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Meta-analysis

Statin use and Severity of Knee Osteoarthritis: A Systematic Review and Meta-Analysis

Reza Noktehsanj[1], Farzad Amouzadeh-Omrani[3], Sayed-Mohammad-Amin Nourian[2]

1. Department of Surgery and Orthopedics, Ardabil University of Medical Sciences, Ardabil, Iran.

2. California State University Stanislaus, Turlock, CA, USA.

3. Department of Orthopedics, School of Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Correspondence to:

Reza Noktehsanj, Department of Surgery and Orthopedics, Ardabil University of Medical Sciences, Ardabil, Iran.

Email: rezanoktehsanj@gmail.com

ABSTRACT

Background: Several studies have shown that lipid disturbances could be associated with pathophysiology of knee osteoarthritis (OA). The aim of the study is to assess whether statin use could reduce the risk of the incidence or progression of OA of knee.

Methods: The Scopus, PubMed, Embase, Cochrane databases, EBSCO, and SID were systematically searched for observational studies on the association between statin use and knee OA. ORs and 95% confidence intervals (CIs) were directly collected by two independent authors. The Newcastle-Ottawa quality assessment scale was used to assess the quality of included studies. Statistical analysis and publication bias were performed using Comprehensive Meta-analysis software (CMA. Ver. 3).

Results: A total of six studies (160358 participants) were identified from the systematic literature search of above-mentioned databases. No significant association between statin use and incidence of OA was found in our meta-analysis (OR: 1.051; 95% CI: 0.882 to 1.253; P: 0.575). However, there was a significant association between statin use and progression of OA (OR: 1.381; 95% CI: 1.063 to 1.793; P: 0.016).

Conclusion: Our meta-analysis revealed that statin use may not be associated with a lower risk of incidence of OA of knee. However, the negative effects of statin use on progression of OA of knee were detected in our meta-analysis.

Keywords: Knee osteoarthritis, Incidence, Progression, Statin, Safety, Complication, Systematic review, Meta-analysis.

Introduction

Osteoarthritis (OA) is a degenerative and progressive disorder that affects 9.6% of men and 18% of women aged 60 years or older (1, 2). It most commonly affects the joints including the knees, hands, hips, and spine and is a leading musculoskeletal cause of impaired mobility in the elderly (3). The common clinical symptoms include chronic pain, joint instability, stiffness, joint deformities, and radiographic joint space narrowing

(4). The etiology of OA remains largely unclear. Several studies highlighted that OA is associated with metabolic disorders such as obesity, hypertension, diabetes, dyslipidemia, and others (5). A recent meta-analysis demonstrated an association between dyslipidemia and OA (6). Experimental studies have suggested that lipid disturbances could be involved in OA pathophysiology (7). Although OA does not fit into the classification of a typical inflammatory arthropathy due to a lack of leukocytes found in the synovial fluid of affected joints, studies have shown inflammatory foci present in the synovium with increasing inflammation associated with the increasing severity of OA (8, 9). Statins are types of hydroxymethylglutaryl-coenzyme A reductase inhibitors that are widely used to reduce low-density lipoprotein (LDL) cholesterol to treat cardiovascular diseases. In addition to lowing the circulating level of LDL, statins have a broad range of biological effects including anti-inflammatory properties and bone metabolism effects (10). One meta-analysis demonstrated that statin treatment did not only have a lipid-lowering effect in rheumatoid arthritis patients, but also has an anti-inflammatory effect in rheumatoid arthritis (11). Palmer et al.(12) showed that intraperitoneal simvastatin was of benefit in reducing the mean arthritis score and number of affected paws. Leung et al. (13) found that simvastatin dose-dependently reduced the number of arthritic joints and degree of swelling in affected joints in a murine model. To the best of our knowledge, some observational studies suggested that statin use might be associated with an increased risk of developing incident OA or radiological worsening (14). Other studies (15, 16) showed that statin use did not have protective effects on OA. However, three studies demonstrated that statin use could reduce pain, progression, and joint space narrowing in patients with OA (17, 18). Therefore, the effects of statin use on the incidence and progression of OA remain unclear. Considering the inconsistent conclusions of existing epidemiological studies, we conducted this meta-analysis to summarize the quantitative evidence from observational trials to evaluate the association between statin use and the risk of incidence and progression of OA.

