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Current Rheumatology Reviews, XXXX, *XX*, 1-11

REVIEW ARTICLE

Statin in Clinical and Preclinical Knee Osteoarthritis-What Evidence Exists for Future Clinical Use?-A Literature Review

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Abstract: ***Background*:** Statins are used to lower serum cholesterol. Recent preclinical and clinical research focuses on articular cartilage regeneration aspects of statin. This review summarizes the effects of statins on knee osteoarthritis (OA).

***Methods*:** Published preclinical and clinical literature till November 2021 were searched in PubMed and PubMed Central databases. Articles not written in English, not relevant for the review, and unpublished evidence were excluded. Finally, 27 papers were reviewed and presented in the study.

***Results*:** A total of 27 articles have been included-13 clinical and 14 preclinical studies. Preclinical studies showed statin-induced chondroprotective effects; these included *in vitro* studies on human or animal-derived degenerated articular cartilage as well as OA animal models. Chondroprotective effects of statins are thought to mediate by inhibiting the Wnt/β-catenin signaling pathway, preventing synovial inflammation, and inhibiting catabolic-stress-induced aging of cartilage. Preclinical study outcomes were based on biochemical, macroscopic, and microscopic (histology) assessments and seemed promising in cartilage regeneration. In the 13 clinical studies, the effect of statins on human OA is inconclusive: some showing improvement of OA symptoms, and others depict signs of aggravation and radiological progression. No randomized controlled trial (RCT) has tested the efficacy of intra-articular statins in clinical knee OA, and it seems feasible to avoid oral statin-associated severe adverse effects.

***Conclusion*:** There are no arguments to recommend oral statins in clinical OA-knee. An RCT testing the efficacy of oral statins in patients with OA knee was never done and still seems justified, as well as a prospective phase-II clinical trial for intra-articular statins in different types of OA.

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1. INTRODUCTION

Statins are a class of drugs used to lower serum low-density lipoprotein (LDL) and reduce cardiovascular risks [1]. However, statins may have adverse effects (AEs) on joints and muscles [1, 2]. In muscles, statins activate cysteine/glutamate antiporter and increase intracellular cysteine and glutathione, as well as interstitial glutamate, attenuating statin-induced oxidative stress and peripheral nociception as revealed in a preclinical study [3]. In a cross-sectional study, among US citizens with no arthritis, the prevalence of arthralgia and arthritis was significantly higher among statin users; however, in arthritis patients receiving statin therapy, musculoskeletal complaints were not increased [3, 4]. Some preclinical studies document statin to be promising in regenerating articular cartilage in osteoarthritis (OA), including knee OA (KOA) [5].

OA is not only a disorder of cartilage degeneration but also subchondral bone marrow lesions (BMLs). BMLs in OA lead to persistent and progressive bone pain with compromised quality of life and physical function. In our previous work, we cited how BMLs correlate with cartilage degeneration in KOA [6]. MRI-depicted BMLs correlate with histopathology depicted trabecular bone damage. MRI-BMLs are linked with accelerated cartilage degeneration and pain severity in KOA. OA-BMLs have an increased probability of knee arthroplasty. Besides, cartilage regeneration,

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statin seems to be effective in lowering MRI-depicted BMLs in generalized OA phenotypes [7]. Pro-inflammatory cytokines, for example, interleukin-1 beta (IL-1β), are elevated in synovial fluid and cultured chondrocytes of injured cartilage and degenerated cartilage in OA [5]. Lipophilic statins, for example, simvastatin and mevastatin, can block cartilage degradation by inhibiting geranylgeranylation, a post-translational modification to Rho and Rac GTP-binding proteins, though without affecting cholesterol synthesis [5]. Statins accelerate aggrecan (AGC), matrix proteoglycans, and collagen II synthesis in damaged articular cartilage [8-10]. An *in vitro* study with human articular cartilage tissue harvested during joint replacement and treated in statin-rich media showed the same result [11]. In *animal studies* with induced and spontaneous OA knees, statin proves the potential to regenerate articular cartilage by reducing matrix metalloproteinase (MMP-1, 13) [8-10]. Long-term statin use prevents mesenchymal stem cells (MSC) from differentiating into macrophages, bone, and cartilage cells; it further reduces the DNA repair potential of MSC and accelerates the MSC death rate. The impact of statins on macrophage differentiation appears impressive; however, it does not influence the biologic properties of stem cells [12].

