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Diabetes Progression from "High-Normal" Glucose in School Teachers

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Abstract

Objective High-normal, the intermediate category between normal fasting glucose (NFG) and impaired fasting glucose (IFG), was introduced in the criteria of the disordered glucose metabolism in 2008. The aim of this study was to investigate the risk for future incidence of type 2 diabetes of the subjects with high-normal and to examine how other metabolic variables could be useful for their risk stratification.

Methods A historical cohort study was conducted from 2001 to 2008, inclusive, in 4,165 non-diabetic employees at public schools (2,229 men and 1,936 women; age 45.8±5.9 years, range 25-55 years). They were classified at baseline as NFG with fasting plasma glucose (FPG)<100 mg/dL, high-normal with FPG 100-109 mg/dL, and IFG with FPG 110-125 mg/dL. The incidence of type 2 diabetes (defined either by FPG≥126 mg/dL or by receiving treatments) was measured.

Results The cumulative incidence during a mean follow-up of 5.1 years were 16/3,364 (0.5%), 40/613 (6.5%), and 53/188 (28.2%) in subjects with NFG, high-normal, and IFG, respectively. Multivariate-adjusted odds ratios for the incidence were still significant both in high-normal and IFG compared to NFG. Body mass index (BMI) and alanine aminotransaminase (ALT) were associated with the incidence of type 2 diabetes independently of FPG categories ($p<0.05$).

Conclusion The future incidence of type 2 diabetes in subjects with high-normal was significantly higher than in those with NFG in this population. BMI and ALT can improve risk stratification in high-normal subjects.

Key words: impaired fasting glucose, diabetes, prevention

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Introduction

Impaired fasting glucose (IFG), the intermediate category between the normal and diabetic ranges of fasting plasma glucose (FPG), was first introduced by the American Diabetes Association (ADA) (1) and the World Health Organization (WHO) (2) in the late 1990s. IFG is considered as an intermediate stage in the natural history of the disordered glucose metabolism. Indeed, a number of studies to date have demonstrated that subjects with IFG (FPG of 110-125 mg/dL) are at an increased risk for developing type 2 diabetes (3-7).

In 2003, the American Diabetes Association (ADA) reduced the lower limit of IFG from 110 mg/dL to 100 mg/dL to optimize the prediction of future type 2 diabetes (8), although this change has not been supported by the European Diabetes Epidemiology Group (EDEG) (9) and the last WHO/ International Diabetes Federation consultation (10). This lower threshold was also adopted in the international criteria of the metabolic syndrome (11, 12), a clinical entity that can be used as a predictor of type 2 diabetes (13-15). Along with such changes in the upper limit of normal FPG, the Japan Diabetes Society in 2008 declared the recommen-

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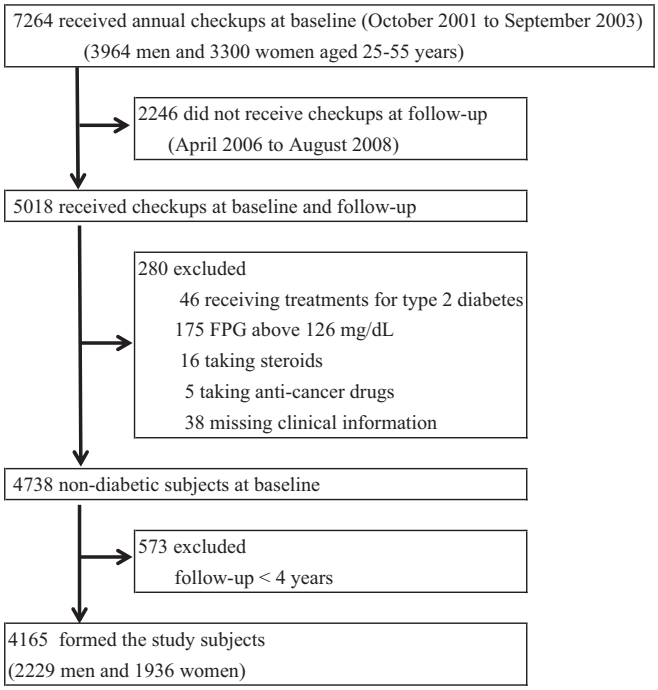

Figure 1. **The study sample.**

dation that subjects with a FPG value of 100 to 109 mg/dL should be classified as "high-normal" and appropriate lifestyle modifications might be implemented (16).

