Association Between Waist-to-Height Ratio and Endothelial Dysfunction in Patients With Morbidity — A Report From the FMD-J Study —

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Background: Waist circumference (WC), waist-to-height ratio (WHtR) and body mass index (BMI) are known as easy anthropometric markers of abnormal obesity and screening tools for predicting cardiovascular outcomes, but which indices are best is unclear. We therefore investigated the superiority and association between each index and low flow-mediated dilatation (FMD) as a surrogate marker for cardiovascular outcomes in patients with morbidity in a large Japanese prospective cohort.

Methods and Results: A total of 1,645 Japanese patients who had coronary artery disease and hypertension or diabetes mellitus were enrolled, and 1,087 of them were analyzed. The high-WHtR group (≥0.5) showed greater morbidity and increased inflammation in association with atherosclerosis compared with the low-WHtR group. High WHtR and advanced age were identified as predictors of low FMD (odds ratio (OR) 1.39, 95% confidence interval (CI) 1.02–1.88, P=0.037 and OR 1.55, 95% CI 1.19–2.01, P=0.001, respectively). However, WC was not associated with that risk in either sex (male: OR 1.37, 95% CI 0.97–1.93, P=0.076; female: OR 1.08, 95% CI 0.68–1.73, P=0.74), and no association was evident between high BMI and low FMD (OR 0.92, 95% CI 0.71–1.19, P=0.54).

Conclusions: WHtR offers a superior predictor of decreased FMD than other anthropometric indices, and progression of atherosclerosis might be detected more sensitively. Further study is needed to investigate the relationship between cardiovascular mortality and WHtR.

Key Words: Body mass index; Endothelial dysfunction; Flow-mediated vasodilatation; Waist circumference; Waist-to-height ratio

Received February 27, 2017; revised manuscript received May 17, 2017; accepted June 6, 2017; released online July 7, 2017
Time for primary review: 35 days

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Obesity, and abdominal adiposity in particular, is related to increased risks of mortality and morbidity. Similarly, recent studies and a systematic review have reported that metabolic syndrome (MetS) causes endothelial dysfunction, oxidative stress, inflammation and is associated with an increased risk of cardiovascular events. Defining optimal cutoffs for waist circumference (WC), which reflects abnormal adiposity and is one of the diagnostic criteria for MetS, appears difficult because of the influences of various factors, such as age, sex, ethnic group, height, and weight. In fact, the current Japanese cutoffs of WC for MetS (85 cm for men; 90 cm for women) remain controversial. Simple anthropometric indices used as markers of abnormal obesity and in screening tools for predicting cardiovascular outcomes include WC, waist-to-height ratio (WHtR) and body mass index (BMI), but which of these works best remains unclear. Atherosclerosis, which leads to cardiovascular disease (CVD) events, is caused by endothelial dysfunction, and because the measurement of flow-mediated dilatation (FMD) is able to clarify endothelial function noninvasively, early detection and treatment of atherosclerosis may be feasible. However, little is known about the comparison of FMD among the anthropometric indices. We therefore investigated the superiority and associations between anthropometric indices and low FMD of the brachial artery as a surrogate marker for endothelial dysfunction (and hence, increased risk of cardiovascular morbidity) in patients with a diagnosis of coronary artery disease (CAD), hypertension or diabetes mellitus (DM) in the Flow-mediated Dilation Japan Registry (FMD-J) study, which recruited a large prospective cohort.

Methods

Study Design and Subjects

The FMD-J study was a prospective multicenter study conducted to examine the utility of FMD assessment using a semi-automatic device at individual institutions in the management of patients at risk of CVD. Groups A and B in that study comprised patients being followed at one of the participating centers (22 university hospitals and affiliated clinics). The ethics committees of the participating institutions approved the study protocol. We obtained written informed consent for participation from all subjects in the FMD-J study.

