# Atherosclerotic Risk Factors in Japanese Subjects With Isolated Impaired Fasting Glucose and Those With Isolated Impaired Glucose Tolerance According to 1997 and 2003 American Diabetes Association Criteria

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Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are different clinical categories of abnormal glucose metabolism (1–3). Both IGT and IFG are similarly associated with increased risk of diabetes, but IGT may be more strongly associated with cardiovascular diseases (4–7). Although insulin secretion and insulin resistance have been shown to differ between these two clinical categories (8,9), mechanisms underlying the differences in the association with cardiovascular diseases are not well determined. There are only a few studies that have tried to identify differences in cardiovascular risk factors among subjects with abnormal glucose metabolism (10–13). The definition of normal glucose tolerance (NGT), IFG, and IGT and the study populations differ among these studies, such that their results do not appear to be uniform.

The aim of this study was to evaluate cardiovascular risk factors in Japanese subjects with IFG and IGT. Two diagnostic criteria defined in 1997 and in 2003 by the American Diabetes Association (ADA) (2,3) were used for the comparison. The measures included pulse-wave velocity (PWV), a noninvasive technique for assessing an aspect of atherosclerosis related to arterial stiffness (14,15).

## RESEARCH DESIGN AND METHODS

— Of 1,934 Japanese subjects who visited the Kinki Central Hospital between April and October 2003 for periodic health examinations, we evaluated 1,541 subjects (955 men and 586 women, aged 30–77 years) after exclusion of subjects with diabetes, malignant diseases, chronic or acute inflammatory diseases, elevated serum creatinine levels ($\geq$106 μmol/l), or autoimmune disorders.

Brachial-ankle PWV (baPWV) was measured with the use of a Waveform analyzer (VaSera VS-1000; Fukuda Denshi, Tokyo, Japan) (16,17) after at least 5 min of rest. In this study, PWV was defined as the mean of right and left baPWV readings.

Laboratory data included single measurements of fasting plasma glucose (FPG), 2-h plasma glucose in a 75-g oral glucose tolerance test (2-h glucose), serum insulin, and lipids. Plasma high-sensitivity C-reactive protein (CRP) was determined by nephelometry. Homeostasis model assessment (HOMA) indexes of insulin sensitivity (HOMA-%S) and β-cell function (HOMA-%β) were estimated by the correct HOMA evaluation (18).

Unadjusted comparisons for continuous variables were performed among groups using ANOVA, and the Bonferroni method was used to estimate the level of significance of differences between means. Comparisons for categorized variables were made using Fisher's exact test. A $P$ value $<0.05$ defined statistical significance.

## RESULTS

— The demographic characteristics of subjects in each group according to 1997 ADA criteria are shown in Table 1 and 2003 ADA criteria in Table 2. In both analyses, there were significant differences between the four groups with respect to variables except for LDL cholesterol.

By both the 1997 and 2003 ADA criteria, subjects with IFG and IGT had higher BMI, FPG, 2-h glucose, logCRP, and systolic and diastolic blood pressure and lower HOMA-%S than subjects with NGT. HOMA-%β were lower in subjects with IFG than in subjects with NGT and IGT.

Age, triglycerides, total cholesterol, and PWV were higher and HDL cholesterol lower in subjects with IGT, unlike in IFG, than in subjects with NGT according to the 1997 ADA criteria. According to the 2003 ADA criteria, age, triglycerides, and PWV were higher and HDL cholesterol lower in subjects with IFG and those with IGT than in subjects with NGT. Total cholesterol was lower in subjects with IGT but not in subjects with IFG.

## CONCLUSIONS

— The present study has shown that according to the 1997 ADA criteria, subjects with IGT, but

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**Abbreviations:** ADA, American Diabetes Association; baPWV, brachial-ankle PWV; CRP, C-reactive protein; FPG, fasting plasma glucose; HOMA, homeostasis model assessment; HOMA-%β, HOMA of β-cell function; HOMA-%S, HOMA of insulin sensitivity; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; PWV, pulse-wave velocity.

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

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Table 1—*Clinical characteristics of 1,541 nondiabetic Japanese subjects categorized into NGT, isolated IFG, isolated IGT, and combined IGT/IFG: 1997 ADA criteria*

