Association of Knee Osteoarthritis with the Accumulation of Metabolic Risk Factors Such as Overweight, Hypertension, Dyslipidemia, and Impaired Glucose Tolerance in Japanese Men and Women: The ROAD Study

NORIKO YOSHIMURA, SHIGEYUKI MURAKI, HIROYUKI OKA, HIROSHI KAWAGUCHI, KOZO NAKAMURA, and TORU AKUNE

ABSTRACT. Objective. To clarify the association of knee osteoarthritis (KOA) with overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT), which are components of metabolic syndrome (MS), in a Japanese population.

Methods. We enrolled 1690 participants (596 men, 1094 women) from the large-scale cohort study Research on Osteoarthritis Against Disability (ROAD), begun in 2005 to clarify epidemiologic features of OA in Japan. KOA was evaluated by the Kellgren-Lawrence grade, minimum joint space width (MJSW), minimum joint space area (JSA), and osteophyte area (OPA). OW, HTN, DL, and IGT were assessed using standard criteria.

Results. The prevalence of KOA in the total population in the age groups ≤ 39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. Logistic regression analyses after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercise, and history of knee injuries revealed that the OR of KOA significantly increased according to the number of MS components present (1 component: OR 1.21, 95% CI 0.88–1.68, p = 0.237; 2 components: OR 1.89, 95% CI 1.33–2.70, p < 0.001; 3 or more components: OR 2.72, 95% CI 1.77–4.18; p < 0.001). The number of MS components was inversely related to medial MSJW (β = –0.148, R² = 0.21, p < 0.001), medial JSA (women only; β = –0.096, R² = 0.18, p = 0.001), and positively related to OPA (β = 0.12, R² = 0.11, p < 0.001).

Conclusion. The accumulation of MS components is significantly related to presence of KOA. MS prevention may be useful to reduce cardiovascular disease and KOA risk. (First Release Feb 15 2011; J Rheumatol 2011;38:921–30; doi:10.3899/jrheum.100569)

Key Indexing Terms: EPIDEMIOLOGY RISK FACTORS METABOLIC SYNDROME KNEE OSTEOARTHRITIS ROAD STUDY

Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly that affects activities of daily living (ADL) and quality of life, leading to increased morbidity and mortality1,2,3. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and longterm care4.

In the same report, cardiovascular disease (CVD) is...
Knee OA (KOA) and MS share age and obesity as risk factors. Many investigators have considered the association of OA with other components of MS. In an early population study, Lawrence first reported that diastolic blood pressure was associated with KOA in women. Regarding DL, Kellgren reported a significant association between women with hand OA and above-average serum cholesterol levels in the 1960s. Cimmino and Cutolo examined the role of glucose and OA, and observed significantly higher levels of plasma glucose in women with OA than in those without OA. Although contradictory findings regarding the association of such metabolic factors with OA have been reported, Hart et al. found that metabolic factors such as blood glucose, hypercholesterolemia, and even treated HTN were associated with the development of KOA. Based on that evidence, they proposed that the etiology of OA had an important systemic and metabolic component. This hypothesis has been supported by data from several population-based studies performed in the United States. However, to our knowledge, few population-based studies have demonstrated a dose-response relationship between the severity of KOA and an increasing number of the components of MS. Our first purpose was to clarify the association between the presence of KOA, defined using the Kellgren-Lawrence (KL) scale, and the number of MS components in a Japanese population.

Moreover, in most of these studies that confirmed the association between the presence of KOA and the components of MS, KOA was defined according to KL grade. KL grade is the most conventional system for measuring the radiographic severity of KOA, but does not separately assess joint space narrowing and osteophyte formation. Accumulating evidence has shown that osteophytosis and joint space narrowing have distinct etiologic mechanisms, and their progression is neither constant nor proportional. Thus, to examine the factors associated with KOA, these 2 OA features should be assessed separately. However, no reports to date have clarified the association of indices of KOA, such as minimum joint space width (MJSW), joint space area (JSA), and osteophyte area (OPA), with the accumulation of the number of components of MS. Our second purpose was to determine whether the accumulation of MS components influenced the values of MJSW, JSA, and OPA.

