Prevalence of Diabetes Estimated by Plasma Glucose Criteria Combined With Standardized Measurement of HbA_{1c} Among Health Checkup Participants on Miyako Island, Japan

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OBJECTIVE — To estimate the prevalence of diabetes in participants of an annual health checkup in the district of the Miyako Public Health Center (Okinawa, Japan) by using the revised criteria of the Japan Diabetes Society (JDS).

RESEARCH DESIGN AND METHODS — The subjects studied here were all Japanese and 45–75 years of age at the time of the health examination in 1998. Diagnosis of diabetes was based on the following: *1*) fasting plasma glucose ≥7.0 mmol/l, *2*) casual plasma glucose ≥11.1 mmol/l, *3*) HbA_{1c} ≥6.1%, and *4*) self-report on a special questionnaire given at the examination. The HbA_{1c} value was standardized by the measurement of 2 standard samples provided by the JDS.

RESULTS — Among the 2,621 subjects, 59.7% had their fasting blood glucose levels measured. Of the subjects diagnosed as having diabetes, 154 (12.6%) were men and 115 (8.6%) women. Among the subjects newly diagnosed with diabetes from their fasting blood glucose levels, 27.5% of the men and 21.9% of the women had diagnoses based on HbA_{1c} alone. Overall, 34.9% of the subjects with newly diagnosed diabetes were identified by plasma glucose (PG) alone and 33.0% were diagnosed by HbA_{1c} alone.

CONCLUSIONS — The combination of PG and HbA_{1c} resulted in a considerable increase in newly diagnosed diabetes as compared with the use of only one of these parameters. Considering the convenience and correlation with vascular complications, use of the 2 tests may be beneficial in epidemiological studies of the Japanese population to identify high-risk groups for micro- and macrovascular diseases.

Diabetes Care 23:1092–1096, 2000

Type 2 diabetes is a disease associated with lifestyle changes (1,2) as well as genetic predisposition (3). The oral glucose tolerance test (OGTT) has long been the "gold standard" for the diagnosis of diabetes, but it is difficult to perform in a large population study. The usefulness of fasting plasma glucose (FPG) or HbA_{1c} as an alternative means of diagnosis was considered in the Pima Indians (4), and its validity has been intensively argued. Recently, it has been reported that the combined use of FPG and HbA_{1c} in the Chinese population can replace 80% of OGTT use, suggesting the usefulness of HbA_{1c} as a diagnostic criterion in Asian people (5). One of the major problems with measuring glycated hemoglobin is the difference in the methods of assay and the wide variation in the actual values measured (6), suggesting a need for standardization.

In 1997, the American Diabetes Association (ADA) established new criteria for diagnosing diabetes. A major revision of the criteria allowed for the diagnosis of diabetes by FPG alone (7). The Japan Diabetes Society (JDS) has recently revised their diagnostic criteria (8), which coincide with the ADA's criteria in many respects. However, one difference is that the JDS has used HbA_{1c} ≥6.5% as one of the supporting diagnostic criteria. Furthermore, the JDS has announced that HbA_{1c} ≥6.1% can be used for the estimation of the prevalence of diabetes in epidemiological studies, based on the fact that an HbA_{1c} concentration of 6.1% corresponds to both an FPG of 7.0 mmol/l and a 2-h value of a 75-g OGTT of 11.1 mmol/l in Japanese people (9). Before the JDS announcement, the ADA reported a similar correlation between FPG and HbA_{1c}, but it was not included in the diagnostic criteria (7). Assay of HbA_{1c} is widely available in Japan, and the measurement of HbA_{1c} among different laboratories has been standardized by 2 standard samples of HbA_{1c} (5.5 and 10.5%) provided by the JDS (10).

We conducted a diabetes survey in 1998, which was a part of a broader study in a population-based Japanese cohort (Japan Public Health Center–based Prospective Study on Cancer and Cardiovascular Diseases [JPHC Study]) (11). In this survey, we used the JDS's new criteria on plasma glucose (PG) and HbA_{1c} because it was difficult

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Received for publication 19 October 1999 and accepted in revised form 2 May 2000.