Human observational study outcomes were not consistently depicting improvement with statin treatment in KOA. Some studies showed clinical and radiological improvement with statin use. Other studies indicated worsening of clinical and radiology-based OA outcomes with statin use. To our knowledge, no prospective study of the effect of oral statins in patients with knee OA was done. A randomized controlled trial (RCT) could answer the effect of statin in patients with OA knees. As there are no successful disease-modifying drugs available for daily practice, it would be nice if statins could reduce the risk and progression of OA, including OA-knee [13].

In the present literature review, we aim to summarize preclinical and clinical research outcomes of statins in induced and spontaneous knee OA to make the scientific community aware of this. We wanted to know how statins work in animal OA models and clinical OA. A future area of statin research in clinical OA has also been explored.

2. MATERIALS AND METHODS

We performed a preclinical and clinical literature search on statin use in KOA published till November 2021. For this purpose, the following keywords and phrases were used-lipid-lowering agents in the treatment of osteoarthritis knee, statin in treating osteoarthritis knee, atorvastatin, rosuvastatin, simvastatin, and pravastatin in OA treatment. Two authors (MAB and IJ) accessed and reviewed the papers; when they faced a problem regarding article access, another author (JJR) was contacted. Any disagreement was discussed with JJR until a consensus was reached. A total of 494 articles were found in PubMed and PubMed Central databases (PubMed-24, PubMed Central-470); among them, 34 described the effects of statins in OA articular cartilage, OA clinical features (symptom improvement or aggravation), radiological outcomes (progression or improvement), the association of OA with dyslipidemia (Fig. **1**). As we are studying the possible effects of statins on articular cartilage, all included articles were original research papers (clinical, *in vitro*, and *in vivo* preclinical research) describing the effect of statins (atorvastatin, mevastatin, pravastatin, rosuvastatin, and simvastatin) in OA. Excluded articles fell into any of the following categories: not written in English, not relevant for the review, research protocols on a statin in OA, expert opinions, and correspondence regarding previously published works. We did not include any unpublished evidence. Finally, 27 papers were included for the analysis (Fig. **1**), and all were checked with the Critical Appraisal Skills Program (CASP) [14]. In this literature review-13 describing clinical- and 14 describing preclinical studies; these include three articles relating *in vitro* analysis of IL-1β stimulated normal human articular cartilage chondrocytes and degenerated articular cartilage chondrocytes in statin-rich media. Tables **1-3** present statin-related preclinical and clinical studies. Table **4** depicts the comparative analysis of statin-related preclinical and clinical studies.

2.1. Outcome Measures as Applied in Research among Patients and Controls

Incidence of radiographic knee OA, radiological joint space narrowing (JSN > 0.5 mm) based on Kellgren-Lawrence (KL) scoring, dose-dependent OA symptoms aggravation, and radiological OA changes (for simvastatin and pravastatin doses of 10-40 mg and 10-20 mg per day, respectively) [15-19]. Further outcome measures were: requiring physician consultation and or surgical interventions for KOA, improvement of the pain and physical function scores of the Western Ontario and McMaster Universities Arthritis Index (WOMAC), the risk of total knee arthroplasty (TKA) revision, and the incidence of non-traumatic knee pain among statin users [20-24]. OA-knee patients receiving statin therapy were found to have increased serum silicon and decreased serum calcium [13, 25]. Serum silicon was measured spectrophotometrically (Tables **1-3**) [25]. Serum lipid profile in statin users with or without knee pain [26]. Mahajer *et al.* described the effect of statin on BMLs in generalized OA with Heberden nodes (HN). BML score with semi-quantitative MRI Osteoarthritis Knee Scores was measured at baseline and after 24 months [7].

2.2. Outcome Measures in Preclinical Studies (Animal Study and *In Vitro* Analysis of Human Articular Cartilage)

In vitro studies of human degenerated OA cartilage involved the culture of chondrocytes in statin-rich media [11, 27, 28]. Animal OA models of rabbit, rat, mouse, and bovine had been treated with oral and intra-articular (IA) statin [8-10, 29-36]. The Pelletier classification and the Mankin histopathological classification demonstrate macroscopic and microscopic changes in cartilage following statin therapy [29]. The Osteoarthritis Research Society International (OARSI) cartilage histopathology assessment system scores help detect statin-mediated cartilage specimen changes [35]. Histological assessment depicted cartilage and synovial cell

