Review Article

Metabolic Syndrome Increases the Risk for Knee Osteoarthritis: A Meta-Analysis

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Background. Studies revealed that metabolic factors might contribute substantially to osteoarthritis (OA) pathogenesis. There has been an increasing interest to understand the relationship between knee OA and the metabolic syndrome (MetS). The purpose of this study was to explore the association between metabolic syndrome and knee osteoarthritis using meta-analysis. Methods. Databases, including PUBMED, EMBASE, and the Cochrane Library, were searched to get relevant studies. Data were extracted separately by two authors and pooled odds ratio (OR) with 95% confidence interval (CI) was calculated. Results. The meta-analysis was finished with 8 studies with a total of 3202 cases and 20968 controls finally retrieved from the database search. The crude pooled OR is 2.24 (95% CI = 1.38–3.64). Although there was significant heterogeneity among these studies, which was largely accounted for by a single study, the increase in risk was still significant after exclusion of that study. The pooled adjusted OR remained significant with pooled adjusted OR 1.05 (95% CI = 1.03–1.07, p < 0.00001). No publication bias was found in the present meta-analysis. Conclusions. The synthesis of available evidence supports that metabolic syndrome increases the risk for knee osteoarthritis, even after adjustment for many risk factors.

1. Introduction

Knee osteoarthritis (KOA) is a prevalent chronic joint disease affecting about 28% of the population in the USA at 45 years of age. It is estimated to rise up to 37% in adults aged over 65 years [1] within the next years. KOA affects joint tissues, including synovium, ligaments, tendons, muscle, and subchondral bone, causing cartilage and osteophyte formation at joints, eventually leading to arthralgia, stiffness, and limitations in the articular function, severely affecting patients’ physical functioning and quality of life [2, 3]. KOA is a heterogeneous disease, and risk factors include sex, age, mechanical factors, or obesity. Understanding the role each of the risk factors plays is important for KOA prevention.

Recently, studies revealed that metabolic factors might contribute substantially to OA pathogenesis [4]. There has been an increasing interest to understand the relationship between knee OA and the metabolic syndrome (MetS). Some studies supported the link between OA and characteristics of MetS, including hypertension, type 2 diabetes, and dyslipidemia [5, 6]. Additionally, several studies were inclined to recognize metabolic phenotype to be a common subtype of OA. Some studies support MetS as a contributing factor to an increased risk of OA. However, literature results are
controversial as there are other groups that do not support this belief. The purpose of this study was to provide a summary and analysis of published studies based on the association between OA and MetS.

2. Materials and Methods

2.1. Search Strategy. The authors did an intensive search on PUBMED, EMBASE, and the Cochrane Library for published studies until June 3, 2015. Relevant available articles were obtained using keywords such as ("Osteoarthritis" [Majr]) AND "Metabolic Syndrome X" [Majr], "osteoarthritis metabolism syndrome", and "osteoarthritis metabolic syndrome". No language restrictions were applied. A reference list of relevant papers was also screened.

2.2. Study Selection Criteria. A study was included if it met the following inclusion criteria: (1) It is cohort, case-control, or cross-sectional study investigating the association between MetS and risk of OA; (2) relative risk (RR) or odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) could be directly extracted or calculated from the available data; and (3) if there is duplicated data, the larger sample size was adopted. Two investigators independently applied the selection criteria to each reference identified by the search strategy. Any discrepancies regarding eligibility or quality were resolved by the third reviewer.

The following information was collected from each available article: year of publication, ethnicity of the studied population, numbers of cases and controls, mean age of case and control groups, and MetS criteria and OA criteria adopted adjusted OR and adjusted variables. All articles were independently reviewed by two investigators. Data was extracted independently and entered into separate databases. Results were compared and any discrepancy was resolved by the third investigator as well.

2.3. Definition of Metabolic Syndrome. The National Cholesterol Education Program-ATPIII (NCEP-ATPIII) definition was used to define metabolic syndrome (MetS) [14]. MetS is defined as the presence of any three out of five components: that is, abdominal obesity defined as the presence of any three out of five components: (1) It is cohort, case-control, or cross-sectional study investigating the association between MetS and risk of OA; (2) relative risk (RR) or odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) could be directly extracted or calculated from the available data; and (3) if there is duplicated data, the larger sample size was adopted. Two investigators independently applied the selection criteria to each reference identified by the search strategy. Any discrepancies regarding eligibility or quality were resolved by the third reviewer.

2.4. Definition of Knee Osteoarthritis. Kellgren and Lawrence grade (K-L grade) classified KOA into four grades (0, normal, to 4, severe). Radiographic knee OA is defined as K-L grade 2 or above [16]. The American Rheumatism Association (ACR) proposed an alternative definition for OA based on a clinical or self-reported approach [17].

