Original Article

Association of Metabolic Factors with Symptomatic Hand Osteoarthritis in the Chinese Han Population Aged 40 Years and above

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Abstract

Background: The relationship between hand osteoarthritis (HOA) and systemic metabolic factors is unclear. The aim of this study was to investigate the prevalence of systemic metabolic factors including obesity, hypertension, diabetes mellitus, and atherosclerosis in symptomatic patients with HOA and the association between these systemic metabolic factors and symptomatic HOA in the Chinese Han population aged 40 years and above.

Methods: A cross-sectional survey was conducted on Chinese Han population aged 40 years and above in six centers in China. The sociodemographic features, lifestyle of the participants, and medical history of hypertension, diabetes mellitus, and atherosclerosis were collected. The cases with hand symptoms underwent anteroposterior radiographic examination of both hands to obtain a diagnosis. The correlations between systemic metabolic factors and symptomatic HOA were analyzed using Logistic regression analysis.

Results: Overweight (39.3% vs. 30.5%, $P < 0.001$), hypertension (34.7% vs. 18.6%, $P < 0.001$), diabetes mellitus (11.2% vs. 3.3%, $P < 0.001$), and atherosclerosis (19.8% vs. 8.3%, $P < 0.001$) were more prevalent in symptomatic patients with HOA than those in the population without HOA. Overweight (odds ratio [*OR*] = 1.35, 95% confidence interval [*CI*]: 1.10–1.65, $P = 0.005$), hypertension (*OR* = 1.47, 95% *CI*: 1.18–1.83, $P < 0.001$), and diabetes mellitus (*OR* = 2.45, 95% *CI*: 1.74–3.45, $P < 0.001$) were associated with a higher prevalence of symptomatic HOA and the *OR* of symptomatic HOA significantly increased with the accumulated number of the three metabolic factors. Symptomatic HOA was associated with a higher prevalence of atherosclerosis (*OR* = 1.39, 95% *CI*: 1.05–1.85, $P = 0.023$).

Conclusions: Overweight, hypertension, and diabetes mellitus were associated with a higher prevalence of HOA, showing cumulative effects. Atherosclerosis risk should be assessed in patients with HOA.

Key words: Atherosclerosis; Diabetes Mellitus; Hand; Hypertension; Osteoarthritis; Overweight

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder and affected 151 million individuals globally in 2000. It is the major cause of pain and chronic disability worldwide.[1] Moreover, OA incidence is still rapidly increasing largely because of the increase in obesity rates and the aging population.[2] The hands are the third most common sites of OA, following the knees and hips. The health-related quality of life in patients with hand osteoarthritis (HOA) could be considerably affected because of pain and limitations in daily activities as demonstrated in a study by Kwok *et al*.[3] OA is caused by abnormal stress to the joint, based on systemic susceptible factors, including genetics, age, gender, and nutrition.[4]

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Obesity is considered one of the most important predisposing factors for OA in the weight-bearing joints, especially the knees and hips, because of increased load on joint surface that accelerates wear.[5] However, several studies have also linked obesity to OA in nonweight-bearing areas, especially the finger joints,[6,7] suggesting that systemic effects exerted by metabolic factors other than simple local biomechanics possibly play a

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role in the high prevalence of OA in the obese population. Investigators also have reported the association of OA with other systemic metabolic factors, including hypertension, diabetes mellitus, and elevated blood lipid levels.[8-15]

Research on the relationship between OA and systemic metabolic risk factors will deepen our understanding of OA and is important for both prevention and treatment of OA. To date, most researchers have focused on the metabolic factors in patients with hip, knee, or generalized OA, while only a few reports have evaluated patients with HOA, and the results are conflicting. Furthermore, there is no report on these relationships in the Chinese population or in Asian people. Therefore, the purpose of our study was to examine the association of HOA with systemic metabolic factors in the Chinese Han population. Because the possibility exists that atherosclerosis and OA may share pathogenic mechanisms involving metabolic abnormalities, and studies have suggested that OA is associated with atherosclerosis and significantly predicted cardiovascular deaths,[16,17] we also examined the association between HOA and atherosclerosis.

Methods

Study population

This study utilized data of cases from the Prevalence of Osteoarthritis in the Population Aged 40 years and above in China (TPOAPC), which was under the support of the National Science and Technology Department's Tenth Five-year Plan (No. 2004BA702B06). TPOAPC was a cross-sectional survey conducted from July 1, 2005, to August 31, 2005, to investigate the epidemiology of OA in a representative sample of the Han population aged 40 years and above in China.

