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# Relationships Between Body Mass Index, Fat Mass, Muscle Mass, and Musculoskeletal Pain in Community Residents

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***Objective.*** **To evaluate the relationships between fat mass, muscle mass, fat:muscle mass ratio, metabolic syndrome, and musculoskeletal pain in community residents.**

***Methods.*** **In the Korean Health and Genome Study, 1,530 participants (mean ± SD age 60.8 ± 8.60 years) completed pain questionnaires and underwent dual x-ray absorptiometry to calculate body composition. Pain was categorized according to the number of pain regions, such that widespread pain, defined as pain above the waist, below the waist, on both sides of the body, and in the axial region, represented the most severe pain. Metabolic syndrome was defined using the International Diabetes Federation 2005 recommendations, and the association between metabolic syndrome and pain was evaluated by dividing the population into 4 groups, according to the presence/absence of metabolic syndrome and of high body mass index (BMI).**

***Results.*** **Total fat mass and fat:muscle mass ratio were significantly and positively associated with musculoskeletal pain among female subjects only. Compared to the lowest quartile of fat:muscle mass ratio, the odds ratios for widespread pain among subjects in other quartiles were significantly increased after adjustment for confounders. Widespread pain was more prevalent among subjects with metabolic syndrome whether their BMI was high or normal, especially among female subjects.**

***Conclusion.*** **Increased fat mass and fat:muscle mass ratio were significantly associated with musculoskeletal pain among women. Widespread pain was significantly associated with a high fat:muscle mass ratio after adjustment for confounders. Understanding the relationship between fat mass and pain may provide insights into preventative measures and therapeutic strategies for musculoskeletal pain.**

Musculoskeletal pain, one of the most common chronic conditions in older adults (1), reduces health-related quality of life and is the largest contributor of disability in all regions of the world, thus representing a major burden to individuals and to health care and social service systems (2,3). As the population ages, musculoskeletal pain would be expected to become the most serious public health problem. There are multiple, heterogeneous pathologies involved in musculoskeletal pain, including arthritis, soft tissue rheumatic disorders, degenerative spinal disease, and fibromyalgia. The reported prevalence of musculoskeletal pain varies because of diverse case definitions and differences in study methods. In a recent epidemiologic review it was reported that musculoskeletal pain affects between 13.5% and 47% of the general population, with the prevalence of chronic widespread pain, the most severe type, varying between 11.4% and 24% (4). We previously reported the prevalence of widespread pain in the Korean population as 12% (16.2% among females and 5.5% among males) (5). Reported risk factors for musculoskeletal pain include older age, female sex, high physical and psychosocial workload, and low physical activity (5–8).

Obesity, another major concern in contemporary

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health care, affecting ~500 million adults worldwide, is also closely related to musculoskeletal pain and physical dysfunction (9,10). Specifically, increasing severity of pain is observed at higher body mass index (BMI) classifications, from low-normal BMI through obesity class III (BMI $\geq$40 kg/m$^2$) (11,12). Many studies have shown an association between obesity and specific musculoskeletal diseases such as osteoarthritis (OA) (13–15), rheumatoid arthritis (RA) (16,17), and fibromyalgia (18,19).

The strong association between obesity and arthritis affecting weight-bearing joints, such as the knee, supports the classic hypothesis that obesity promotes joint damage due to increased biomechanical loading. Thus, worsening of joint damage associated with obesity has been considered a factor in the higher prevalence of pain in the obese population. Obesity is currently considered to be a low-grade systemic inflammatory state, and recent studies suggest that metabolic factors associated with obesity alter systemic levels of proinflammatory cytokines (20). Obesity has been associated with markers of chronic inflammation, such as levels of C-reactive protein, tumor necrosis factor $\alpha$, amyloid A, and interleukin-6, and white blood cell counts (21–23). Thus, the impact of obesity on various musculoskeletal conditions may stem not only from the biomechanical stress of obesity, but also from systemic effects. In a study of 407 individuals $\geq$70 years of age, abdominal obesity was significantly associated with chronic pain after adjustment for pain-related comorbidities such as OA and neuropathy, suggesting that increased inflammation caused by obesity per se may play a role in pain (24). However, it is difficult to unravel the independent influence of mechanical and metabolic/inflammatory factors on pain, and the underlying mechanism linking obesity and musculoskeletal pain still remains to be addressed.

