078
Systolic blood pressure (10 mmHg)	0.150	0.067	0.030
HbA_{1c} (1%)	0.412	0.163	0.011

Model 1 includes age, systolic blood pressure and fasting plasma glucose as independent variables. Model 2 includes age, systolic blood pressure and hemoglobin A1c (HbA_{1c}) as independent variables.

Prevalence of Retinopathy by Glucose Categories on FPG or HbA_{1c}

Figure 1 shows the relationship between the crude prevalence of retinopathy and the six glucose categories based on FPG or HbA_{1c}. The prevalence of retinopathy increased with deterioration of glucose categories for each of HbA_{1c} and FPG ($P < 0.001$ for

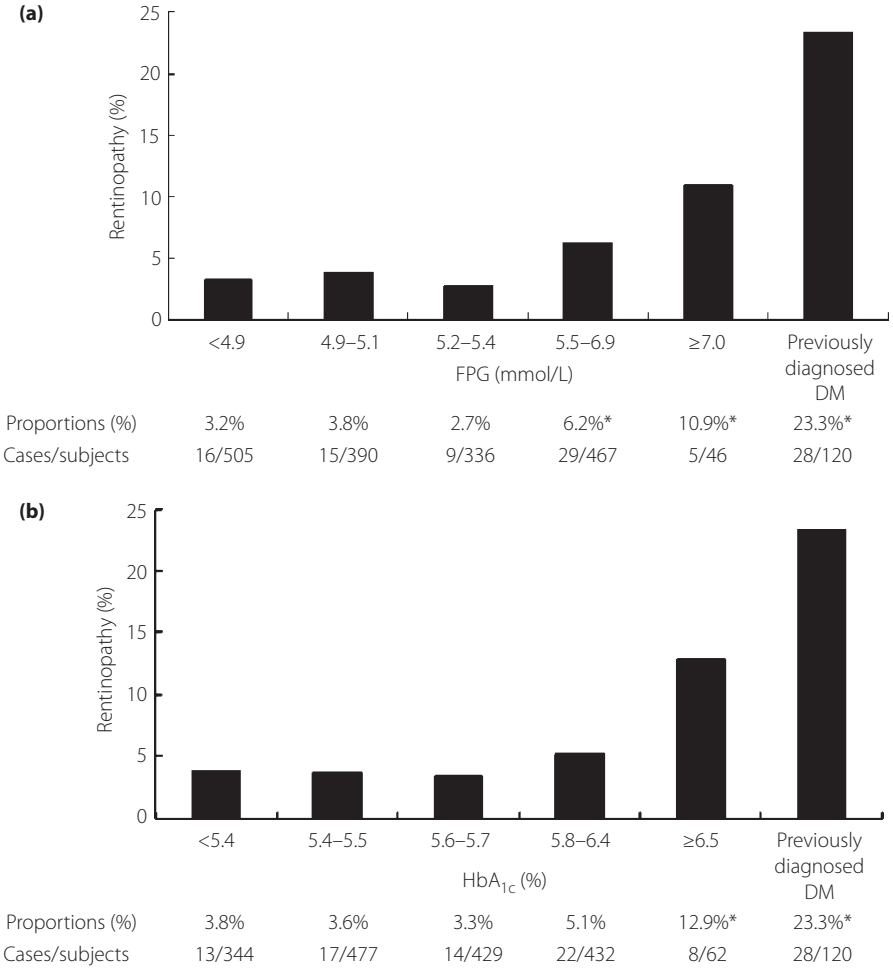

Figure 1 | The prevalence of retinopathy based on six glucose categories for (a) fasting plasma glucose (FPG) and (b) hemoglobin A1c (HbA_{1c}). *$P < 0.05$. DM, diabetes mellitus.

FPG or HbA1c category) (Figure 1) and FPG or HbA_{1c} category was significantly associated with retinopathy. When no adjustment was made, the statistically significant increase in the risk of retinopathy was observed in participants with the category of FPG ≥5.5 mmol/L or HbA_{1c} ≥6.5% in comparison with participants in the category of the lowest FPG or HbA_{1c}. However, this statistically significant increased risk of retinopathy remained only in participants with FPG ≥7.0 mmol/L or HbA_{1c} ≥6.5% compared with participants with the lowest FPG or HbA_{1c} after adjusting for age and SBP.

DISCUSSION

The current study has shown that the prevalence of retinopathy in Japanese health check-up examinees without previously diagnosed diabetes was low at 4.2%, and FPG or both HbA_{1c} and SBP were positive and independent risk factors for retinopathy in this group. The significantly increased adjusted risk for retinopathy in comparison with the lowest quartile for FPG or HbA_{1c} was shown only in the current newly diagnostic glucose categories for FPG or HbA1c.