The study design and patient enrollment of the FMD-J have been described in detail. A total of 1,645 Japanese patients who had CAD (n=679 from Study A) or hypertension or DM (n=966 from Study B) who gave informed consent for their vascular function to be measured were enrolled in the FMD-J Registry between 1 April 2010 and 31 August 2012 at 3 hospitals in Japan. We excluded subjects for whom measurements of WC were unavailable. The final study population was 1,087 patients for this analysis (Figure).

Definitions

The meta-analysis showed that the area under receiver operator characteristic analyses indicated that mean boundary values for WHtR, covering all cardiometabolic outcomes, from studies in 14 different countries and including Caucasian, Asian and Central American subjects, were 0.5 for men and 0.5 for women. For this reason, we adopted 0.5 as the cutoff point of WHtR.

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure ≥90 mmHg in a seated position on at least 3 different occasions. We excluded patients with secondary hypertension. Diabetes was defined according to the criteria of the American Diabetes Association. CAD included angina pectoris, unstable angina and myocardial infarction. Unstable angina was defined as present if a history of prolonged ischemic chest pain (>15 min in duration) was observed with transient ischemic ST-segment and T-wave abnormality on ECGs without development of Q-wave abnormality or elevation.
of serum enzyme with myocardial necrosis. Framingham Risk score was computed using the following risk factors: age, total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, SBP and smoking status. Definitions of other diseases were as previously reported.12

### Measurement of FMD

All measurements were taken in the morning, after over-

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**Table 1. Baseline Characteristics of Study Patients Subdivided by WHtR <0.5 vs. ≥0.5**

| Variables                                | All (n=1,087) | WHtR <0.5 (n=234) | WHtR ≥0.5 (n=853) | P value |
|-------------------------------------------|---------------|-------------------|-------------------|---------|
| Age (years)                               | 61.9±9.3      | 60.8±9.95         | 62.2±9.10         | 0.054   |
| ≥65 years                                 | 462 (43)      | 87 (37)           | 375 (44)          | 0.063   |
| Male (n (%))                              | 715 (66)      | 153 (65)          | 562 (66)          | 0.89    |
| BMI (kg/m²)                               | 24.9±3.7      | 21.7±2.82         | 25.8±3.41         | <0.0001 |
| Waist (cm)                                | 88.0±10.3     | 76.0±6.6          | 91.3±8.5          | <0.0001 |
| Height (cm)                               | 161.8±8.7     | 163.0±8.9         | 161.5±8.6         | 0.018   |
| WHtR                                      | 0.54±0.06     | 0.47±0.03         | 0.57±0.05         | <0.0001 |
| Systolic BP (mmHg)                        | 133.7±15.3    | 134.1±15.3        | 133.6±15.3        | 0.64    |
| Diastolic BP (mmHg)                       | 78.8±10.9     | 78.8±10.9         | 78.8±10.9         | 0.75    |
| Heart rate (beats/min)                    | 71.3±12.4     | 71.5±13.9         | 71.2±12.0         | 0.81    |
| Total cholesterol (mmol/L)                | 4.93±0.87     | 5.02±0.86         | 4.91±0.86         | 0.091   |
| Triglycerides (mmol/L)                    | 1.23 (0.87–1.75) | 0.95 (0.73–1.36) | 1.32 (0.94–1.84) | <0.0001 |
| HDL-C (mmol/L)                            | 1.44±0.39     | 1.67±0.46         | 1.38±0.35         | <0.0001 |
| LDL-C (mmol/L)                            | 3.20±0.79     | 3.12±0.78         | 3.22±0.79         | 0.071   |
| Glucose (mmol/L)                          | 5.61 (5.22–6.23) | 5.42 (5.17–5.83) | 5.67 (5.28–6.39) | <0.0001 |
| Uric acid (mg/dL)                         | 5.81±1.35     | 5.48±1.35         | 5.90±1.33         | <0.0001 |
| eGFR (mL/min/1.73m²)                      | 75.0±18.3     | 77.7±18.8         | 74.2±18.1         | 0.009   |
| Framingham risk score                     | 6.04±3.00     | 5.42±0.20         | 6.21±2.92         | 0.0006  |
| Hypertension (n (%))                      | 1,037 (95)    | 209 (89)          | 828 (97)          | <0.0001 |
| Dyslipidemia (n (%))                      | 535 (49)      | 85 (36)           | 450 (53)          | <0.0001 |
| Diabetes mellitus (n (%))                 | 169 (16)      | 17 (7.3)          | 152 (18)          | <0.0001 |
| Cardio- and cerebrovascular disease (n (%)) | 366 (34)  | 63 (27)          | 303 (36)          | 0.014   |
| Current smoking (n (%))                   | 150 (14)      | 41 (18)           | 109 (13)          | 0.061   |
| Chronic kidney disease (n (%))            | 190 (17)      | 28 (12)           | 162 (19)          | 0.012   |
| Flow-mediated vasodilatation (%)          | 4.48±2.59     | 4.86±2.74         | 4.38±2.54         | 0.011   |
| Baseline brachial artery diameter (mm)    | 4.16±0.63     | 4.02±0.58         | 4.20±0.65         | 0.0002  |
| Mean ankle-brachial index                 | 1.14±0.08     | 1.14±0.07         | 1.15±0.09         | 0.41    |
| hs-CRP (mg/mL)                            | 0.52 (0.26–1.08) | 0.36 (0.16–0.74) | 0.57 (0.29–1.15) | <0.0001 |
| Small dense LDL (mg/dL)                   | 36.6±15.6     | 31.9±12.8         | 37.9±16.1         | <0.0001 |
| Oxidized LDL (U/L)                        | 119.7±39.7    | 111.9±35.6        | 121.8±40.5        | 0.0003  |