Measures of obesity used in previous studies have included weight, BMI, waist circumference, and waist-hip index; these measures do not provide information about specific components of body composition, such as fat and lean body mass, which are increasingly being shown to have distinct roles in the pathogenesis of musculoskeletal disease (25–27). A recent study examining the relationship between BMI, fat mass, lean mass, and quality of life in patients with fibromyalgia (28) showed that each factor was associated with different domains of the Short Form 36 health survey (29). For example, BMI was associated with emotional role functioning, while fat mass was associated with bodily pain. Another potential factor that could link obesity to musculoskeletal health is metabolic syndrome. Although metabolic syndrome and obesity defined as high BMI are strongly associated, in some individuals, metabolic syndrome does not coincide with high BMI. For example, "metabolically obese but normal-weight" (MO/NW) individuals have abnormal metabolic status despite low-to-normal BMI (30). The importance of this phenotype classification is based on findings that abnormal metabolic status, rather than high BMI, confers an increased risk of developing type 2 diabetes mellitus (DM) (31) or cardiovascular disease (19,30,31).

In this study, we sought to delineate the relationship between fat mass parameters and musculoskeletal pain, including widespread pain, in residents of a Korean community. In addition, we examined the influence of metabolic syndrome on musculoskeletal pain independent of BMI, by assessing risk of musculoskeletal pain in 4 categories of individuals defined by low-to-normal or high BMI and the presence or absence of metabolic syndrome.

## SUBJECTS AND METHODS

**Study population.** In the ongoing prospective Korean Health and Genome Study, a rural farming community (Ansung) in Korea was selected for the present study. Ansung, a county ~70 km south of Seoul, had a population of 132,906 in 2000 (32). The methods of the Korean Health and Genome Study have been described previously (33). Briefly, the eligibility criteria included an age of 40–79 years, residence within the borders of the survey area for at least 6 months before testing, and the mental and physical ability to participate. Cluster sampling was conducted, and 5 representative subcounties were selected. Among the 7,192 residents of the 5 subcounties who were ages 40–79 years, 5,018 were surveyed in the first wave of the study (years 2001 and 2002; response rate 70%). Subjects were invited by both telephone and mail to participate, with the announcement that "This is a study evaluating general health and physical function in the adult." Pain and arthritis were not mentioned in the study advertisement. The present study involved 3,431 subjects participating in the third wave of the Korean Health and Genome Study (2007 and 2008). Beginning in 2008, subjects were examined by dual x-ray absorptiometry (DXA) to measure fat and muscle mass; 1,535 subjects underwent DXA. Compared to the subjects from 2007 who were not examined by DXA, the 2008 subject group was not significantly different in terms of sex composition and BMI. A flow chart illustrating the numbers of subjects participating in each wave of the study is shown in Figure 1.

**Baseline data and health interview.** Demographic and clinical information including education, occupation, exercise, and comorbidities was collected at baseline, using a standard questionnaire administered during a face-to-face interview. Education was dichotomized into $\geq$12 years (finished high school, finished vocational school, some college, finished col-