Abbreviations: ADA, American Diabetes Association; CV, coefficient of variation; CPG, casual plasma glucose; FPG, fasting plasma glucose; HPLC, high-performance liquid chromatography; JDS, Japanese Diabetes Society; JPHC, Japan Public Health Center; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; PG, plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Prevalence of diabetes classified by age and sex*

	Men				Women			
	Diabetic subjects	Nondiabetic subjects	Total	Prevalence (%)	Diabetic subjects	Nondiabetic subjects	Total	Prevalence (%)
Age (years)								
45–54	13 (6)	131	144	9.0	12 (6)	219	231	5.2
55–64	56 (31)	335	391	14.3	31 (21)	457	488	6.4
65	85 (53)	599	684	12.4	72 (40)	611	683	10.5
Total	154 (93)	1,065	1,219	12.6	115 (67)	1,287	1,402	8.2

Data are *n* or %. Data in parentheses indicate the number of subjects who had a prior diagnosis of diabetes.

to obtain fasting blood samples from all of the participants. We are reporting a pilot study on Miyako Island to estimate the frequency of diabetes as defined by the combined use of these 2 variables.

RESEARCH DESIGN AND METHODS

In the district of the Miyako Public Health Center, all of the residents in Gusukube-cho and Hirara City who were 40–69 years of age on 31 December 1992 were initially registered on the basis of their resident cards. They belonged to part of the JPHC Study cohort (designated as cohort II), and a total of 7,081 men and 7,028 women in this district had been followed up for cancer, cardiovascular disease, and cerebrovascular disease since 1993 (11). Research on diabetes was initiated in 1998, and the subjects in the present study were limited to those who participated in a survey of diabetes simultaneously carried out at the annual health checkup in 1998. It is of note that the participants visited the health examination at their own choice, and therefore, the sampling was not randomized.

Questionnaire and examination

A special questionnaire for diabetes was given at the annual health checkup between 24 July and 20 November 1998. The questionnaire ascertained the following: *1*) family history of diabetes, *2*) experiences on diagnostic examination for diabetes, *3*) age at the diagnosis of diabetes, *4*) hospital(s) where diagnosis or medication was performed, *5*) treatments (diet, exercise, tablets, insulin, or others), *6*) diabetic complications, *7*) maximal body weight in the past and corresponding age, and *8*) physical activities. In the district of the Miyako Public Health Center, brief questions about current medications for hypertension and hyperlipidemia were attached to the questionnaire. Public health nurses assisted with the questionnaire, and written informed consent was obtained at the same time. Annual examination in this district was performed in one laboratory and was composed of anthropometry, blood chemistry (plasma glucose, serum lipids, and others), and urinary tests. Blood examination was performed regardless of current medication for diabetes and, according to the ADA criteria for FPG, the blood samples taken after a >8-h fast were defined as fasting blood samples. All of the fasting samples were taken during the morning session; part of the samples taken during the morning session and all of the samples taken during the afternoon session were casual blood samples. Subjects lacking written informed consent, blood sampling, or information about fasting intervals were excluded from the analysis.

Standardization of HbA_{1c}

The measurement of HbA_{1c} was carried out by high-performance liquid chromatography (HPLC) (Kyoto-Daiichi Kagaku, Kyoto, Japan). Sets of 2 standards corresponding to HbA_{1c} levels of 5.5 and 10.5% were prepared by Kokusai Shiyaku (Kobe, Japan) and were kindly provided by the JDS (10). Each standard was measured 10 times at every change of the apparatus for HPLC columns, including changes of filters and elution buffers. For calibration, averages of the 2 standards were calculated with exclusion of the maximal and minimal values, and actual values of HbA_{1c} were calibrated on the basis of linear regression using the averages for the 2 standards (10). Calibration was renewed 8 times during the examination period. Coefficient of variation (CV) in intra-assay ranged from 0.76 to 1.73% for the HbA_{1c} 5.5% standard and from 0.46 to 1.8% for the HbA_{1c} 10.5% standard. CVs of the average in interassay were 0.6 and 0.5%, respectively.

The sensitivity and specificity of the HbA_{1c} test on the basis of the incidence of diabetic microvascular complications are not available to us. Instead, in another Japanese cohort defined by 1999 JDS diagnostic criteria on a 75-g OGTT, the diabetic group (n = 3,100) and the nondiabetic group (n = 6,121) under 65 years of age were analyzed for the HbA_{1c} test. Those who had current medication for diabetes or had previous gastrectomy were excluded from analysis. HbA_{1c} was measured using the HPLC method since the beginning in 1984 and was calibrated using the standards provided by the JDS (10). The sensitivity and specificity of the HbA_{1c} test for the diagnosis of diabetes were 56.9 and 95.3%, respectively, when the cutoff value was 6.1%. When Japanese subjects younger than 60 years of age were analyzed for the correlation between PG and HbA_{1c} (n = 6,275) (9), a strong correlation was observed in the following linear regression equations: FPG = [-9.5 + 21.9 × HbA_{1c} (%)]/18 (r = 0.852, $P < 0.0001$), and 2-h PG on OGTT = [-125.4 + 53.1 × HbA_{1c} (%)]/18 (r = 0.806, $P < 0.0001$).