Medications

- Calcium antagonists (n (%))
- ACEI/ARB (n (%))
- β-blockers (n (%))
- Diuretics (n (%))
- Aldosterone antagonists (n (%))
- Statins
- Fibrate preparations
- EPA preparations
- Oral antidiabetic agents
- Use of insulin
- Aspirin
- Ticlopidine
- Clopidogrel
- Nitrate agents
- Nicorandil

Continuous variables are shown as mean±SD or median (interquartile range). Categorical variables were compared with the chi-square test or Fisher’s exact test. Continuous variables were compared using Student’s t-test or the Wilcoxon rank-sum test based on distributions. ACEI, angiotensin converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; WHtR, waist-to-height ratio.
### Table 2. Adjusted Effect of WHtR for FMD <4.8%

| Variables          | N of events/present N of patients | N of events/absent N of patients | Univariate          | Multivariate          |
|--------------------|----------------------------------|----------------------------------|---------------------|-----------------------|
|                    |                                  |                                  | OR (95% CI)         | P value               | OR (95% CI)         | P value               |
| WHtR ≥0.5          | 515/853 (60%)                   | 122/234 (52%)                   | 1.40 (1.05–1.87)    | 0.024                 | 1.39 (1.02–1.88)    | 0.037                 |
| Age ≥65 years      | 299/462 (65%)                   | 338/625 (54%)                   | 1.56 (1.22–2.00)    | 0.0004                | 1.55 (1.19–2.01)    | 0.001                 |
| Male               | 428/715 (60%)                   | 209/372 (56%)                   | 1.16 (0.90–1.50)    | 0.24                  | 1.30 (0.98–1.73)    | 0.071                 |
| Uric acid ≥7.0 mg/dL | 119/205 (58%)                  | 518/880 (59%)                   | 0.97 (0.71–1.32)    | 0.83                  | 0.85 (0.61–1.20)    | 0.36                  |
| Hypertension       | 611/1,037 (59%)                 | 26/50 (52%)                     | 1.32 (0.75–2.34)    | 0.33                  | 1.22 (0.67–2.19)    | 0.51                  |
| Dyslipidemia       | 308/535 (58%)                   | 329/552 (60%)                   | 0.92 (0.72–1.17)    | 0.5                   | 0.85 (0.63–1.16)    | 0.31                  |
| Diabetes mellitus  | 101/169 (60%)                   | 536/918 (58%)                   | 1.06 (0.76–1.48)    | 0.73                  | 1.02 (0.71–1.46)    | 0.93                  |
| Current smoking    | 90/150 (60%)                    | 539/920 (59%)                   | 1.06 (0.75–1.51)    | 0.74                  | 1.14 (0.79–1.64)    | 0.49                  |
| Chronic kidney disease | 122/190 (64%)                 | 515/897 (57%)                   | 1.33 (0.96–1.84)    | 0.082                 | 1.26 (0.90–1.80)    | 0.18                  |
| Cardio- and Cerebrovascular disease | 213/366 (58%)             | 424/721 (59%)                   | 0.98 (0.76–1.26)    | 0.85                  | 0.90 (0.64–1.26)    | 0.53                  |