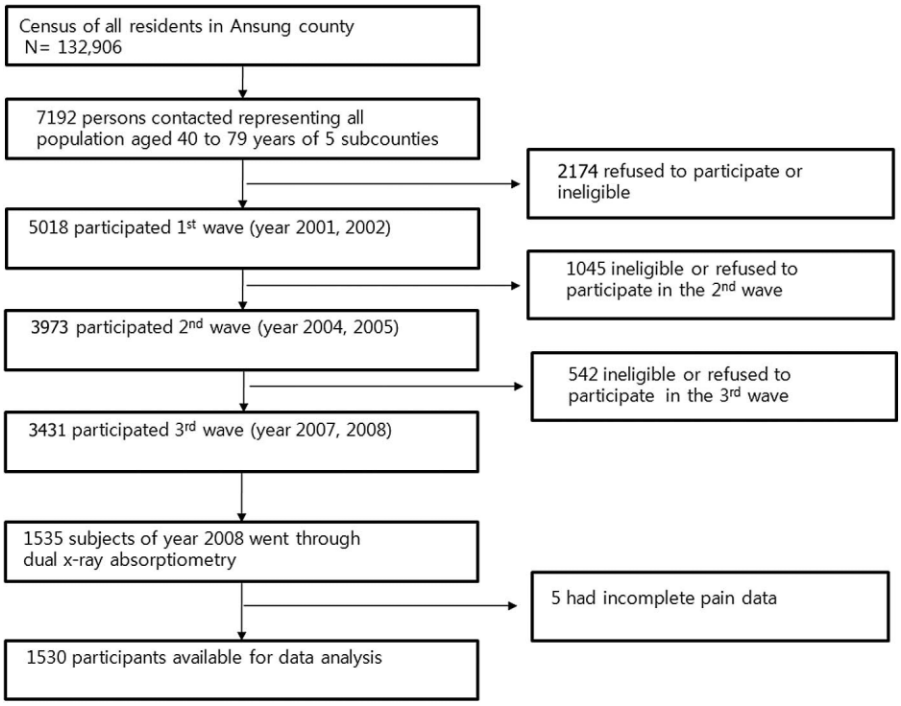


**Figure 1.** Recruitment, enrollment, and followup of the study participants.

lege, some graduate school, and higher) or <12 years. Exercise was self-reported and classified as none or at least once per week (once per week, 2–3 times per week, and daily). Participants who had either a fasting glucose level of ≥126 mg/dl or a glucose level of ≥200 mg/dl 2 hours after 75-gm oral glucose loading, or were receiving treatment for previously diagnosed DM, were classified as having DM. Hypertension was defined as either a systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg after 3 sphygmomanometer measurements with the second and third measurements averaged to estimate systolic and diastolic pressure, or specific treatment for previously diagnosed hypertension. Data on hand or knee arthritis were collected based on responses to a question asking participants whether they had ever been diagnosed by a physician as having hand or knee arthritis.

**Anthropometric measurement.** For calculation of BMI, height (cm) and body weight (kg) were measured to the nearest 0.1 cm and 0.1 kg, respectively, with the subject wearing light clothing and no shoes. Obesity was defined as a BMI of ≥25 kg/m$^2$. DXA (Prodigy; GE Healthcare) was used to calculate body composition.

**Determination of metabolic syndrome components and grouping according to metabolic syndrome and BMI.** Metabolic syndrome was defined according to the International Diabetes Federation 2005 recommendations (waist circumference >90 cm in men or >80 cm in women, serum triglyceride ≥150 mg/dl or specific treatment for this lipid abnormality, high-density lipoprotein cholesterol <40 mg/dl in men or <50 mg/dl in women or specific treatment for this lipid abnormality, fasting blood glucose ≥100 mg/dl or treatment for previously diagnosed type 2 DM, and systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or treatment for previously diagnosed hypertension) (34). Participants were divided into groups according to the presence or absence of metabolic syndrome and normal or high BMI. Metabolic obesity was defined as the presence of at least 3 features of metabolic syndrome; BMIs between 18.5 and 25 kg/m$^2$were considered normal weight and those >25 kg/m$^2$were considered obese. The 4 groups were categorized as follows: metabolically normal/normal weight (MN/NW), metabolically obese/normal weight (MO/NW), metabolically normal/obesity (MN/OB), and metabolically obese/obesity (MO/OB).

**Determination of pain categories.** This study measured pain by the number of locations of frequent pain, as described by Leveille et al (35). Briefly, participants were asked if they had pain, aching, or stiffness in any of their joints on most days. Persons who responded "yes" were asked to mark painful joints with circles on a homunculus showing upper and lower extremity joints and 4 areas of the back and neck (9). Pain was categorized according to the number of pain regions, and with this method, the most severe category of pain was widespread pain, defined, as described in the American College of Rheumatology preliminary criteria for fibromyalgia (36), as pain above the waist, below the waist, on both sides of the body, and in the axial region. The 3 other categories of pain in these analyses were pain in 2 or more regions that did not meet the criteria for widespread pain, pain in 1 region, and no pain.

**Statistical analysis.** The significance of between-group differences was evaluated using Student's *t*-test for continuous variables and Pearson's chi-square test for categorical variables. Descriptive statistics, means, and percentages, were used

for exploring the relationships between pain categories and demographic characteristics. To test for association across categories of pain constellations and body composition, means and (SEMs) were assessed by analysis of covariance (ANCOVA) after adjustment for age. Interaction by sex with the features being analyzed was also assessed using ANCOVA. Statistical tests were first performed for the total group of participants, and the results were then reexamined in separate groups of male and female subjects. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were derived using multivariate logistic regression methods examining the association between widespread pain and body composition after adjustment for factors found to be significantly associated with widespread pain in univariate analyses (age, sex, and history of arthritis) (5). Body composition was analyzed by quartile, and ORs in other quartiles were calculated compared to the lowest quartile of total fat mass or fat:muscle mass ratio after adjustment for confounders. To analyze the association between metabolic syndrome and pain independent of BMI, we examined the distribution of pain categories within each of the 4 groups (MN/NW, MO/NW, MN/OB, and MO/OB) and calculated the OR and 95% CI for widespread pain within the MO/NW, MN/OB, and MO/OB groups relative to the MN/NW group by multivariate logistic regression analysis. Statistical analyses were performed using SPSS 12.0. *P* values less than 0.05 (2-tailed) were considered significant.