| | NGT[1] | IFG[2] | IGT[3] | IGT/IFG[4] | [1] vs. [2] | [1] vs. [3] | [1] vs. [4] | [2] vs. [3] | [2] vs. [4] | [3] vs. [4] | ANOVA *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *n* | 1,188 | 47 | 244 | 62 | | | | | | | |
| Sex (M/F) | 701/487 | 37/10 | 169/75 | 47/15 | 0.01 | 0.004 | 0.01 | 0.26 | 0.90 | 0.39 | — |
| Age (years) | 50.9 ± 6.7 | 52.6 ± 6.5 | 52.8 ± 6.0 | 54.1 ± 5.2 | 0.07 | <0.001 | <0.001 | 0.79 | 0.23 | 0.19 | <0.001 |
| BMI (kg/m$^2$) | 23.2 ± 2.7 | 24.8 ± 3.5 | 24.3 ± 3.0 | 25.4 ± 2.7 | <0.001 | <0.001 | <0.001 | 0.24 | 0.31 | 0.007 | <0.001 |
| Systolic blood pressure (mmHg) | 113 ± 13 | 118 ± 13 | 118 ± 14 | 123 ± 16 | 0.008 | <0.001 | <0.001 | 0.89 | 0.08 | 0.01 | <0.001 |
| Diastolic blood pressure (mmHg) | 72 ± 10 | 77 ± 10 | 75 ± 11 | 77 ± 11 | 0.001 | <0.001 | <0.001 | 0.26 | 0.98 | 0.19 | <0.001 |
| Triglycerides (mg/dl) | 115 ± 70 | 121 ± 54 | 145 ± 84 | 160 ± 100 | 0.63 | <0.001 | <0.001 | 0.04 | 0.007 | 0.17 | <0.001 |
| Total cholesterol (mg/dl) | 211 ± 33 | 216 ± 38 | 216 ± 31 | 220 ± 32 | 0.32 | 0.03 | 0.03 | 0.98 | 0.49 | 0.37 | 0.03 |
| HDL cholesterol (mg/dl) | 59 ± 15 | 58 ± 12 | 56 ± 13 | 58 ± 15 | 0.93 | 0.005 | 0.56 | 0.24 | 0.74 | 0.40 | 0.047 |
| LDL cholesterol (mg/dl) | 130 ± 30 | 133 ± 33 | 132 ± 30 | 133 ± 28 | 0.42 | 0.35 | 0.43 | 0.74 | 0.94 | 0.79 | 0.60 |
| Fasting plasma glucose (mg/dl) | 96 ± 6 | 114 ± 4 | 99 ± 6 | 116 ± 6 | <0.001 | <0.001 | <0.001 | <0.001 | 0.09 | <0.001 | <0.001 |
| 2-h plasma glucose in OGTT (mg/dl) | 109 ± 18 | 116 ± 16 | 158 ± 14 | 161 ± 15 | 0.01 | <0.001 | <0.001 | <0.001 | <0.001 | 0.14 | <0.001 |
| HOMA-%S (%) | 138 ± 65 | 109 ± 45 | 115 ± 67 | 95 ± 37 | 0.003 | <0.001 | <0.001 | 0.56 | 0.26 | 0.03 | <0.001 |
| HOMA-%β (%) | 73 ± 22 | 60 ± 18 | 82 ± 28 | 63 ± 19 | <0.001 | <0.001 | <0.001 | <0.001 | 0.44 | <0.001 | <0.001 |
| logCRP (mg/l) | −0.451 ± 0.402 | −0.305 ± 0.374 | −0.325 ± 0.392 | −0.228 ± 0.428 | 0.01 | <0.001 | <0.001 | 0.76 | 0.32 | 0.09 | <0.001 |
| PWV (m/s) | 12.41 ± 1.54 | 12.64 ± 1.42 | 12.97 ± 1.75 | 13.51 ± 1.79 | 0.32 | <0.001 | <0.001 | 0.20 | 0.005 | 0.02 | <0.001 |

Data are means ± SD unless otherwise indicated. NGT was defined as FPG and 2-h plasma glucose in an oral glucose tolerance test (OGTT) of <110 and <140 mg/dl, isolated IFG 110–125 and <140 mg/dl, isolated IGT <110 and 140–199 mg/dl, and combined IFG/IGT 110–125 and 140–199 mg/dl, respectively.

not IFG, had abnormal serum lipid profiles and higher PWV compared with subjects with NGT. PWV is shown to be influenced by age, blood pressure, diabetes, insulin resistance, smoking, serum creatinine, and triglycerides (15,17,19,20) and to predict future cardiovascular mortality (21). Therefore, differences of this parameter in IFG and IGT may support the association of IGT but not IFG with cardiovascular diseases (4–7).

In contrast, subjects with IFG and IGT similarly had abnormal lipid profiles and higher PWV according to the 2003 ADA criteria. It indicates that IFG and IGT, based on the 2003 ADA criteria, carries strong risks for atherosclerosis. Many subjects classified as NGT and IGT by the 1997 ADA criteria were shifted into IFG and IFG/IGT groups by the 2003 ADA criteria. These were predominantly male subjects, and they could have caused the change in cardiovascular risk. Differences in numbers of IFG subjects (47 vs. 410) according to the two criteria may also influence the statistical analyses.

HOMA-%S was lower in both IFG and IGT compared with subjects with NGT, while HOMA-%β was lower in IFG and rather higher in subjects with IGT. This indicates that there is defective insulin secretion in IFG but not in IGT. These results appear consistent with a study involving Pima Indians (22) but not with other studies (8,9).

CRP, a known marker associated with cardiovascular risk factors (23), was elevated in subjects with IFG and those with IGT according to the 1997 and 2003 ADA criteria. CRP is shown to be related to BMI and insulin resistance (24,25). In our analyses, BMI was higher and HOMA-%S lower in subjects with IFG and IGT. Thus, CRP may more strongly reflect high BMI and increased insulin resistance rather than atherosclerosis per se.