A multiple logistic regression model was used to identify the effect of WHtR on low FMD (<4.8%), with effects expressed as ORs and 95% CIs. CIs, confidence intervals; FMD, flow-mediated dilatation; ORs, odds ratios; WHtR, waist-to-height ratio.

### Table 3. Adjusted Effect of WC ≥85 cm for FMD <4.8% in Males

| Variables          | N of events/present N of patients | N of events/absent N of patients | Univariate          | Multivariate          |
|--------------------|----------------------------------|----------------------------------|---------------------|-----------------------|
|                    |                                  |                                  | OR (95% CI)         | P value               | OR (95% CI)         | P value               |
| WC ≥85 cm          | 316/512 (62%)                   | 112/203 (55%)                   | 1.31 (0.94–1.82)    | 0.11                  | 1.37 (0.97–1.93)    | 0.076                 |
| Age ≥65 years      | 186/280 (66%)                   | 242/435 (56%)                   | 1.58 (0.46–0.86)    | 0.004                 | 1.59 (1.15–2.21)    | 0.005                 |
| Uric acid ≥7.0 mg/dL | 108/186 (58%)                  | 320/528 (61%)                   | 0.90 (0.64–1.27)    | 0.54                  | 0.83 (0.58–1.20)    | 0.32                  |
| Hypertension       | 412/683 (60%)                   | 16/32 (50%)                     | 1.52 (0.25–3.11)    | 0.25                  | 1.43 (0.68–3.01)    | 0.34                  |
| Dyslipidemia       | 216/376 (57%)                   | 212/339 (63%)                   | 0.81 (0.60–1.09)    | 0.17                  | 0.78 (0.52–1.17)    | 0.24                  |
| Diabetes mellitus  | 69/117 (59%)                    | 359/598 (60%)                   | 0.96 (0.64–1.44)    | 0.83                  | 0.99 (0.65–1.52)    | 0.96                  |
| Current smoking    | 74/122 (61%)                    | 350/583 (60%)                   | 1.03 (0.69–1.54)    | 0.9                   | 1.08 (0.72–1.64)    | 0.71                  |
| Chronic kidney disease | 88/136 (65%)                  | 340/579 (59%)                   | 1.29 (0.88–1.91)    | 0.2                   | 1.29 (0.85–1.97)    | 0.23                  |
| Cardio- and Cerebrovascular disease | 178/309 (58%)              | 250/406 (62%)                   | 0.85 (0.63–1.15)    | 0.28                  | 0.91 (0.61–1.38)    | 0.67                  |

Multiple logistic regression modeling was used to examine the association of WC with low FMD (<4.8%) in male, expressed as ORs and 95% CIs. WC, waist circumference. Other abbreviations as in Table 2.