Definition of diseases

At the follow-up examination in the JPHC cohort, diabetes was defined by the following: *1*) FPG ≥7.0 mmol/l, *2*) casual plasma glucose (CPG) ≥11.1 mmol/l, *3*) HbA_{1c} ≥6.1%, and *4*) self-reported history of diabetes. Those who met any of these 4 criteria were defined as having diabetes.

Our criteria for hypertension included the following: *1*) systolic blood pressure >140 mmHg, *2*) diastolic blood pressure >90 mmHg, and *3*) taking medication for hypertension. Those who met any of these criteria at the 1998 examination were defined as having hypertension.

Data analysis

A database was constructed with the Japanese version of Microsoft Excel 97 and Access 97 (Microsoft Japan, Tokyo). Statistical analysis was performed with the Japanese version of SAS software (SAS

Table 2—*Plasma glucose and HbA_{1c} values in diabetic and nondiabetic subjects*

	Without diabetes		Newly diagnosed diabetes		Self-reported diabetes	
	n	Means ± SD (range)	*n*	Means ± SD (range)	*n*	Means ± SD (range)
Men						
FPG	664	5.4 ± 0.6 (4.1–6.9)	40	7.6 ± 2.0 (4.6-13.0)	62	8.4 ± 3.0 (5.2–17.6)
CPG	401	6.1 ± 1.2 (3.5–10.7)	21	11.2 ± 3.2 (5.8-18.7)	31	10.9 ± 4.7 (3.8–22.1)
HbA_{1c}	1,065	4.9 ± 0.4 (3.7–6.0)	61	6.4 ± 1.1 (4.9-9.3)	93	6.6 ± 1.6 (4.4–14.2)
Women						
FPG	725	5.2 ± 0.5 (4.2–6.9)	32	7.7 ± 1.2 (5.7-10.7)	42	9.2 ± 2.9 (5.0–20.4)
CPG	562	5.8 ± 1.0 (3.1–10.6)	16	9.3 ± 3.1 (5.8-15.6)	25	9.0 ± 3.2 (5.4–19.9)
HbA_{1c}	1,287	4.9 ± 0.3 (3.8–6.0)	48	6.3 ± 0.9 (4.5-9.3)	67	7.0 ± 1.4 (4.6–12.5)

Data are *n* or means ± SD (range).

Institute Japan, Tokyo), and $P < 0.05$ was considered significant. Mean, SD, and the range of variables were calculated by the univariate procedure. Stepwise logistic regression analysis was used to adjust multiple variables for the estimation of the potential risk factors for diabetes. Entry of a variable into the models was determined by a corresponding P value <0.2.

RESULTS

Prevalence of diabetes in the study participants

A total of 1,219 men (17.2% of the male cohort) and 1,402 women (19.9% of the female cohort) completed the 1998 health examination. A total of 766 men (62.8%) and 799 women (57.0%) had FPG, and the rest of the participants had CPG. The frequency of diabetes is indicated in Table 1. The means and ranges of FPG, CPG, and HbA_{1c} are indicated in Table 2. In every category of age, the frequency of diabetes was higher in men than in women (Table 1). The type of diabetes was not determined specifically, but there were only 8 subjects requiring insulin injections. Six of these patients were diagnosed as having diabetes at 48 years of age or later; the other 2 subjects did not give their ages at diagnosis.

Before the survey, 93 men and 67 women had been diagnosed with diabetes (Table 1); of these, 62 men (66.7%) and 55 women (82.1%) were confirmed by the examination. Among the 31 men and 12 women diagnosed by self-report alone, 37 subjects were currently or previously on medication. In another cohort, we tested the validity of a questionnaire on diabetes similar to the questionnaire in this study. Medical records of about half of 167 subjects with self-reported diabetes were checked after obtaining informed consent from them, and ~95% were confirmed on the basis of the 1985 World Health Organization criteria (Y. Matsumura, M.N., and S. Sasaki, unpublished data). Based on this finding, we speculate that most of the subjects with self-reported diabetes had a correct previous diagnosis.