However, there have been only a few longitudinal studies on the progression of type 2 diabetes in Japanese subjects meeting with this new category, high-normal (17-19). They and other investigators have also reported that metabolic variables such as A1c (18, 19), blood pressure (20), liver enzymes (21), and waist circumference (22) predicted the future development of type 2 diabetes independent of FPG levels in non-diabetic subjects. How these predictors other than FPG are associated with type 2 diabetes incidence in each category is not fully known.

The aim of this study, therefore, was to determine the cumulative incidence of type 2 diabetes among middle-aged Japanese men and women with high-normal and with IFG, respectively. We also examined how the combined assessment of FPG levels and other predictors could be useful for risk stratification of these subjects.

Methods

Study subjects

A historical cohort study was conducted in a dataset of the Health Service Department of the Hokuriku Central Hospital where public school employees receive annual medical checkups. We set the baseline period to be between October 2001 and September 2003 and the follow-up period to be between April 2006 and August 2008. During the baseline period, 7,264 persons underwent a checkup at least once during this period (Fig. 1). If subjects received more than one checkup, the initial checkup data were used. During the follow-up period, 9,165 persons underwent at least one checkup. If subjects underwent more than one checkup during the follow-up period, the last checkup data were used. Follow-up data were merged with baseline data, yielding 5,018 persons who had been examined during both periods. Of these, 46 persons receiving treatments for type 2 diabetes or 175 persons with FPG≥126 mg/dL, 16 persons taking steroids or 5 persons on anti-cancer drugs, and 38 with missing clinical information were excluded. Among the remaining 4,738 persons, 573 with <4 years between their baseline and follow-up checkups were excluded, so that, ultimately, 4,165 subjects formed the study sample.

Information on smoking and drinking habits and medical histories was obtained through a questionnaire. Subjects were considered current smokers if they smoked at least one cigarette per day at baseline. Alcohol use was defined by the number of days per week for drinking regardless of its amount. Signed informed consent was obtained from all subjects, and the hospital review board approved the study protocol.

Measurements of anthropometric indices and laboratory assays

All of the evaluations, including the baseline and the follow-up, were performed in the morning at the health check department of the Hokuriku Central Hospital. Subjects were ordered not to take any food or drink after 21:00 on the day before the checkup and to come to the hospital by 8:30 am. Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by nurses. Weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Blood pressure (BP) was measured using an automatic device (Colin Model BP-203RV, Colin, Tokyo, Japan) after at least 5 minutes of rest in a seated position.

Blood samples were drawn after an overnight 12 hour fast and assays were performed in the hospital's laboratory. Plasma glucose (PG) was determined using the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160, Arkray, Kyoto). Triglycerides, high-density lipoprotein (HDL)-cholesterol, alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), and γ-glutamyltransferase (GGT) were measured using enzymatic analytical chemistry (Auto analyzer BioMajesty JCA-BM 1650, JEOL Ltd., Tokyo, Japan). The serum hepatitis B virus surface antigen was detected using an immunoprecipitation method and the presence of the hepatitis C virus antibody was assessed by the recombinant immunoblot assay using commercial kits (Fujirebio, Inc., Tokyo, Japan).