### Table 4. Adjusted Effect of WC ≥90 cm for FMD <4.8% in Females

| Variables          | N of events/present N of patients | N of events/absent N of patients | Univariate          | Multivariate          |
|--------------------|----------------------------------|----------------------------------|---------------------|-----------------------|
|                    |                                  |                                  | OR (95% CI)         | P value               | OR (95% CI)         | P value               |
| WC ≥90 cm          | 69/119 (58%)                     | 140/253 (55%)                   | 1.11 (0.72–1.73)    | 0.63                  | 1.08 (0.68–1.73)    | 0.74                  |
| Age ≥65 years      | 113/182 (62%)                    | 96/190 (51%)                     | 1.60 (1.06–2.43)    | 0.025                 | 1.56 (1.00–2.43)    | 0.049                 |
| Uric acid ≥7.0 mg/dL | 11/19 (59%)                     | 198/352 (56%)                   | 1.07 (0.42–2.82)    | 0.89                  | 0.97 (0.37–2.63)    | 0.95                  |
| Hypertension       | 199/354 (56%)                    | 10/18 (56%)                     | 1.03 (0.38–2.66)    | 0.96                  | 1.00 (0.37–2.63)    | 0.99                  |
| Dyslipidemia       | 92/159 (58%)                     | 117/213 (55%)                   | 1.13 (0.74–1.71)    | 0.57                  | 1.00 (0.61–1.62)    | 0.99                  |
| Diabetes mellitus  | 32/52 (62%)                      | 177/320 (55%)                   | 1.29 (0.71–2.39)    | 0.4                   | 1.04 (0.53–2.09)    | 0.91                  |
| Current smoking    | 16/28 (57%)                      | 189/337 (56%)                   | 1.04 (0.48–2.32)    | 0.91                  | 1.19 (0.53–2.72)    | 0.67                  |
| Chronic kidney disease | 34/54 (63%)                      | 175/318 (55%)                   | 1.39 (0.77–2.55)    | 0.27                  | 1.20 (0.64–2.29)    | 0.56                  |
| Cardio- and Cerebrovascular disease | 22/57 (61%)                   | 174/315 (55%)                   | 1.29 (0.73–2.32)    | 0.39                  | 1.03 (0.52–2.03)    | 0.94                  |

Multiple logistic regression modeling was used to identify the effect of WC on low FMD (<4.8%) in males, expressed as ORs and 95% CIs. Abbreviations as in Table 2.
Measurement of Small-Dense Low-Density Lipoprotein (LDL) and Oxidized LDL

The small-dense LDL levels were measured with a rapid assay using a modified version of a previously described heparin-magnesium precipitation method by Hirano et al. Serum levels of malondialdehyde-modified LDL

Table 5. Baseline Characteristics of Study Patients Subdivided by BMI <25 kg/m² vs. ≥25 kg/m²

| Variables                                      | All (n=1,087) | BMI <25 (n=618) | BMI ≥25 (n=469) | P value |
|------------------------------------------------|---------------|-----------------|-----------------|---------|
| Age (years)                                    | 61.9±9.3      | 63.0±8.9        | 60.5±9.6        | <0.0001 |
| ≥65 years                                      | 462 (43)      | 290 (47)        | 172 (37)        | 0.0007  |
| Male (n (%))                                   | 715 (66)      | 382 (62)        | 333 (71)        | 0.002   |
| BMI (kg/m²)                                    | 24.9±3.7      | 22.5±1.8        | 28.2±3.0        | <0.0001 |
| Waist (cm)                                     | 88.0±10.3     | 82.5±7.4        | 95.3±8.9        | <0.0001 |
| Height (cm)                                    | 161.8±8.7     | 161.2±8.6       | 162.5±8.8       | 0.014   |
| WHtR                                           | 0.54±0.06     | 0.51±0.05       | 0.59±0.06       | <0.0001 |
| Serum levels of malondialdehyde-modified LDL   |               |                 |                 |         |
| Night fasting, in a quiet, dark, air-conditioned room (constant temperature, 22–25°C). Subjects remained supine throughout all FMD measurements. Vascular response to reactive hyperemia in the brachial artery was used for assessment of endothelium-dependent FMD. Details of measurements are provided in our previous report.12