A total of 61 men and 48 women were newly diagnosed diabetic subjects (Table 3), which was more than one-third of diabetic subjects. Thus, a considerable number of people with diabetes were undiagnosed until the 1998 examination. As shown in Table 3, approximately two-thirds of the newly diagnosed diabetic subjects were diagnosed based on either PG or HbA_{1c} alone. In particular, even in subjects who were newly diagnosed with fasting blood samples, 27.5% of men and 21.9% of women were diagnosed by HbA_{1c} alone, whereas 42.5% of men and 40.6% of women were diagnosed by FPG alone. Thus, the number of newly diagnosed diabetic subjects who had fasting blood sampling and met both of the diagnostic criteria (FPG and HbA_{1c}) was unexpectedly small (30.0% in men and 37.5% in women). Also, the measurement of HbA_{1c} greatly increased the number of diabetic subjects newly diagnosed with casual blood sampling (Table 3). It was reported that plasma glucose values were significantly higher after an oral glucose load than after a mixed meal load (12). Thus, we speculate that CPG (≥11.1 mmol/l) is less sensitive for diagnosing diabetes than the 2-h value of OGTT (≥11.1 mmol/l), and our results suggest that some additional tests may be required for diagnosis with casual blood sampling.

Profiles of diabetic and nondiabetic subjects available from the health examination

The profiles of diabetic and nondiabetic subjects are given in Table 4. When age, BMI, male sex, hypertension, and a family history of diabetes were adjusted in a multiple logistic regression model, these variables were all significantly associated with diabetes, as defined here ($P < 0.01$ for age, BMI, sex, and family history, and $P = 0.027$ for hypertension; detailed data not shown).

CONCLUSIONS

— Our present study shows a frequency of diabetes that was determined by combined use of PG and HbA_{1c}, as well as self-reports. One of the problems was that not all of the subjects had fasting blood samples taken and also that the participants who had given fasting blood samples or casual blood samples were not randomly assigned. CPG is thought to be less sensitive and less reproducible than FPG, and an increase in the number of participants with CPG may lead to lower estimations of the prevalence of diabetes. To minimize the oversight of diabetes, we used HbA_{1c} as an additional diagnostic tool. McCance et al. (4) discussed the benefit of the single measurement of FPG or HbA_{1c} in terms of the incidence and prevalence of diabetes-specific microvascular complications. An additional observation was shown in the ADA's expert committee report (7); FPG, 2-h glucose value on OGTT, and HbA_{1c} had a similar correlation to the prevalence of diabetic retinopathy in the Third National Health

Table 3—*Classification of newly diagnosed diabetic subjects by diagnostic procedures*

	Men				Women			
Sampling	PG alone	HbA_{1c} alone	Both	Total	PG alone	HbA_{1c} alone	Both	Total
Fasting	17 (42.5)	11 (27.5)	12 (30.0)	40 (100)	13 (40.6)	7 (21.9)	12 (37.5)	32 (100)
Casual	7 (33.3)	7 (33.3)	7 (33.3)	21 (100)	1 (6.3)	11 (68.7)	4 (25.0)	16 (100)
Total	24 (39.3)	18 (29.5)	19 (31.1)	61 (100)	14 (29.2)	18 (37.5)	16 (33.3)	48 (100)

Data are *n* (%). Newly diagnosed diabetic subjects were categorized according to the type of blood sampling (fasting blood sampling or casual blood sampling) and on the basis of diagnosis.

Table 4—*Profiles of diabetic and nondiabetic subjects*

Variables	Men (n = 1,219)		Women (n = 1,402)	
	Diabetic subjects	Nondiabetic subjects	Diabetic subjects	Nondiabetic subjects
Age	64.6 ± 6.7 (45–75)	64.2 ± 7.4 (45–75)	64.9 ± 6.4 (47–75)	62.7 ± 7.8 (45–75)
BMI	25.0 ± 2.8 (19.2–40.0)	24.2 ± 3.1 (15.7–39.3)	25.5 ± 3.7 (14.9–36.0)	24.7 ± 3.3 (16.3–38.1)
MXBMI*	27.2 ± 3.2 (21.2–41.0)	26.0 ± 3.0 (19.0–41.4)	28.0 ± 3.5 (18.9–37.6)	26.2 ± 3.2 (18.5–40.6)
sBP	136.1 ± 14.9 (102–190)	134.1 ± 17.4 (90–208)	133.0 ± 16.7 (90–180)	129.0 ± 16.9 (88–210)
dBP	78.5 ± 8.6 (50–100)	78.2 ± 10.6 (40–120)	75.2 ± 11.0 (50–110)	75.7 ± 10.0 (40–116)
Hypertension	61.0	55.0	63.5	47.9
Family history	20.8	7.4	33.0	11.3

Data are means ± SD (range) or %. MXBMI, past maximal BMI; sBP, systolic blood pressure (mmHg); dBP, diastolic blood pressure (mmHg). *MXBMI values of 1 man with diabetes, 10 men without diabetes, and 9 women without diabetes are missing.

and Nutrition Examination Survey (NHANES III). Furthermore, the Diabetes Control and Complications Trial has demonstrated a tight correlation between HbA_{1c} and long-term diabetic complications (13). Based on these findings, HbA_{1c} may reduce the oversight of diabetic subjects who were examined by postprandial blood sampling and were susceptible to diabetic microvascular complications.

