from 1980 for the 75–79 cohort. The cumulative incidence rates of laser photocoagulation and blindness in each group were analysed by the Kaplan–Meier method, and the log-rank test was used to compare the survival curves. In addition, to evaluate the cumulative incidence rates of blindness after receiving laser photocoagulation, the cumulative incidence rates of blindness in each group were analysed in those subjects who received laser photocoagulation. In this analysis, the follow-up time was calculated from the time when laser photocoagulation was performed. Using Cox proportional hazard models, the hazard ratio and its 95% confidence interval for the time of diagnosis for blindness were calculated after adjusting for age of onset and sex. The status of laser photocoagulation and its interaction with the year-of-diagnosis group were further included into models. The status of laser photocoagulation was analysed as a time-dependent covariant. A dummy variable was incorporated for the year-of-diagnosis groups. All statistical analyses were performed using SAS software (version 9; SAS Institute, Cary, North Carolina, USA). A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient background

The study subjects comprised 285 patients (115 male and 170 female) in the 65–69 cohort and 769 patients (316 male and 453 female) in the 75–79 cohort. Of those, 29 and 76 subjects in the 65–69 and 75–79 cohorts, respectively, died during the follow-up. These subjects were treated as censored at their deaths unless they had developed blindness or received laser photocoagulation before their deaths.

The history of laser photocoagulation was ascertained in 224 subjects (ascertainment rate 78.6%) in the 65–69 cohort and 692 subjects (90.0%) in the 75–79 cohort (table 1). The status of blindness was confirmed in 257 subjects (90.2%) in the 65–69 cohort and 703 subjects (91.4%) in the 75–79 cohort as of 1 January 1995 (table 1).

The onset age of diabetes was not different between the subjects with the missing information and the traced subjects on blindness and laser photocoagulation in the 65–69 cohort. Subjects in the 75–79 cohort with missing information on laser photocoagulation were younger at the onset age of diabetes (8.5 (SD 4.1) years) than the subjects traced (9.9 (SD 4.2) years, $p<0.01$) and the results were the same for those missing information on blindness (8.6 (SD 4.1) years) as the subjects traced (9.7 (SD 4.2) years, $p<0.05$). Sex distributions of blindness and laser photocoagulation were not different between the subjects with the missing information and the traced subjects in both the 65–69 and 75–79 cohorts.

Distribution of sex (135 male and 219 female) in the subgroup (354 patients) diagnosed between 1970 and 1974 that was excluded from the study showed no significant difference from those in the 65–69 cohort and 75–79 cohort ($p = 0.64$). The age at onset of diabetes (8.6 (SD 4.2) years old) in the subgroup diagnosed between 1970 and 1974 showed no significant difference from that in the 75–79 cohort (8.7 (SD 4.1) years old) ($p = 0.69$).

Response of attending physicians to the survey

A total of 735 attending physicians returned information on their patients' clinical status at the time point of questionnaire survey in 1995, including those who had treated multiple patients. No regional difference was observed in the number of answers from attending physicians who responded to our survey. It was confirmed that not only urban but also rural physicians were performing laser photocoagulation at the time point of this survey in Japan.

Cumulative incidence rate of laser photocoagulation

Laser photocoagulation was performed in 107 subjects (47.8%) in the 65–69 cohort and 112 subjects (16.2%) in the 75–79 cohort by the end of follow-up (table 2). In the 65–69 cohort, the cumulative incidence rates of the therapy (%) were 1.3 (95% CI 0 to 2.8), 5.9 (0.05 to 9.0), 22.8 (17.3 to 28.4), 39.4 (32.9 to 45.9) and 49.3 (42.6 to 56.0) at 5, 10, 15, 20 and 25 years follow-up, respectively. The rates were 0.7 (0.1 to 1.4), 5.9 (4.2 to 7.7) and 16.3 (13.6 to 19.1) at 5, 10 and 15 years follow-up in the 75–79 cohort, respectively. There was no statistically significant difference in the incidence of laser photocoagulation between the 65–69 cohort and the 75–79 cohort ($p = 0.51$) (fig 1A).

Cumulative incidence rate of blindness

Blindness developed in 60 subjects (23.3%) in the 65–69 cohort and 15 (2.1%) in the 75–79 cohort (table 2). The cumulative incidence rate of blindness (%) were 0.4 (95% CI 0 to 1.2), 3.6 (1.3 to 5.9), 13.0 (8.8 to 17.2), 22.0 (16.8 to 27.2) and 24.5 (19.1 to 29.9) at 5, 10, 15, 20 and 25 years follow-up in 65 to 69 cohort, respectively, and 0.1 (0 to 0.4), 0.7 (0.1 to 1.3) and 2.0 (1.0 to 3.1) at the follow-up at 5, 10 and 15 years follow-up in the 75–79 cohort, respectively. There was a statistically significant difference in the incidence of blindness between the 65–69 cohort and the 75–79 cohort ($p<0.0001$) (fig 1B).

