Risk for Future Diabetes among Individuals with High-normal Glycemia at 40 Years of Age

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Abstract

Objective The present study investigated the risk for future diabetes among individuals with high-normal glycemia (fasting plasma glucose (FPG) of 100-109 mg/dL) in an early middle-aged population.

Methods We retrospectively observed a workplace cohort all aged 40 and followed the incidence of diabetes according to the FPG levels at baseline. A total of 901 non-diabetic males were included in the analysis. The 10-year cumulative incidence of diabetes was calculated. The hazard ratios of developing diabetes were calculated using a Cox proportional hazards regression.

Results The proportions of those with high-normal glycemia and impaired fasting glucose (IFG) (FPG of 110-125 mg/dL) at baseline were 21.5% and 4.7%. The 10-year cumulative incidence of diabetes was 14.7% and 48.9%, respectively, in these individuals. After adjustment for possible confounders, the hazard ratios of developing diabetes among individuals with high-normal glycemia and IFG were 5.2 (95% CI=2.4-11.2) and 21.3 (95% CI=9.2-49.5) relative to those with an FPG of <90 mg/dL.

Conclusion High-normal glycemia is a risk for future diabetes even in the relatively young and healthy workplace population. Although the relative risk is much higher in those with IFG, the absolute number of incident diabetes developing from those with high-normal glycemia seems to be considerable given the prevalence of this condition.

Key words: fasting plasma glucose, high-normal glycemia, impaired fasting glucose, risk for future diabetes

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Introduction

The definition of impaired fasting glucose (IFG) is not consistent worldwide. According to the American Diabetes Association (ADA) criterion, IFG is defined as fasting plasma glucose (FPG) levels of 100 to 125 mg/dL, whose threshold was lowered in 2003 for a better prediction of future diabetes (1). On the other hand, other organizations, including the European Diabetes Epidemiology Group and the Japan Diabetes Society (JDS) retain the original diagnostic range for IFG at FPG of 110 to 125 mg/dL (2, 3). The risk for future diabetes among those with an FPG of 100 to 109 mg/dL, who were categorized in different ways across organizations, remains controversial. Several population-based studies from different ethnic groups have reported that FPG

levels of 100 to 109 mg/dL are associated with an increased risk for future diabetes (4-13). However, most studies were performed among older adults. It therefore remains unclear whether or not the evidence holds true for the early middle-aged population, since aging is a potent risk factor for diabetes and can modify the association between the FPG levels and the risk for future diabetes.

Recently, Japan has implemented an annual special health screening (*tokutei kenshin*) and health counseling (*tokutei hoken shidou*) system. Under this system, everyone aged 40 years old or older is required to undergo an annual special health checkup focusing on metabolic syndrome. If they are diagnosed as being at high-risk for metabolic syndrome, health guidance regarding lifestyle modification is provided (14). As a result of the implementation of this system, an increased number of people are being found to have an

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FPG of 100 to 109 mg/dL at the age of 40. According to the JDS, these people are categorized as having “high-normal” glycemia (15). However, a practical estimate of developing diabetes among those with high-normal glycemia in the early middle-aged population has not been provided yet. There is a high demand for a new study estimating the incidence and the risk for developing diabetes among early middle-aged individuals with high-normal glycemia.

In the present study (the Tokyo Businessman Study), we retrospectively observed one Japanese workplace cohort, all who were 40 years of age, and followed the incidence of diabetes in this population for more than 10 years. We next examined whether or not those with high-normal glycemia at 40 years of age are at an increased risk for future diabetes.

Materials and Methods

The data from the annual health checkup program conducted by Marubeni Corporation, which is one of the largest trading companies in Japan, from October 1989 to June 2011 were obtained. The data included information on the results of the Marubeni Corporation employees’ annual health checkups. Males who underwent the medical checkup at 40 years of age between October 1989 and March 2000 were selected from the data set. A total of 937 individuals were included in the cohort. Of these 937 individuals, we excluded 26 individuals who had diabetes (FPG levels ≥ 126 mg/dL or treating diabetes) and 10 individuals with missing data at baseline. Finally, 901 non-diabetic individuals who were all 40 years of age at baseline were included in the present study.