Further, MS is an emerging epidemic in both men and women worldwide, and with the increase in the global population of Asians, an understanding of the epidemiology of diseases as they relate to Asian populations is required. We have reported that the prevalence of KOA was much higher in a Japanese population than in elderly whites in the United States and Europe, although not largely different from that of African American and Chinese populations. In contrast, the prevalence of MS in East Asian countries including China, Korea, and Japan was reported to be lower than in white populations. In light of the rapid increase in the population of Asian countries, prevention strategies for obesity-related chronic diseases such as MS and KOA should be implemented immediately. Our final aim was to clarify the association between MS and KOA.
outward to the joint level, and the area that was medially prominent
calculated. The medial outline of the tibia from the inflection point was
drawn. Inflection points for these outlines were then
inside rims. Medial and lateral JSA were determined as areas surrounded by
regression line for the lower rim outline was then drawn, and the intersec-
tion of the lower rim outline and the regression line were designated as the
axis of the femur. Similarly, the straight regression line of the middle line of the tibia from the bottom
to the inflection points was designated as the axis of the tibia. The lateral
angle between the two axes lines was calculated as FTA. In general clinical
practice, this system can quantify the major features of knee OA on stan-
dard radiographs and allows objective, accurate, simple, and easy assess-
ment of the structural severity of knee OA without any manual operation.

Regarding the relationship between the measurements of KOA, we
have confirmed the correlation values were more than 0.5 between medial
JSA and medial MJSW, and between lateral JSA and lateral MJSW, indi-
cating that these are confounding factors for each other. Osteophyte area
was not significantly associated with either medial JSA or medial MJSW.
Further, JSA and MJSW on the lateral side were positively correlated with
those on the medial side. These measurements showed good correlation
between KL grades (p < 0.0001)31.

Further, to evaluate the KOA severity using quantitative measurements,
the medial and lateral MJSW, medial and lateral JSA, and OPA were meas-
ure separately, using a KOA computer-assisted diagnostic system (KOA-
CAD). The KOACAD was programmed to measure MJSW and JSA in the
tibiofemoral joint space, a vertical neighborhood difference filter was
applied to identify points with high absolute values for difference of scales.
The centers of all points were then calculated, and the ROI was selected.

Next, to determine the region of interest (ROI) including the
medial side. These measurements showed good correlation
between KL grades (p < 0.0001)31.

Further, JSA and MJSW on the lateral side were positively correlated with
those on the medial side. These measurements showed good correlation
between KL grades (p < 0.0001)31.

For the samples of participants in the baseline study, the following
items were measured: blood counts, hemoglobin, hemoglobin Alc
(HbA1c), blood sugar, total protein, aspartate aminotransferase, alanine
aminotransferase, γ-glutamyltransferase, high-density lipoprotein
(HDL) cholesterol, total cholesterol, triglycerides (TG), blood urea nitrogen,
uric acid, and creatinine. These analyses were performed at the same
laboratory within 24 hours after the extraction (Osaka Kessei Research
Laboratories Inc., Osaka, Japan).

Definition of MS components. This definition was based mainly on the cri-
teria of the Examination Committee of Criteria for Metabolic Syndrome in
Japan33. According to these criteria, an abdominal circumference ≥ 85 cm
in men and ≥ 90 cm in women is a necessary condition for MS. HTN was
diagnosed as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg,
DL as serum TG level ≥ 150 mg/dl and/or serum HDL cholesterol level <
40 mg/dl, and IGT as fasting serum glucose ≥ 110 mg/dl. Because there has
been considerable debate regarding the measurement of abdominal circum-
cumference, we decided to use BMI ≥ 25 instead as an indicator of over-
weight, based on the criteria of the Japan Society for the Study of
Obesity33. Also, because not all blood samples were obtained under fasting
conditions, we did not use participants’ data concerning serum levels of
glucose and TG, because of their large variation depending on hours after
eating. Instead, we used a serum HDL cholesterol level < 40 mg/dl to indi-
cate DL, and serum HbA1c level ≥ 5.5% to indicate IGT. These are indices
used in the National Health and Nutrition Survey in Japan, and they were
adopted as criteria for MS in this national screening based on the difficulty
of collecting the samples under fasting conditions33. Further, subjects being
treated with medication for HTN, DL, or diabetes mellitus were regarded as
having the respective disorder.