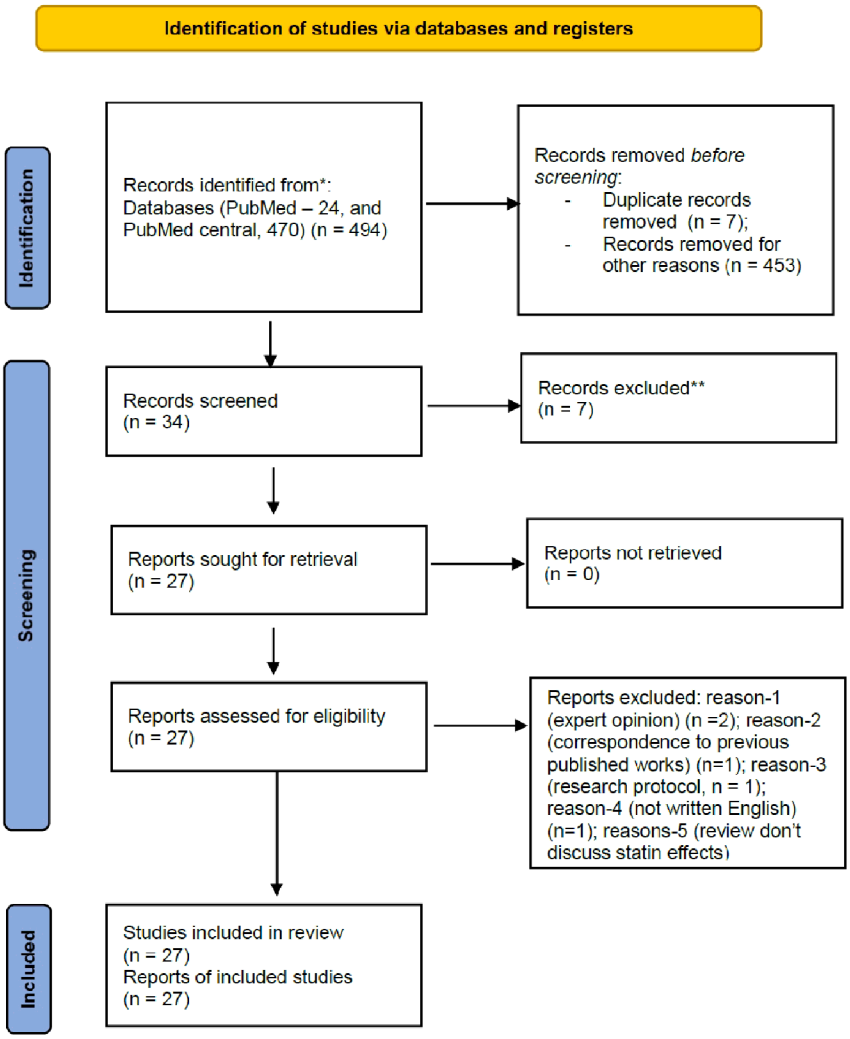

Fig. (1). Flow chart of article screening for the review. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Analysis of the statin-related clinical study in osteoarthritis.

Study Types	Country	Study Design	Outcome Measures	Remarks
Valdes *et al*. 2014 [13]	United Kingdom	Case control study	Nodal OA (Heberden's or Bouchard's nodes are seen in more than 2 X-rays of hand; knee OA based on KL score ≥2 at TFJ; generalised knee OA defined as knee OA in addition to nodal status	The use of statins is associated with a lower prevalence of the generalized OA phenotype, hope could be true for OA knee
Haj-Mirzaian *et al*. 2019 [15]	USA	Prospective study, cohort in nodal OA	Radiological OA knee progression based on KL score	Statin was associated with a reduced risk of radiographic knee OA JSN
Eymard *et al*. 2018 [16]	France	Post hoc analysis	Radiological progressive	Radiological worsening of knee OA following statin use regardless of potential confounding factors
Clockaerts *et al*. 2012 [17]	Netherlands	Population-based cohort	Based on the KL score of the OA knee	Statin use is associated with more than a 50% reduction in the overall progression of OA knee, but not of the hip.