TPOAPC used a nationwide, stratified, four-stage, cluster sampling method. Six centers belonging to six administrative divisions of China (North China, Northeast China, East China, South Central China, Southwest China, and Northwest China) were selected, and in Shijiazhuang, Harbin, Shanghai, Guangzhou, Chengdu, and Xi'an, respectively. The population of each center was divided into urban and rural strata. A half-ratio observation per stratum was allocated, taking a multistage, random cluster sampling in each stratum (three-stage sampling: the first stage of sampling was in cities, the second stage of sampling in districts, and the third stage in communities). Finally, 1008, 1190, 997, 998, 1017, and 1008 people in Shijiazhuang, Harbin, Shanghai, Guangzhou, Chengdu, and Xi'an respectively were sampled.

The study was conducted with the approval of the Ethics Committee of the Beijing Hospital and other centers. All participants obtained written and oral information about the study and provided written informed consents before any study-related procedure was conducted.

Data collection

All participants completed an interviewer-controlled questionnaire of 94 items, including questions about sociodemographic features and lifestyle information such as occupation, most frequently used tools, smoking habit, alcohol consumption, diet, family history, medical history, physical activity, hand pain, and hand function. In addition, participants with hand symptoms (defined as hand pain, aching, or stiffness for a few days or more in the last month) underwent radiographic examination of both hands using an anteroposterior view positioning. Similarly, those with symptoms in the knee/knees, cervical or lumbar joints underwent radiographic examination of both knees and the cervical or lumbar spine using anteroposterior and lateral view positioning. Anthropometric measures included height and weight. Subsequently, the body mass index (BMI) was calculated (kg/m^2) (BMI: weight [kg]/height [m]^2). The interviewers were uniformly trained professional staff.

Variables definitions

Overweight and obesity were defined based on the WHO criteria (overweight: BMI ≥25 kg/m^2; preobese: 25 kg/m^2≤BMI <30 kg/m^2; obesity: BMI ≥30 kg/m^2).[18] Hypertension, diabetes mellitus, and atherosclerosis were defined as a history, medical diagnosis made by a physician, or regular use of corresponding medication. Type 1 diabetes and Type 2 diabetes were not differentiated.

Hand osteoarthritis diagnosis

Radiographs were read by one of the two experienced orthopedists without the knowledge of the participants' clinical status. The bilateral 2nd–5th distal and proximal interphalangeal, thumb interphalangeal, and 1st–5th metacarpophalangeal and carpometacarpal joints were graded according to the Kellgren-Lawrence grading scale.[19] Symptomatic HOA was defined as at least one joint with existing radiographic HOA (Kellgren-Lawrence grade ≥2) and pain/aching/stiffness in the same joint(s). Persons with secondary OA were excluded from the study.

Similarly, knee, cervical, or lumbar OA was defined as existing radiographic OA (Kellgren-Lawrence grade ≥2) and symptoms (pain/aching/stiffness) in the same joint(s).

Statistical analysis

Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were calculated including the mean and standard deviation (SD) of continuous variables and frequencies of categorical variables. For categorical variables, the Chi-square statistic was used to test the statistical significance between groups. Logistic regression analysis was performed to test the association of symptomatic HOA with systemic metabolic factors and the cumulative number of metabolic factors present. The results were expressed as odd ratios (*OR*s), 95% confidence intervals (*CI*s), and *P* values. Because the prevalence of HOA is associated with OA in other areas (like knee OA) and the incidence of OA is already known to increase with age and may be influenced by many other factors, the effect of OA in other areas (knee, cervical spine, and lumbar spine), age, gender, level of education, occupation, most frequently used tools, smoking habit, alcohol consumption, diet, and

family history were included in the regression model. We also examined whether symptomatic HOA was associated with atherosclerosis using Logistic regression. For all tests, $P < 0.05$ was considered statistically significant.

