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Short Communication

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Comparison between Prediabetes Defined by Hemoglobin A1c (A1C) 5.7-6.4% and that Defined by Impaired Fasting Glucose (IFG) in a Japanese Population

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Abstract

Objective: To investigate prevalence and cardiovascular risk profiles of prediabetes defined by hemoglobin A1c (A1C) 5.7-6.4% and that defined by impaired fasting glucose (IFG) in Japanese.

Subjects and Methods: We calculated the prevalence of isolated A1C 5.7-6.4%, isolated IFG, and overlap of A1C 5.7-6.4% and IFG and compared cardiovascular risk profiles of each group in non-diabetic Japanese 2,274 men and 1,417 women.

Results: The prevalence of isolated A1C 5.7-6.4%, isolated IFG, and their overlapping was 6.1%, 11.9%, and 9.5%, respectively in men and 13.3%, 4.0%, and 6.4%, respectively in women. HDL cholesterol (p=0.004 in men and 0.03 in women), systolic blood pressure (p=0.047 in men and 0.0005 in women), and total bilirubin (p=0.0001 in men and 0.013 in women) were significantly lower in subjects with isolated A1C 5.7-6.4% compared with those with isolated IFG.

Conclusions: Overlap of A1C 5.7-6.4% and IFG was not uncommon in Japanese. There were gender differences in the prevalence of isolated A1C 5.7-6.4% and isolated IFG. A1C 5.7-6.4% was associated with lower HDL cholesterol and lower bilirubin.

Keywords: Prediabetes; Hemoglobin A1c; Impaired fasting glucose; HDL cholesterol; Total bilirubin

Introduction

Hemoglobin A1c (A1C) at a range of 5.7-6.4% was proposed as a marker of prediabetes [1] in addition to impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) although the World Health Organisation has not recommended using A1C for diagnosis of prediabetes. A1C was significantly associated with risks of cardiovascular disease (CVD) and death from any cause adjusting for fasting glucose (FG), while FG was not significantly associated with risks of CVD and death from any cause adjusting for A1C in non-diabetic adults [2]. Saukkonen et al reported that overlap between A1C 5.7-6.4%, IFG, and IGT was uncommon and isolated A1C 5.7-6.4% was associated with higher BMI, higher triglycerides, and lower HDL cholesterol compared with isolated IFG among an aging white population [3]. The overlap between A1C 5.7-6.4% and IFG was only 2% in their population [3]. In the present study, we investigated prevalence and cardiovascular risk profiles of prediabetes defined by A1C 5.7-6.4% and that defined by IFG in a Japanese population.

Subjects and Methods

Subjects

Between April 2008 and March 2009, 2,444 men and 1,442 women visited our medical check-up center for health screening and gave informed consent. Excluding diabetic subjects from them, 2,274 men and 1,417 women were the subjects in this study. Diabetes was diagnosed as FG ≥ 7.0 mmol/L, A1C ≥ 6.5% or antidiabetic medication. The protocol for the study was approved by the ethics committee at Tachikawa Medical Center.

Measurements

After an overnight fast, blood samples were obtained to measure blood levels of A1C, FG, triglycerides, HDL cholesterol, LDL cholesterol, high-sensitivity C-reactive protein (CRP), and total bilirubin. High-sensitivity CRP was measured with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). A1C was measured with latex aggregation immunoassay using Determiner HbA1c (Kyowa Medex, Tokyo, Japan). This A1C measuring technique aligned with current recommendations for diagnosis of diabetes by the Japanese Diabetes Society (JDS) and measured A1C values are presented in JDS%. The intra- and inter-assay coefficients of variation were 0.79% and 0.85%. Corresponding values in NGSP% are obtained by adding 0.4 to values in JDS%. In this paper, A1C values are shown in NGSP%. LDL cholesterol was measured with a direct surfactant method using Choletest-LDL (Sekisui Medical Inc., Tokyo, Japan). An average systolic blood pressure (BP) and diastolic BP was calculated from two measurements with the subjects in a sitting position after 5 minutes rest. Waist circumference was measured at the level of the umbilicus in standing position. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

