Combined Measurement of Fasting Plasma Glucose and A1C Is Effective for the Prediction of Type 2 Diabetes

The Kansai Healthcare Study

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OBJECTIVE — We prospectively assessed whether the combined measurements of fasting plasma glucose (FPG) and A1C were effective for predicting type 2 diabetes.

RESEARCH DESIGN AND METHODS — Study participants included 6,736 nondiabetic Japanese men aged 40–55 years. Type 2 diabetes was diagnosed in those who had an FPG ≥126 mg/dl or who were being treated with an oral antidiabetic agent or insulin. The models including FPG, A1C, and both were compared using the area under the receiver operating characteristic (AUROC) curves.

RESULTS — During the 4-year follow-up period, we confirmed 659 diabetes cases. In multivariate analysis, both FPG and A1C were independently associated with the risk of type 2 diabetes. The model including both FPG and A1C had a greater AUROC curve than that including FPG alone (0.853 vs. 0.818; $P < 0.001$) or A1C alone (0.853 vs. 0.771; $P < 0.001$).

CONCLUSIONS — The combined measurement of FPG and A1C was effective for predicting type 2 diabetes.

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It is urgently necessary and important to identify individuals who might develop type 2 diabetes in order to prevent and delay its development. A1C has been used as an indicator to monitor glycemic control in patients with known diabetes (1,2). It is not clear whether A1C measurement is useful for detecting subjects with pre-diabetes independent of fasting plasma glucose (FPG). Our specific purposes were *1*) to examine whether both FPG and A1C were independently associated with the risk of type 2 diabetes and *2*) to assess the utility of both FPG and A1C measurements for predicting the incidence of type 2 diabetes using receiver operating characteristic curve analysis.

RESEARCH DESIGN AND METHODS

— The Kansai Healthcare Study is an ongoing cohort investigation designed to clarify the risk factors for cardiometabolic diseases (3,4). The details of the study have been described previously (3,4). The protocol for the Kansai Healthcare Study was reviewed by the human subjects review committee at Osaka City University.

For the current analysis, study participants consisted of 9,116 Japanese men aged 40–55 years with FPG <126 mg/dl who were not taking an oral antidiabetic agent or insulin at study entry. The follow-up examination was conducted annually, and the follow-up period was 4 years. We excluded 2,312 men because of loss to follow-up. Thus, the study population consisted of 6,804 men.

Blood samples were drawn after an overnight 12-h fast. A1C was measured in the same laboratory by high-performance liquid chromatography standardized to the Japan Diabetes Society Committee for the Standardization of Glycohemoglobin, using an HA-8150 automatic glycohemoglobin analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan) (5). The relationship is described by the following regression equation: A1C (%) of the National Glycohemoglobin Standardization Program = 0.0915 × {10.39 × [A1C (%) of Japan Diabetes Society] − 16.8} + 2.15 (6).

Participants were questioned about physical activity including the duration of their walk to work and how often they engaged in leisure-time physical activity. Participants were classified as engaging in regular leisure-time physical activity at least once weekly or less than once weekly. The validation of these questionnaire measures has been described in detail previously (3,4). Regarding smoking habits, participants were classified as nonsmokers, past smokers, or current smokers. Alcohol intake assessed by questionnaire was converted to total alcohol consumption (in grams of ethanol per day) using standard Japanese tables.

Type 2 diabetes at baseline and follow-up examinations was diagnosed in participants who had an FPG ≥126 mg/dl or were taking an oral antidiabetic agent or insulin (7).

We used multiple logistic regression analysis to estimate the odds ratio (OR) for the incidence of type 2 diabetes in relation to baseline variables, and we calculated the 95% CI for each OR. The models including FPG, A1C, and both for predicting type 2 diabetes were compared using the area under the receiver operating characteristic (AUROC) curves. The AUROC curve is used to evaluate clinical utility for predictive models (8,9). It can range from 0.5 (no predictive ability) to 1 (perfect discrimination) (8). A value $0.8 \leq \text{AUROC} < 0.9$ is considered excel-

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Table 1—*ORs of FPG with A1C and AUROC curve for various models to predict incidence of type 2 diabetes*