Risk of blindness and age of onset

The risk of blindness significantly increased by 1.09 times (95% CI 1.03 to 1.15, $p<0.005$) with an increase in the age of onset by 1 year when adjusted for sex and time of diagnosis using a Cox proportional hazard model (table 3).

Risk for blindness and the calendar years of diagnosis

Using a Cox proportional hazard model, the risk of blindness by the calendar year of diagnosis was analysed after adjustment for age of onset, sex, and presence or absence of laser photocoagulation. The hazard ratio for blindness decreased significantly to 0.18 times (95% CI 0.09 to 0.33, $p<0.0001$) in the 75–79 cohort compared with the 65–69 cohort when adjusted for the age of onset and sex (table 3). The hazard ratio attenuated to 0.21 times (0.10 to 0.45, $p<0.0001$) after further adjustment

Table 1 Demographic characteristics by time of diagnosis for diabetes

	Laser photocoagulation			Blindness		
Characteristic	1965–9	1975–9	p Value	1965–9	1975–9	p Value
Number of subjects	224	692		257	703	
Sex (male) (%)	50 (46.7)	41 (36.6)	0.13	25 (41.7)	5 (33.3)	0.56
Onset age (years)	9.2 (4.2)	10.5 (3.5)	0.02	10.5 (4.0)	10.5 (3.3)	0.98

Values are mean (SD) or n (%).
p Values for sex and onset age were calculated by chi-square test and t test for the 1965–9 cohort vs 1975–9 cohort, respectively.

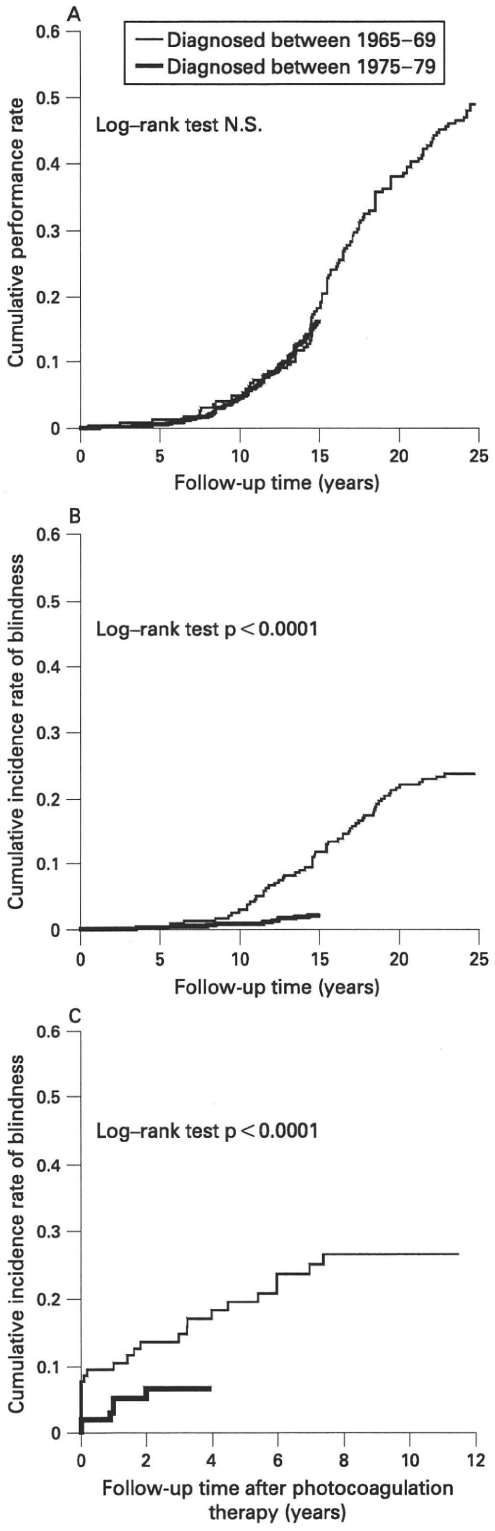

Figure 1 Cumulative performance rates of retinal photocoagulation therapy (A), cumulative incidence rates of blindness (B) and cumulative incidence rates of blindness after photocoagulation therapy (C). The data were followed-up by the Kaplan–Meier method for those diagnosed in 1965–9 and 1975–9. NS, not significant.

for the time-dependent status of laser photocoagulation (table 3).

Risk of blindness and receiving laser photocoagulation

The hazard ratio for the blindness significantly increased to 17.75 (95% CI 8.76 to 35.96, p<0.0001) for those receiving laser photocoagulation compared with those not receiving laser photocoagulation when adjusted for the age of onset, sex and time of diagnosis (table 3). The risk of blindness was significantly higher in subjects who needed laser photocoagulation than in those who did not, even after adjustment for the year of diagnosis.