The prevalence of retinopathy in non-diabetes varies between different Asian ethnic groups, being 6.0% in the Singapore Malay Eye Study[6], 17.2% in Chinese in the Multi-Ethnic Study of Atherosclerosis[7] and 9.0% in the Funagata Study from Japan[8]. As for diabetic retinopathy in subjects with diabetes and non-diabetes, it has been reported as 2.3% in the Hisayama Study from Japan[18]. The reason for the variation in prevalence might be a result of differences in the retinal grading methodology used, the studies' diagnostic criteria for diabetes, the distribution of clinical characteristics and the frequency of examinations. These factors might in part explain the difference in the prevalence of retinopathy within the same ethnic group. A combination of FPG and 2-h PG was used in the two Japanese population-based studies[8,18], whereas either FPG or HbA_{1c} was used to diagnose diabetes in the present study. Participants in the Funagata Study were non-diabetics[8], whereas those in the Hisayama Study included both diabetics and non-diabetics[18], and those in the present study were subjects without previously diagnosed diabetes. Furthermore, participants in the Hisayama Study[18] and the present study were approximately

10 years younger than those in the Funagata Study[8]. Alternatively, the participants analyzed in the present study received health check-ups twice annually, and the potential risks for complications might be low.

Previous studies have identified various risk factors for retinopathy in subjects without diabetes as a history of heart attack[6,9], the presence of stroke[9,10], SBP[6,11], hypertension[6,7,9,12–15], BMI[6,8,11], internal carotid arterial intima–media thickness[7,9], carotid arterial plaque[9], age[8,16], glucose intolerance[8] and dyslipidemia[11]. These findings suggest that retinopathy and cardiovascular diseases (CVD) share a common pathophysiology. In the current study, age, glucose indicators and SBP had a significant positive and independent relationship to retinopathy in participants without previously diagnosed diabetes or CVD. In contrast, the presence of hypertension based on the combination of systolic and diastolic blood pressure was not an independent risk factor of retinopathy among non-diabetics of the Funagata Study, where participants with previous CVD were included[8]. This shows that the magnitude of the same risk factor for retinopathy varies even in the same ethnicity. In the present study, SBP was an independent risk factor for retinopathy in the model including age and HbA_{1c} as covariates, whereas it was a borderline risk factor in the model including age and FPG as covariates. The reason is not known; however, this might be a result of a lower proportion of newly diagnosed diabetes by FPG than HbA_{1c}. Furthermore, SBP was no longer an independent risk factor for retinopathy when excluding participants taking antihypertensive medications in the present study (data not shown).

Some reports have shown the significant sex difference for having retinopathy[6,19]. The retinal signs were consistently more prevalent among men than women in the Singapore Malay Eye Study[6] and Beaver Dam Eye Study[19]. This sex difference might be a reflection of the higher CVD risks in men than women[20]. However, the present results were in contrast to the findings of the Singapore Malay Eye Study and Beaver Dam Eye Study, as sex was not identified as a significant risk factor in logistic regression models. The reason is not known, but this might be because of a selection bias, as our participants had been repeatedly examined in health check-ups. Further research will be required to clarify the sex difference in the prevalence of retinopathy.

The limitations of the present study should be noted. First, only one single angle retinal photograph per one health check-up examination was used for the present study, and this might have led to misclassification of retinopathy. However, two independent well-trained ophthalmologists have confirmed the retinal findings. Furthermore, we selected people who have examined their retina on two occasions per year. This might have increased cumulative time information about the retina and helped to distinguish drusen and hard exudates. Thus, our grading might be justified. Retinal fundus photography is a common, inexpensive and useful tool for assessing early atherosclerotic vascular changes in a general health check-up program, such as that used in Japan. Second, this was a cross-sectional study and therefore needs to be replicated using longitudinal data. Third, our participants were general health check-up examinees, so we had no 2-h PG data to analyze. The Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) Study[21] reported a narrow threshold range for diabetic retinopathy was identified for FPG and HbA1c but not for 2-h PG. While the Hisayama Study from Japan has suggested that measuring FPG or HbA_{1c} was as useful as 2-h PG for the diagnosis of diabetes[18], as the area under the receiver operating characteristic curves for 2-h PG was slightly, but not significantly, larger than that for FPG or HbA_{1c} with respect to the prevalence of diabetic retinopathy. Thus, even without 2-h PG data, we believe our data were worthwhile. Fourth, the DETECT-2 Study has suggested that the current diabetes diagnostic level for FPG could be lowered from 7.0 mmol/L to 6.5 mmol/L, with regard to the prevalence of retinopathy[21]. The lowered diagnostic cut-off for FPG of 6.4 mmol/L (and HbA_{1c} of 6.1%) has also been suggested in the Hisayama Study[18]. However, it was inclusive in the present study because we could not focus on diabetic retinopathy or further stratify our participants because of the small sample size.

In conclusion, the prevalence of retinopathy was 4.2%, and FPG or both HbA_{1c} and SBP were positive and independent risk factors for retinopathy in health check-up examinees without previously diagnosed diabetes. FPG 7.0 mmol/L or HbA_{1c} 6.5% seem to be appropriate cut-off values to diagnose diabetes with respect to prevalence of retinopathy.

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