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Statistical analysis

Prevalence of isolated A1C 5.7-6.4% and isolated IFG was calculated and compared by chi-squared tests. Means of cardiovascular risk factors were compared by ANOVA among subjects with isolated A1C 5.7-6.4%, isolated IFG, overlapping A1C 5.7-6.4% and IFG, and normal FG (NFG) and by subsequent Turkey's tests between subjects with isolated A1C 5.7-6.4% and isolated IFG. Triglycerides and high-sensitivity CRP were compared after log transformation. Statistical analyses were performed with Dr SPSS-2 (IBM Japan Inc., Tokyo, Japan). P values of less than 0.05 were considered as significant.

Results

The means (SDs) or the medians (lower to upper quartiles) of FG and A1C were 5.19 (0.48) mmol/L or 5.2 (4.9-5.4) mmol/L and 5.39 (0.29)% or 5.4 (5.2-5.5)%, respectively in men and 4.93 (0.46) mmol/L or 4.9 (4.6-5.2) mmol/L and 5.40 (0.30)% or 5.4 (5.2-5.6)%, respectively in women. The mean FG was significantly higher in men than in women ($p < 0.0001$), but the mean A1C was not significantly different between men and women ($p = 0.127$). Prediabetes data are presented in (Table 1 and Table 2). The prevalence of total prediabetes, isolated A1C 5.7-6.4%, isolated IFG, and their overlapping was 27.5%, 6.1%, 11.9%, and 9.5%, respectively in men and 23.7%, 13.3%, 4.0%, and 6.4%, respectively in women. The prevalence of isolated A1C 5.7-6.4% was significantly lower in men and higher in women than that of isolated IFG. Thus, if A1C was used as the only diagnostic tool instead of fasting glucose, then the prevalence of prediabetes would decrease in men, but increase in women. However, their overlapping was not uncommon. HDL cholesterol (p=0.004 in men and 0.03 in women), systolic blood pressure (p=0.047 in men and 0.0005 in women), and total bilirubin (p=0.0001 in men and 0.013 in women) were significantly lower in subjects with isolated A1C 5.7-6.4% compared with those with isolated IFG in both men and women. Diastolic BP was significantly lower in subjects with isolated A1C 5.7-6.4% compared with those with isolated IFG in women (p=0.0002). Age, BMI, waist circumference, and triglycerides were not significantly different between subjects with isolated A1C 5.7-6.4% and isolated IFG in both men and women. HDL cholesterol was not significantly different between isolated A1C 5.7-6.4% and overlapping A1C 5.7-6.4% and IFG both in men (p=0.96) and women (p=0.95). While total bilirubin was not significantly different between the two groups in women (p=0.999), it was significantly lower in isolated A1C 5.7-6.4% than in overlapping A1C 5.7-6.4% and IFG in men (p=0.039).

Discussion

In contrast to the results reported by Saukkonen et al in an aging white population [3], overlap of A1C 5.7-6.4% and IFG was not uncommon and the prevalence of isolated A1C 5.7-6.4% was

	isolated A1C 5.7-6.4%	isolated IFG	overlapping	NFG	p*
A1C (%)	5.82 (0.13)	5.41 (0.17)	5.92 (0.21)	5.28 (0.21)	<0.0001
FG (mmol/L)	5.17 (0.24)	5.81 (0.28)	5.99 (0.34)	4.99 (0.31)	<0.0001
n (%)	138 (6.1)	271 (11.9)	217 (9.5)	1,648 (72.5)	<0.0001
age (years)	54.8 (9.8)	53.9 (8.5)	56.0 (8.4)	50.3 (9.6)	0.832
BMI (kg/m^2)	24.1 (3.8)	23.9 (2.9)	24.6 (2.8)	22.8 (2.6)	0.884
waist circumference (cm)	86.8 (9.4)	86.7 (7.9)	88.1 (7.6)	83.0 (7.5)	0.998
systolic BP (mmHg)	124 (16.9)	128 (18.4)	127 (18.0)	120 (16.8)	0.047
diastolic BP (mmHg)	78.6 (9.6)	80.8 (10.9)	80.3 (10.7)	76.5 (10.5)	0.183
triglycerides (mmol/L)	1.32 (0.93-1.92)	1.25 (0.90-1.76)	1.45 (1.06-2.01)	1.11 (0.79-1.56)	0.841#
HDL cholesterol (mmol/L)	1.37 (0.33)	1.50 (0.36)	1.39 (0.34)	1.51 (0.37)	0.004
LDL cholesterol (mmol/L)	3.31 (0.78)	3.18 (0.79)	3.28 (0.78)	3.10 (0.75)	0.349
total bilirubin (mmol/L)	12.2 (4.4)	14.9 (6.1)	14.0 (5.4)	14.9 (6.4)	0.0001
high-sensitivity CRP (mg/L)	0.49 (0.27-0.81)	0.35 (0.19-0.63)	0.46 (0.24-0.80)	0.28 (0.15-0.57)	0.136#