Cumulative incidence rate of blindness in those who received laser photocoagulation

According to the subjects who received laser photocoagulation, blindness developed in 27 subjects (25.5%) in the 65–69 cohort and seven subjects (6.3%) in the 75–79 cohort. The cumulative incidence rate of blindness in those who received laser photocoagulation (%) were 20.2 (95% CI 12.2 to 28.1) and 26.9 (17.7 to 36.1) at 5- and 10-years follow-up, respectively, after receiving laser photocoagulation in the 65–69 cohort, and 7.9 (2.0 to 13.9) at 5-years follow-up after receiving laser photocoagulation in the 75–79 cohort. There was a statistically significant difference in the incidence of blindness between the 65–69 cohort and the 75–79 cohort (p<0.0001) (fig 1C).

Risk of blindness in those who received laser photocoagulation

The hazard ratio for blindness in those who received laser photocoagulation in the 75–79 cohort decreased significantly to 0.55 (95% CI 0.36 to 0.84, p<0.01) compared with those in the 65–69 cohort after adjusting for the age of onset, sex and time of diagnosis (table 4).

DISCUSSION

To our knowledge this study presents the first estimate of the incidence rate of blindness in Japanese type 1 diabetes patients with a large number of study subjects nationwide and with a high ascertainment rate.[9]

This study revealed that there was a significant improvement of blindness in the 75–79 cohort. A study based at Hvidore Hospital in Denmark showed a 7% cumulative incidence of blindness at 25-year follow-up, when the visual acuity of blindness was defined to be 0.1 or worse, in type 1 diabetes patients diagnosed in 1965–9, and 1% at 15-year follow-up in patients diagnosed in 1975–9.[11] In Japan, visual impairment, semi-blindness and blindness are defined according to the following decimal visual acuity scales: worse than 0.3 to a lower limit of 0.04, worse than 0.04 to a lower limit of 0.02, and worse than 0.02, in both eyes with the best possible correction. Considering that the definition of blindness in the present study was light perception level, we conclude that the incidence rate of 24.5% of blindness at the 25-year follow-up in the 65–69 cohort was extremely high compared with the similar data from the previous study.[11] The present study is based on a nationwide survey whereas Hvidore Hospital is a referral hospital. These differences indicate that there is room to improve prognosis or vision among Japanese patients.

The cumulative incidence of laser photocoagulation was the same for those diagnosed in the 1965–9 and 1975–9 cohorts. The finding is consistent with the aforementioned report of the Hvidore Hospital: the cumulative incidence of proliferative retinopathy was 11–16% and that of laser-treated retinopathy

Table 2 Laser photocoagulation and blindness outcomes in total and 15-year observation periods by the year of diagnosis of diabetes

	Laser photocoagulation		Blindness	
Variable	**1965–9**	**1975–9**	**1965–9**	**1975–9**
As of the end of 1994				
Number of events (%)	107 (47.8)	112 (16.2)	60 (23.3)	15 (2.1)
Duration of diabetes at event (years)	16.1 (4.9)	11.3 (2.9)	15.2 (4.5)	9.9 (4.4)
Age at event (years)	27.5 (5.7)	24.3 (3.8)	28.3 (5.8)	23.6 (4.8)
Calendar year at event (years)	1985.7 (4.9)	1990.9 (2.9)	1984.7 (4.5)	1989.4 (4.4)
Follow-up period (years)	24.1 (2.6)	14.9 (0.7)	20.3 (4.8)	13.9 (2.3)
At 15-year follow-up				
Number of events (%)	53 (18.6)	112 (14.6)	33 (11.6)	15 (2.0)
Duration of diabetes at event (years)	12.4 (3.6)	11.3 (2.9)	12.0 (3.0)	9.9 (4.4)
Age at event (years)	24.6 (4.9)	24.3 (3.8)	25.3 (4.5)	23.6 (4.8)
Calendar year at event (years)	1981.9 (3.6)	1990.9 (2.9	1981.4 (3.0	1989.4 (4.4)

Values are mean (SD) or n (%).

was 12–21% at 15 years of diabetes duration among type 1 diabetes patients diagnosed in 1965–9, 1970–4 and 1975–9.[11] The cumulative incidence of laser photocoagulation was a little higher in our population. Regarding the subgroup excluded from the study, we confirmed that there was no significant difference in the distribution of sex compared with the 65–69 and 75–79 cohorts, and no significant difference in the onset age compared with the 75–79 cohort. These findings suggest that this excluded subgroup did not differ in any other important demographic or clinical features from the groups investigated further in this study.

The risk of advanced retinopathy and blindness increased significantly with an increase in age of onset when adjusted for sex and time of diagnosis. There seems to be no established agreement on an increased risk of advanced retinopathy and blindness in age of onset.

In the subjects who received laser photocoagulation, the cumulative incidence rate of blindness after receiving the therapy decreased significantly in the 75–79 cohort compared with the 65–69 cohort. Given that there was no change in the frequency of laser photocoagulation, we consider two possible explanations.

