

Metabolic Syndrome is a Poor Predictor of Incident Diabetes Compared with Hemoglobin A1c (HbA1c) in a General Japanese Population

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Abstract

Aims: To evaluate the usefulness of metabolic syndrome (MetS) as a predictor of incident diabetes comparing with other predictors of diabetes including hemoglobin A1c (HbA1c).

Materials and Methods: It is a retrospective five-year follow-up study from annual health examination data in a community including 1,997 Japanese subjects without diabetes at baseline. Logistic regressions using incident diabetes as a dependent variable were calculated for each predictor adjusted for age, sex and drinking status. Area under receiver operating characteristic curves (AUCs) and population attributable risk fractions (PAFs) of incident diabetes were calculated for each predictor.

Results: The odds ratios (95% confidence interval) of incident diabetes for MetS, fasting plasma glucose (FPG) \geq 5.6 mmol/L and HbA1c \geq 6.0% were 5.39 (2.72-10.7), 9.52 (5.08-17.9), and 33.5 (13.0-86.4), respectively. The AUCs (95% confidence interval) of diagnosing incident diabetes for FPG, HbA1c, and MetS were 0.82 (0.76-0.88), 0.89 (0.82-0.95) and 0.63 (0.53-0.72) respectively. The optimal cutoff points of FPG, HbA1c, and body mass index were 5.3 mmol/L, 6.0% and 23.5 kg/m² respectively. The sensitivity and specificity of FPG, HbA1c and MetS for predicting diabetes were 0.67 and 0.80, 0.88 and 0.83, and 0.33 and 0.93, respectively. The PAFs of FPG \geq 5.3 mmol/L, HbA1c \geq 6.0%, and MetS were 59%, 86%, and 27%, respectively.

Conclusions: MetS was a poor predictor of diabetes compared with FPG or HbA1c and A1C was the best predictor of diabetes in a general Japanese population.

Keywords: Diabetes; Metabolic syndrome; Hemoglobin A1c

Introduction

Metabolic syndrome (MetS) [1-6] is considered to be a risk factor of diabetes and cardiovascular disease (CVD). However, its predictive value for diabetes beyond fasting plasma glucose (FPG) per se is questioned [7-9]. The American Diabetes Association and the European Association for the Study of Diabetes criticized that it is antimony that MetS definition includes diabetes if it is a risk factor of diabetes [2]. Even for the purpose of predicting CVD, it may be dangerous for individuals to be diagnosed with MetS [2,3]. Recently, the World Health Organization Expert Consultation Group reported that MetS is a concept that focuses attention on complex multifactorial health problems, but it has limited practical utility as a diagnostic or management tool and there is limited utility in epidemiological studies in which different definitions of MetS are compared [5]. MetS is a pre-morbid condition rather than a clinical diagnosis, and should thus exclude individuals with established diabetes or known CVD [5]. Cameron et al reported that MetS was not a better predictor of diabetes than prediabetes because the risk for incident diabetes among those with prediabetes but not MetS was almost triple that of those with MetS but not prediabetes in a study among Australian adults [9]. On the other hand, the usefulness of hemoglobin A1c (HbA1c) for predicting diabetes has been reported in several studies [10-12]. In the present study, we evaluated the usefulness of MetS as a predictor of incident diabetes comparing with other predictors of incident diabetes including HbA1c in a general Japanese population.

Subjects and Methods

Study subjects

This community-based, retrospective cohort study was based on

annual health examinations at the Niigata Health Foundation [13]. The annual health examination consisted of a medical history, physical examination, blood examination, chest x-ray, and electrocardiography. This report includes 2,153 subjects who took the health examination including FPG and HbA1c in 1998 as a baseline study and subsequently received the examination in 2003. Forty eight subjects who were with diabetes at baseline were excluded. Diabetes was diagnosed as FPG \geq 7.0 mmol/L and HbA1c \geq 6.5% and/or antidiabetic medication according to new criteria of diabetes based on a single blood test recommended by the Japan Diabetes Society. This study was approved by the ethics committees at Tachikawa Medical Center and Niigata University Graduate School of Medical and Dental Sciences.

Measurements

After an overnight fast, blood samples were obtained to measure FPG, HbA1c, triglycerides, high-density lipoprotein (HDL) cholesterol, alanine aminotransferase (ALT), and gamma glutamyltransferase

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(GGT). Blood pressure was measured in supine position after a five minutes rest. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Values of HbA1c are presented as NGSP %.