The cohort was categorized into four groups according to the FPG level at baseline (<90 mg/dL, 90-99 mg/dL, 100-109 mg/dL, or 110-125 mg/dL). The follow-up for incident diabetes was based on the annual health checkup data. Follow-up began on the date of the health examination at the age of 40. The data in the present study were collected by June 2011. The follow-up was completed at the last examination date or the date of a diagnosis of diabetes, whichever came first. The endpoint was the development of diabetes, which was defined as self-reported diabetes and/or an FPG of 126 mg/dL or higher.

The study protocol followed the Japanese Government’s ethical guidelines for epidemiological research. It was reviewed and approved by the ethics committee of Saiseikai Central Hospital.

Statistical analysis

The baseline characteristics of the patients are shown after they were stratified into the four categories based on the FPG levels. The differences across the FPG categories were examined using a one-way analysis of variance (ANOVA). Multiple comparisons were conducted using Scheffe’s test. The frequency of incident diabetes, person-years and the incidence rate of developing diabetes were calculated. The 10-

year cumulative incidence of diabetes was calculated using the Kaplan-Meier method. Kaplan-Meier curves comparing the cumulative incidence are shown for up to 15 years of follow-up. The log-rank test was used to examine the differences in the incidence of diabetes across FPG categories. Hazard ratios (HRs) of developing diabetes were calculated using a Cox proportional hazards regression analysis with the follow-up time as a dependent time variable.

First, a univariate model was generated that included the body mass index (BMI), systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. All variables except the HDL cholesterol were proven to have a statistical significance of <0.10 . Then, these variables were fitted in a multivariate model with the categorical FPG variable. The proportional hazard assumption of the multivariate model was confirmed by Schoenfeld’s global test, which produced $p > 0.05$. Population-attributable fractions (PAFs) for incident diabetes were calculated as $1 - 1/\sum_{i=0}^k p_i (RR_i)$ (16), where p_i refers to the proportion of each FPG category in the study population and RR_i refers to the relative risk of incident diabetes when comparing each FPG category with the FPG category of <90 mg/dL. Regarding the relative risk of each FPG category, the multiple-adjusted hazard ratio was used in the calculation. All analyses were performed using the STATA software program (version 11; StataCorp, Texas, USA).

Results

Table 1 shows the baseline characteristics of the study participants at the age of 40 years, groups according to their FPG levels. Among the 901 non-diabetic individuals, the proportions of those with an FPG of 110-125 mg/dL and those with an FPG of 100-109 mg/dL were 4.7% (43 subjects) and 21.5% (194 subjects). The FPG levels increased with BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, and triglycerides.

During a median follow-up period of 12.0 years (7.0 years in incident diabetes cases), a total of 87 incident diabetes cases were reported, yielding 10,228 person-years (Table 2).

The Kaplan-Meier curve shows that individuals with increased FPG levels have higher incidence rates of diabetes. The log rank test gave $p < 0.001$ (Figure). The 10-year cumulative incidence of diabetes increased with FPG levels, with percentages of 1.9% (FPG of <90 mg/dL), 3.2% (FPG of 90-99 mg/dL), 14.7% (FPG of 100-109 mg/dL) and 48.9% (FPG of 110-125 mg/dL) of subjects developing diabetes (Table 2).

Table 3 displays the HRs of developing diabetes. In the multivariate model, individuals with an FPG of 100-109 mg/dL and 110-125 mg/dL had an increased risk for developing diabetes, with HRs of 5.2 [95% Confidence Interval (CI)=2.4-11.2] and 21.3 (95% CI=9.2-49.5), respectively, relative to those with an FPG of <90 mg/dL. On the other hand,

Table 1. Baseline Characteristics according to FPG Levels at the Age of 40

FPG(mg/dL)	< 90		90 - 99		100 - 109		110 - 125		Overall ANOVA p value
<i>n</i>	258	(28.6%)	406	(45.1%)	194	(21.5%)	43	(4.7%)	
BMI (kg/m ²)	23.6	(23.2-23.9)	23.8	(23.6-24.1)	24.9	(24.4-25.3)	24.8	(23.8-25.7)	< 0.001
Systolic blood pressure (mmHg)	117	(115-118)	117	(116-118)	122	(120-124)	125	(120-129)	< 0.001
Diastolic blood pressure (mmHg)	76	(75-77)	77	(76-78)	80	(79-82)	83	(80-86)	< 0.001
Total Cholesterol (mg/dL)	194	(190-198)	197	(194-201)	208	(203-213)	213	(204-224)	< 0.001
HDL Cholesterol (mg/dL)	53	(51-54)	52	(51-54)	52	(50-55)	48	(45-52)	0.421
Triglycerides (mg/dL) ^a	107	(100-115)	113	(107-120)	135	(125-147)	179	(148-217)	< 0.001

Data are n (%) or mean (95%CI).