We used plasma glucose and HbA_{1c} in combination rather than separately. As a result, 18 of the participants with fasting blood sampling performed were diagnosed by HbA_{1c} alone and did not meet the FPG criterion (Table 3). Defective insulin secretion after glycemic loads is a feature of diabetes in Japanese people (14), and it is likely that some Japanese diabetic subjects exhibit chronic hyperglycemia without an apparent increase in FPG. Therefore, some subjects who would be diagnosed by a 2-h glucose value on OGTT alone and not by FPG were likely to be captured by HbA_{1c} (5). In our present study, sensitivity and convenience of the diagnostic criteria took priority over specificity, but the combined use of FPG and HbA_{1c} may lead to decreased specificity. Further investigation is needed to address this crucial issue.

In our study, the combined use of FPG and HbA_{1c} in subjects with fasting blood sampling resulted in a rise in the number of newly diagnosed diabetic subjects by 33.3% (54–72 subjects). In Japan, a 42% decrease in the frequency of diabetes defined only by FPG (≥7.0 mmol/l) compared with combined use of FPG and 2-h value of 75-g OGTT (FPG ≥7.0 mmol/l or 2-h value ≥11.1 mmol/l) has been reported (15). In that report, the frequency of diabetes decreased from 13.4 to 7.8% in the same sample population when the diagnosis was based on FPG alone. In the NHANES III Study (16), the prevalence of diabetes (previously diagnosed + undiagnosed) was calculated by the combined use of FPG ≥7.0 mmol/l and a 2-h value of a 75-g OGTT of 15.3%, and the prevalence decreased to 12.3% when only the FPG criterion was used for undiagnosed diabetes. Thus, the use of FPG criterion alone decreased the detection of diabetes more in the Japanese study (by 42.2%) than in the NHANES III Study (by 19.6%). Taken together, there may be a significant difference in the features of diabetes among different ethnic groups, and the prevalence of diabetes in Japan may have to be ideally estimated with a 75-g OGTT. The combined use of PG and HbA_{1c} may be an alternative method. In 1997, the Ministry of Health and Welfare in Japan conducted a survey about diabetes in which both HbA_{1c} and a questionnaire were used for diagnosis. The report estimated the number of probable diabetic subjects at 6.9 million (17), but in this regard, it may have considerably underestimated the number of diabetic subjects.

Another problem inherent in our diagnostic criteria for an epidemiological study is a possible oversight of the older diabetic subjects who would be diagnosed by a 2-h value of OGTT and who are at high risk of cardiovascular disease (18). Macrovascular diseases such as myocardial infarction and stroke are not specific for, but are closely associated with, diabetes and causes of death (19). Therefore, identification of the high-risk group for macrovascular complications is important in public health. A recent report has indicated that impaired glucose tolerance, but not impaired fasting glucose, is a risk factor for death from cardiovascular disease in Japanese subjects (20). Thus, FPG may not be an appropriate predictor of Japanese subjects at risk for ischemic heart disease. In the present study, those who did not have increased FPG but had raised HbA_{1c} may be candidates for such a high-risk group. This notion is in part supported by the Framingham Heart Study, which showed a correlation between HbA_{1c} values and ischemic heart disease in women (21).

In summary, we have described a pilot study before the estimation of the prevalence of diabetes in cohort II of the JPHC Study. The combined use of PG and HbA_{1c} in Japanese subjects resulted in a considerable increase in the number of newly diagnosed diabetic subjects as compared with the use of PG or HbA_{1c} alone.

Acknowledgments — This study was supported by health sciences research grants (Research on Health Services, H10-074) and a grant-in-aid for cancer research from the Ministry of Health and Welfare of Japan.

We are indebted to T. Sobue and S. Yamamoto at the National Cancer Center Research Institute for overall management of the study of cohort II as well as for the critical reading of this manuscript; to S. Baba at the National Cardiovascular Center for providing part of the data; and to N. Onga at Miyako Prefectural Hospital and his staff for overall management of the residents' health check programs. We also thank J. Ishihara, F. Furuya, N. Kodera, M. Iizuka, K. Masuda, Y. Yamaguchi, F. Yamada, T. Suda, and M. Ohyama at the National Cancer Center Research Institute for help in data collection.

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