(Table 1) contd…

Study Types	Country	Study Design	Outcome Measures	Remarks
Kadam *et al.* 2013 [18]	United Kingdom	Cohort	Cox and discrete time survival analysis to determine clinically defined OA at 2, 4, and 10-year follow-up	higher statin dose and larger statin dose increments were associated with a reduction in clinically defined OA outcome
Campion 2008 [19]	United Kingdom	Case report	Raised knee pain on exposure to higher statin doses	Incremental doses of pravastatin and simvastatin caused knee pain
Michaëlsson *et al.* 2017 [20]	Sweden	Pooled analysis of 4 cohort study	Risk of consultation or surgery for OA hip or knee	Statin use is not associated with a reduced risk of consultation or surgery for OA of the hip or knee
Riddle *et al.* 2013 [21]	USA	Community-based cohort	The changes in WOMAC Pain and Physical Function scores, pain intensity and KL radiographic grade for knee OA	Statin use was not associated with improvements in knee pain, function, or radiological progression over the 4 years
Cook *et al.* 2020 [22]	United Kingdom	Time-event analysis	Cox regression models were used to assess the link between statin exposure and TKA revision risk at different points in time	Statin may reduce the risk of revision knee arthroplasty.
Makris *et al.* 2018 [23]	USA	Retrospective cohort	Non-traumatic arthropathies, use-related injury, undergoing rehabilitation in statin users and non-users and expressed as OR at 95% CI	Statin use was associated with an increased risk of non-traumatic arthropathies and use-related injury.
Veronese *et al.* 2019 [24]	Northern America	Longitudinal cohort	Radiographic knee OA (ROA) and symptomatic knee OA (SxOA) and ROA, worsening of WOMAC score	Atorvastatin has a lower risk of developing knee pain, however, rosuvastatin has a higher risk of knee pain
Horecka *et al.* 2016 [25]	Poland	Case control study	Plasma concentration of simvastatin, calcium and silicon.	Increased serum simvastatin concentration is associated with reduced serum calcium an OA knee
Zhou *et al.* 2017 [26]	China	Cross-sectional study	Incidence of knee pain, clinical knee OA in hyperlipidemia with or without statin uses	Hyperlipidemia without statin use had higher risks of knee pain and clinical KOA and hyperlipidemia with statin use had the highest risks of knee pain. No hyperlipidemia but taking statin for other indications had no increased risk of knee pain

Note: OA, osteoarthritis; KOA, knee OA; TFJ, tibiofemoral joint; ROA, radiographic OA; WOMAC, Western Ontario and McMaster Universities Arthritis Index; KL, Kellgren Lawrence radiological score.

Table 2. Statin in *in vitro* study with human tissue.

Study	Country	Study Type	Outcome Measures	Interpretition
Baker *et al.* 2012 [11]	Ireland	*In vitro* culture of normal human chondrocytes	Expression of MMP-3 and MMP-9 mRNA was measured using PCR and MMP enzyme activity was assessed using a fluorescent MMP-specific substrate	Human chondrocytes treated with pravastatin cause a significant reduction in selected MMP genes and a non-significant reduction in MMP enzyme activity.
Simopoulou 2010 [27]	Greece	*In vitro* human tissue from damaged OA cartilage	MMP-13, COL2a1, AGC mRNA expression levels were evaluated by PCR, and protein expression levels by Western blot analysis. IL-1beta levels with ELISA.	Statins have a chondroprotective effect
Lazzerini *et al.* 2004 [28]	Italy	*In vitro* analysis of damaged articular cartilage in OA	Concentration of MMP-3 in simvastatin treated chondrocyte culture irrespective of IL1ß level, and whether MMP-3 level changed after adding mevalonate or farnesol	Statin could repair OA cartilage through a different mechanism than IL1ß-mediated MMP-3 concentration

Note: MMP, matrix metalloproteinases; COL2a, collagen 2a; IL-1β, interleukin-1beta; OA, osteoarthritis; PCR, polymerase chain reaction; AGC, agreecan.

Table 3. Statin and animal study.