First, the change in quality of laser photocoagulation could explain the decreased incidence of blindness observed over time. The results of two large clinical trials[12 13] of laser photocoagulation showed that the technical advances in laser photocoagulation prevented the progression of retinopathy. In Japan, the laser coagulation instrument was first introduced in 1968 and spread rapidly throughout the country during the 1970s through 1990s.[16] The long-term prognosis for blindness may have been improved by technical advances in laser photocoagulation in the late 1980s and early 1990s in Japan.[14]

Second, the earlier introduction of laser photocoagulation relative to the disease process may also have contributed to the reduction of the incidence of blindness, on which our data do not provide any detailed information. The early introduction of laser photocoagulation was optimally timed by the development of fluorescein fundus angiography.[15] It rapidly became available in Japan in the late 1970s[16] and made early diagnosis of proliferative retinopathy possible.

As a result, the risk of blindness was significantly higher in subjects who received laser photocoagulation than in those who did not, even after adjustment for the year of diagnosis. It is appropriate that patients receiving laser photocoagulation have advanced retinopathy, and this may explain the markedly higher risk of blindness compared with those not receiving the therapy. Zaninetti *et al* emphasised that eyes requiring vitrectomy because of vitreous haemorrhage or retinal detachment in proliferative retinopathy after laser photocoagulation were often a result of incomplete photocoagulation.[17] Various surgeries introduced by Machemer in 1971[18] were performed from about 1979 in Japan.[19] Photocoagulation therapy and progress in the treatment of advanced retinopathy, such as the technical improvement in vitreous surgery, might have contributed to the reduced incidence of blindness.

This study has the following limitations. First, information evaluated in this study was limited to reports on the status of blindness, any type of laser photocoagulation therapies and presence or absence of vitreous surgery. Second, our data did not include other known clinical risk factors for retinopathy, including hyperglycaemia,[20] hypertension[21] and so on. Better management of clinical risk factors may play an important role in reducing the progression of retinopathy in this study.

Table 3 Analyses of risk factors for blindness using Cox proportional hazard models

	Model 1		Model 2		Model 3	
Variable	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**	**p Value**
Age at onset (per year)	1.09 (1.03 to 1.15)	0.0047	1.04 (0.96 to 1.11)	0.35	1.03 (1.00 to 1.11)	0.38
Sex (female/male)	1.14 (0.71 to 1.82)	0.58	1.05 (0.59 to 1.89)	0.86	1.04 (0.58 to 1.87)	0.91
Calendar time period of diagnosis (1975–9/1965–9)	0.18 (0.09 to 0.33)	<0.0001	0.21 (0.10 to 0.45)	<0.0001	0.16 (0.05 to 0.50)	0.002
Laser photocoagulation (presence/absence)	–	–	17.75 (8.76 to 35.96)	<0.0001	15.45 (6.91 to 34.52)	<0.0001
Calendar time period of diagnosis × laser photocoagulation	–	–	–	–	1.65 (0.38 to 7.17)	0.51

Laser photocoagulation was analysed as a time-dependent covariant.
Three levels of adjustment were made as follows. Model 1: age at onset (per year), sex (female/male) and calendar time period of diagnosis (1975–9/1965–9); Model 2: Model 1+ laser photocoagulation (presence/absence); Model 3: Model 2 + calendar time period of diagnosis × laser photocoagulation].

Table 4 Analyses of risk factors for blindness after laser photocoagulation using Cox proportional hazard model

Variable	Hazard ratio (95% CI)	p Value
Age at onset (per year)	1.06 (0.97 to 1.15)	0.23
Sex (female/male)	1.25 (0.62 to 2.54)	0.54
Calendar time period of diagnosis (1975–9/1965–9)	0.55 (0.36 to 0.84)	<0.01

In summary, the incidence of blindness has decreased significantly for the subjects observed over time. This decrease might partially be attributed to technical advances in laser photocoagulation.

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Hemoglobin A1c in predicting progression to diabetes☆

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ABSTRACT

The predictive value of hemoglobin A1c (HbA1c) in comparison to fasting plasma glucose (FPG) is evaluated for 5-year incident diabetes (DM), as HbA1c may be more practical than FPG in the screening for DM in the future. Of 1189 non-DM subjects aged 35–89 years old from the Funagata Study, 57 subjects (4.8%) had developed DM on the WHO criteria at 5-year follow-up. The odds ratio (95% confidence interval: CI) for a one standard deviation increase in FPG/HbA1c was 3.40 (2.44–4.74)/3.49 (2.42–5.02). The area under the receiver operating characteristic curve for FPG/HbA1c was 0.786 (95% CI: 0.719–0.853)/0.785 (0.714–0.855). The HbA1c corresponding to FPG 5.56 mmol/l was HbA1c 5.3%. There was no statistical difference in sensitivity between FPG 5.56 mmol/l and HbA1c 5.3% (61.4% vs. 56.1%), while specificity was higher in HbA1c 5.3% than FPG 5.56 mmol/l (87.8% vs. 82.5%, p-value < 0.001). 0.001). The fraction of incident case from those with baseline IGT was similar between the groups, however the fraction of people above the cut-off was significantly lower in HbA1c 5.3% than FPG 5.56 mmol/l (14.3% vs. 19.6%, p-value < 0.001). HbA1c is similar to FPG to evaluate DM risk, and HbA1c could be practical and efficient to select subjects for intervention.