Data are presented as means (SD) or medians (interquartile range); FG, fasting glucose; IFG, impaired FG; NFG, normal FG; BP, blood pressure; CRP, C-reactive protein; p*, isolated A1C 5.7-6.4 vs. isolated IFG; # compared after log transformation

Table 1: Cardiovascular risk factors of participants with isolated A1C 5.7-6.4%, isolated IFG, overlapping A1C 5.7-6.4% and IFG, and NFG in men.

	isolated A1C 5.7-6.4%	isolated IFG	overlapping	NFG	p*
A1C (%)	5.82 (0.14)	5.43 (0.14)	5.93 (0.20)	5.29 (0.22)	<0.0001
FG (mmol/L)	5.07 (0.29)	5.75 (0.24)	5.92 (0.34)	4.78 (0.33)	<0.0001
n (%)	188 (13.3)	56 (4.0)	90 (6.4)	1,083 (76.4)	<0.0001
age (years)	56.3 (8.1)	55.7 (9.9)	58.6 (8.6)	49.7 (9.5)	0.981
BMI (kg/m^2)	22.7 (3.7)	22.7 (3.2)	23.3 (4.2)	21.3 (2.8)	0.999
waist circumference (cm)	82.1 (9.2)	81.1 (8.9)	84.4 (10.2)	77.8 (8.0)	0.861
systolic BP (mmHg)	114 (17.6)	124 (19.9)	123 (20.1)	111 (16.0)	0.0005
diastolic BP (mmHg)	70.7 (10.6)	77.1 (11.2)	75.5 (11.7)	69.3 (9.9)	0.0002
triglycerides (mmol/L)	0.98 (0.70-1.30)	0.86 (0.67-1.13)	0.97 (0.77-1.32)	0.79 (0.60-1.05)	0.567#
HDL cholesterol (mmol/L)	1.65 (0.33)	1.81 (0.51)	1.62 (0.37)	1.77 (0.37)	0.030
LDL cholesterol (mmol/L)	3.23 (0.68)	3.34 (0.88)	3.41 (0.68)	3.08 (0.77)	0.853
total bilirubin (mmol/L)	11.2 (3.6)	13.3 (4.0)	11.3 (4.0)	12.6 (4.7)	0.013
high-sensitivity CRP (mg/L)	0.30 (0.16-0.61)	0.21 (0.12-0.44)	0.39 (0.18-0.89)	0.20 (0.10-0.41)	0.344#

Data are presented as means (SD) or medians (interquartile range); FG, fasting glucose; IFG, impaired FG; NFG, normal FG; BP, blood pressure; CRP, C-reactive protein; p*, isolated A1C 5.7-6.4 vs. isolated IFG; # compared after log transformation

Table 2: Cardiovascular risk factors of participants with isolated A1C 5.7-6.4%, isolated IFG, overlapping A1C 5.7-6.4% and IFG, and NFG in women.

significantly lower in men and higher in women than that of isolated IFG in our Japanese population. HDL cholesterol, systolic BP, and total bilirubin were significantly lower in subjects with isolated A1C 5.7-6.4% than those with isolated IFG. But, BMI, waist circumference, and triglycerides were not significantly different between subjects with isolated A1C 5.7-6.4% and isolated IFG in our Japanese population. It may be related with a substantially lower prevalence of obesity in Japanese compared with white populations [4]. The reason why total bilirubin was significantly lower in isolated A1C 5.7-6.4% than in overlapping A1C 5.7-6.4% and IFG in men (p=0.039) was unknown. It may possibly be a chance finding resulted from multiple comparisons.