## RESULTS

**Characteristics of the study subjects.** Of the 1,535 participants in the Korean Health and Genome Study who underwent DXA in 2008, complete data on pain were available for 1,530. These 1,530 individuals (682 men and 848 women; mean age 60.8 years) comprised the study population for the present investigation. Demographic and clinical characteristics are shown in Table 1. Mean BMI, mean total fat mass, mean fat:muscle mass ratio, prevalence of obesity, and prevalence of self-reported arthritis were higher in women compared to men.

**Association between body composition and musculoskeletal pain.** We analyzed the association between body composition features and extent of pain distribution after adjustment for age (Table 2). Total fat mass and fat:muscle mass ratio were significantly and positively associated with musculoskeletal pain, with a corresponding significant negative association between total lean mass and musculoskeletal pain. Because there was significant interaction by sex between lean body mass and extent of pain, the association was reexamined in male and female subjects separately. In this analysis, although total fat mass and fat:muscle mass ratio were positively associated with pain in both sexes, the association reached statistical significance only among women.

**Multivariate logistic regression analysis of the association between fat mass and widespread pain.** We next performed multivariate logistic regression analysis to assess the association between total fat mass or fat:muscle mass ratio and widespread pain (Table 3). While total fat mass was significantly associated with widespread pain in unadjusted analysis, after adjustment for age and sex the association was significant only in the highest quartile of fat mass (OR 1.67 [95% CI 1.04–

**Table 1.** Demographic characteristics of the study participants

| Characteristic* | Men (n = 682) | Women (n = 848) | Total (n = 1,530) | *P*, men vs. women |
|---|---|---|---|---|
| Age, mean ± SD years | 60.6 ± 8.49 | 60.9 ± 8.70 | 60.8 ± 8.60 | 0.600 |
| BMI, mean ± SD kg/m$^2$ | 23.8 ± 3.0 | 24.7 ± 3.3 | 24.3 ± 3.2 | <0.001 |
| Total fat mass, mean ± SD kg | 13.7 ± 5.8 | 19.5 ± 6.0 | 16.9 ± 6.6 | <0.001 |
| Total lean mass, mean ± SD kg | 50.1 ± 6.0 | 36.2 ± 3.8 | 42.4 ± 8.5 | <0.001 |
| Fat:muscle mass ratio, mean ± SD | 0.27 ± 0.11 | 0.54 ± 0.15 | 0.42 ± 0.19 | <0.001 |
| Obese, no. (%) | 244 (35.8) | 376 (44.3) | 620 (40.5) | <0.001 |
| Education ≥12 years, no. (%) | 271 (39.7) | 138 (16.3) | 409 (26.7) | <0.001 |
| Alcohol use, no. (%) | 456 (66.9) | 201 (23.7) | 657 (42.9) | <0.001 |
| Smoking, no. (%) | 237 (34.8) | 14 (1.7) | 251 (16.4) | <0.001 |
| Exercise ≥1 time per week, no. (%) | 287 (42.1) | 316 (37.3) | 603 (39.4) | 0.055 |
| Diabetes mellitus, no. (%) | 158 (23.2) | 164 (19.3) | 322 (21.0) | 0.062 |
| Hypertension, no. (%) | 125 (18.3) | 171 (20.2) | 296 (19.3) | 0.366 |
| Self-reported arthritis, no. (%) | 31 (4.5) | 125 (14.7) | 156 (10.2) | <0.001 |

* Obesity was defined as a body mass index (BMI) of ≥25 kg/m$^2$. Alcohol use was defined as drinking of any alcoholic beverages more than once per month. Smoking was defined as >20 packs of cigarettes ever smoked during lifetime. Diabetes mellitus was defined as either a fasting glucose level of ≥126 mg/dl or a 2-hour glucose level of ≥200 mg/dl after 75-gm oral glucose loading, or treatment for previously diagnosed diabetes mellitus. Hypertension was defined as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg after 3 sphygmomanometer measurements, with the second and third measurements averaged to estimate systolic and diastolic pressure, or specific treatment for previously diagnosed hypertension. Self-reported arthritis was defined as a positive response by the subject when asked if he or she had ever been diagnosed by a physician as having hand or knee arthritis.