Statistical analysis. All statistical analyses were performed using Staats sta-
tistical software (Stata Corp., College Station, TX, USA). Differences in
proportion were compared by the chi-square test. Differences in continu-
ous variables were tested for significance using ANOVA for comparisons
among multiple groups, and Scheffe’s least significant difference test for
pairs of groups. Significant items were selected, and multiple regression
and logistic regression analyses were performed by adjusting selected vari-
ables. Various confounding factors were used for the adjustment for each
multivariable analysis.

RESULTS

Study population. Table 1 shows selected characteristics of the
participants including age, height, weight, BMI, systolic

<table>
<thead>
<tr>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 39</td>
<td>45</td>
<td>14</td>
</tr>
<tr>
<td>40–49</td>
<td>149</td>
<td>44</td>
</tr>
<tr>
<td>50–59</td>
<td>316</td>
<td>107</td>
</tr>
<tr>
<td>60–69</td>
<td>482</td>
<td>157</td>
</tr>
<tr>
<td>70–79</td>
<td>539</td>
<td>220</td>
</tr>
<tr>
<td>≥ 80</td>
<td>159</td>
<td>54</td>
</tr>
<tr>
<td>Total, n</td>
<td>1690</td>
<td>596</td>
</tr>
<tr>
<td>Mean (SD) selected characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>66.2 (12.0)</td>
<td>66.3 (11.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.4 (7.2)</td>
<td>163.4 (7.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.2 (10.9)</td>
<td>52.0 (8.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0 (3.4)</td>
<td>23.2 (3.2)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>135.1 (20.7)</td>
<td>137.9 (19.6)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74.2 (11.5)</td>
<td>77.0 (11.6)</td>
</tr>
<tr>
<td>Serum levels of HDL cholesterol, mg/dl</td>
<td>60.8 (15.7)</td>
<td>56.1 (15.8)</td>
</tr>
<tr>
<td>Serum levels of HbA1c, %</td>
<td>5.20 (0.74)</td>
<td>5.23 (0.83)</td>
</tr>
<tr>
<td>Prevalence of selected characteristics, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking habit</td>
<td>13.1</td>
<td>29.9</td>
</tr>
<tr>
<td>Current alcohol consumption</td>
<td>39.8</td>
<td>66.7</td>
</tr>
<tr>
<td>Medication for hypertension</td>
<td>32.3</td>
<td>29.5</td>
</tr>
<tr>
<td>Medication for dyslipidemia</td>
<td>6.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Medication for diabetes mellitus (including insulin injection)</td>
<td>5.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Prevalence of each component of metabolic syndrome, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>25.3</td>
<td>26.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.9</td>
<td>74.8</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>21.5</td>
<td>24.3</td>
</tr>
</tbody>
</table>

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.
and diastolic BP, and serum levels of HDL cholesterol and HbA1c, classified by sex. Two-thirds of the 1690 participants were women, and their mean age was 1.5 years younger than that of the men (p = 0.0098).

Height, weight, and BMI were significantly lower in women than in men (height, p < 0.0001; weight, p < 0.0001; BMI, p = 0.049). Both measurements of systolic BP and diastolic BP were significantly higher in men than in women (systolic BP and diastolic BP, p < 0.0001). However, there was no significant difference in serum levels of HbA1c between men and women (p = 0.2472). The serum level of HDL cholesterol was significantly lower in men than in women (p < 0.0001).

Table 1 also shows the proportion of subjects who smoked (regularly or more than once a month) and consumed alcohol (drinking regularly or more than once a month); medication use; and the prevalence of OW, HTN, DL, and IGT. Smoking and drinking were significantly more common in men than in women (p < 0.001). In the total population, the component of MS with the highest prevalence was HTN, followed by OW, IGT, and DL. The prevalence of HTN and IGT was significantly higher in men than in women (HTN, p = 0.001; IGT, p = 0.039).

Table 2. Mean (SD) of each component of metabolic syndrome in the absence or presence of knee osteoarthritis (KOA).