Continuous variables are shown as mean±standard deviation or median (interquartile range). Categorical variables were compared with the chi-square test or Fisher’s exact test. Continuous variables were compared using Student’s t-test or the Wilcoxon rank-sum test based on distributions. Abbreviations as in Table 1.
(MDA-LDL), a major oxidized LDL, was measured at SRL Co. Ltd., Tokyo. An enzyme-linked immunosorbent assay was used for the detection of MDA-LDL, based on the principles previously reported by Kotani et al.18

**Statistical Analysis**

Descriptive statistics are presented as frequency (percentage) for categorical variables and mean±standard deviation or median (interquartile range (IQR)) for continuous variables. These values were compared between patients who had low-WHtR (<0.5) and high-WHtR (≥0.5) using a chi-square or Fisher’s exact test for categorical variables and using a two-sample t-test or Wilcoxon rank-sum test for continuous variables. Multiple logistic regression modeling was used to identify the effect of WHtR on low FMD (<4.8%), with effects expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

All analyses were conducted using JMP version 12.0 software (SAS Institute, Cary, NC, USA). All statistical analyses were two-tailed and values of P<0.05 were considered statistically significant.

### Results

**Baseline Characteristics and Medications: WHtR <0.5 vs. ≥0.5 (Table 1)**

As compared with patients in the low-WHtR (<0.5) group, age, BMI, WC, triglycerides, HDL-C, glucose, uric acid, and Framingham score were significantly higher in the high-WHtR (≥0.5) group. Furthermore, hypertension, dyslipidemia, DM, chronic kidney disease and cardio- and cerebrovascular disease were more frequent in the high-WHtR group. Regarding baseline medications, use of calcium antagonists, angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), β-blockers, diuretics, statins, oral antidiabetic agents and insulin was more frequent in the high-WHtR group than in the low-WHtR group.

Factors related to inflammation and oxidative stress in association with atherosclerosis such as high-sensitivity C-reactive protein (hs-CRP), small-dense LDL and oxidized LDL were significantly higher in the high-WHtR group.

**High WHtR as a Risk Factor for Low FMD (Table 2)**

The risk factors for low FMD (<4.8%) in univariate analysis by logistic regression model were high WHtR and advanced age. After adjusting for confounders such as male sex, uric acid (≥7.0 mg/dL), hypertension, dyslipidemia, DM, current smoking, chronic kidney disease and cardio- and cerebrovascular disease, high WHtR and advanced age were identified as predictors (OR 1.39, 95% CI 1.02–1.88, P=0.037; OR 1.55, 95% CI 1.19–2.01, P=0.001, respectively).

**Association Between WC, BMI and FMD**

In relation to WC, analysis stratified by sex was performed because definitions of MetS differed between male and female patients.

In male patients, risk factors for low FMD (<4.8%) in the univariate analysis by logistic regression modeling did not include high WC (≥85 cm), only advanced age. After adjusting for confounders such as uric acid (≥7.0 mg/dL), hypertension, dyslipidemia, DM, current smoking, chronic kidney disease and cardio- and cerebrovascular disease, high WC was not confirmed as a predictor (OR 1.37, 95% CI 0.97–1.93, P=0.076), and only advanced age was found to be a predictor (OR 1.59, 95% CI 1.15–2.21, P=0.005; Table 3). Similarly, among female patients, risk factors for low FMD (<4.8%) in the univariate analysis by logistic regression modeling again did not include high WC (≥90 cm), only advanced age. After adjusting for confounders such as uric acid (≥7.0 mg/dL), hypertension, dyslipidemia, DM, current smoking, chronic kidney disease and cardio- and cerebrovascular disease, high WC did not represent a predictor (OR 1.08, 95% CI 0.68–1.73, P=0.74), with only advanced age showing a predictive relationship (OR 1.56, 95% CI 1.00–2.43, P=0.0049) (Table 4).