Materials and methods

This systematic review and meta-analysis followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. Obtaining institutional review board approval or informed patient consent was waived for this study because it was a review of publicly available data.

Literature search

The Scopus, PubMed, Embase, Cochrane databases, EBSCO, and SID were searched to identify observational trials that investigated the association between statin use and OA from their inception to October 8, 2020. There were no language restrictions. The search terms were (hydroxymethylglutaryl CoA reductase inhibitors OR HMG-CoA reductase OR statins OR hydroxymethylglutaryl- coenzyme A) and (arthritis OR osteoarthritis OR OA). We also searched the references of reviews and included studies to ensure that all of the relevant studies were assessed for the meta-analysis.

Selection criteria

All of the eligible studies had to meet the following selection criteria: (1) randomized controlled study, observational study, cohort study, or case-control study; (2) human studies; (3) any definition of OA, ranging from radiological to self-reported or physician-diagnosed, and any evidence of the progression of OA; (4) the exposure variable was any type of statin use; and (5) the interest outcome was the effect of statin use on the incidence or progression of OA. Case reports, editorial letters, science reviews, and expert opinions were excluded.

Data extraction

Two reviewers independently performed data extraction from the included studies using a standardized data extraction form. A third reviewer resolved any divergence by discussion. The data extracted from the included studies included the author name, publication year, country of study, trial design, data source, sample size, age, sex, joint site of OA, definition of OA, statin use, main findings, adjustments, and follow-up period.

Study quality assessment

Two reviewers independently assessed the methodological quality and risk of bias of the included studies. Disagreements were resolved by consulting a third reviewer. The quality of the included studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS), which contained eight items for case-control and cohort

studies. Three parts were assessed: selection, comparability, and exposure. Each item was scored with one or two points and summed to a total score ranging from 0 to 9. A score of more than six points was considered high-quality.