<table>
<thead>
<tr>
<th>Component</th>
<th>Total KOA</th>
<th>KOA+</th>
<th>p</th>
<th>KOA−</th>
<th>KOA+</th>
<th>p</th>
<th>KOA−</th>
<th>KOA+</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62.5 (12.1)</td>
<td>71.5 (8.8)</td>
<td>0.0001</td>
<td>62.5 (12.1)</td>
<td>71.5 (8.8)</td>
<td>0.0001</td>
<td>57.8 (11.8)</td>
<td>70.3 (9.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0 (3.2)</td>
<td>23.5 (3.2)</td>
<td>0.0001</td>
<td>23.0 (3.2)</td>
<td>23.5 (3.2)</td>
<td>0.0931</td>
<td>22.0 (3.1)</td>
<td>23.6 (3.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>134.5 (18.9)</td>
<td>142.5 (19.6)</td>
<td>0.0001</td>
<td>134.5 (18.9)</td>
<td>142.5 (19.6)</td>
<td>0.0001</td>
<td>127.9 (20.0)</td>
<td>138.0 (21.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>77.1 (11.6)</td>
<td>76.8 (11.5)</td>
<td>0.6970</td>
<td>77.1 (11.6)</td>
<td>76.8 (11.5)</td>
<td>0.6970</td>
<td>72.1 (10.4)</td>
<td>73.1 (11.8)</td>
<td>0.1380</td>
</tr>
<tr>
<td>Serum levels of HDL cholesterol, mg/dl</td>
<td>57.5 (16.2)</td>
<td>54.1 (15.0)</td>
<td>0.0001</td>
<td>57.5 (16.2)</td>
<td>54.1 (15.0)</td>
<td>0.0001</td>
<td>6.6 (15.8)</td>
<td>60.8 (13.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum levels of HbA1c, %</td>
<td>5.22 (0.83)</td>
<td>5.23 (0.80)</td>
<td>0.9409</td>
<td>5.22 (0.83)</td>
<td>5.23 (0.80)</td>
<td>0.9409</td>
<td>5.07 (0.53)</td>
<td>5.28 (0.77)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Table 3 shows the prevalence of potential associated lifestyle factors for KOA classified by the absence or presence of KOA. In the overall population, significantly associated factors for KOA included residential area, smoking habit, alcohol consumption, bicycling regularly as a factor of physical activity, and regular exercises. These factors should be taken into consideration as confounders for the following multivariate analysis.

Then, logistic regression analysis was repeated using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age, sex, regional difference, smoking habit, alcohol consumption, physical activities including regular bicycling in the past 12 months, regular exercises such as football, tennis, baseball, and golf; and history of knee injuries. The analysis revealed that OW and HTN were significantly positively associated with KOA (OW: OR 2.74, 95% CI 1.07–3.62, p < 0.001; HTN: OR 1.43, 95% CI 1.09–1.86, p < 0.001). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that OW and HTN were positively associated with KOA in men (OW: OR 1.76, 95% CI 1.13–2.74, p < 0.05; HTN: OR 1.77, 95% CI 1.11–2.84, p < 0.05), and only OW in women (OR 3.63, 95% CI 2.51–5.25, p < 0.001). These results suggest that all components of MS were not equally associated with the presence of KOA.

Then, to clarify the association between all the components of MS and KOA, logistic regression analysis was repeated using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT, as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, the analysis revealed that only OW was significantly positively associated with KOA (OR 2.33, 95% CI 1.79–3.04, p < 0.001). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that only HTN was positively associated with KOA in men (OR 1.61, 95% CI 1.03–2.53, p = 0.038), and only OW in women (OR 3.48, 95% CI 2.42–5.01, p < 0.001).
OW was significantly positively associated with KOA (OR 2.65, 95% CI 1.98–3.54, p < 0.001). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that, in both sexes, OW was the only factor that was significantly associated with KOA (men: OR 1.64, 95% CI 1.04–2.59, p < 0.05; women: OR 3.64, 95% CI 2.48–5.34, p < 0.001), while in men, there was weak but not significant association between HTN and KOA (OR 1.61, 95% CI 0.99–2.60, p = 0.053). These results suggest that obesity, among the various components for MS, was most significantly correlated to KOA.