1. Introduction

The prevalence of type 2 diabetes (T2DM) is increasing rapidly worldwide, and emerging as a serious health issue [1]. Recent clinical trials have demonstrated that lifestyle or pharmacological interventions in subjects with impaired glucose tolerance (IGT) can delay or prevent T2DM [2–4]. More recent epidemiological study [5] and clinical trial [6] have shown that aggressive glycemic control should be started as early as possible to delay or prevent serious diabetes-related complications in subjects with DM. Thus, high-risk subjects for T2DM should be identified at early stage of the disease for intensive interventions.

In Japan, people with possible (hemoglobin A1c [HbA1c] 5.6–6.0%) and probable (HbA1c ≥6.1% and under treatment of diabetes) DM increased from 16.2 million in 2002 to 22.1 million in 2007 among the general population over 20 years old, representing an average 7.3% increase in rate per year [7]. The high-risk approach where either FPG or HbA1c is

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Abbreviations: ADA, American Diabetes Association; CI, confidence intervals; BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; JDS, Japan Diabetes Society; OGTT, oral glucose tolerance test; OR, odds ratio; ROC, receiver operating characteristic; Wc, Waist circumference; WHO, World Health Organization; 2 h PG, 2 h plasma glucose.

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incorporated into the general health check targeted future lifestyle-related diseases including DM has been launched in 2008 [8]. Although 2 h plasma (2 h PG) on an oral glucose tolerance test (OGTT) is a better predictor of DM than FPG [9,10], an OGTT is abandoned at opportunistic screening for DM. The simple and inexpensive substitutes would be required at primary health care. To date, both HbA1c and FPG are significant predictors of DM in some studies [11,12]. However, these studies used the American Diabetes Association (ADA) criteria [13] for the diagnosis of DM and the impact of HbA1c on incident DM based on 2 h PG was not taken into account. Thus, the aim of the current study was to assess the predictabilities of baseline FPG and HbA1c for DM based on the World Health Organization (WHO) criteria [14] at 5-year follow-up, by comparing baseline 2 h PG on an OGTT. Moreover, the cut-off points on baseline HbA1c were examined with respect to the prediction of DM at 5-year follow-up.

2. Subjects and methods

Funagata Study has been described previously [15]. Briefly, the Funaga Study is a population-based study conducted in an agricultural area 400 km north of Tokyo to clarify the risk factors, related conditions, and consequence of type 2 DM. The baseline data from the 2nd survey performed between 18th June1995 and 6th July 1997 consisted of 2154 subjects aged 35–89 years (participation rate: 48.4%). Of those, 1189 subjects without DM on the 1999-WHO criteria [14] were repeatedly performed an OGTT at the 3rd survey conducted between 16th June 2000 and 7th June 2002.

In both baseline and 5-year follow-up, blood samples were drawn from the antecubital vein after overnight fasting for measurement of FPG and lipids (enzymatic and direct methods) followed by an 75 g OGTT (Trelan-G®, Shimizu Pharmaceutical, Shimizu) in subjects without a treatment of DM. HbA1c was measured after the calibration standardized of the Japan Diabetes Society (JDS) [16,17] and the JDS assigned HbA1c values, which is 0.3% lower than the National Glycoprotein Standardization Program assigned values [18], were used in the present study. Intra-assay coefficient of variation for HbA1c was 1.0% at values 5.2% and 10.5%. Waist circumference (Wc) was measured at the navel level at the end of expiration under normal breathing in a standing position. Systolic and diastolic blood pressures were measured in the sitting position after a 5 min rest using a mercury sphygmomanometer. All participants were questioned about their smoking and alcohol habits.

2.1. *Statistical analyses*

McNemar's test was used to compare proportions between dependent samples. The 5-year cumulative incidence of DM was calculated as the number of subjects who developed DM at 5-year follow-up divided by the sum of duration of follow-up for each subject, in the three glucose categories for FPG, 2 h PG and HbA1c, respectively, as follows: FPG <5.05, 5.05–5.55, 5.56–6.99 mmol/l, 2 h PG <5.60, 5.60–7.79, 7.80-11.09 mmol/l, and HbA1c <5.0, 5.0–5.2, ≥5.3%. The FPG 5.56 mmol/l and 2 h PG 7.80 mmol/l were chosen, as they are defined as the lower limit of abnormal glucose metabolism in non-DM glucose range [14]. The HbA1c 5.3% was chosen, as it corresponds to FPG 5.56 mmol/l in the receiver operating characteristic (ROC) curve analysis [19] described below. The below these cut-offs, subjects were equally divided into cited group for FPG, 2 h PG and HbA1c, respectively.