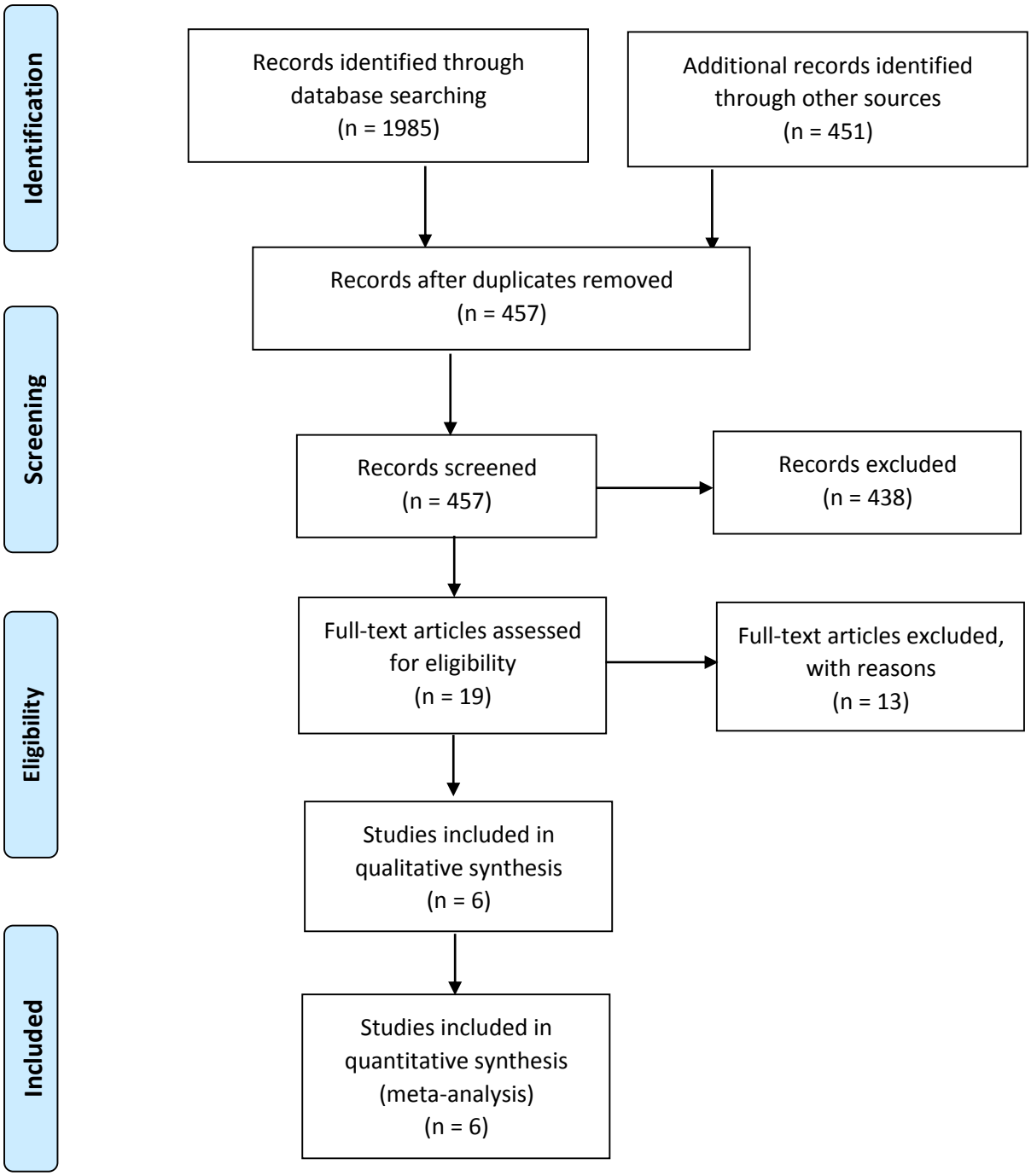

Figure 1. PRISMA flowchart of the literature search and selection of studies that reported effects of statin use on incidence or progression of knee osteoarthritis.

Statistical analysis and publication bias

Publication bias was assessed graphically using a funnel plot and with Egger test**.** The pooled proportions of overall and major complications were assumed as the principal indices in our meta-analysis. Heterogeneity among studies was determined by calculating the $\chi 2$ statistic for the pooled estimates ($p<0.05$ indicated significant heterogeneity) and the inconsistency index I2. An I2

value of 50 % or greater and/or a Q-statistic value of $P < 0.05$ suggest the presence of heterogeneity. Pooled proportions with 95 % confidence intervals (CIs) were obtained with the random or fixed effects modeling based on the results of heterogeneity assessment. Publication bias was visually assessed using funnel plot, and statistical significance was evaluated by Egger's test. All the statistical analysis was performed using Comprehensive Meta-Analysis software (CMA, ver. 3).

Results

Characteristics of the included studies

Fig. 1 shows a flow diagram of the literature selection. Overall, 2436 records were retrieved. After excluding the duplicate publications, reviews, letters, comments, titles, and abstracts, 13 potential articles were full-text reviewed for further assessment. Three study was excluded for not reporting the OR, RR, and HR and no sufficient data to calculate the OR. Two was a study protocol l36. One study was excluded as that analyzed based on people in the same area and during the same period and reported the association between non-traumatic arthropathies and statin use. Finally, six studies met the criteria for inclusion in this meta-analysis. Table 1 shows the main characteristics of the six studies included in this meta-analysis. The six studies, published between 2012 and 2020, included 160358 subjects. Five studies reported the association between statin use and the incidence of knee OA. Three studies reported the progression of knee OA. Most of the studies defined the incidence or progression of OA based on the radiological criteria.

Table 1. Characteristics of the included studies in the meta-analysis.

Authors	Year	Number of Subjects	OR (95% CI) Incidence	OR (95% CI) Incidence
Clockaerts et al. (19)	2012	2921	0/62 (0/33-1/19)	0/69 (0/27-1/73)
Kadam et al. (20)	2013	16609	1/04 (0/51-2/10)	-
Valdes et al. (16)	2014	3171	1/07 (0/87-1/32)	-
Michaelsson et al. (15)	2017	132607	1/04 (0/99-1/10)	-
Eymard et al. (14)	2018	336	-	1/49 (1/10-2/02)
Veronese et al. (17)	2019	4448	1/31 (0/83-2/09)	0/97 (0/93-1/02)
Haj-Mirzaian et al. (18)	2019	602	0/8 (0/19-3/44)	1/37 (0/74-2/53)

All the studies investigated knee OA. All of the extracted data from the included studies were adjusted for potential confounders, except Haj-Mirzaian's study (18), which did not report this. However, the potential confounders used for adjustment were different among the included studies. The Newcastle-Ottawa quality assessment scores of the included studies ranged from 5 to 9. Most of the studies were rated as high quality.