Definition of MetS

MetS was defined as the clustering of three or more of the following components [4]. 1) high BMI: BMI ≥ 25 kg/m², 2) high BP: systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg and/or antihypertensive medication, 3) high triglycerides: triglycerides ≥ 1.7 mmol/L, 4) low HDL cholesterol: HDL cholesterol < 1.0 mmol/L in men and < 1.3 mmol/L in women, and 5) high FPG: FPG ≥ 5.6 mmol/L. We used BMI instead of waist circumference as an obesity marker because waist circumference was not available. Because of the differences in obesity between Japanese and Western populations, BMI of ≥ 25 kg/m² was used as the cutoff point in contrast to ≥ 30 kg/m² in Western populations according to the criteria of the Japan Society for the Study of Obesity [14].

Statistical analysis

Logistic regressions were performed using incident diabetes as a dependent variable adjusted for sex, age and drinking status. Areas under receiver operating characteristic curves (AUCs) for diagnosing incident diabetes were calculated. Population attributable risk fractions (PAFs) were calculated for each predictor. Statistical analyses were

	diabetes	non-diabetes	p
n	43	1,954	
male sex (%)	37.2	22.9	0.03
age (years)	65.3 \pm 7.6	61.6 \pm 8.9	0.006
fasting plasma glucose (mmol/L)	5.56 \pm 0.56	4.92 \pm 0.48	<0.0001
hemoglobin A1c (%)	6.3 \pm 0.5	5.6 \pm 0.4	<0.0001
body mass index (kg/m ²)	23.9 \pm 2.7	22.6 \pm 2.7	0.002
systolic blood pressure (mmHg)	133.3 \pm 14.0	128.9 \pm 15.5	0.07
diastolic blood pressure (mmHg)	79.8 \pm 11.7	78.0 \pm 10.0	0.3
HDL cholesterol (mmol/L)	1.47 \pm 0.30	1.67 \pm 0.40	0.002
triglycerides (mmol/L)	1.49 \pm 0.74	1.14 \pm 0.73	0.002
alanine aminotransferase (U/L)	26.3 \pm 21.9	19.1 \pm 12.8	0.0004
gamma glutamyltransferase (U/L)	21.7 \pm 15.6	16.7 \pm 18.8	0.08
total cholesterol (mmol/L)	5.74 \pm 0.79	5.62 \pm 0.87	0.4
smoker (%)	14.0	11.0	0.5
everyday drinker (%)	20.9	18.5	0.7
antihypertensive medication (%)	34.9	14.2	0.0002

mean \pm SD or %

Table 1: Baseline data stratified by incident diabetes.

	diabetes	non-diabetes	p
metabolic syndrome	32.6	7.0	<0.0001
high fasting plasma glucose	51.2	9.3	<0.0001
high body mass index	39.5	18.5	0.0005
high blood pressure	62.8	53.3	0.2
high triglycerides	32.6	12.7	0.0001
low HDL cholesterol	18.6	7.8	0.01

*defined as the clustering of three or more of the following components: 1) high body mass index (BMI): BMI ≥ 25 kg/m², 2) high blood pressure (BP): systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg and/or antihypertensive medication, 3) high triglycerides: triglycerides ≥ 1.7 mmol/L, 4) low HDL cholesterol: HDL cholesterol < 1.0 mmol/L in men and < 1.3 mmol/L in women, and 5) high fasting plasma glucose (FPG): FPG ≥ 5.6 mmol/L

Table 2: Prevalence of metabolic syndrome* and its components by incident diabetes.

odds ratio* (95% confidence interval)	p	
fasting plasma glucose	2.23 (1.80-2.76)	<0.0001
hemoglobin A1c	3.67 (2.72-4.96)	<0.0001
body mass index	1.58 (1.19-2.11)	0.002
systolic blood pressure	1.17 (0.86-1.59)	0.3
diastolic blood pressure	1.14 (0.84-1.55)	0.4
HDL cholesterol	0.61 (0.43-0.88)	0.008
triglycerides	1.25 (1.06-1.47)	0.008
alanine aminotransferase	1.21 (1.06-1.39)	0.006
gamma glutamyltransferase	1.15 (0.96-1.38)	0.1