Results

A total of 6218 cases met the inclusion criteria. Among them, 484 met our diagnostic criteria of symptomatic HOA, and the prevalence of symptomatic HOA was 7.8%. The mean age of the general population was 54.8 years (SD, 10.0; range, 40–94 years). The demographic data of participants are shown in Table 1. Men and women were comparably distributed in the general population (women 53.1%); urban and rural residents were also equally distributed (rural 48.1%). Demographic data of the non-HOA population and patients with HOA showed significant differences in age and gender distribution. Cases with symptomatic HOA tended to be significantly older and were more often women (69.2% vs. 51.7%, $P < 0.001$). The mean age of the population with symptomatic HOA was 60.7 years (SD, 9.9), compared with 54.3 years (SD, 9.8) in the general non-HOA population.

Prevalence of individual metabolic factors

The prevalence of overweight, hypertension, diabetes mellitus, and atherosclerosis in the total population was 31.2%, 19.8%, 3.9%, and 9.2%, respectively [Table 1]. As shown in Figure 1a, symptomatic patients with HOA had significantly greater prevalence of overweight (39.3% vs. 30.5%, $P < 0.001$), obesity (8.3% vs. 3.5%, $P < 0.001$), hypertension (34.7% vs. 18.6%, $P < 0.001$), diabetes mellitus (11.2% vs. 3.3%, $P < 0.001$), and atherosclerosis (19.8% vs. 8.3%, $P < 0.001$) than the general population without HOA. Figure 1b and 1c compare the prevalence of overweight, obesity, hypertension, diabetes mellitus, and atherosclerosis in men versus women, in the populations with HOA and without HOA, and similar results were observed except in men, where there was no significant difference in the prevalence of obesity.

Association of metabolic factors with hand osteoarthritis

Multivariate logistic regression analysis revealed that overweight (*OR* = 1.35, 95% *CI*: 1.10–1.65, $P = 0.005$), hypertension (*OR* = 1.47, 95% *CI*: 1.18–1.83, $P < 0.001$), and diabetes mellitus (*OR* = 2.45, 95% *CI*: 1.74–3.45, $P < 0.001$) were significantly associated with the prevalence of symptomatic HOA after adjusting for potential confounders [Table 2]. Logistic regression analysis with the same objective and explanatory factors and stratified according to gender indicated that overweight (*OR* = 1.71, 95% *CI*: 1.18–2.48, $P = 0.004$), hypertension (*OR* = 1.59, 95% *CI*: 1.07–2.35, $P = 0.022$), and diabetes mellitus (*OR* = 2.15, 95% *CI*: 1.17–3.97, $P = 0.014$) were still associated with symptomatic HOA in men; however, only obesity (*OR* = 2.01, 95% *CI*: 1.31–3.10, $P = 0.002$), hypertension (*OR* = 1.44, 95% *CI*: 1.11–1.87, $P = 0.007$), and diabetes mellitus (*OR* = 2.58, 95% *CI*: 1.70–3.91, $P < 0.001$) were associated with symptomatic HOA in women.

To clarify the accumulative effect of metabolic factors on the presence of symptomatic HOA, logistic regression analysis using the presence of symptomatic HOA as the objective variable and the number of metabolic factors present as explanatory variables was conducted after adjustment for age, gender, level of education, occupation, most frequently used tools, smoking habit, alcohol consumption, diet, family history, and knee OA. Figure 2 shows the *OR* (95% *CI*) of the association between an accumulative number of metabolic factors and HOA. Compared to the reference condition (no metabolic factor), increasing the number of metabolic factors significantly increased the *OR* for symptomatic HOA (compared to no metabolic factors, one metabolic factor: *OR* = 1.17, 95% *CI*: 0.94–1.47, $P = 0.162$; two metabolic factors: *OR* = 2.37, 95% *CI*: 1.82–3.09,