Diagnosis of IFG and diabetes

The diagnosis of high-normal, IFG and type 2 diabetes was based on FPG and treatment information according to the criteria of the Japan Diabetes Society (16). At baseline, the subjects were classified into three categories: normal

Table 1. Baseline Characteristics of the Participants according to the Fasting Plasma Glucose Categories

	Total	NFG < 100 mg/dL	High-normal 100-109 mg/dL	IFG 110-125 mg/dL	p value for trend
	n = 4165	n = 3364	n = 613	n = 188	
Anthropometry					
Age (yrs)	45.8 ± 5.9	45.5 ± 5.9	47.0 ± 5.6	47.8 ± 5.4	<0.001
Male (%)	2229 (53.5)	1671 (49.7)	424 (69.2)	134 (71.3)	<0.001
Body Mass Index (kg/m^2)	23.3 ± 3.1	22.9 ± 2.9	24.5 ± 3.1	25.2 ± 2.9	<0.001
Systolic blood pressure (mmHg)	121.9 ± 16.9	119.9 ± 16.1	129.7 ± 17.3	132.7 ± 18.7	<0.001
Diastolic blood pressure (mmHg)	75.0 ± 11.2	73.7 ± 10.8	79.7 ± 10.6	81.9 ± 12.4	<0.001
Biochemistry					
Fasting plasma glucose (mg/dL)	92.2 ± 9.3	88.9 ± 6.3	103.5 ± 2.9	115.4 ± 4.4	<0.001
AST (U/L)	23.2 ± 10.4	22.5 ± 9.0	24.9 ± 10.6	30.4 ± 22.6	<0.001
ALT (U/L)	25.2 ± 19.6	23.5 ± 16.5	29.6 ± 21.5	41.0 ± 42.6	<0.001
GGT (U/L)	40.9 ± 58.6	36.4 ± 53.6	55.5 ± 66.3	72.2 ± 92.3	<0.001
Triglycerides (mg/dL)	63.0/93.0/137.0	61.0/87.0/129.0	79.5/117.0/172.0	88.3/125.0/175.0	<0.001
HDL-cholesterol (mg/dL)	60.5 ± 15.3	61.5 ± 15.4	55.9 ± 14.1	56.1 ± 14.0	<0.001
Habits and Medications					
Anti-hypertensive drugs	216 (5.2)	152 (4.5)	49 (8.0)	15 (8.0)	<0.001
Lipid-lowering drugs	112 (2.7)	77 (2.3)	28 (4.6)	7 (3.7)	0.004
Current smokers (%)	893 (21.4)	679 (20.2)	154 (25.1)	60 (31.9)	<0.001
Former smokers (%)	592 (14.2)	424 (12.6)	127 (20.7)	41 (21.9)	<0.001
Drinking everyday(%)	965 (23.2)	738 (21.9)	172 (28.1)	55 (29.3)	<0.001
Drinking 1-6 days per week (%)	1020 (24.5)	814 (24.2)	156 (25.4)	50 (26.6)	0.340
Others					
Hepatitis B virus antigen positive	77 (1.9)	65 (2.0)	10 (1.7)	2 (1.1)	0.378
Hepatitis C virus antibody positive	29 (0.7)	24 (0.7)	4 (0.7)	1 (0.5)	0.778

Data are expressed as mean ± SD, 25/50/75th percentile value, or number(%). NFG, normal fasting glucose; IFG, impaired fasting glucose; AST, aspartate aminotransaminase; ALT, alanine aminotransaminase; GGT, γ-glutamyl transferase.

fasting glucose (NFG) with FPG<100 mg/dL; high-normal with FPG of 100-109 mg/dL; and IFG with FPG of 110-125 mg/dL. At the follow-up assessment, incident diabetes was defined as FPG≥126 mg/dL or receiving treatments for type 2 diabetes.