Prevalence of KOA and its association with the number of components for MS. Table 4 shows the prevalence of KOA classified by the number of components: the prevalence of KOA tended to increase with the increase in the number of MS components (p for trend < 0.001) in the total population. However, the prevalence of KOA in men and women did not tend to increase monotonically. Thus, in men, the prevalence of KOA in the group with 2 MS components was lower than that in the groups with 1 component. Similarly, in women, the prevalence of KOA in the group with 2 MS components was higher than that in the group with 3 or more components.

To clarify the effect of the accumulation of MS components on the prevalence of KOA, logistic regression analysis was performed using the prevalence of KOA as the objective variable and the presence of MS components (OW, HTN, DL, and IGT) as explanatory variables. Compared to the reference condition (no MS component), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.18, 95% CI 0.87–1.61, p = 0.273; 2 components: OR 1.74, 95% CI 1.25–2.44, p = 0.001; more than 3 components: OR 2.15, 95% CI 1.44–3.23; p < 0.001). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no component; 1 component: OR 1.94, 95% CI 1.11–3.39, p = 0.021; 2 components: OR 1.61, 95% CI 0.89–2.91, p = 0.117; more than 3 components: OR 2.96, 95% CI 1.5–5.85, p = 0.002). In contrast, in women, no significant difference was observed between the presence of no components and 1 component; however, 2 or more components of MS increased the risk of KOA significantly (vs no component; 1 component: OR 0.89, 95% CI 0.61–1.29, p = 0.527; 2 components: OR 1.94, 95% CI 1.27–2.96, p = 0.002; more than 3 components: OR 1.71, 95% CI 1.01–2.87, p = 0.044).

Logistic regression analysis was performed using the presence of KOA as the objective variable and the number of MS components present (OW, HTN, DL, and IGT) as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. Figure 1 shows the OR of the association between accumulation of components of MS and presence of KOA. Compared to the reference condition (no components of MS), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.21, 95% CI 0.88–1.68, p = 0.237; 2 components: OR 1.89, 95% CI 1.33–2.70, p < 0.001; > 3 components: OR 2.72, 95% CI 1.77–4.18, p < 0.001). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no component; 1 component: OR 1.21, 95% CI 0.88–1.68, p = 0.237; 2 components: OR 1.89, 95% CI 1.33–2.70, p < 0.001; > 3 components: OR 2.72, 95% CI 1.77–4.18, p < 0.001). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no component; 1 component: OR 1.21, 95% CI 0.88–1.68, p = 0.237; 2 components: OR 1.89, 95% CI 1.33–2.70, p < 0.001; > 3 components: OR 2.72, 95% CI 1.77–4.18, p < 0.001).
ponent; 1 component: OR 2.07, 95% CI 1.15–3.74, p = 0.016; 2 components: OR 1.68, 95% CI 0.89–3.17, p = 0.110; more than 3 components: OR 3.88, 95% CI 1.87–80.6, p < 0.001). In contrast, in women, no significant difference was observed between the presence of no component and 1 component; however, 2 or more components of MS increased the OR of KOA significantly (vs no component; 1 component: OR 0.88, 95% CI 0.59–1.32, p = 0.541; 2 components: OR 2.13, 95% CI 1.36–3.34, p = 0.001; > 3 components: OR 2.17, 95% CI 1.25–3.77, p = 0.006).

Joint space narrowing and areas of osteophytes in the knee, and their association with components of MS. Tables 5A and 5B show the mean measurements of indices for KOA, medial MJSW (mm), lateral MJSW (mm), medial JSA (mm²), lateral JSA (mm²), and OPA (mm²), classified by the number of components of MS. The values of medial MJSW tended to be significantly lower, and those of OPA significantly higher, with the increasing number of components of MS. The values of medial JSA in women belonging to the group with no component of MS were significantly higher than in those belonging to the groups with 1, 2, 3, or more components of MS, but no such tendency was observed in men. There was no relationship between the values of lateral MJSW, lateral JSA, and the number of components of MS.

Multiple regression analysis was performed using values of medial MJSW as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, we found that the number of components of MS was inversely related to the values of medial MJSW (β = −0.148, R² = 0.21, p < 0.001). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: β = −0.152, R² = 0.14, p < 0.001; women: β = −0.149, R² = 0.18, p < 0.001).