Odds ratios (ORs) for the presence of DM at 5-year follow-up were estimated by using logistic regression analysis and reported with their 95% confidence intervals (CIs). The model adjusted for age (continuous), sex (categorical), Wc (continuous), FPG, 2 h PG or HbA1c (categorical) was made and tested by one by one for following explanatory variables: systolic blood pressure (continuous), cholesterol (continuous), triglyceride (continuous), high density lipoprotein cholesterol (continuous), smoking status (categorical, none/past smoker/current smoker), alcohol habits (categorical, none/drink occasionally/drink regularly) and family history of DM (categorical, none/present in first degree relatives). A variable of family history of DM, which came out to be significant in the former model, was fitted in a final model with age, sex, Wc and variables for FPG, 2 h PG or HbA1c. The subsequent logistic regression model, in which a continuous variable for a one standard deviation increase in FPG (0.58 mmol/l), 2 h PG (1.83 mmol/l) or HbA1c (0.4%) was entered, was fitted to see which of the glucose index has the strongest impact on the development of DM.

2.1.1. *Performance of three glucose indices as screening tests for DM at 5-year follow-up*

The ability of baseline FPG, 2 h PG and HbA1c to predict the incidence of DM at 5-year follow-up was determined by computing sensitivity and specificity and plotting them in a ROC curve [19]. The optimal cut-off maximizing sum of sensitivity plus specificity was explored for each glucose indicator. The sensitivity, specificity, positive predictive value (PPV) and false negative predictive value (NPV) for DM at 5-year follow-up and the proportion of subjects above the cut-off were calculated at baseline FPG 5.56 mmol/l and 2 h PG 7.80 mmol/l. The same calculation was made for HbA1c 5.1%, 5.2%, 5.3% and 5.4%.

The study was approved by the Institutional Review Board of Yamagata University and the informed consent to participate was obtained from all participants. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS, Chicago, IL, USA). A p-value < 0.05 was considered as statistically significance.

3. Results

During a 5-year follow-up period, 34 men (6.8% [95% CI: 4.6–9.0]) and 23 women (3.3% [2.0–4.7]) developed DM. The overall cumulative 5-year incidence density of DM was 12.1 (95% CI: 8.9–15.2) per 1000 person years of follow-up for men and women combined (Table 1).

3.1. *Incidence density and risk prediction of DM at 5-year follow-up from baseline FPG, 2 h PG, or HbA1c*

The 5-year cumulative incidence density and the multivariate ORs of DM at 5-year follow-up were significantly higher in subjects with the highest glucose category than the lowest

Table 1 – Incidence density and adjusted odds ratios for the presence of DM at 5-year follow-up according to baseline glucose categories.

	Number of subjects (%)	Number of incident case (incident case from IGT)	Incidence density of DM 1000 person-years (95% CI)	[a] Adjusted ORs for DM (95% CI)
Fasting plasma glucose (mmol/l)				
<5.05	507 (42%)	8 (1)	4.0 (1.2–6.7)	1.00
5.05–5.55	449 (38%)	14 (9)	7.9 (3.8–12.0)	1.72 (0.71–4.19)
5.56–6.99	233 (20%)	35 (25)	37.8 (25.5–50.1)	7.53 (3.35–16.93)
2 h plasma glucose (mmol/l)				
<5.60	512 (43%)	6 (0)	3.0 (0.6–5.3)	1.00
5.60–7.79	541 (46%)	16 (0)	7.5 (3.8–11.1)	2.38 (0.91–6.26)
7.80–11.09 (IGT)	136 (11%)	35 (35)	64.8 (44.1–85.6)	20.64 (8.13–52.37)
HbA1c (%)				
<5.0	559 (47%)	8 (2)	3.6 (1.1–6.1)	1.00
5.0–5.2	460 (39%)	17 (7)	9.3 (4.9–13.7)	2.14 (0.91–5.05)
≥5.3	170 (14%)	32 (26)	47.4 (31.4–63.4)	10.06 (4.44–22.79)
Total				
	1189 (100%)	57 (35)	12.1 (9.0–15.2)	

[a] Adjusting for age, sex, waist circumference, and family history of DM.

glucose category for FPG, 2 h PG and HbA1c (Table 1). There was no difference in the 5-year cumulative incidence density between three glucose indicators for each of the lowest, middle and the highest glucose category.

Modeling with continuous FPG, 2 h PG or HbA1c, the risk for DM at 5-year follow-up related to a one standard deviation increase in FPG, 2 h PG and HbA1c were 3.40 (2.44–4.74), 4.76 (3.30–6.86) and 3.49 (2.42–5.02), respectively.