Statin Use and the Incidence of Knee OA

Five articles were included in the analysis of statin use and the incidence of knee OA defined based on The pooled results indicated no association between statin use and the incidence of hand, knee, and hip OA defined based on the radiographic criteria or disease code (OR: 1.051; 95% CI: 0.882 to 1.253; P: 0.575). Low but non-significant heterogeneity was observed between the studies (I^2:0, heterogeneity P: 0.457) (Fig. 2).

Statin Use and the Progression of Knee OA

Three articles investigated the association between statin use and the progression of knee OA defined based on radiographs or symptoms. The summary OR for the association between statin use and the progression of knee OA defined based on radiographs of the symptoms was 1.381 (95% CI: 1.063 to 1.793; P: 0.016) with a low heterogeneity (I^2:16/14, heterogeneity P: 0.303) (Fig. 3).

Publication Bias

Visual inspection of the funnel plot identified substantial asymmetry (Fig. 4). However, Begg's rank correlation test (P: 0.327) and Egger's linear regression test (P: 0.520) also indicated no evidence of publication bias among the studies.

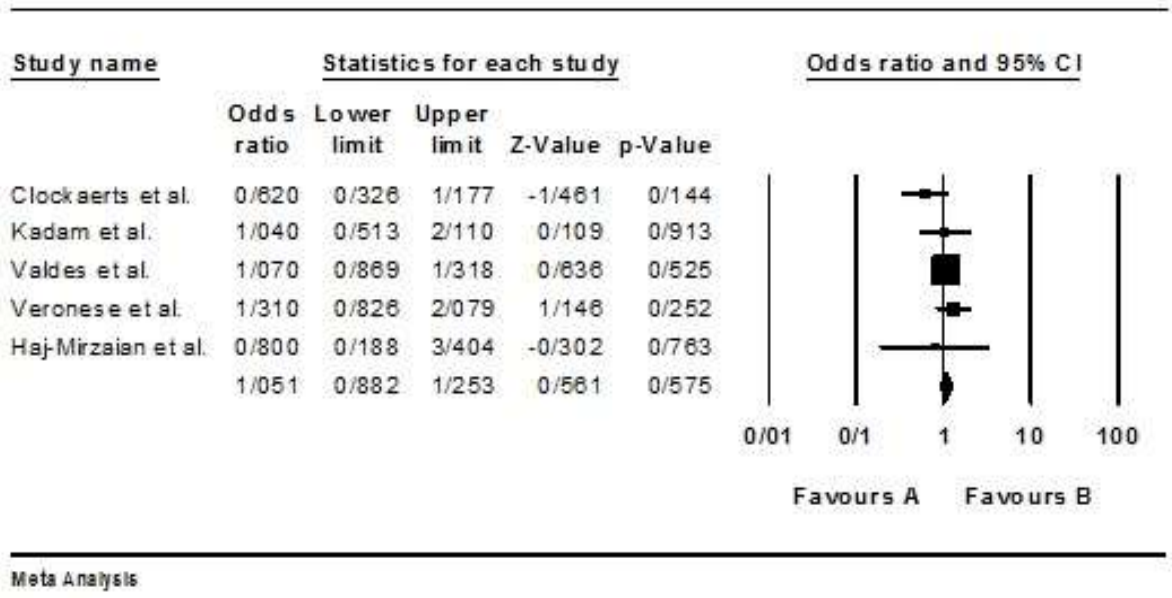

Figure 2. Effect of statin use on incidence of knee osteoarthritis.

Discussion

Our pooled analysis revealed that statin use may not be associated with a lower risk of incidence of OA of knee. However, the negative effects of statin use on progression of OA of knee were detected in our meta-analysis. Statins may play a potentially protective role in OA due to their anti-inflammatory effects, and these results were confirmed in different types of the studies (21). However, our meta-analysis of 5 articles with 160358 subjects confirmed that statin use may not be associated with a reduced risk of incidence of knee OA, although we detected that statin use have opposite effects on progression of knee OA.