Regarding BMI in both males and females, a risk factor for low FMD (<4.8%) in the univariate analysis by logistic regression modeling was not low BMI (<25.0), only advanced age. After adjusting for confounders such as uric acid (≥7.0 mg/dL), hypertension, dyslipidemia, DM, current smoking, chronic kidney disease and cardio- and cerebrovascular disease, high BMI was not found to be a predictor (OR 0.92, 95% CI 0.71–1.19, P=0.54), only advanced age

### Table 6. Adjusted Effect of BMI <25.0 kg/m² for FMD <4.8%**

| Variables                          | Present N of events/ N of patients | Absent N of patients | Univariate OR (95% CI) | P value | Multivariate OR (95% CI) | P value |
|------------------------------------|-----------------------------------|----------------------|------------------------|---------|-------------------------|---------|
| BMI <25.0 kg/m²                    | 360/637 (57%)                     | 258/450 (57%)        | 0.97 (0.76–1.23)       | 0.79    | 0.92 (0.71–1.19)        | 0.54    |
| Age ≥65 years                      | 299/462 (65%)                     | 338/625 (54%)        | 1.56 (1.22–2.00)       | 0.0004  | 1.57 (1.21–2.05)        | 0.0007  |
| Male                               | 428/715 (60%)                     | 209/372 (56%)        | 1.16 (0.90–1.50)       | 0.24    | 1.28 (0.96–1.71)        | 0.088   |
| Uric acid ≥7.0 mg/dL               | 119/205 (58%)                     | 518/880 (59%)        | 0.97 (0.71–1.32)       | 0.83    | 0.87 (0.62–1.22)        | 0.42    |
| Hypertension ≥1.037 (59%)          | 61/1.037 (59%)                    | 26/50 (52%)          | 1.32 (0.75–2.34)       | 0.33    | 1.32 (0.74–2.37)        | 0.34    |
| Dyslipidemia ≥308/535 (58%)        | 329/552 (60%)                     | 536/918 (58%)        | 0.92 (0.72–1.17)       | 0.5     | 0.87 (0.64–1.18)        | 0.38    |
| Diabetes mellitus 101/169 (60%)    | 536/918 (58%)                     | 101/169 (60%)        | 1.06 (0.75–1.48)       | 0.73    | 1.03 (0.72–1.49)        | 0.86    |
| Current smoking 90/150 (60%)       | 539/920 (59%)                     | 536/918 (58%)        | 1.06 (0.75–1.51)       | 0.74    | 1.12 (0.78–1.62)        | 0.54    |
| Chronic kidney disease 122/190 (64%) | 515/857 (57%)                      | 122/190 (64%)        | 1.33 (0.96–1.84)       | 0.082   | 1.28 (0.91–1.82)        | 0.16    |
| Cardio- and cerebrovascular disease | 213/366 (58%)                     | 424/721 (59%)        | 0.98 (0.76–1.26)       | 0.85    | 0.90 (0.64–1.27)        | 0.56    |

A multiple logistic regression model was used to identify the effect of waist circumference on low FMD (<4.8%) in males, with effects expressed as ORs and 95% CIs. Abbreviations as in Table 2.
was found as a predictor (OR 1.57, 95% CI 1.21–2.05, P=0.0007) (Tables 5,6).

Discussion
This study showed that: (1) the high-WHtR group displayed a greater risk of morbidity and increased inflammation in association with atherosclerosis relative to the low-WHtR group; (2) high WHtR was predictive of low FMD (<4.8%), but neither WC nor BMI was associated with a risk of morbidity in either sex.