Table 1: Baseline demographic data of participants included in the study

Features	General population (n = 6218)	Non-HOA population (n = 5734)	HOA population (n = 484)	P*
Age (years), mean ± SD	54.8 ± 10.0	54.3 ± 9.8	60.7 ± 9.9	<0.001
Female, *n* (%)	3302 (53.1)	2967 (51.7)	335 (69.2)	<0.001
Rural residents, *n* (%)	2993 (48.1)	2782 (48.5)	211 (43.6)	0.037
Education, *n* (%)				
Primary school or less	2533 (40.7)	2279 (39.7)	254 (52.5)	<0.001
Middle school	2010 (32.3)	1888 (32.9)	122 (25.2)	
High school or more	1675 (26.9)	1567 (27.3)	108 (22.3)	
Current smoking, *n* (%)	1791 (28.8)	1689 (29.5)	102 (21.1)	<0.001
Current alcohol consumption, *n* (%)	1525 (24.5)	1455 (25.4)	70 (14.5)	<0.001
Overweight, *n* (%)				
BMI ≥25 kg/m^2	1937 (31.2)	1747 (30.5)	190 (39.3)	<0.001
Preobese (25 kg/m^2≤BMI <30 kg/m^2)	1694 (27.2)	1544 (26.9)	150 (31.0)	0.054
Obesity (BMI≥30 kg/m^2)	243 (3.9)	203 (3.5)	40 (8.3)	<0.001
Hypertension, *n* (%)	1233 (19.8)	1065 (18.6)	168 (34.7)	<0.001
Diabetes, *n* (%)	243 (3.9)	189 (3.3)	54 (11.2)	<0.001
Atherosclerosis, *n* (%)	572 (9.2)	476 (8.3)	96 (19.8)	<0.001

Data are number (frequency) except age. *Statistical significance between HOA and non-HOA population using the Chi-square test except for age (Student's *t*-test). HOA: Hand osteoarthritis; BMI: Body mass index; SD: Standard deviation.

Table 2: Association of HOA with overweight, hypertension, and diabetes*

Factors	Total			Men			Women		
	OR	95% *CI*	*P*	*OR*	95% *CI*	*P*	*OR*	95% *CI*	*P*
BMI									
BMI <25 kg/m^2	1.00			1.00			1.00		
Overweight (BMI ≥25 kg/m^2)	1.35	1.10–1.65	0.005	1.71	1.18–2.48	0.004	1.21	0.94–1.55	0.138
Preobese (25 kg/m^2≤BMI <30 kg/m^2)	1.23	0.99–1.54	0.062	1.67	1.14–2.44	0.009	1.07	0.82–1.41	0.609
Obesity (BMI ≥30 kg/m^2)	2.11	1.44–3.09	<0.001	2.31	1.00–5.33	0.050	2.01	1.31–3.10	0.002
Hypertension									
No	1.00			1.00			1.00		
Yes	1.47	1.18–1.83	<0.001	1.59	1.07–2.35	0.022	1.44	1.11–1.87	0.007
Diabetes									
No	1.00			1.00			1.00		
Yes	2.45	1.74–3.45	<0.001	2.15	1.17–3.97	0.014	2.58	1.70–3.91	<0.001

*Multivariate logistic regression model: Adjusted for age, gender, level of education, occupation, most frequently used tools, smoking habit, alcohol consumption, diet, family history, and knee OA. HOA: Hand osteoarthritis; *OR*: Odds ratio; *CI*: Confidence interval; BMI: Body mass index; OA: Osteoarthritis.

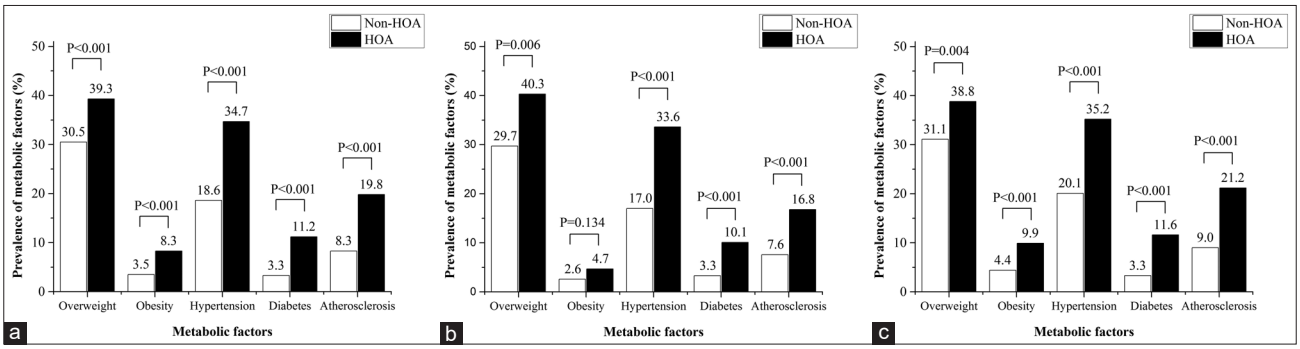

Figure 1: Frequencies of overweight, obesity, hypertension, diabetes mellitus, and atherosclerosis in the population with HOA and without HOA, in (a) total population, (b) men, and (c) women. HOA: Hand osteoarthritis; BMI: Body mass index.