	Total	Case	Model 1	Model 2	Model 3	Model 4*	Model 5*	Model 6*
All participants								
FPG (mg/dl)								
≤99	4,147	118 (2.8)	1.00	—	1.00	1.00	—	1.00
100–109	1,863	207 (11.1)	4.27 (3.38–5.39)	—	3.50 (2.75–4.45)	4.06 (3.20–5.14)	—	3.28 (2.57–4.18)
110–125	794	334 (42.1)	24.79 (19.68–31.23)	—	16.00 (12.55–20.40)	22.52 (17.73–28.60)	—	14.54 (11.31–18.68)
A1C (%)								
≤4.9 (5.3)†	2,125	63 (3.0)	—	1.00	1.00	—	1.00	1.00
5.0–5.4 (5.4–5.7)†	3,157	204 (6.5)	—	2.26 (1.70–3.02)	1.82 (1.35–2.46)	—	2.11 (1.58–2.83)	1.71 (1.26–2.31)
5.5–5.9 (5.8–6.2)†	1,239	255 (20.6)	—	8.48 (6.37–11.29)	4.87 (3.60–6.58)	—	7.86 (5.86–10.54)	4.50 (3.30–6.14)
6.0–6.4 (6.3–6.7)†	215	90 (41.9)	—	23.57 (16.29–34.09)	11.72 (7.80–17.59)	—	22.50 (15.27–33.13)	11.04 (7.23–16.87)
≤6.5 (6.8)†	68	47 (69.1)		73.25 (41.33–129.83)	33.14 (17.23–63.75)		75.58 (41.66–137.10)	33.58 (16.88–66.78)
AUROC curve of each model (95% CI)			0.818 (0.800–0.837)	0.771 (0.751–0.792)	0.853 (0.836–0.870)	0.831 (0.814–0.849)	0.789 (0.770–0.809)	0.859 (0.842–0.876)
P value for reference‡			Ref.	<0.001	<0.001	<0.001	0.072	<0.001
Stratified analysis according to FPG								
Participants with FPG ≤99 mg/dl								
FPG, per 5 mg/dl			1.29 (1.06–1.58)	—	1.24 (1.02–1.51)	1.27 (1.04–1.56)	—	1.21 (0.99–1.48)
A1C (%)								
≤4.9 (5.3)†	1,568	21 (1.3)	—	1.00	1.00	—	1.00	1.00
5.0–5.4 (5.4–5.7)†	1,955	37 (1.9)	—	1.42 (0.83–2.44)	1.35 (0.79–2.33)	—	1.32 (0.76–2.27)	1.26 (0.73–2.17)
5.5–5.9 (5.8–6.2)†	535	45 (8.4)	—	6.77 (3.99–11.47)	6.43 (3.79–10.92)	—	6.51 (3.76–11.30)	6.17 (3.54–10.74)
6.0–6.4 (6.3–6.7)†	72	10 (13.9)	—	11.88 (5.37–26.30)	11.30 (5.09–25.08)	—	12.21 (5.32–28.00)	11.44 (4.96–26.37)
≤6.5 (6.8)†	17	5 (29.4)		30.69 (9.93–94.89)	31.89 (10.21–99.59)		39.77 (12.17–129.98)	41.63 (12.68–136.72)
AUROC curve of each model (95% CI)			0.581 (0.526–0.636)	0.717 (0.663–0.770)	0.713 (0.659–0.767)	0.672 (0.621–0.722)	0.740 (0.688–0.792)	0.738 (0.686–0.791)
P value for reference‡			Ref.	<0.001	<0.001	0.004	<0.001	<0.001
Participants with FPG ≥100 mg/dl								
FPG, per 5 mg/dl			2.12 (1.95–2.29)	—	1.92 (1.77–2.09)	2.11 (1.94–2.29)	—	1.93 (1.76–2.10)
A1C (%)								
≤4.9 (5.3)†	557	42 (7.5)	—	1.00	1.00	—	1.00	1.00
5.0–5.4 (5.4–5.7)†	1,202	167 (13.9)	—	1.98 (1.39–2.82)	2.01 (1.39–2.90)	—	1.85 (1.29–2.65)	1.87 (1.29–2.71)
5.5–5.9 (5.8–6.2)†	704	210 (29.8)	—	5.21 (3.66–7.42)	4.27 (2.95–6.18)	—	4.83 (3.36–6.93)	3.94 (2.70–5.74)
6.0–6.4 (6.3–6.7)†	143	80 (55.9)	—	15.57 (9.87–24.57)	10.93 (6.72–17.77)	—	14.40 (8.96–23.16)	10.15 (6.12–16.83)
≤6.5 (6.8)†	51	42 (82.4)		57.22 (26.08–125.53)	28.72 (12.58–65.54)		53.29 (23.86–119.03)	25.51 (10.99–59.23)
AUROC curve of each model (95% CI)			0.749 (0.724–0.773)	0.738 (0.714–0.763)	0.804 (0.782–0.825)	0.773 (0.749–0.796)	0.756 (0.732–0.780)	0.814 (0.792–0.835)
P value for reference‡			Ref.	0.970	<0.001	<0.001	0.995	<0.001