Statistical analysis

The subjects were classified into three FPG categories as described above. Trend tests were performed to compare their characteristics by assigning the median value within each category and by treating the categories as a continuous variable. The cumulative incidence of type 2 diabetes (%) was calculated in each category. Multiple logistic regression analyses were performed to estimate adjusted odds ratios (ORs) for incident diabetes. Following covariates were used; age, sex, BMI, systolic blood pressure, triglycerides, HDL-cholesterol, ALT, smoking (a three-level variable: current, former, never a smoker), alcohol use (a three-level variable: drinking everyday, drinking 1-6 days per week, drinking less than 1 day per week), taking any medications for hypertension (yes or no), and taking any medications for dyslipidemia (yes or no). Since ALT yielded the highest correlation with the diabetes incidence among liver enzymes (ALT, AST, and GGT), we included only ALT in the model to avoid multicollinearity problems. Regarding the covariates that showed independent associations, the risk for type 2 diabetes was determined by joint categories of FPG and such independent predictors. A receiver operating characteristics (ROC) curve for predicting the future incidence of type 2 diabetes was derived by plotting the sensitivity vs. 1-specificity for the baseline FPG in all subjects. All analyses were conducted using SPSS software version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics of the study subjects are shown in Table 1. Of the 4,165 study subjects, 3,364 (80.8%) subjects were NFG, 613 (14.7%) subjects were high-normal, and 188 (4.5%) subjects were IFG at baseline. There were significant trends toward higher age, higher proportions of males, higher BMIs, higher levels of liver enzymes, and other adverse metabolic profile across NFG, high-normal, and IFG categories. Overall, 109 (2.6%) subjects developed type 2 diabetes during a mean follow-up of 5.1 years. Of those, 28 were identified because they were taking medications for type 2 diabetes and 81 were identified based on FPG (≥126 mg/dL). The cumulative incidences of type 2 diabetes were 0.5% in NFG, 6.5% in high-normal, and 28.2% in IFG (Table 2). Adjustments for age, gender, BMI and other metabolic variables still provided significantly elevated odds ratios in both high-normal and IFG relative to NFG. When the logistic regression analyses were conducted in men and women separately, the progression rates of type 2 diabetes from high-normal and IFG were 8.5% and 27.6% in men,

Table 2. Cumulative Incidences and Odds Ratios for the Progression to Type 2 Diabetes during a Mean Follow-up of 5.1 Years by Fasting Plasma Glucose Categories

	Fasting Plasma Glucose		
	NFG	High-normal	IFG
	<100 mg/dL	100-109 mg/dL	110-125 mg/dL
	n = 3364	n = 613	n = 188
Number of incident cases of diabetes (%)	16 (0.5)	40 (6.5)	53 (28.2)
Follow-up period (years)	5.1 ± 0.6	5.2 ± 0.6	5.1 ± 0.6
Unadjusted odds ratio (95% CI)	1.0	14.6 (8.1-26.3)	82.1 (45.8-147.4)
Adjusted odds ratio (95% CI)			
for age and gender	1.0	13.0 (7.2-23.5)	72.5 (40.0-131.4)
for age, gender, and BMI	1.0	10.5 (5.7-19.0)	55.9 (30.7-101.8)
for age, gender, BMI and other metabolic variables*	1.0	10.0 (5.4-18.4)	47.8 (25.7-88.8)

*Metabolic variables were triglycerides, HDL-cholesterol, systolic blood pressure, alanine aminotransaminase, smoking status, alcohol use, taking anti-pertensive drugs, and taking lipid-lowering drugs. NFG, normal fasting glucose; IFG, impaired fasting glucose; CI, confidence interval.

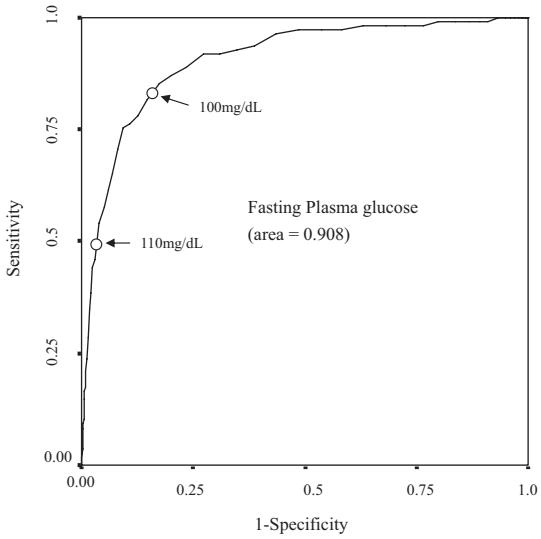

Figure 2. The ROC curve for the baseline FPG to predict the future incidence of type 2 diabetes.

with multivariable-adjusted odds ratios of 10.8 (5.3-21.8) in high-normal and 36.3 (17.4-76.0) in IFG. For women, they were 2.1% and 29.6%, with multivariable-adjusted odds ratios of 6.8 (1.7-27.4) in high-normal and 129.7 (37.6-447.9) in IFG. Figure 2 shows the analysis of the ROC characteristics for the incidence of type 2 diabetes. The cut-off point maximizing the sum of sensitivity and specificity was 100 mg/dL. The sensitivity and the specificity were 47.2% and 96.9% for 110 mg/dL and 83.5% and 83.9% for 100 mg/dL, respectively.