*for 1 SD increment adjusted for age, sex, and drinking status

Table 3: Odds ratios of incident diabetes for numerical variables.

odds ratio* (95% confidence interval)	p	
metabolic syndrome	5.39 (2.72-10.7)	<0.0001
fasting plasma glucose ≥ 5.6 mmol/L	9.52 (5.08-17.9)	<0.0001
body mass index ≥ 25 kg/m ²	2.98 (1.59-5.58)	0.0006
high blood pressure [†]	1.17 (0.61-2.24)	0.6
triglycerides ≥ 1.7 mmol/L	3.07 (1.59-5.92)	0.0008
low HDL cholesterol [#]	1.88 (0.76-4.67)	0.2
hemoglobin A1c $\geq 6.0\%$	33.5 (13.0-86.4)	<0.0001
alanine aminotransferase ≥ 22 U/L	2.05 (1.10-3.83)	0.02

*for the positive status compared with the negative status adjusted for age, sex, and drinking status, [†]systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or antihypertensive medication, [#] < 1.0 mmol/L in men and < 1.3 mmol/L in women

Table 4: Odds ratios of incident diabetes for categorical variables.

performed with Dr SPSS-2 (IBM Japan Inc., Tokyo, Japan). P values of less than 0.05 were considered as significant.

Results

The subjects of this study were 463 men and 1,534 women aged 61.7 \pm 8.8 years at baseline. The means \pm SD of FPG, HbA1c, BMI, systolic BP, diastolic BP, triglycerides, HDL cholesterol, ALT, and GGT were 4.9 \pm 0.5 mmol/L, 5.6 \pm 0.3%, 22.6 \pm 2.8 kg/m², 129 \pm 16 mmHg, 78 \pm 10 mmHg, 1.15 \pm 0.73 mmol/L, 1.66 \pm 0.40 mmol/L, 19.3 \pm 13.1 U/L, and 16.8 \pm 18.8 U/L respectively at baseline. During the follow-up, 43 subjects developed diabetes. Baseline data stratified by incident diabetes (Table 1). The frequency of male sex, age, FPG, HbA1c, BMI, triglycerides, ALT, and the frequency of antihypertensive medication were significantly higher in subjects who developed incident diabetes than in those who did not. HDL cholesterol was significantly lower in subjects who developed incident diabetes than in those who did not. The prevalence of MetS and its components stratified by incident diabetes (Table 2). The prevalence of MetS and its components except for low HDL cholesterol was higher in subjects who developed incident diabetes than in those who did not. Odds ratios (ORs) of incident diabetes for numerical variables (Table 3). The ORs of incident diabetes for FPG, HbA1c, BMI, HDL cholesterol triglycerides, and ALT were significant. The OR of incident diabetes for HbA1c was significantly higher than that for FPG. ORs of incident diabetes for categorical variables (Table 4). The ORs (95% confidence interval (CI)) of incident diabetes for MetS, FPG ≥ 5.6 mmol/L, and HbA1c $\geq 6.0\%$ were 5.39 (2.72-10.7), 9.52 (5.08-17.9), and 33.5 (13.0-86.4), respectively. AUCs of incident diabetes (Table 5). The AUCs (95% CI) of predicting incident diabetes for FPG, HbA1c, MetS, BMI and ALT were 0.82 (0.76-0.88), 0.89 (0.82-0.95), 0.63 (0.53-0.72), 0.66 (0.57-0.74) and 0.60 (0.50-0.69) respectively. The optimal cutoff points and their sensitivity and specificity and the PAFs for incident diabetes (Table 6). The

AUC (95% confidence interval)		p
fasting plasma glucose	0.82 (0.76-0.88)	<0.0001
hemoglobin A1c	0.89 (0.82-0.95)	<0.0001
metabolic syndrome	0.63 (0.53-0.72)	0.004
body mass index	0.66 (0.57-0.74)	0.0005
alanine aminotransferase	0.60 (0.50-0.69)	0.03

Table 5: Area under receiver operating characteristic curves (AUCs) for predicting incident diabetes.

	cutoff point	sensitivity; specificity	PAF*
fasting plasma glucose	5.3 mmol/L	0.67; 0.80	59%
hemoglobin A1c	6.0%	0.88; 0.83	86%
metabolic syndrome		0.33; 0.93	27%
body mass index	23.5 kg/m ²	0.63; 0.66	43%#
alanine aminotransferase	22 U/L	0.42; 0.75	22%