Multiple regression analysis was then performed using OPA values as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was positively related to OPA values (β = 0.12, R² = 0.11, p < 0.001). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: β = 0.15, R² = 0.08, p < 0.001; women: β = 0.11, R² = 0.11, p < 0.001).

In women, multiple regression analysis was performed using values of medial JSA as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was inversely related to the values of medial JSA in women (β = −0.096, R² = 0.18, p = 0.001).

DISCUSSION

We found that an increase in the number of components of MS was significantly associated with the presence of KOA diagnosed by using the KL scale in Japanese men and women. We also clarified that the values of medial MJSW and OPA in men and women, and medial JSA in women as features of KOA, were significantly associated with the increase in the number of MS components.

KOA and MS share age and OW as risk factors.\cite{1,7,8,9,10,11} We have already reported that higher BMI was associated with radiographic KOA based on an analysis using the same population evaluated in our study\cite{36}, and it was also clarified that OW was the strongest factor that influenced the prevalence of KOA.

Regarding the association between clustering of metabolic factors and KOA, Hart, et al found that metabolic factors including blood glucose, hypercholesterolemia, and HTN were associated with both unilateral and bilateral KOA and were independent of OW\cite{20}. Sowers, et al\cite{21} defined the presence of ≥ 2 of the following criteria as cardiometabolic clustering: low levels of HDL cholesterol, elevated levels of low-density lipoprotein cholesterol, TG, BP, C-reactive protein, waist/hip ratio, glucose levels, and dia-
Betes mellitus, and assessed the association between cardiometabolic clustering and KOA. They found that KOA was significantly more frequent in obese women with cardiometabolic clustering compared with those without it. Using data from the National Health and Nutrition Examination Survey III (NHANES III), Singh, et al suggested that adults with OA in the United States have a high prevalence of CVD risk factors, and Puenpatom and Victor demonstrated that each of the 5 cardiovascular risk factors that comprise MS, HTN, abdominal OW, hyperglycemia, elevated TG, and low HDL cholesterol, was more prevalent in the population with OA than in the population without OA. However, to our knowledge, few population-based studies have shown a dose-response relationship between the presence of KOA and the accumulation of the number of MS components.

In our study, the logistic regression analysis revealed that only OW was significantly associated with KOA, and other components were not significant, using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT as explanatory variables and after adjustment for potential confounders. However, we found that the higher the number of components of MS, the greater the OR of the presence of KOA. This result indicates that, even if the effect of each component of MS on KOA may be weak, accumulation of the number of components may significantly worsen KOA.

In addition, we found that medial MJSW values in men and women, and medial JSA values in women tended to be significantly lower with the increase in the number of components of MS. In contrast, OPA values became significantly higher with the increase in the number of components of MS. Regarding the association between JSW and KOA, Sowers, et al used statistical models that included variables representing obesity, cardiometabolic status, and lateral and medial JSW differences to show that a 1-mm increase in the difference between lateral and medial JSW was associated with 2.1 times greater odds of having KOA, and subjects who were obese with cardiometabolic clustering had 4.5 times greater odds of having KOA. However, no other reports have addressed direct associations between indices of KOA, such as MJSW, JSA, and OPA values, with the accumulation of the number of components of MS. In our study, we confirmed that the accumulation of the number of MS components present influenced the values of both MJSW, JSA (women only), and OPA, which determine the features and severity of KOA.

Regarding the association of clustering of components for MS and KOA, a few hypotheses have been suggested. Hart, et al attributed the effect of excess endogenous estrogens to the aromatization of estrone in fat tissue. Regarding the endogenous secreted products, Sowers, et al suggested that leptin and adiponectin levels influenced the development of OA. They stated that leptin concentrations

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**Table 5A.** Mean (SD) of medial and lateral minimum joint space width (MJSW) classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