3.2. *ROC curve analyses predicting DM from baseline FPG, 2 h PG, or HbA1c*

The area under the ROC curve for DM at 5-year follow-up was not statistically different across three glucose indicators: 0.830 (0.767–0.893) for 2 h PG, 0.786 (0.719–0.853) for FPG and 0.785 (0.714–0.855) for HbA1c (Fig. 1). The optimal cut-offs for FPG, 2 h PG and HbA1c were 5.36 mmol/l, 7.52 mmol/l and 5.1%, respectively. The HbA1c 5.3% gave the same sum of sensitivity plus specificity as FPG 5.56 mmol/l/l.

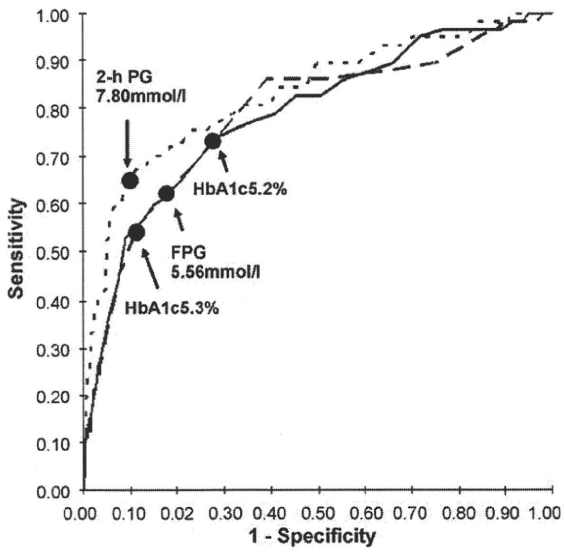

Fig. 1 – Receiver operating characteristic curves for incident diabetes at 5-year follow-up: baseline FPG (solid line), 2 h PG (dotted line) and HbA1c (solid and dotted line) among 1189 non-diabetes subjects at baseline.

3.3. *Performance as the screening test for future DM at various Pre-DM glucose cut-offs*

There was no statistical difference in sensitivity and 100-PPV between FPG 5.56 mmol/l, 2 h PG 7.80 mmol/l, HbA1c 5.2% and HbA1c 5.3%. The specificity was the highest in 2 h PG 7.80 mmol/l, the second highest in HbA1c 5.3%, followed by FPG 5.56 mmol/l, and the lowest in HbA1c 5.2% (all p-values <0.01). There was a precise reverse order in the proportion of subjects above the cut-off (all p-values <0.05).

The distribution of incident case of DM from subjects with baseline IGT was almost similar between the categories for baseline FPG and baseline HbA1c (Table 1). The proportion of incident case of DM from subjects with baseline IGT was significantly higher in those with baseline HbA1c 5.2% (89%, 31/35)(p-values <0.001) than that in those with baseline FPG 5.56 mmol/l (71%, 25/35) or baseline HbA1c 5.3% (74%, 26/35).

4. Discussion

The FPG is an established predictor of DM and considered as a relevant screening test for DM in the future [9–12]. However, blood sampling at fasting state in the morning is oftentimes difficult to perform in general population. Our study has shown that HbA1c has a similar ability to FPG for evaluating future DM risk and for detecting incident cases of DM, especially from the group of subjects with IGT at baseline. Obtained data also demonstrated that 2 h PG on an OGTT had a slightly better predictability for future DM than FPG or HbA1c, which is partly accordance with European reports [9,10]. However, its use as an initial screening test is unrealistic. In the screening at non-fasting state, HbA1c could be practically

and efficiently used to identify subjects at high-risk for DM who should be targeted for intensive prevention intervention.

The 2 h PG depends on insulin secretary capacity of pancreatic beta cells, peripheral insulin sensitivity, and hepatic glucose output and uptake whereas FPG largely depends on hepatic glucose production. While HbA1c reflects glucose metabolism over the past 1–2 months [16], can be converted into the estimated average glucose levels [20], has smaller variability than FPG and 2 h PG [21], and is closely correlated with post-load glucose in its low range and correlated with FPG in its high range [22]. Thus, HbA1c could cover a wider range of pathophysiological processes of DM than FPG. In our study, HbA1c showed almost the same overall predictability for DM in the future as FPG. In some previous studies, HbA1c seemed to be inferior to FPG with respect to the risk prediction and detection [11,12]. This might partly be due to the application of ADA criteria for the diagnosis of DM [11,12]. In our data, 70% of new cases of DM was identified by isolated 2 h PG (data not shown) and these subjects would not be identified as DM by the ADA criteria. In our country, HbA1c ≥6.5% has been used as a supportive test for the diagnosis of DM for past 10 years [23]. The International Expert Committee appointed by the ADA, the European Diabetes Association for the Study of Diabetes, and the International Diabetes Federation has recommended diagnosing DM by using HbA1c, since June 2009 [24]. Moreover, HbA1c has been provided a treatment target for patients with DM in many organizations including JDS [23]. Thus, HbA1c could be used in different stages of the diseases: screening, diagnosis and treatment. Meanwhile, HbA1c measurement by enzymatic method (Arkray, Kyoto) has become possible at a reasonable cost [25]. This satisfactorily correlates with HbA1c measurement by the HPLC method, does not need standardization, and is more economical than it measurement by HPLC method. This might be a rationale for recommending HbA1c in evaluating future DM risk.