**Table 2.** Association between body composition and extent-of-pain distribution after adjustment for age*

| | No pain | Pain in 1 region | Pain in 2–3 regions | Widespread pain | *P* |
|---|---|---|---|---|---|
| All subjects | | | | | |
| Total fat mass, kg | 15.9 ± 0.3 | 15.9 ± 0.3 | 18.5 ± 0.4 | 19.1 ± 0.4 | <0.001 |
| Total lean mass, kg | 44.0 ± 0.3 | 42.4 ± 0.4 | 41.2 ± 0.5 | 39.6 ± 0.5 | <0.001 |
| Fat:muscle mass ratio | 0.38 ± 0.01 | 0.39 ± 0.01 | 0.47 ± 0.01 | 0.50 ± 0.01 | <0.001 |
| Male subjects | | | | | |
| Total fat mass, kg | 13.9 ± 0.30 | 13.0 ± 0.4 | 13.9 ± 0.6 | 14.6 ± 0.8 | 0.249 |
| Total lean mass, kg | 50.5 ± 0.3 | 49.3 ± 0.4 | 49.9 ± 0.6 | 51.1 ± 0.8 | 0.038 |
| Fat:muscle mass ratio | 0.27 ± 0.01 | 0.26 ± 0.01 | 0.29 ± 0.01 | 0.29 ± 0.02 | 0.375 |
| Female subjects | | | | | |
| Total fat mass, kg | 18.6 ± 0.4 | 18.7 ± 0.4 | 20.8 ± 0.4 | 20.2 ± 0.5 | <0.001 |
| Total lean mass, kg | 35.7 ± 0.2 | 36.0 ± 0.3 | 36.9 ± 0.3 | 36.4 ± 0.3 | 0.005 |
| Fat:muscle mass ratio | 0.52 ± 0.01 | 0.52 ± 0.01 | 0.56 ± 0.01 | 0.55 ± 0.01 | 0.001 |

* Values are the mean ± SEM. *P* values (for trend) were determined by analysis of covariance.

2.68]). After further adjustment for self-reported arthritis, the association between fat mass and widespread pain was no longer significant. In contrast, compared to the lowest quartile of fat:muscle mass ratio, the ORs for quartiles 2, 3 and 4 were all statistically significant and remained so after adjustment for age, sex, and arthritis.

**Association between metabolic syndrome and pain.** Finally, to analyze the association between metabolic syndrome and pain independent of BMI, we examined the extent-of-pain distribution within each of the 4 subgroups (MN/NW, MO/NW, MN/OB, and MO/OB) (Table 4). The MN/NW, MO/NW, MN/OB, and MO/OB phenotypes accounted for 43.1%, 16.4%, 15.7%, and 24.8% of the study population, respectively. MO/NW subjects comprised 12.7% of the male population and 19.4% of the female population. Compared to MN/NW subjects, widespread pain was more common in MO/NW subjects (17.2% in MO/NW versus 11.0% in MN/NW [7.0% versus 6.6% in men, and 22.6% versus 16.0% in women, respectively]). In addition, compared to MN/OB subjects, widespread pain was more common in MO/OB subjects (19.6% in MO/OB subjects versus 16.7% in MN/OB subjects). This tendency toward a higher prevalence of widespread pain among those with metabolic syndrome was more pronounced among female subjects.

The OR and 95% CI for widespread pain within the MO/NW, MN/OB, and MO/OB groups relative to the MN/NW group, determined by multivariate logistic regression analysis, are shown in Table 5. In unadjusted analysis, ORs for widespread pain were greater in all 3 groups compared to the MN/NW group; the association was nonsignificant in the MO/NW group after adjustment for age and sex. After further adjustment for

**Table 3.** Association of total fat mass and fat:muscle mass ratio with widespread pain*

| | Unadjusted | | Model 1† | | Model 2‡ | |
|---|---|---|---|---|---|---|
| Characteristic | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Total fat mass | | | | | | |
| Quartile 1 | Referent | – | Referent | – | Referent | – |
| Quartile 2 | 1.77 (1.14–2.76) | 0.011 | 1.46 (0.91–2.33) | 0.113 | 1.45 (0.91–2.32) | 0.120 |
| Quartile 3 | 1.68 (1.07–2.61) | 0.023 | 1.35 (0.83–2.19) | 0.223 | 1.24 (0.76–2.03) | 0.380 |
| Quartile 4 | 2.42 (1.58–3.70) | <0.001 | 1.67 (1.04–2.68) | 0.034 | 1.50 (0.93–2.43) | 0.099 |
| *P* for trend | – | <0.001 | – | <0.001 | – | <0.001 |
| Fat:muscle mass ratio | | | | | | |
| Quartile 1 | Referent | – | Referent | – | Referent | – |
| Quartile 2 | 2.18 (1.30–3.67) | 0.003 | 1.86 (1.08–3.21) | 0.026 | 1.83 (1.06–3.17) | 0.031 |
| Quartile 3 | 3.93 (2.41–6.41) | <0.001 | 2.18 (1.21–3.93) | 0.009 | 2.07 (1.14–3.75) | 0.016 |
| Quartile 4 | 4.33 (2.66–7.05) | <0.001 | 2.20 (1.19–4.05) | 0.012 | 1.94 (1.04–3.59) | 0.037 |
| *P* for trend | – | <0.001 | – | <0.001 | – | <0.001 |