Data are *n*, *n* (%), or OR (95% CI) unless otherwise indicated. *Model included age, BMI, smoking habit (nonsmokers, past smokers, and current smokers), regular leisure-time physical activity, daily alcohol consumption (nondrinkers, light drinkers, moderate drinkers, and heavy drinkers), walk to work (0–10, 11–20, ≥21 min), and parental history of diabetes. †A1C of the National Glycohemoglobin Standardization Program is indicated in parentheses. See research design and methods for help converting A1C (%) of the Japan Diabetes Society to that of the National Glycohemoglobin Standardization Program. ‡*P* value compared with AUROC curve of model 1 by the Sidak method.

lent discrimination (10). All *P* values were two tailed. Statistical analyses were performed using Stata SE, version 10.0 (Stata, College Station, TX).

RESULTS — During the 4-year follow-up period, we confirmed 659 cases of type 2 diabetes. The baseline characteristics of the study population are summarized in Table A1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-1631/DC1).

In multiple logistic regression models, FPG was divided into three categories: ≤99, 100–109, and 110–125 mg/dl; and A1C was divided into five categories: ≤4.9, 5.0–5.4, 5.5–5.9, 6.0–6.4, and ≥6.5%. Both FPG and A1C were independently associated with the risk of type 2 diabetes. Even after stratifying participants by FPG (≤99 or ≥100 mg/dl), elevated A1C had an increased risk of type 2 diabetes (Table 1). The Pearson correlation coefficient between FPG and A1C at baseline was not strong ($r = 0.305$; $P < 0.001$). There was no multicollinearity in all models of Table 1 because the variance inflation factor for independent variables was <4.0 (11). There was no interaction between FPG and A1C at baseline.

In the AUROC curve analyses used to predict the incidence of type 2 diabetes, FPG and A1C were treated as continuous variables. In all participants, the model including both FPG and A1C had a greater AUROC curve than those including FPG alone (0.853 vs. 0.818; $P < 0.001$) or A1C alone (0.853 vs. 0.771; $P < 0.001$) (Table 1). After stratifying participants according to FPG, the combined measurement of FPG and A1C was effective to predict type 2 diabetes in each group. After excluding 17 participants who were confirmed as having type 2 diabetes based on use of an oral antidiabetic agent or insulin, we examined all analyses again, and the associations did not change.

CONCLUSIONS — Three prospective studies have reported the utility of A1C in predicting type 2 diabetes (12–14). Of these, two studies did not show whether both FPG and A1C were independently associated with the risk of type 2 diabetes (12,13). Droumaguet et al. (14) showed that A1C was a significant risk factor for type 2 diabetes in French men and women with FPG ≥110 mg/dl, not with FPG <110 mg/dl. In our study, even in those with FPG <100 mg/dl, A1C was associated with an increased risk of type 2 diabetes. This might have been due to ethnicity differences.

A1C is commonly considered to reflect the previous 8–12 weeks' average blood glucose concentrations. Several previous studies in diabetic patients have shown the contribution of FPG and postprandial blood glucose to A1C (15). In the present study, the correlation between A1C and FPG at baseline was not strong; therefore, A1C is not a surrogate marker of FPG. We think that it is effective to use the combined measurement of FPG and A1C to predict type 2 diabetes.

Because all participants were registered employees of the same company and of a single ethnic group, our results may not be representative of the general population but may apply to Japanese-American men and also, possibly, other Asian-American and native Asian men. In conclusion, our results provide evidence that the combined measurement of FPG and A1C is effective for predicting type 2 diabetes.

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