Recently, we have shown that FPG ≥5.56 mmol/l is the better predictor than metabolic syndrome or a constellation of cardiovascular risk factors except for FPG ≥5.56 mmol/l regardless of abdominal adiposity in the Funagata Study [26]. The same trend was obtained when HbA1c ≥5.3% replaced FPG ≥5.56 mmol/l (data not shown). This highlighted glucose itself as the screening test for DM in the future. In our data, HbA1c 5.3% corresponded to FPG 5.56 mmol/l for predicting DM (Fig. 1 and Table 2) and both cut-offs identified similar risk of DM (Table 1) and had equal detection rate of DM, especially from the group of subjects with baseline IGT (Tables 1 and 2). On the other hand, the proportion of people above the cut-off was significantly lower in HbA1c 5.3% than FPG 5.56 mmol/l. Thus, HbA1c 5.3% rather than FPG 5.56 mmol/l might be efficient to identify those targeted for intensive intervention. Since the decision of the screening cut-off is tentative, the cut-off for HbA1c applied in Japan of 5.2% [8] might be too low in our study subjects. Since HbA1c 5.2% could identify significantly more incident cases from those with IGT than FPG 5.56 mmol/l or HbA1c 5.3%, the use of HbA1c 5.2% would make markedly high proportion of subjects (= one third of the entire screened population) who would be followed by intensive intervention.

There are limitations in our study. First, despite concerted efforts to maximize follow-up, the participation rate at 5-year of follow-up was 60%, which, although comparable to other studies of this nature, could potentially bias our results. When comparing baseline characteristics between those who did and did not participate in follow-up, the participants were younger and were healthier than non-participants (data not shown). This is in line with the frequent observation of "healthy participants' effect", which has also been reported in other studies [27]. This would lead to an underestimation of the true cumulative incidence in the general population, and thus our results are conservative. Second, the study population is approximately 10-years older than the representative sample of the Japanese general population [7], and this may have influenced our results. The relevance of Japanese cut-off of 5.2% for HbA1c to screen subjects requiring health guidance in the screening program [8] should be further examined in other Japanese studies. Third, FPG and 2 h PG in this population were assessed only once at both baseline and follow-up. The inter- and intra-coefficients of variations in glucose values may have caused some random misclassification in glucose categories [21], and thereby influenced our results. Fourth, the total number of incident cases is too small to obtain conclusive cut-off discriminating risks and performance as the screening between different strata. Fifth, we did not run sex-stratified analysis due to limited number of incident cases but did adjustment by sex. Since the crude proportion of incident case in men was double-folds higher than women, the overall predictabilities of DM based on ROC curve analysis did not differ between sexes for each glucose indicators or not differ across three glucose indicators in both

Table 2 – Performance (%) [95% confidence interval] of cut-offs on three glucose indicators for predicting DM at 5-year follow-up.

Variables	Cut-offs	Number (%)	% Sensitivity	% Specificity	100-Positive predictive value (%)	100-Negative predictive value (%)
FPG	5.56 mmol/l	233 (19.6)	61.4 [48.8–74.0]	82.5 [80.3–84.7]	85.0 [80.4–89.6]	2.3 [1.4–3.3]
2 h PG	7.80 mmol/l	136 (11.4)	61.4 [48.8–74.0]	91.1 [89.4–92.7]	74.3 [66.9–81.6]	2.1 [1.2–3.0]
HbA1c	5.1%	490 (41.2)	86.0 [76.9–95.0]	61.0 [58.2–63.9]	90.0 [87.3–92.7]	1.1 [0.4–1.9]
	5.2%	360 (30.3)	73.7 [62.3–85.1]	71.9 [69.3–74.5]	88.3 [85.0–91.6]	1.8 [0.9–2.7]
	5.3%	170 (14.3)	56.1 [43.3–69.0]	87.8 [85.9–89.7]	81.2 [75.3–87.1]	2.5 [1.5–3.4]
	5.4%	113 (9.5)	45.6 [32.7–58.5]	92.3 [69.3–74.5]	77.0 [69.2–84.8]	2.9 [1.9–3.9]

FPG: fasting plasma glucose, 2 h PG: 2 h plasma glucose.

sexes (data not shown). Sixth, the application of micro- and macro-vascular complication as the hard end point was not unable in the current study. However, notwithstanding the limitations, our study has notable strengths, being population-based, consisting of both men and women, having FPG and 2 h PG to enable rigorous biochemical diagnosis of DM based on either FPG or 2 h PG criteria and a well-phenotyped sample at baseline and follow-up.

In conclusion, HbA1c can be practically used to screen high-risk of future DM in a general Japanese population. It could also effectively be used in association with IGT who could be targeted for intensive prevention intervention.

Conflicts of interest

The authors declare that they have no conflict of interest.

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