Study	Country	Study Type	Outcome Measures	Conclusion
Dinc *et al*. 2012 [8]	Turkey	*In vivo* experimental animal study	Chondral and synovial tissues of induced OA knee rabbit models were examined macroscopically and histopathologically.	Statins have chondroprotective effects over tetracycline
Zhang *et al*. 2016 [9]	China	*In vivo* and *in vitro* animal study	Histological analysis of graft-bone healing with evidence of angiogenesis and osteogenesis in the SIM/COL/polyethylene terephthalate (PET) group with an increase in the ultimate failure load and stiffness in the SIM/COL/PET group.	Collagen containing low-dose SIM microsphere coating on the surface of PET artificial ligaments could be potentially applied for ACL reconstruction.
Yu *et al*. 2018 [10]	South korea	*In vitro* study of rabbits	MMP-1, 13, NO and NO synthetase inhibited and increase the synthesis of collagen II.	Simvastatin could minimize articular cartilage degeneration by inhibiting MMPs in NO-treated chondrocytes, a potential treatment for OA
Bayyurt *et al*. 2015 [29]	Turkey	*In vivo* animal study with New Zealand rabbit models	Total lesion points obtained in medial tibial plateau cartilage tissue and electron microscopic examination of impaired articular cartilage tissue	Chondroprotective effect of statin on degenerative cartilage tissue could be mediated by protecting the structure of the endoplasmic reticulum and the Golgi complex
Akasaki *et al*. 2009 [30]	Japan	*In vivo* and *in vitro* study with rabbit OA knee model	Morphological, histological (less thickened synovial tissue with reduced infiltration of CD68+monocyte lineage cells) immunohistochemical (mRNA expressions of MCP-1, IL-1beta, MMP-3, and MMP-13), and biochemical methods were used to assess knee joints	Statin reduces inflammatory cell infiltration and matrix-degrading enzyme expression, but not articular cartilage chondrocytes thus limiting cartilage degradation.
Tanaka *et al*. 2019 [31]	Turkey	*In vivo* study of murine OA model	Decreased MMP -13 and IL-1β expression, increase synthesis of collagen II. The effects of simvastatin on gene expression and autophagy in the mouse primary chondrocytes were also examined in the presence or absence of IL-1β	Our findings suggest IA simvastatin-conjugated gelatin hydrogel could be used as a new OA treatment strategy
Terabe *et al*. 2019 [32]	USA	*In vivo* study with Bovine chondrocytes	Articular chondrocytes (Bovine, human knee, rat chondrosarcoma chondrocytes) treated with simvastatin; passaged bovine chondrocytes under simvastatin increased expression of SOX9, ACAN, BMP2 and inhibited the expression of COL1 and α-smooth muscle actin. Co-treatment of chondrocytes with simvastatin together with mevalonate, geranylgeranylpyrophosphate and to a lesser extent, farnesylpyrophosphate, pro-differentiation effects of simvastatin is blocked. Human knee OA chondrocytes increased the expression of SOX9 and COL2a and enhanced SOX9 protein.	Blocking of critical protein prenylation events is required for the positive effects of simvastatin on the re-differentiation of chondrocytes
Yu *et al*. 2019 [33]	South Korea	*In vivo* experimental study with rabbit	Dose dependent expression of Chondrocyte II collagen, sulphated proteoglycan synthesis; reduced expression and translocation of β-catenin into the nucleus from the cytoplasm based-on luciferase assay and immunofluorescence staining and the luciferase assay	Simvastatin increases the differentiation of rabbit articular chondrocytes *via* the β-catenin pathway
Pathak *et al*. 2015 [34]	India	Original research	Oral gavage, the pain was assessed on days 0, 1, 3, 7, 14 and 21. Histopathology of ipsilateral knee joint; oxidative markers (level of lipid peroxidation, superoxide, protein carbonyl); decreased activity of antioxidants in plasma was assessed on day 21.	Atorvastatin attenuates MIA-induced OA pain and protects cartilage from degrading through inhibiting oxidative stress
Aktas *et al*. 2011 [35]	Turkey	*In vivo* animal experimental study with Wistar rats	OA changes based on Osteoarthritis Research Society International (OARSI) OA cartilage histopathology assessment system scores; percentage of MMP-3 expression in chondrocytes.	Simvastatin showed beneficial effects on OA progression and extent by reducing cartilage degradation in post-traumatic knee
Yudoh *et al*. 2010 [36]	Japan	*In vivo* and *in vitro* animal study	The concentration of chondrocytes IL-1β, MMP -1, 13 and cellular senescence in chondrocytes *in vitro*. *In vivo* study with STR/OrtCrlj mouse (spontaneously OA knee) model unveiled statin mediated reduced articular cartilage degeneration	Statin, a potential therapeutic agent to protect against cartilage damage

Note: OA, osteoarthritis; MMP, matrix metalloproteinases; OARSI, Osteoarthritis Research Society International; RCT, randomized controlled trial; MRI, magnetic resonance imaging; WOMAC, Western Ontario and McMaster Universities Arthritis Index; KL, Kellgren Lawrence radiological score.

Table 4. Comparison between statin-associated clinical and preclinical research.