Mostafa et al compared the two different cutoff points of A1C for prediabetes in a UK population and concluded that A1C 5.7-6.4% was better than A1C 6.0-6.4% in white Europeans, but A1C 6.0-6.4% is a reasonable option in south Asians [5]. In the present Japanese population, the prevalence of isolated A1C 6.0-6.4% and its overlapping with IFG were 1.1% and 3.6% in men and 2.5% and 2.7% in women. From ROC curve analysis, the optimal cutoff point for detecting IFG was A1C ≥ 5.5% (sensitivity/specificity 71.9%/71.4%) in men and A1C ≥ 5.6% (sensitivity/specificity 74.7%/76.1%) in women. Thus, A1C ≥ 5.7% may be better than A1C ≥ 6.0% as the cutoff point of prediabetes. Mann et al reported that the prevalence of isolated A1C 5.7-6.4%, isolated IFG, and their overlapping was 4.9%, 20.5%, and 7.7% in a US population and concluded that clinicians and health systems should understand the differences and similarities in using A1C or IFG in diagnosis of prediabetes [6].

A1C was significantly associated with risks of CVD and death from any cause adjusting for FG, while FG was not significantly associated with risks of CVD and death from any cause adjusting for A1C in non-diabetic adults [2]. The additional CVD risks of A1C beyond FG may be partly contributed by adverse lipid profiles. A1C levels appear to increase with age [7] and will be influenced by any condition that changes red cell turnover [8]. Higher prevalence of A1C 5.7-6.4% in women than men may be partly associated with a relatively anemic state of women compared with men. In case of pre-menopausal women, Koga et al reported that erythrocyte indices are associated with A1C, independently of plasma glucose levels, in pre-menopausal women even when they are not anemic [9]. We reported that total bilirubin was negatively associated with A1C independently of other cardiovascular risk factors in apparently healthy Japanese men and women [10]. Bilirubin is a potent antioxidant in human body [11] and increased serum levels of total bilirubin are reported to be associated with reduced risk for CVD in some epidemiological studies [12-16]. Thus, total bilirubin is suggested to be an independent negative risk factor for CVD.

Heianza et al reported that diagnosis of prediabetes by both A1C 5.7-6.4% and IFG identified individuals with an increased risk of progression to diabetes and the predictive value for progression to diabetes assessed by isolated A1C 5·7-6·4% was similar to that assessed by isolated IFG in a general Japanese population and the two tests used together could efficiently target people who are most likely to develop diabetes [17]. We reported that the odds ratios (95% confidence interval) of incident diabetes for metabolic syndrome (MetS), FG ≥ 5.6 mmol/L, and A1C ≥ 6.0% were 5.39 (2.72-10.7), 9.52 (5.08-17.9), and 33.5 (13.0-86.4), respectively, the areas under receiver operating characteristic curve (95% confidence interval) of diagnosing incident diabetes for FG, A1C, 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 FG and A1C were 5.3 mmol/L and 6.0% respectively, and the population attributable risk fractions of FG ≥ 5.3 mmol/L, A1C ≥ 6.0%, and MetS were 59%, 86%, and 27%, respectively among a general Japanese population [18]. Thus, A1C 5.7-6.4% may be a valuable marker of both future diabetes and CVD.

Limitations

The present study is a cross-sectional one. It is better to study further and for longer time intervals in order to investigate whether people with A1C 5.7-6.4% are most likely to develop future diabetes and CVD. We were unable to study IGT because OGTTs were not performed. The subjects were not randomly recruited from a community but took the health screening tests voluntarily. Thus, they might be more health-conscious than a general population and the present results should be evaluated by future studies in a more general population.

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