<table>
<thead>
<tr>
<th>No. MS Components</th>
<th>Medial MJSW, mm</th>
<th>Lateral MJSW, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Men Women</td>
<td>Total Men Women</td>
</tr>
<tr>
<td>0</td>
<td>2.98 (0.81) 3.33 (0.66)</td>
<td>2.85 (0.82) 4.00 (1.18)</td>
</tr>
<tr>
<td>1</td>
<td>2.69 (1.01) 3.05 (0.97)</td>
<td>2.49 (0.98) 3.96 (1.13)</td>
</tr>
<tr>
<td>2</td>
<td>2.43 (1.19) 2.87 (1.10)</td>
<td>2.15 (1.17) 3.85 (1.19)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>2.42 (1.22) 2.73 (1.24)</td>
<td>2.22 (1.17) 4.06 (1.27)</td>
</tr>
</tbody>
</table>

* Significantly different from values obtained in the absence of components (p < 0.05). b Significantly different from values obtained with 1 component (p < 0.05).

**Table 5B.** Mean (SD) of medial and lateral joint space area (JSA) and area of osteophytosis (OPA), classified by number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

<table>
<thead>
<tr>
<th>No. MS Components</th>
<th>Medial JSA, mm²</th>
<th>Lateral JSA, mm²</th>
<th>OPA, mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Men Women</td>
<td>Total Men Women</td>
<td>Total Men Women</td>
</tr>
<tr>
<td>0</td>
<td>96.3 (27.6) 111.4 (25.6)</td>
<td>98.8 (26.2) 111.0 (33.2)</td>
<td>1.81 (6.42) 0.93 (2.97) 2.13 (7.26)</td>
</tr>
<tr>
<td>1</td>
<td>90.2 (31.7) 104.0 (30.7)</td>
<td>82.3 (29.6) 111.0 (32.4)</td>
<td>132.2 (34.2) 103.3 (29.2) 1.81 (6.42) 0.93 (2.97) 2.13 (7.26)</td>
</tr>
<tr>
<td>2</td>
<td>85.2 (36.7) 101.1 (34.3)</td>
<td>75.0 (34.6) 111.7 (32.2)</td>
<td>128.9 (29.6) 100.6 (28.8) 5.34 (11.25) 2.45 (5.36) 7.18 (13.44)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>88.2 (39.3) 102.0 (40.1)</td>
<td>79.1 (36.0) 118.2 (35.3)</td>
<td>132.5 (34.7) 108.8 (32.5) 6.26 (9.59) 3.82 (8.70) 7.86 (9.85)</td>
</tr>
</tbody>
</table>

* Significantly different from values obtained in the absence of components (p < 0.05). b Significantly different from values obtained with 1 component (p < 0.05).
in the synovial fluid of patients with OA correlated with their BMI, and levels of adiponectin are low in obese individuals and in those with CVD. Another hypothesis states that atherosclerotic change may play a role in the development of OA. Kornat, et al reported the association between increased popliteal artery vessel wall thickness and generalized OA. It has been hypothesized that atherosclerotic changes and obesity-associated metabolic changes in the subchondral bone are associated with OA. In obese subjects, metabolic changes in the striated muscles induced by the interaction of insulin resistance and systemic inflammation might lead to fatigue and muscle weakness, which influences the balance between damage and repair mechanisms leading to OA. In our study, we could not substantiate these hypotheses because of the lack of relevant measurements. However, in the followup study, we will obtain the ankle brachial pressure index and pulse wave velocity of the ROAD subjects, and thus we will further the evidence regarding the association between arteriosclerosis and KOA.

In our study, a sexual dimorphism pattern was shown in prevalence of KOA (women > men) and components of MS such as values of BMI (men > women), BP (men > women), and HDL cholesterol (women > men). Regarding KOA, being female is well known as a strong risk factor, according to our previous survey and other studies. In our study, we could not substantiate these hypotheses because of the lack of relevant measurements. However, in the followup study, we will obtain the ankle brachial pressure index and pulse wave velocity of the ROAD subjects, and thus we will further the evidence regarding the association between arteriosclerosis and KOA.

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ROAD study and revealed that the presence of KOA was significantly associated with increases in the number of components of MS. Additionally, the number of components of MS was inversely related to medial MSJW values and positively related to OPA values. The prevention of MS may be useful for both CVD and KOA in Asian populations. Further investigations, along with continued longitudinal surveys in the ROAD study, will elucidate the components of MS and occurrence or progress of KOA.

REFERENCES