* Odds ratios (ORs) are for the likelihood of widespread pain in the given quartile relative to that in the lowest quartile. 95% CI = 95% confidence interval.
† Adjusted for age and sex.
‡ Adjusted for age, sex, and self-reported arthritis.

**Table 4.** Distribution of anatomic extent of pain in 4 groups classified by the presence and absence of metabolic syndrome and of obesity*

| Group | No pain | Pain in 1 region | Pain in 2–3 regions | Widespread pain | Total | *P* |
|---|---|---|---|---|---|---|
| All | | | | | | <0.001 |
| MN/NW | 296 (45.1) | 184 (28.0) | 105 (16.0) | 72 (11.0) | 657 (43.1) | |
| MO/NW | 104 (41.6) | 69 (27.6) | 34 (13.6) | 43 (17.2) | 250 (16.4) | |
| MN/OB | 93 (38.8) | 60 (25.0) | 47 (19.6) | 40 (16.7) | 240 (15.7) | |
| MO/OB | 125 (33.1) | 80 (21.2) | 99 (26.2) | 74 (19.6) | 378 (24.8) | |
| Total | 618 (40.5) | 393 (25.8) | 285 (18.7) | 229 (15.0) | 1,525 (100) | |
| Men | | | | | | 0.919 |
| MN/NW | 175 (50.0) | 103 (29.4) | 49 (14.0) | 23 (6.6) | 350 (51.6) | |
| MO/NW | 47 (54.7) | 23 (26.7) | 10 (11.6) | 6 (7.0) | 86 (12.7) | |
| MN/OB | 51 (52.6) | 28 (28.9) | 10 (10.3) | 8 (8.2) | 97 (14.3) | |
| MO/OB | 74 (51.0) | 36 (24.8) | 25 (17.2) | 10 (6.9) | 145 (21.4) | |
| Total | 347 (51.2) | 190 (28.0) | 94 (13.9) | 47 (6.9) | 678 (100) | |
| Women | | | | | | <0.001 |
| MN/NW | 121 (39.4) | 81 (26.4) | 56 (18.2) | 49 (16.0) | 307 (36.2) | |
| MO/NW | 57 (34.8) | 46 (28.0) | 24 (14.6) | 37 (22.6) | 164 (19.4) | |
| MN/OB | 42 (29.4) | 32 (22.4) | 37 (25.9) | 32 (22.4) | 143 (16.9) | |
| MO/OB | 51 (21.9) | 44 (18.9) | 74 (31.8) | 64 (27.5) | 233 (27.5) | |
| Total | 271 (32.0) | 203 (24.0) | 191 (22.6) | 182 (21.5) | 847 (100) | |

* Values are the number (%). *P* values (for trend) were determined by Pearson's chi-square test. MN/NW = metabolically nonobese/normal weight (≤2 metabolic syndrome features and body mass index [BMI] <25 kg/m$^2$); MO/NW = metabolically obese/normal weight (≥3 metabolic syndrome features and BMI <25 kg/m$^2$); MN/OB = metabolically nonobese/obesity (≤2 metabolic syndrome features and BMI ≥25 kg/m$^2$); MO/OB = metabolically obese/obesity (≥3 metabolic syndrome features and BMI ≥25 kg/m$^2$).

self-reported arthritis, the association remained significant only in the MO/OB group. Since there was significant interaction by sex in the association between the 4 phenotypes and widespread pain, the data were analyzed separately by sex, and the association of MO/OB phenotype with widespread pain was found to be significant among women only (data not shown).