^a Geometric mean

ANOVA: analysis of variance, BMI: body mass index, CI: confidence interval, FPG: fasting plasma glucose, HDL: high-density lipoprotein

Table 2. Incidence of Diabetes according to FPG Levels at the Age of 40

FPG categories (mg/dL)	<i>n</i>	Number of incident cases	Time at risk (person-years)	Incidence rate (per 1,000 person-year)	10-year cumulative incidence (%)	(95%CI)
< 90	258	8	3,021	2.6	1.9	(0.7-5.0)
90 - 99	406	21	4,681	4.5	3.2	(1.8-5.8)
100 - 109 (High-normal)	194	37	2,179	17.0	14.7	(10.3-20.9)
110 - 125 (IFG)	43	21	347	60.4	48.9	(34.8-65.4)
Total	901	87	10,228	8.5	7.6	(6.0-9.7)

CI: confidence interval, FPG: fasting plasma glucose, IFG: impaired fasting glucose

Figure. Kaplan-Meier curve estimates of developing diabetes according to FPG levels at the Age of 40.

those with an FPG of 90-99 mg/dL had a non-significant increased risk, with a HR of 1.6 (95% CI=0.7-3.5). A positive trend between the FPG levels and the risk for developing diabetes was also observed (p for trend <0.001). Based on

these HRs in combination with the distribution of the FPG, the PAF of an FPG of 90 mg/dL or more for incident diabetes was 68.0% compared with an FPG of <90 mg/dL. The PAFs of the FPG of 90-99 mg/dL, 100-109 mg/dL and 110-

Table 3. HRs of Developing Diabetes according to FPG Levels at the Age of 40

FPG categories (mg/dL)	Crude HR	(95% CI)	Adjusted HR ^a	(95% CI)	p for trend
< 90	1.0	reference	1.0	reference	< 0.001
90 - 99	1.7	(0.7 -3.8)	1.6	(0.7 -3.5)	
100 - 109 (High -normal)	6.4	(3.0 -13.7)	5.2	(2.4 -11.2)	
110 - 125 (IFG)	23.7	(10.5 -53.7)	21.3	(9.2 -49.5)	

^a Adjusted for BMI, systolic blood pressure, total cholesterol, and triglyceride.

BMI: body mass index, CI: confidence interval, FPG: fasting plasma glucose, HR: hazard ratio, IFG: impaired fasting glucose

Table 4. Studies on the Risk for Developing Diabetes among Individuals with High-Normal Glycaemia

Study	Cohort selection	Sample size M/F	Age at baseline (years)	Follow- up (years)	FPG category of interest (mg/dL)	Incidence rate of diabetes (per 1,000 person-years)
Qiao et al, 2003 (4)	Persons from general population in Finland	3,404 (1,654/1,750)	45-64	10	98-109	5
Balkau et al, 2005 (12)	Persons participating in the French D.E.S.I.R. study	4,452 (2,176/2,276)	30-64	6	100-109	6
Ryu et al, 2006 (13)	Workplace employees in Korea	13,189 (15,079/0)	30-59	4	100-109	13
Kato et al, 2009 (7)	Persons from general population in Omiya, Japan	11,369 (3,315/8,054)	62 ± 6	7	100 - 104 105 - 109	16 30
Noda et al, 2010 (8)	Persons from general population in several cities, Japan	2,207 (821/1,386)	62 ± 5	5	100 - 104 105 - 109	12 30
Oizumi et al, 2011 (9)	Persons from general population in Funagata, Japan	3,413 (1,516/1,897)	56 ± 12	12	101- 105	18
The present study	Workplace employees in Japan	901 (901/0)	40	12	100-104 105-109 100-109	16 19 17

125 mg/dL were 8.2%, 28.7% and 31.1%, respectively.