*population attributable risk fractions, #PAF was 25% for body mass index \geq 25 kg/m²

Table 6: Optimal cutoff points (sensitivity; specificity) and PAFs* for incident diabetes.

optimal cutoff points of FPG, HbA1c, BMI and ALT were 5.3 mmol/L, 6.0%, 23.5 kg/m² and 22 U/L respectively. The sensitivity and specificity of predicting incident diabetes for FPG, HbA1c, MetS, BMI, and ALT were 0.67 and 0.80, 0.88 and 0.83, 0.33 and 0.93, 0.63 and 0.66 and 0.42 and 0.75, respectively. The PAFs of FPG \geq 5.3 mmol/L, HbA1c \geq 6.0%, MetS, BMI \geq 25 kg/m², BMI \geq 23.5 kg/m² and ALT \geq 22 U/L, were 59%, 86%, 27%, 25%, 43%, and 22% respectively.

Discussion

In the present five-year follow-up study among a general Japanese population, MetS was a poor predictor of incident diabetes compared with FPG or HbA1c (AUC; 0.63 vs. 0.82 or 0.89) and was comparable to BMI or ALT (AUC; 0.63 vs. 0.66 or 0.60). The PAFs of FPG \geq 5.3 mmol/L, HbA1c \geq 6.0%, and MetS were 59%, 86%, and 27%, respectively. The optimal cutoff point of FPG for predicting incident diabetes was not 5.6 but 5.3 mmol/L (sensitivity and specificity; 0.67 and 0.80, respectively). Thus, HbA1c was superior to MetS as a predictor of diabetes.

The predictive value of MetS for incident diabetes beyond FPG per se is questioned [7-9]. Ford et al reviewed prospective studies examining the association between MetS and incident diabetes [7]. The relative risks of incident diabetes were 3.53-5.17 in various definitions of MetS [7]. AUCs of MetS for predicting incident diabetes were ranging from 0.68 to 0.85; sensitivity ranged from 0.224 to 0.722, and specificity ranged from 0.613 to 0.939 [7]. They concluded that limited evidence suggests FPG alone may be as good as MetS for diabetes prediction and the clinical value of MetS for diabetes prediction remains uncertain though MetS has a stronger association with incident diabetes than that with CVD [7]. Cheung et al. studied the association between MetS and incident diabetes in Chinese subjects and reported that hazard ratios (HRs) (95% CI) for the National Cholesterol Education Program (NCEP) and International Diabetes Federation (IDF) definitions of MetS were 4.1 (2.8-6.09) and 3.5 (2.3-5.29), respectively and HRs (95% CI) for FPG \geq 6.1 and \geq 5.6 mmol/l were 6.9 (4.1-11.5) and 4.1 (2.8-6.0), respectively and that the sensitivity/specificity of NCEP and IDF criteria of MetS for predicting diabetes were 0.419/0.875 and 0.317/0.902, respectively [8]. Cameron et al compared the ability of MetS, a diabetes prediction model (DPM), a noninvasive risk questionnaire, and individual glucose measurements to predict incident diabetes in a five-year longitudinal cohort study among an adult Australian population [9]. In their results,

MetS was not a better predictor of incident diabetes than the DPM or FPG and the risk for diabetes among those with prediabetes but not MetS was almost triple that of those with MetS but not prediabetes [9]. They concluded that a single FPG measurement may be more effective and efficient than published definitions of MetS or other risk constructs in predicting incident diabetes and that diagnosis of MetS did not confer increased risk for incident diabetes independent of its individual components, with an exception for the European Group for the Study of Insulin Resistance definition of MetS in men [9]. In Japanese, Mukai et al reported that the multivariate adjusted HRs (95% CI) of incident diabetes for MetS and FPG \geq 5.6 mmol/l were 2.58 (1.85-3.59) and 3.76 (2.57-5.52), respectively in men and 3.69 (2.58-5.27) and 3.50 (2.45-5.00), respectively in women [15]. The HRs (95% CI) of incident diabetes were 2.37 (1.45-3.88) in subjects with MetS alone, 3.49 (2.57-4.74) in those with FPG \geq 5.6 mmol/l alone, and 6.76 (4.75-9.61) in subjects with both MetS and FPG \geq 5.6 mmol/l compared with those without MetS and with FPG $<$ 5.6 mmol/L [15]. They suggested that MetS significantly increases the risk of incident diabetes independent of FPG, and is therefore a valuable tool to identify individuals at high risk of diabetes, but they did not measure HbA1c and did not calculate AUCs or PAFs of MetS and FPG to compare their ability to predict incident diabetes [15].