In conclusion, according to the 1997 ADA criteria (also adopted by the Japan Diabetes Society), subjects with IGT, but not IFG, had higher levels of atherosclerotic risk factors than NGT subjects, whereas according to the 2003 ADA criteria, subjects with IFG and those with IGT were fraught with cardiovascular risk. Criteria for the metabolic syndrome include abnormal glucose metabolism, but its definitions differ depending on the organization developing the criteria (26–28). Our results, studying Japanese nondiabetic subjects, suggest that a FPG cutoff level of 100 mg/dl, rather than 110 mg/dl, is suitable for differentiating be-

tween individuals with and those without high atherosclerotic risks.

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**Table 2—*Clinical characteristics of 1,541 nondiabetic Japanese subjects categorized into NGT, isolated IFG, isolated IGT, and combined IGT/IFG: 2003 ADA criteria***

| | NGT[1] | IFG[2] | IGT[3] | IGT/IFG[4] | [1] vs. [2] | [1] vs. [3] | [1] vs. [4] | [2] vs. [3] | [2] vs. [4] | [3] vs. [4] | ANOVA *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *n* | 825 | 410 | 130 | 176 | | | | | | | |
| Sex (M/F) | 440/385 | 301/99 | 87/43 | 129/47 | <0.001 | 0.005 | <0.001 | 0.08 | 0.69 | 0.28 | — |
| Age (years) | 50.4 ± 6.7 | 52.0 ± 6.5 | 53.3 ± 6.6 | 52.8 ± 5.7 | <0.001 | <0.001 | <0.001 | 0.05 | 0.14 | 0.59 | <0.001 |
| BMI (kg/m$^2$) | 22.8 ± 2.7 | 24.1 ± 2.8 | 24.0 ± 3.0 | 24.9 ± 2.9 | <0.001 | <0.001 | <0.001 | 0.57 | <0.001 | 0.002 | <0.001 |
| Systolic blood pressure (mmHg) | 112 ± 13 | 115 ± 13 | 117 ± 14 | 120 ± 14 | <0.001 | <0.001 | <0.001 | 0.17 | <0.001 | 0.05 | <0.001 |
| Diastolic blood pressure (mmHg) | 71 ± 10 | 74 ± 10 | 75 ± 11 | 76 ± 11 | <0.001 | <0.001 | <0.001 | 0.75 | 0.14 | 0.38 | <0.001 |
| Triglycerides (mg/dl) | 108 ± 67 | 131 ± 73 | 144 ± 88 | 151 ± 87 | <0.001 | <0.001 | <0.001 | 0.07 | 0.002 | 0.39 | <0.001 |
| Total cholesterol (mg/dl) | 210 ± 34 | 213 ± 32 | 217 ± 31 | 217 ± 31 | 0.11 | 0.03 | 0.01 | 0.29 | 0.23 | 1.00 | 0.02 |
| HDL cholesterol (mg/dl) | 60 ± 16 | 56 ± 13 | 56 ± 14 | 56 ± 14 | <0.001 | 0.002 | 0.002 | 0.94 | 0.66 | 0.78 | <0.001 |
| LDL cholesterol (mg/dl) | 129 ± 31 | 132 ± 29 | 133 ± 29 | 131 ± 30 | 0.09 | 0.17 | 0.31 | 0.80 | 0.84 | 0.71 | 0.24 |
| Fasting plasma glucose (mg/dl) | 93 ± 4 | 105 ± 4 | 94 ± 4 | 108 ± 7 | <0.001 | 0.02 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| 2-h plasma glucose in OGTT (mg/dl) | 108 ± 18 | 113 ± 18 | 157 ± 14 | 160 ± 15 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.18 | <0.001 |
| HOMA-%S (%) | 148 ± 69 | 114 ± 48 | 128 ± 74 | 98 ± 50 | <0.001 | <0.001 | <0.001 | 0.02 | 0.006 | <0.001 | <0.001 |
| HOMA-%β (%) | 75 ± 22 | 69 ± 21 | 84 ± 30 | 73 ± 24 | <0.001 | <0.001 | 0.45 | <0.001 | 0.05 | <0.001 | <0.001 |
| logCRP (mg/l) | −0.482 ± 0.406 | −0.373 ± 0.384 | −0.356 ± 0.387 | −0.267 ± 0.407 | <0.001 | <0.001 | <0.001 | 0.69 | 0.003 | 0.05 | <0.001 |
| PWV (m/s) | 12.33 ± 1.55 | 12.58 ± 1.50 | 12.94 ± 1.76 | 13.18 ± 1.77 | 0.01 | <0.001 | <0.001 | 0.02 | <0.001 | 0.20 | <0.001 |

Data are means ± SD unless otherwise indicated. NGT was defined as FPG and 2-h plasma glucose <100 and <140 mg/dl, isolated IFG 100–125 and <140 mg/dl, isolated IGT <100 and 140–199 mg/dl, and combined IFG/IGT 100–125 and 140–199 mg/dl, respectively.

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