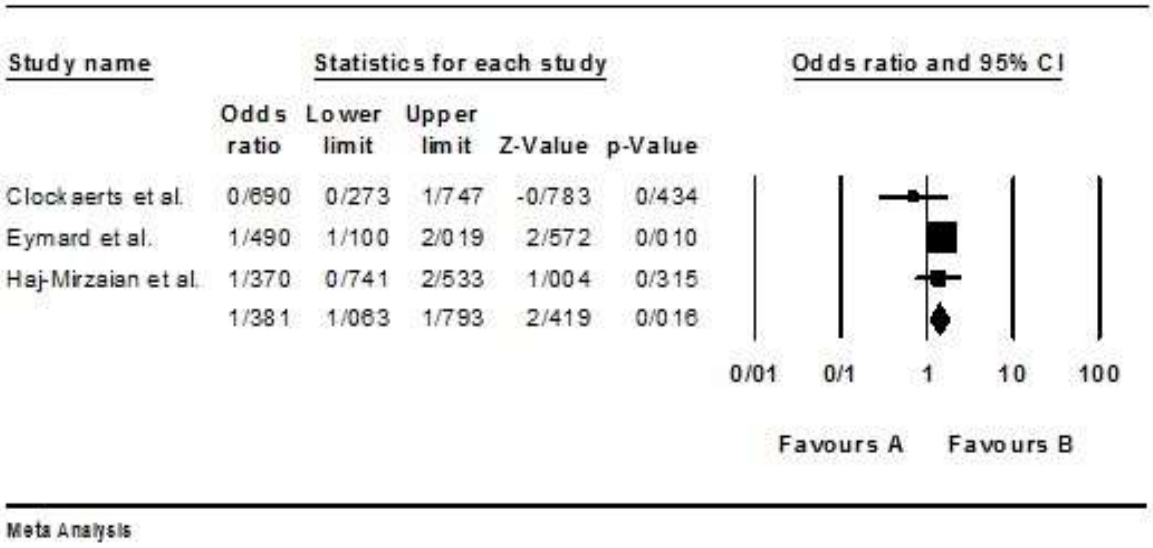

Figure 3. Effect of statin use on progression of knee osteoarthritis.

Although there are very plausible mechanisms by which statins may produce beneficial effects on OA joints, most of the evidence of the beneficial effects of statins was provided by in vitro or animal studies. Most of the studies used animal models of induced OA, but not the model of spontaneous OA (22, 23). Wei et al. (23) did not find any impact of statin use on systemic inflammation, cartilage degradation, or subchondral bone thickness based on a spontaneous OA murine model. All of the included observational studies on human statin use demonstrated conflicting evidence with some suggesting a reduction in the progression of OA (18, 19), other studies finding no effect (17), and yet others an increased risk of OA (14). Thus, whether or not statin use had potentially protective effects on OA was rarely answered by primary research as each study was often one single study design or setting. However, the meta-analysis could answer this question because of its advantage that it can examine different study designs and settings by reviewing the published literature.