## DISCUSSION

In this study, fat mass and fat:muscle mass ratio were significantly associated with musculoskeletal pain. When separate analyses were performed by sex, the association remained significant only among women. The most severe pain category, widespread pain, was significantly associated with high fat:muscle mass ratio after adjustment for confounders. Although widespread pain tended to be more prevalent in subjects with metabolic syndrome regardless of BMI, the association between metabolic syndrome and widespread pain became nonsignificant after adjustment for age and sex.

With obesity reaching epidemic proportions worldwide, its detrimental influence on many health-related conditions has recently become a focus of research. The proinflammatory effect of obesity in the pathogenesis of musculoskeletal diseases, independent of its biomechanical effect, has also been gaining interest. Several studies have demonstrated that BMI is associated with the development of OA in non–weight-

**Table 5.** Association between metabolic syndrome and widespread pain*

| | Unadjusted | | Model 1† | | Model 2‡ | |
|---|---|---|---|---|---|---|
| Group (n) | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| MN/NW (368) | Referent | – | Referent | – | Referent | – |
| MO/NW (147) | 1.70 (1.10–2.64) | 0.018 | 1.04 (0.64–1.68) | 0.874 | 1.04 (0.63–1.70) | 0.885 |
| MN/OB (133) | 1.77 (1.13–2.78) | 0.013 | 1.76 (1.07–2.90) | 0.026 | 1.63 (0.98–2.72) | 0.062 |
| MO/OB (199) | 2.43 (1.65–3.58) | <0.001 | 1.91 (1.25–2.93) | 0.003 | 1.88 (1.21–2.91) | 0.005 |

* Odds ratios (ORs) are for the likelihood of widespread pain in the given group relative to that in the MN/NW group. 95% CI = 95% confidence interval (see Table 4 for other definitions).
† Adjusted for age and sex.
‡ Adjusted for age, sex, and self-reported arthritis.

bearing joints such as the hands (13,37). In a 6-year followup study of hand OA, a high baseline adiponectin level was associated with radiographic progression of hand OA after adjustment for age, sex, and BMI (25), indicating a role of adipokines in arthritis pathogenesis independent of joint loading. Additionally leptin and other adipokines associated with excess fat have been linked to complex physiologic processes involving inflammation that can lead to painful conditions (26).

Although distinguishing the biomechanical and inflammatory mechanisms by which obesity contributes to painful conditions is challenging, two recent studies shed light on the systemic metabolic effects of obesity in knee OA. In one study (38), mice were fed either a control diet or a very high-fat diet, and half of the mice in each diet group were housed with running wheels. Obesity due to a very high-fat diet induced knee OA and systemic inflammation in proportion to body fat. In the high-fat diet subgroup subjected to wheel running exercise, however, this exercise mitigated the severity of knee OA, improved glucose tolerance, and disrupted the coexpression of proinflammatory cytokines without a significant change in body weight. This provided evidence that knee OA in the obese mice could not be explained by biomechanical load only. In the other study, a cross-sectional study of 2,893 human subjects, the association between knee OA and obesity with or without sarcopenia was examined. Sarcopenic obesity was found to be more closely associated with knee OA than was nonsarcopenic obesity (39).

We can speculate that the association between fat mass and musculoskeletal pain observed in the present study may be caused by the greater severity of OA resulting from increased joint load. However, since the association between widespread pain and fat:muscle mass ratio remained significant after adjustment for self-reported arthritis, and pain from knee OA and widespread pain may not have the same pathophysiology, aggravation of OA by increased fat mass might only partially account for increase in pain in our study subjects. In addition, a recent study showed that clinically relevant weight loss in older obese patients with knee OA reduced pain independent of muscle strength, knee joint alignment, or structural damage at baseline as assessed by imaging (40), which corroborates our hypothesis that obesity has a role in pain aggravation independent of joint damage.

Few studies have examined the association between body composition in terms of fat and muscle mass, which can be assessed by DXA or bioelectric impedance, and musculoskeletal status. In studies of patients with early RA (disease duration $\leq$12 months) (41,42), the patients were observed to have lower lean mass of the arms and legs, higher total body fat mass, and higher truncal fat distribution than age- and sex-matched controls, and antiinflammatory treatment for 2 years ameliorated these potentially harmful alterations and improved symptoms as assessed by the Health Assessment Questionnaire (HAQ) (43). In a study of the associations of measures of fat and lean mass with disability in RA patients, HAQ score was strongly associated with body composition, with increasing fat and decreasing lean mass associated with higher HAQ scores after adjustment for demographic and clinical characteristics (44).