P < 0.001; and three metabolic factors: *OR* = 5.09, 95% *CI*: 2.81–9.23, *P* < 0.001).

Association of hand osteoarthritis with Atherosclerosis

Using multivariate logistic regression modeling, controlling for age, gender, registered residence, occupation, BMI, hypertension, diabetes mellitus, smoking habit, alcohol consumption, diet, family history, and knee OA, patients with symptomatic HOA were more likely to have atherosclerosis, with an *OR* of 1.39 (95% *CI*: 1.05–1.85, *P* = 0.023). Analysis stratified according to gender revealed that symptomatic HOA was associated with a higher prevalence of atherosclerosis in women (*OR* = 1.43, 95% *CI*: 1.01–2.01, *P* = 0.043), but not in men.

Discussion

Our results show that in the Chinese Han population aged 40 years and above, overweight, hypertension, and diabetes mellitus were more prevalent in the symptomatic patients with HOA and were associated with symptomatic HOA with an accumulative effect. Symptomatic HOA was associated with a higher prevalence of atherosclerosis.

A population-based study including 7714 adult cases in the US by Puenpatom and Victor[10] found that metabolic syndrome had higher prevalence in patients with OA, regardless of gender or race, and each of the five cardiovascular risk factors comprising metabolic syndrome was more prevalent in patients with OA compared to the population without OA. Nevertheless, only a few population-based studies have shown the relationship between the presence of HOA and these metabolic factors. Kalichman and Kobyliansky[20] reported that women with obesity had an approximately three-fold higher risk of HOA compared to those with normal BMI; however, no association of prevalence of HOA with BMI was found in men. However, a previous longitudinal prospective study on 70-year-old individuals observed a significant association of radiographic HOA with BMI in men.[21] A recent study in Korea found that fat percentage was associated with radiographic HOA in both male and female cases while the distribution of fat tissue was the most significant factor in female cases.[22] Another study showed that being overweight or obese increased the risk of HOA.[23] In the current study, our findings confirm the previous results and show that overweight in men and obesity in women were associated with symptomatic HOA. A study by Nieves-Plaza *et al*.[14] revealed that patients with diabetes mellitus had a higher risk (*OR* = 2.18) of having hand or knee OA than nondiabetic cases, which is

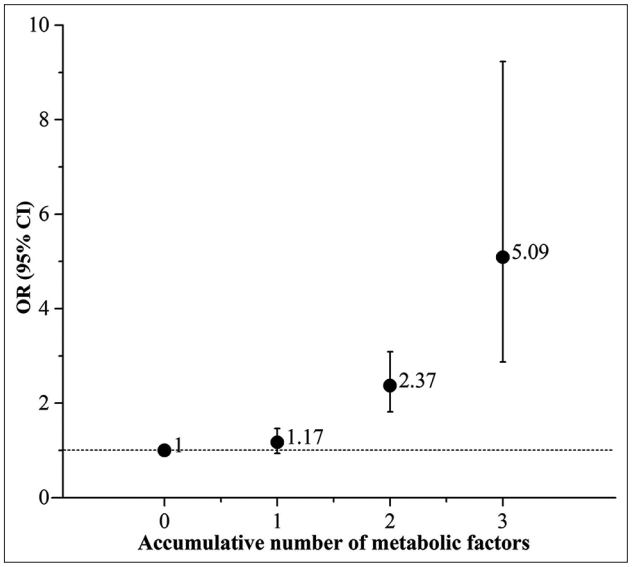

Figure 2: Association between an accumulative number of metabolic factors and the presence of HOA. Logistic regression analysis using the presence of symptomatic HOA as the objective variable and the number of metabolic factors present (compared to no metabolic factor) as explanatory variables after adjustment for age, gender, level of education, occupation, most frequently used tools, smoking habit, alcohol consumption, diet, family history, and knee OA. Systemic metabolic factors include overweight, hypertension, and diabetes mellitus. *OR*: Odds ratio; *CI*: Confidence interval; HOA: Hand osteoarthritis; OA: Osteoarthritis.

consistent with our results, showing that diabetes mellitus is associated with symptomatic HOA in both men and women.