Among the covariates in the multiple logistic regression model, ALT and BMI showed independent associations with the incidence of type 2 diabetes, while triglycerides, HDL-cholesterol, systolic BP, smoking, or alcohol use did not reach statistical significance. The joint analyses of these two independent factors (ALT and BMI) and FPG category for the incidence were shown in Table 3. Tertiles were used for stratifying the levels of ALT and the limitations 23.0 kg/m^2 and 27.5 kg/m^2 were used for BMI according to the recommendations of WHO consultation for the Asian populations (23). Both in high-normal and IFG categories, higher ALT level was associated with an increased risk of type 2 diabetes incidence. Similar results were obtained when the analyses were performed for the 3,975 subjects whose hepatitis B or C marker tests were negative (data not shown). In the joint analysis of FPG category and BMI, higher BMI was associated with an increased risk of type 2 diabetes incidence in NFG and high-normal categories, but in IFG category, the adjusted odds ratios were comparably high among different BMI groups.

Table 3. The Risk for Type 2 Diabetes according to Joint Categories of FPG and Predictors

	FPG		
	NFG	High-normal	IFG
	< 100 mg/dL	109-109 mg/dL	110-125 mg/dL
ALT (U/L)			
Case/n (%)			
tertile 1 (<16)	3/1167 (0.3)	2/115 (1.7)	2/25 (8.0)
tertile 2 (16-24)	2/1179 (0.2)	12/206 (5.8)	9/38 (23.7)
tertile 3 (25≦)	11/1018 (1.1)	26/292 (8.9)	42/125 (33.6)
*Adjusted odds ratio (95% CI)			
tertile 1 (<16)	1.0	5.2 (0.8-31.7)	24.6 (3.8-157.8)
tertile 2 (16-24)	0.5 (0.1-3.2)	14.2 (3.8-53.1)	77.4 (18.8-319.1)
tertile 3 (25≦)	2.3 (0.6-8.8)	17.5 (4.8-64.5)	89.7 (24.8-323.8)
BMI (kg/m^2)			
Case/n (%)			
<23.0	3/1817 (0.2)	7/204 (3.4)	13/48 (27.1)
23.0-27.5	7/1327 (0.5)	22/314 (7.0)	26/105 (24.8)
27.5≦	6/220 (2.7)	11/95 (11.6)	14/35 (40.0)
*Adjusted odds ratio (95% CI)			
<23.0	1.0	16.5 (4.2-65.8)	160.9 (42.6-607.7)
23.0-27.5	2.2 (0.5-8.5)	25.6 (7.3-89.9)	103.6 (29.5-364.3)
27.5≦	7.8 (1.8-33.1)	35.8 (9.2-139.6)	128.5 (31.0-532.0)

*Adjusted for age, gender, triglycerides, HDL-cholesterol, systolic blood pressure, smoking status, alcohol use, taking anti-hypertensive drugs, and taking lipid-lowering drugs, and BMI or ALT. NFG, normal fasting glucose; IFG, impaired fasting glucose; FPG, fasting plasma glucose; ALT, alanine aminotransaminase; BMI, body mass index; CI, confidential interval.

Discussion

In this historical cohort study of middle-aged Japanese men and women during a mean follow-up of 5.1 years, we revealed that 6.5% of the subjects with high-normal (100-109 mg/dL) progressed to type 2 diabetes, with a crude odds ratio of 14.6 (8.1-26.3) compared to NFG. Among the subjects with IFG (110-125 mg/dL), we found 28.2% progressed to type 2 diabetes, with a crude odds ratio of 82.1 (45.8-147.4) compared to NFG. We also showed that ALT and BMI can be utilized to stratify the risk for future incidence of type 2 diabetes in each FPG category. Our results may help clinicians to evaluate the risk of the subjects with high-normal in terms of future incidence of type 2 diabetes.