In our present study, HbA1c was the best predictor of incident diabetes. HbA1c has been suggested to be superior to FPG for the prediction of vascular disease and death from any cause among nondiabetic subjects [16,17]. Cheng et al studied the diabetes predicting ability of HbA1c and reported that HbA1c increments of 0.5% between 5.0% and 6.4% had adjusted ORs of 1.70 [5.0-5.4%], 4.87 [5.5-5.9%], and 16.06 [6.0-6.4%] when compared with the reference group [HbA1c $<$ 4.5%] in an eight-year follow-up study among 12,375 subjects [10]. Choi et al also evaluated the usefulness of HbA1c as a predictor of incident diabetes and reported that the optimal cutoff point of HbA1c was 5.6% with the sensitivity and specificity of 0.59 and 0.77, respectively in a six-year follow-up study among 9,466 Korean subjects [11]. Heianza et al. reported that diagnosis of prediabetes by both the HbA1c criterion (5.7-6.4%) and the FPG criterion (5.6-6.9 mmol/L) identified individuals with an increased risk of progression to diabetes and the predictive value for progression to diabetes assessed by HbA1c 5.7-6.4% was similar to that assessed by impaired fasting glucose alone in a general Japanese population [12]. Thus, the two tests used together could efficiently target people who are most likely to develop diabetes and allow for early intervention [12].

FPG levels of 5.6-6.9 mmol/L is called impaired fasting glucose and are considered to be a marker of prediabetes. However, in our present study, the optimal cutoff point of FPG for predicting diabetes was not 5.6 but 5.3 mmol/L. Brambilla et al suggested that FPG between 5.1 and 5.5 mmol/L is a strong independent predictor of diabetes and should be used to identify people to be further investigated and aided with preventive measures [18]. Our present results support their suggestion. Individuals with normal fasting glucose (FPG $<$ 5.6 mmol/L) should not be excluded from the target subjects of preventive measures.

In Japanese, the predictive value of MetS for CVD mortality beyond other cardiovascular risk factors is also poor [19-21]. Higashiyama et al reported that the prevalence of smoking was 49.5% and that of MetS was 19.8%, respectively, the HR for CVD incidence compared with non-smoking and non-MetS participants was 2.07 (1.26-3.40) in those who smoked, 2.09 (1.08-4.04) in those with MetS, and 3.56 (1.89-6.72) in those with both, and the PAF of CVD incidence was 21.8% for smoking, 7.5% for MetS, and 11.9% for both in urban Japanese men

[22]. The PAF of CVD mortality due to smoking or hypertension was 35.1% for men and 22.1% for women in NIPPON DATA80, a 19-year follow-up nation-wide study in Japan [23]. Thus, the usefulness of MetS diagnosis is low for either predicting diabetes compared with FPG or HbA1c or predicting CVD compared with hypertension or smoking in Japanese where obesity is not prevailing.

Limitations

Our results are hypothetical because the subjects in the present study were not randomly recruited from the community but recruited because their information about diabetic history and other relevant data were retrospectively available, and the number of subjects was relatively small. We lost original data and have now only incomplete data in 1998 and 2003 where 14,244 subjects were included. However, information about medical history remained in only 1997 subjects and biased regarding sex and age. Accordingly, the present study was based on logistic regression using data at only two time points. Thus, drop-out subjects were ignored. Prospective studies in a large number of randomly recruited subjects from a community through a longer period of follow-up using Kaplan-Meier analysis and Cox proportional hazard model are required to provide confident findings. We used BMI instead of waist circumference as an obesity marker because waist circumference was not available. However, cutoff points of waist circumference have not yet been determined for any ethnic group [4] and BMI and waist circumference are not significantly different as an obesity marker for the clustering of cardiovascular risk factors in a general Japanese population [24].

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Declaration of Competing Interests

Nothing to declare.

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