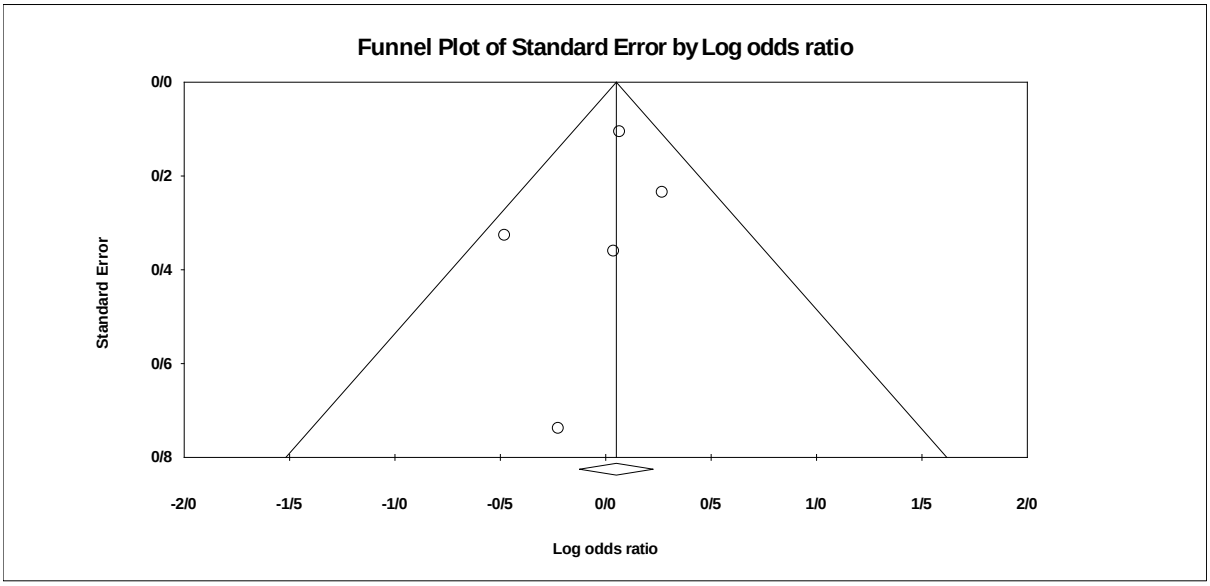

Figure 4. Funnel plot of results of association between statin use and incidence of knee osteoarthritis.

Our meta-analysis did not find any protective effects of statin use for symptomatic OA. One possible explanation was the side effects of statin on muscle pain and weakness (24), masking the protective effects of statins on OA-related symptomatic outcomes. The other explanation was the different diagnostic criteria used for the definition of symptomatic OA and the covariates used for adjustment between studies. OA diagnoses by disease code might be subject to considerable misclassification, leading to null findings. However, we excluded the studies using the disease code for OA diagnoses, but we still found no association between statin use and the incidence of knee OA. Therefore, future studies on this topic should be differentiate between the joint pain caused by OA and the muscle pain caused by statin use to achieve a definite definition of symptomatic OA. In addition, it is important to distinguish different diagnostic methods of OA to reduce selection bias. Michaelsson et al.'s study (15) included 132321 participants, which accounted for 82.5% of our meta-analysis sample size. This large study might have driven the negative results of our meta-analysis. Obesity is thought to induce OA in weight-bearing joints, especially the knee, due to mechanical strains on these joints (25). This concept seems logical because OA patients feel symptomatic relief after weight loss (26). Studies have shown that OA is a much more complex disease with inflammatory mediators released by the cartilage, bone, and synovium (27). Low-grade inflammation induced by the metabolic syndrome, innate immunity, and inflammation are some of the more recent arguments in favor of the inflammatory theory of OA (28). Taken together, the current results might be changed by adding future studies. These results should be interpreted with caution. The possible explanations of these heterogeneities were the different definitions of OA among the included studies and the limitations of the observational studies due to selection bias, information bias, and confounding. Because of the small number of included studies in each outcome, a subgroup

analysis or meta-regression could not be conducted to seek the source of heterogeneity. Since all of the included studies did not examine the potential influence of dyslipidemia on the association between statin use and OA, we posit that whether statin use was related to OA by regulating dyslipidemia was inconclusive. However, one meta-analysis including 48 observational studies indicated that the risk of dyslipidemia was twofold greater with than without OA (6). To investigate this issue further, more well-designed studies should be conducted. Visual inspection of the funnel plot identified substantial asymmetry, but Begg's test and Egger's test showed no publication bias. This difference might be attributed to a lack of test power because of the small number of included studies. Another explanation might be that we synthesized the data before the final analysis within some included studies. Our results must be interpreted with caution because of the following limitations. First, there were differences in the definition of the incidence or progression of knee OA and differences in the period of statin use among the included studies that might have contributed to the heterogeneity. Second, our results might not fit for those in developing countries because all of the included studies were conducted in developed countries. Third, only cohort studies and case control studies were found through the electronic search. These observational studies weakened the level of evidence. Large, rigorous randomized controlled trials are required to improve the evidence. Finally, potential publication bias was demonstrated by the funnel plot, although the results of Begg's test and Egger's test were not significant. The influence on the results should not be ignored.

Conclusion

In summary, our results showed that statin use may not be associated with a lower risk of incidence of knee OA. However, the opposite effects of statin use were detected on knee OA. However, prospective randomized controlled trials need to be conducted to confirm the findings of our meta-analysis.

Declarations

Acknowledgement

The authors thank all those who contributed to this study.

Author Contribution

Reza Noktehsanj: Study design, data collection, writing draft of study.

Farzad Amouzadeh-Omrani: Study design, data collection, writing draft of study.

Sayed-Mohammad-Amin Nourian: Study design, data collection, writing draft of study.

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Conflict of interest

There is no conflict of interest.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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