Discussion

The aim of the present study was to examine the risk for developing diabetes among individuals with high-normal glycemia at the age of 40. As mentioned previously, an increased number of people have been diagnosed to have this condition after the implementation of the annual special health screening system in Japan. However, a realistic risk estimate of developing diabetes among the early middle-aged population is lacking. The novelty of the present study was that we followed a cohort of subjects who were all 40 years of age at baseline for more than 10 years and showed

a pragmatic risk estimate. We demonstrated that the 10-year cumulative incidence of diabetes among those with high-normal glycemia was approximately 15%, which was significantly associated with a 5-fold increase in the risk for future diabetes compared to those with an FPG of <90 mg/dL. Compared with other studies reporting the incidence rate of diabetes among individuals with high-normal glycemia (Table 4), our study showed a consistent result with the studies conducted in Japan and Korea (7-9, 13). Although the average age of participants in each study varied, individuals with high-normal glycemia had a similar incidence of diabetes. This means that high-normal glycemia might be a risk factor for future diabetes, regardless of age. On the other hand, studies performed in European populations (4, 12) have re-

ported a lower incidence of diabetes than those in Japan and Korea. This finding suggests that ethnic differences, which might reflect differences in physical traits or lifestyle choices, could modify the association between the FPG and the risk for future diabetes.

Regarding the relationship between the baseline FPG levels and the risk for future diabetes, a positive and continuous association was observed. In terms of the relative risk for future diabetes, the subjects with IFG had a much higher risk than those with high-normal glycemia. However, as shown in the PAFs, the importance of high-normal glycemia is not negligible. In the present study, the prevalence of high-normal glycemia was higher than that of IFG (21.5% vs. 4.7%). Therefore, if the 10-year cumulative incidence of diabetes in the corresponding categories (15% in those with high-normal glycemia and 49% in those with IFG) were applied to the prevalence, the absolute number of incident diabetes cases in 10 years would be larger in those with high-normal glycemia than in those with IFG. In fact, incident diabetes cases were most frequently observed in the baseline high-normal FPG category (Table 2). Similar findings were also observed in other studies (8, 9).

In the special health counseling system (*tokutei hoken shidou*), health guidance on lifestyle modification is provided to those at high-risk for metabolic syndrome. In terms of the FPG levels, not only those with IFG, but also those high-normal glycemia are considered to be high-risk individuals, which seems rational considering the number of diabetes cases arising from the FPG category of high-normal glycemia.

There are several limitations that should be considered when interpreting the results of the present study. First, the definition of diabetes in the present study was based on a single measurement of FPG or self-reporting, which may involve misclassification. Our definition could also miss those who would have been diagnosed as diabetics if a 2-hour value of the oral glucose tolerance test (OGTT) was available. Although the OGTT is a standard diagnostic method, it is impractical to perform the test for the annual health checkup. In practice, it will be easier and more appropriate to estimate the risk for future diabetes using the FPG without knowing the 2-hour value. Second, there might have been heterogeneity in the cohort because of the long entry period. The study participants were born between 1949 and 1960, a period during which Japanese society changed dramatically in terms of nutrition and public hygiene. Such changes may have had an influence on the incidence of diabetes. To address this point, we further examined the incidence, dividing the cohort into two groups according to their birth years. No significant difference was found in the incidence of diabetes between those born in earlier years and those born later (p for log rank=0.965). Although no difference was observed, the long entry period may have affected how representative the study participants, current early-middle-aged Japanese businessmen, were of the general population. Third, those who did not undergo the health

checkup annually might have brought a bias to the study, which could have led to the underestimation of the cumulative incidence of diabetes. In a total of 87 incident diabetes cases, 14 cases were diagnosed with diabetes after over one year had passed since the previous checkup. If they had not skipped the annual checkup, diabetes would have been diagnosed earlier. Fourth, there could be an issue of generalizability since the study participants were restricted to men. We also analyzed the data on female employees. No effect modification by gender on the association between the FPG levels and the risk for future diabetes was observed (data not shown). However, the number of female employees and incident diabetes cases in females during the same follow-up period was too small to conduct an adequate statistical analysis. Further research is therefore required to confirm the risk in females. Finally, it remains unknown whether the health advice given to those with high-normal glycemia and IFG modulated their risk for future diabetes, which would lead to an underestimation of the result.

In summary, the present study showed that individuals with high-normal glycemia at the age of 40 had a significant increase in their risk for future diabetes. From the perspective of an individual's risk perception, high-normal glycemia without any symptoms may not be considered a serious condition. However, from the viewpoint of public health, the impact of those with high-normal glycemia on the incidence of future diabetes seems to be considerable. The results of the present study provide practical information on the risk for future diabetes, which enables individuals with high-normal glycemia to perceive their risk more realistically. As a next step, an early intervention program directed toward these patients is key for preventing future diabetes.

The authors state that they have no Conflict of Interest (COI).

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