2.5. Statistical Analysis. The crude pooled OR was calculated. Adjusted ORs controlling for potential confounding factors in the greatest degree were also extracted whenever available. The adjusted OR was converted by using the natural logarithm and the SEs and their corresponding 95% CIs were calculated from these logarithmic numbers. Pooled adjusted OR was also calculated. When \( I^2 > 50\% \), heterogeneity was significant, and random-effects model was applied to estimate the pooled ORs and 95% CI. We considered \( I^2 \) of <50% as "heterogeneity might not be important," and a fixed-effects model will be conducted. Cochrane Collaboration's Review Manager Software Package (RevMan 5, Version 5.0, Cochrane Collaboration, Oxford, United Kingdom) was used for the meta-analysis.

3. Results

A flow chart of literature search and study selection is shown in Figure 1. After a systematic search in PUBMED, EMBASE, and the Cochrane Library, 371 articles were retrieved. After a systematic review, 8 studies with a total of 3,202 cases and 20,968 controls were finally included. Among these studies, there were two prospective studies [7, 13], three cross-sectional studies [9, 10, 12], and three case-control studies [8, 11]. One study was excluded for lack of data [18]. The characteristics of the included studies are summarized in Table 1.

The pooled ORs result suggested that MetS seemed to significantly increase overall KOA risk (pooled OR = 2.24, 95% CI = 1.38–3.64) (Figure 2). The Egger test did not suggest the presence of publication bias (\( p = 0.555 \) (Figure 3). However, the individual estimates of the ORs were significantly heterogeneous (\( I^2 = 96\% \), \( p < 0.00001 \) in random-effects model). The Galbraith plot showed that the study by Puenpatom and Victor largely accounted for heterogeneity (Figure 4). After excluding this study, the interstudy heterogeneity decreased (\( I^2 = 0\% \), \( p = 0.48 \), with the OR attenuated but remaining statistically significant (pooled OR, 1.74, 95% CI = 1.57–1.92; \( p < 0.00001 \) in a fixed effect model).

Four studies described the adjusted OR [7, 11–13]. After pooling the adjusted ORs, the results remained significant (pooled adjusted OR = 1.05, 95% CI = 1.03–1.07, and \( p < 0.00001 \) (Figure 5). No significant interstudy heterogeneity was observed (\( I^2 = 0\% \), \( p \) for heterogeneity = 0.86) and there was no publication bias (\( p = 0.649 \) (Figure 6).

4. Discussion

KOA is the most prevalent form of arthritis and a major cause of pain and disability that affected 151 million individuals globally in 2000 [1, 2]. It has long been considered a “wear-and-tear” disease leading to loss of cartilage and used to be considered the sole consequence of any process leading to overloading pressure on knee joint. In recent studies, increasing evidence supports that MetS is associated with knee OA [4, 5]. MetS is a clustering of risk factors, including dyslipidemia, high blood pressure, impaired glucose tolerance, and abdominal obesity [15]. It is reported that MetS is prevalent in 59% of patients with OA and in 23% of...
| Study                                                                 | Study design and population | Ethnic       | MetS criteria | OA criteria | Number of KOA/control | Age (KOA/control) | Gender | Waist circumference (KOA/control) (cm) | Weight (KOA/control) (kg) | BMI (KOA/control) (kg/m²) | Adjusted OR, 95% CI | Adjusted variables |
|----------------------------------------------------------------------|----------------------------|-------------|---------------|-------------|-----------------------|-------------------|--------|----------------------------------------|--------------------------|-----------------------|----------------------|---------------------|
| Engströmet al. 2009 [7]                                              | Population-based cohort    | Sweden      | NCEP-ATPIII   | A first knee arthroplasty or high tibial osteotomy and diagnosis of OA (715 or 117 according to ICD-9 and ICD-10) | 89/5082 | (59.7 ± 5.3)/(57.6 ± 6.0)¹           | Male and female | NE                                  | NE                       | 28.9 ± 4.6/25.7 ± 3.9* | 1.1 (0.7-1.8)         | Age, sex (all participants), smoking, CRP, physical activity, BMI |
| Han et al. 2013 [8]                                                  | Case-control               | Korean      | NCEP-ATPIII   | NR          | 270/1964              | (64.5 ± 10.1)/(53.2 ± 11.0)¹ | Male and female | 85.0 ± 9.5/82.7 ± 8.7* Female: 85.3 ± 9.5/82.0 ± 10.1* | 24.6 ± 3.3/23.8 ± 3.1* | NE                                  | NE                                  | NE                                  |
| Inoue et al. 2011 [9]                                                | Cross-sectional            | Japan       | NCEP-ATPIII   | K-L grade   | 251/532               | NR                             | Male and female | 84.5 ± 7.9/84.6 ± 7.4 Female: 84.6 ± 7.4/80.5 ± 8.2* | NE | NE                                  | NE | NE                                  |
| Michishita et al. 2008 [10]                                          | Cross-sectional study      | Japan       | NCEP-ATPIII   | K-L grade   | 35/37                 | (60.1 ± 6.7)/(58.6 ± 5.3)² | Female | 91.7 ± 8.0/87.2 ± 9.0* 68.9 ± 10.0/60.9 ± 8.2* | 28.2 ± 3.7/26.2 ± 2.8* | NE UFO                             | NE                                  |
| Puenpatom and Victor 2009 [11]                                       | Case-control               | American    | NCEP-ATPIII   | K-L grade   | 975/6739              | Age 18-65 years: (43.1% versus 92%)* Age 65 years: (56.9%/9.8%)*¹ | Male and female | NE                                  | NE                       | 1.05 (1.03–1.07)       | Age, controlled for BMI |
| Shin 2014 [12]                                                      | Cross-sectional study      | Korean      | NCEP-ATPIII   | K-L grade   | 919/1444              | 67.2 ± 8.4/60.0 ± 8.1 81.0 ± 10.2/60.6 ± 9.9 | Male | 85.3 ± 8.8/82.2 ± 8.9 61.0 ± 10.2/60.6 ± 9.9 | 24.7 ± 3.2/23.5 ± 2.9 | 0.92 (0.74–1.13)       | Age, sex, income, smoking, alcohol consumption, physical activity, BMI |
| Visser et al. 2015 [13]                                              | Population-based prospective cohort | Netherland | NCEP-ATPIII   | ACR criteria | 663/5170              | 58/55 | Male and female | 80.4 ± 12.6/77.8 ± 10.2 | 26.9 ± 0.8/25.5 ± 2.5 | 1.08 (0.85–1.39)       | Age, sex, smoking, education, ethnicity, height, weight |