Studies examining the association between body composition and pain include a recent cross-sectional study of 135 participants ages 25–62 years showing that greater fat mass, but not lean tissue mass, was associated with the degree of intensity of low back pain and disability (45), and another study of 136 middle-aged adults showing that foot pain was positively associated with BMI, fat mass, and fat mass index, but not with muscle mass or fat-free mass index (46). Although many studies have revealed the detrimental effects of obesity on clinical aspects of fibromyalgia, only one has identified associations of BMI, fat mass, and lean mass with distinct domains of quality-of-life measures (28). In the present study the fat:muscle mass ratio was more strongly associated with pain than was fat mass after adjustment for confounders, lending more credence to the hypothesis that the proportion of fat mass to total body mass contributes to pain.

The association between fat mass and pain was stronger in female subjects than in male subjects in our study. Frequently observed differences between men and women in the prevalence and consequences of pain may thus be explained by body fat mass. In a study of whether BMI influences RA disease activity in a sex-specific manner, while the mean 28-joint Disease Activity Score (47) increased with increasing BMI among women, the opposite trend was observed among men (48). This may result from the greater contribution of fat mass to BMI in females than males. Although research regarding sex differences in pain has proliferated in recent decades (49), the specific etiologic basis of these sex differences is unknown. Recent studies have shown that obesity was associated with the reproductive axis and that circulating adiponectin levels were related to levels of sex hormones (50–52). In a recent review it was suggested that the interactive effects of the gonadal hormones with the opioidergic system might be an

important determinant of sex-based difference in pain (49). Adiposity, gonadal hormones, and the opioidergic system may provide a hidden link to underlying mechanisms of sex differences in musculoskeletal pain.

Another plausible mechanism linking obesity and pain is metabolic syndrome, which is known to be associated with chronic pain and inflammation (53,54). However, the influence of high BMI cannot be easily segregated because of its strong association with both metabolic syndrome and pain. For this purpose, analyzing a subset of subjects who are affected either by metabolic syndrome or obesity, but not both, would be appropriate. The MO/NW phenotype is of special interest because this subgroup allows examination of the relationship between metabolic syndrome and pain in subjects with normal BMI (30,31).

Although compared to MN/NW subjects, MO/NW subjects, and especially female MO/NW subjects, tended to have more widespread pain, this association became nonsignificant after adjustment for confounders. MO/OB subjects also tended to have more widespread pain compared to MN/OB subjects; however, this association was also not significant after adjustment for confounders. The lack of association between metabolic syndrome and pain would be caused by the varying influence of each metabolic syndrome component on pain. Among the 5 items included in the metabolic syndrome definition, fasting glucose and waist circumference were significantly associated with the extent-of-pain distribution only among women (detailed data available from the corresponding author upon request). In the normal BMI group, BMI was significantly higher among those with metabolic syndrome (mean ± SEM 23.17 ± 1.46 kg/m$^2$, versus 21.86 ± 2.05 kg/m$^2$ in those without metabolic syndrome); thus, the slight association we observed may be explained by excess BMI. Further adjustment for either BMI or abdominal circumference eliminated the association between metabolic syndrome and pain in each of the 4 categories (data not shown).

Our study had strengths and limitations. It is the first large-scale population-based study of the association between body composition, specifically fat and muscle mass, and the extent of musculoskeletal pain distribution. We examined the association of metabolic syndrome with pain independently of BMI by comparing subsets of the population, MO/NW and MN/OB, which are not generally considered in studies of the effects of obesity. However, the cross-sectional design of our study precluded elucidation of the causative role of fat mass, because chronic pain might lead to decreased physical activity which leads to increases in fat mass, resulting in reverse causality. The presence of arthritis, which was a significant risk factor for widespread pain, was self-reported because physical examination for formal evaluation of arthritis could not be performed due to limited budget and other logistical issues; thus, diagnostic inaccuracy and bias inflating the risk might have been introduced. The study area included only rural communities, reducing the representativeness of the study sample. Psychological factors, such as depression or anxiety, which play an important role in the development of widespread pain, and neuropathy and analgesic use were not assessed.

In conclusion, greater fat mass and fat:muscle mass ratio were significantly associated with musculoskeletal pain overall, and when examined separately in men and women this association remained significant only among women. The most severe pain category, widespread pain, was significantly associated with high fat:muscle mass ratios after adjustment for confounders. The presence of metabolic syndrome tended to be associated with musculoskeletal pain. Understanding the relationship between fat mass and pain may provide insights into preventative measures and therapeutic strategies for musculoskeletal pain.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Yoo, Cho, Kim.
**Acquisition of data.** Lim, Kim.
**Analysis and interpretation of data.** Cho, Lim, Kim.

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