A previous study demonstrated that overweight (BMI >27.4 kg/m^2) alone increased the likelihood of HOA with an *OR* of 1.4, while the concurrent presence of hypertension, and diabetes mellitus and being overweight led to an even higher risk of HOA (*OR* = 2.3) compared to absence of these characteristics,[24] suggesting an additional combined effect of hypertension and diabetes mellitus. However, to the best of our knowledge, no previous study has demonstrated the association between HOA and the accumulation of metabolic factors. Nevertheless, a prospective study of knee OA in Japan indicated that the risk of knee OA significantly increased with the number of metabolic syndrome components present (compared to no component: one component, *OR* = 2.33; two components, *OR* = 2.82; and equal to or more than three components, *OR* = 9.83).[25] Similarly, we found that the *OR* for the prevalence of HOA tended to increase with the accumulative number of systemic metabolic factors. The result suggests that even if the impact of each systemic metabolic factor on HOA may be weak, accumulation of the metabolic factors may significantly worsen HOA. These findings, suggesting the importance of systemic metabolic factors, may be of great clinical significance, implying that the metabolic factors in patients with HOA should be assessed and intervention targeted at metabolic factors may be helpful in the prevention of HOA. Whether the adequate control of each of these metabolic factors can contribute to the treatment of HOA or improving the quality of life in patients with HOA is unclear. Future longitudinal research is required to further evaluate the role of systemic metabolic factors in HOA.

The underlying mechanisms behind the association between symptomatic HOA and systemic metabolic factors remain unclear. Metabolic factors, such as obesity and diabetes mellitus, cause low-grade systemic inflammation which may lead to OA initiation or aggravation.[26] Studies have shown that abnormal activation of pro-inflammatory and neuroendocrine pathways existing in obesity results in altered metabolism,[27] increasing the expression of pro-inflammatory cytokines, as well as adipokines.[28] Studies on these mediators have indicated that they promote inflammation and catabolism during the pathophysiological processes of OA and lead to damage of joint cartilage.[27,28] Moreover, high glucose concentration increases the production of matrix metalloproteinases and reactive oxygen species in OA chondrocytes, which promotes the chondrocyte catabolic program and injury.[29,30] Advanced glycation end products accumulating in diabetes mellitus have been demonstrated to increase the production of interleukin (IL)-6 and IL-8 in OA chondrocytes,[31] and lead to increased stiffness of the cartilage matrix, thus becoming more sensitive to mechanical stress.[32] In addition, obesity, hypertension, and diabetes mellitus increase the risk of vascular pathology and episodically reduce blood flow through the small vessels within the subchondral bone, and these may facilitate the initiation and/or development of the OA.[33]

Some studies have reported an association between HOA and atherosclerosis in women,[16,34] which was supported by the present study. It appears that the pathology of OA and atherosclerosis have some similarities. It is now known that in patients with OA, inflammatory mediators synthesized by chondrocytes, bone, and synovial membrane diffuse into the articular cavity and ultimately into the circulation, and subsequently amplify the low-grade systemic inflammation, which probably induces or facilitates atherosclerosis.[26]

There were several strengths of the study. The current study was carried out on a large representative sample of people, allowing us to study the association of systemic metabolic factors with HOA in the Chinese population. The diagnosis of HOA in the present study relied on clinical and imaging diagnosis rather than on self-report. The inclusion of a wide range of explanatory factors allowed us to study their association with HOA, with adjustment for possible confounding factors. However, there are also several limitations in our study. First, the study was cross-sectional; therefore, the causal relationship between systemic metabolic factors and HOA remains unclear. Second, patients were categorized as having hypertension, diabetes mellitus, or atherosclerosis solely on the basis of patient-reported medical history; thus, the probability of misclassification bias should be taken into account. Third, the limitations of random cluster sampling not representing the overall population accurately must be considered, and the grading of radiographs was conducted by two assessors and we had

no data on reliability. In addition, in the present study, we had no information about how well hypertension or diabetes mellitus was controlled, and the duration of overweight, hypertension, or diabetes mellitus was not evaluated.

In conclusion, the present study showed that overweight, hypertension, and diabetes mellitus were associated with the prevalence of symptomatic HOA. Increasing the number of metabolic factors significantly increased the *OR* for the presence of symptomatic HOA. In addition, symptomatic HOA was associated with a higher prevalence of atherosclerosis, suggesting that in patients with HOA, assessment for atherosclerosis or cardiovascular disease should be carefully considered.

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Conflicts of interest

There are no conflicts of interest.

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