*: p < 0.05 and #: p > 0.05; K-L grade: Kellgren-Lawrence grade; NR: not recorded; and NE: not evaluated. Values are presented as mean ± SD.
the population without OA, in a population-based cohort study with a sample of 7,714 people across all ages [15]. Studies also proved that people with MetS develop OA at an earlier age and have more generalized pathology, increased inflammation, and augmented intensive pain in the joints, in comparison with patients with OA in the absence of MetS [4–6, 8, 14–16]. On the contrary, some literature results are controversial as there are other groups that do not support this belief [12]. Thus, it is meaningful to provide a summary and analysis of published studies based on the association between OA and MetS.

This study showed that MetS increases the risk of KOA, even after adjusting many of the risk factors. In our meta-analysis, one article was excluded for not providing the data for analysis. However, in the excluded article, it was indicated that MetS was prevalent in 59% of patients with OA, whereas
As parts of the metabolic syndrome, insulin resistance, hyperglycaemia, and hyperinsulinemia are also strongly related to OA pathogenesis. In clinic, diabetes has been proved to be an independent predictor for osteoarthritis by the population-based cohort study followed over 20 years [30]. There is an increasing recognition of the mechanistic link between OA and DM include advanced glycation endproducts (AGEs), dyslipidemia, adipokines, and cytokines act through oxidative stress and inflammatory mechanisms [24–27]. Dyslipidemia with increased free fatty acid and decreased high density lipoprotein and adiponectin is associated with OA development by decreased vascular reactivity and endothelial dysfunction [31, 32]. Inflammatory transformation and proinflammatory cytokines could result in fibrosis of the synovium through the NFκB signalling pathway which plays a critical role during OA development [19, 33].

All of the above highlight the association between MetS and KOA. MetS not only increases the susceptibility to KOA but also exerts influence on its progression and prognosis. Yoshimura et al. demonstrated not only a dose-response relationship between MetS and KOA but also the relationship between MetS components accumulation and KOA progression and occurrence [15, 34]. Our study results could draw attention to the role of MetS in aetiopathology of KOA and give rise to new potential treatments.

This study has several limitations. First, the number of studies evaluated was very small. Future studies should include a more comprehensive analysis of the topic. Second, although genetic risk factors for OA have been found to contribute to the establishment and progression of this condition [35], in this study, we could not establish the effects of genetic factors and other risk factors potentially influencing MS and KOA.

5. Conclusion

For the first time, with meta-analysis, the synthesis of available evidence supports that metabolic syndrome increases the risk for knee osteoarthritis, even after adjustment for many risk factors. As a result, OA is a heterogeneous disease and metabolic factors contribute substantially to its pathogenesis. Furthermore, understanding that MetS contributes to KOA patients will be useful in assessing KOA patients’ individual conditions and selection of precision therapeutic strategies.

Competing Interests

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this paper.

Authors’ Contributions

Huajun Wang and Zhengang Zha designed the study and drafted the paper. Huajun Wang and Yanmei Cheng searched databases for the articles and screened them accordingly and analysed the data. Decheng Shao, Junyuan Chen, and Yuan...
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Sang helped design the study, analysed and tabulated data, and helped draft and edit the paper. Tao Gui, Simin Luo, and Jieruo Li searched databases for the articles and screened them accordingly and tabulated data. Chao Chen, Yongguang Ye, Yong Yang, and Yikai Li helped analyse and tabulate data. Chao Chen, Yongguang Ye, and Jieruo Li searched databases for the articles and screened them accordingly and tabulated data. Tao Gui, Simin Luo, and Jieruo Li helped design the study, analysed and tabulated data. Chao Chen, Yongguang Ye, Yong Yang, and Yikai Li helped analyse and tabulate data. All authors read and approved the final paper.

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