Overall or central obesity is related to cardiovascular risk factors such as DM, hypertension and dyslipidemia. BMI is reflective of overall obesity, but has difficulty in distinguishing between fat and muscle. In contrast, previous reports have shown that WC is significantly associated with central obesity and visceral fat. However, WC appears to be influenced by factors such as age, sex, ethnicity, height, and weight. In particular, height seems to cause deviations in WC and visceral fat. In fact, the current Japanese cutoffs for WC in defining MetS (85 cm for men, 90 cm for women) remain controversial. In the present study, WC and BMI were not associated with a risk of low FMD (<4.8% in both sexes). This was attributed to height causing deviations in WC and visceral fat, as stated above. Similarly, BMI is calculated from height and overall body weight, which can lead individuals with low levels of adiposity being identified as obese by mistake. In addition, endothelial dysfunction appears to be more significantly associated with abnormal fat distributions than with obesity per se. In fact, Hashimoto et al reported that subjects with visceral-type obesity, rather than subcutaneous-type, showed a stronger association with impaired flow-mediated endothelial-dependent vasodilatation of the brachial artery. In addition, a systematic review based on meta-analysis reported WHtR as a better screening tool than WC and BMI for adult cardiometabolic risk factors. On the other hand, Joseph et al reported no clear correlation among older sedentary men between adiposity or body fat distribution and impairment of flow-mediated endothelial-dependent vasodilation. However, this result may have been because the subjects in that study were limited to older men. Because of the absence of easy and appropriate anthropometric indices for predicting endothelial dysfunction, we consider that better indices are needed.

In this study, the high-WHtR group showed a higher risk of morbidity relative to the low-WHtR group, related to increased inflammatory markers and oxidative stress in association with measures of atherosclerosis such as hs-CRP, small-dense LDL and oxidized LDL. Furthermore, high WHtR was predictive of low FMD (<4.8%), which is strongly associated with endothelial dysfunction. These results suggested that visceral adiposity causes inflammation and oxidative stress, leading to endothelial dysfunction. The mechanisms by which endothelial dysfunction is caused by obesity appear complicated, but previous reports have implied that increased oxidative stress from accumulated fat plays a dominant role in eliciting endothelial dysfunction in obesity.

The current study differs from previous studies in several ways. The current study analyzed only baseline data as a cross-sectional study, whereas the FMD-J study was a prospective multicenter study in Japan, and no large cohort studies had been conducted prior to that investigation. FMD has been assessed by many individual institutions, but the reliability of FMD assessment has been increased using various methods. We therefore believe that the accuracy of the present results is significantly higher than in previous reports. WHtR is able to be measured easily, as are BMI and WC, during periodic health examinations, and does not require separation by sex. Furthermore, our findings indicated superior predictive ability of this factor for endothelial dysfunction compared with WC and BMI.

Study Limitations
Some limitations to this study need to be considered when interpreting the results. First, subjects in this study only comprised patients with morbidities such as DM, hypertension and CAD, and healthy individuals were not included. Second, because we did not obtain any data on other factors that are known to affect FMD (such as vitamin and phosphate levels) and other as-yet-unidentified confounding factors, the results of this study might have been inadvertently affected. Finally, this study used a cross-sectional design, which does not allow for definitive determinations of the direction of any relationship between high WHtR and low FMD.

Conclusions
WHtR was a superior predictor of decreased FMD compared with other anthropometric indices (i.e., WC and BMI), and progression of atherosclerosis might be detected more sensitively. Accordingly, we propose that WHtR should be used more positively in clinical practice. Further study is needed to clarify the relationship between cardiovascular mortality and WHtR.

Acknowledgments
The authors acknowledge the valuable contributions of the FMD-J collaborative investigators.

Disclosures
The authors declare that there are no conflicts of interest.

Grant Support
The present study was supported by the Japanese Atherosclerosis Prevention Research Fund (A study of Multi-center Assessment on the Clinical Usefulness of Semi-automatic Measurement of Flow-mediated Vasodilatation of the Brachial Artery: FMD-J study).

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