The future risk of type 2 diabetes progression was significantly elevated from high-normal (100-109 mg/dL) in this study, consistent with prior studies in Japanese subjects (17-19) as well as in Western populations (24, 25). Adjusted odds ratios in high-normal compared to NFG have been reported to be 17.9 in Japanese workers (18), 4.2 in the Kansai Healthcare Study (19), and 3.9 in a Spanish population (26). Although sex and age were different by each cohort, their odds ratios for the incidence of type 2 diabetes in high-normal were consistently significantly elevated compared to NFG. The result of the ROC analysis also showed that the optimal point maximizing its sensitivity and specificity for predicting future diabetes was as low as 100 mg/dL. Given that we assign equal weight to sensitivity and specificity, the lower threshold (100 mg/dL) rather than the original one (110 mg/dL) may be preferred to predict future diabetes.

On the other hand, the prevalence of high-normal was approximately 3 fold that of IFG at baseline in this study. A two- to three-fold higher prevalence has been also reported in other populations including Asians (27). Thus, when introducing high-normal category in clinical settings, its social and economic impacts should be considered, such as the cost of follow-up and distress at being labeled as "abnormal". Moreover, it should be remembered that most studies demonstrating the efficacy of interventions have been carried out in subjects with IGT (28-30), which is not necessarily concordant with IFG even if the lower limit of IFG was reduced to 100 mg/dL (27).

As expected, BMI was an independent predictor for the incidence of type 2 diabetes in subjects with high-normal glucose. Although BMI is generally recognized as an index for overall obesity, we have shown in the previous study that BMI and waist circumference were comparable in the correlation with visceral adipose tissue directly measured by a CT scan in a Japanese population (31). Excess visceral adipose tissue could release several bioactive molecules that affect the action of insulin (32), thereby bringing about systemic insulin resistance and the onset of type 2 diabetes.

ALT facilitated the stratification of the risk of type 2 diabetes incidence in high-normal and IFG; the adjusted odds ratio had more than 3-fold difference between those with the third tertile of ALT and those with the first tertile of ALT. Earlier epidemiological studies in Japanese populations have already reported that liver enzymes predict the incidence of type 2 diabetes independent of BMI or other metabolic variables (21, 33). Since similar results were obtained even after the exclusion of those who were positive for hepatitis B or C virus infection markers in the present study, the elevated liver enzymes are more likely to be interpreted as a marker of fatty change in the liver. Liver fat content is associated with defects in the insulin's suppression of endogenous glucose production (34). ALT may be a useful predictor to identify individuals at higher risk for future diabetes in high-normal subjects.

Several limitations of this study should be considered. First, subjects were not recruited from a community-based sample but from a population engaging in a specific profession (99% of them were school teachers). The total incidence was relatively less compared to prior community-based studies (18, 19). Generalizability of our results should also be examined in other cohort studies. Second, data on subjects who did not receive checkups in the follow-up period was not available, which could have potentially biased our results. When comparing baseline characteristics, the age of the participants who did not receive checkups in the follow-up period was slightly higher than those who did (45.8±6.0 yrs vs. 45.0±6.6 yrs, $p<0.001$) as was their FPG (92.3±9.3 mg/dL vs. 91.7±9.5 mg/dL, $p=0.012$). Subjects who became diabetic may tend to miss checkups, which could lead to an underestimation of the true incidence. Third, the information of family history of type 2 diabetes, physical activity, and dietary habits was not obtained. Finally, the diagnosis of IFG or type 2 diabetes was, like most epidemiological studies, based on only a single evaluation of FPG, while the WHO requires at least two measurements on separate days (35).

In conclusion, this longitudinal study revealed that the future risk of type 2 diabetes progression was significantly elevated from high-normal (100-109 mg/dL) in a Japanese population. The addition of other clinically available variables, such as BMI and ALT, can better stratify diabetes risk.

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