Parameters	Clinical	Preclinical
Study types	Clinical research includes case-control, cross-sectional, case report/series, cohort	Involves *in vitro* study with human articular cartilage, *in vitro* and *in vivo* study with animal models (spontaneous, induced OA models)
RCT	No RCT tested the efficacy in either generalized nodal or regional OA, for example, OA knee	Not applicable
Outcomes measured	Clinical symptoms (pain aggravation / reduction), radiology (osteophyte formation, reduced or improved joint space, KL score), MRI articular cartilage degeneration, WOMAC pain, physical function scores, frequency of doctors visit, requiring surgical intervention, rehabilitation, and revision of surgery	Macroscopic assessments of articular cartilage; biochemistry of synovial and cartilage tissues for mRNA of tissue specific proteins such as MMP, collagens, SOX9, and aggrecans, reversal of statin-mediated pro-inflammatory cytokines outcome. Microscopic analysis of joint cartilage (OARSI), chondrocytes rich with granulous regular endoplasmic reticulum
Future research direction	RCT is required; IA statin trial with regional OA, for example, OA-knee could be done.	Translation of preclinical study outcomes in clinical trials; more preclinical studies with spontaneous OA are required.
Conclusion	Inconclusive*	Conclusive**

*studies unveiled statin reduced symptoms, some depicted the opposite, **preclinical studies depicted the positive outcomes of statin in halting articular cartilage degeneration.

lining and sub-synovial infiltration of CD68+monocyte lineage cells [30]. Besides, synoviocytes and chondrocytes derived proteins, namely IL-1beta, MMP-3, 13, 21, 99, SOX9 (sex-determining region Y (SRY) gene related protein), monocyte chemoattractant protein-1 (MCP-1), β-catenin, aggrecan (AGC), bone morphogenetic protein-2 (BMP2), collagen 1 (COL1), collagen 2a (*COL2a),* α-smooth muscle actin were measured by Western blot test [8-11, 27-36], and the expression of β-catenin detected using immunofluorescence staining and luciferase assay [33].

3. RESULTS

3.1. Clinical Studies

Among human studies included, seven were cohort- and two were case-control studies; one time-event analysis, one post hoc analysis, one cross-sectional study, and one case report [13, 15-26] (Tables **1-3**). Patients with hand OA with Heberden nodes (HN) receiving statin were followed-up prospectively [15]. In an observational study radiographic OA-knees with progressing JSN were found 46% lower among statin-users nodal OA than matched non-statin users (HR 0.54, 95% CI, p = .02) [15]. In an HN-negative cohort, statin use was not linked with radiographic OA-knee progression (HR, 1.37, 95% CI, p = .32) [15].

In a population-based Dutch (Rotterdam) study, a cohort of 2921 patients with OA-knees aged over 55 years were followed up for a mean of 6.5 years; overall radiological progression was reduced in more than 50% of the cases receiving statins than non-statin users [17]. However, there was no reduction in hip OA incidence and radiological progression [17]. A British cardiovascular disease cohort of 16609 patients, aged over 40-years receiving statin was followed-up longitudinally for 10-years. A higher therapeutic dose of statin for at least two years was associated with reduced clinical OA compared to non-statin users. Increased statin dosages were associated with significant reductions in clinical OA-knee (18% and 40 % after 2 and 4 years, respectively) compared to non-statin users [18].

A population-based study was performed, including 11.3 million UK patients from the CRPC (Clinical Practice Research Datalink) between 1988 and 2016. Among the patients, 164,224 had undergone total knee arthroplasty (TKA), 65,032 (43%), and continued statins at follow-up; among them, only 3500 (2.3%) had revision TKA (HR 0.82, 95% CI 0.75-0.90); those on prolonged statin exposure (five years *versus* < 1 year) had a lower TKA revision risk (HR 0.74, 95% CI 0.62-0.88) [22].

In a community-based cohort with 2207 OA-knee patients (radiology suspected or confirmed), outcome trajectories and probability of statin use were examined throughout 4-years-6.7 % of OA patients used statin in the first year, the figure increased to 16.4% in year four. There was no association of receiving statin with improved knee pain or function or radiographic scores; however, longer use of statin was associated with worse physical function according to the WOMAC (β = 0.161, p = 0.005) [21]. In another study, with a total of 1,127 North American community adults from Osteoarthritis Initiative using statins were followed up prospectively. Any use of statin was not associated with a lower risk of pain worsening or of lower incidence of radiological or symptomatic knee OA (RR = 0.97, 95% CI: 0.93-1.02). Atorvastatin (RR=0.95; 95%CI: 0.91-0.996) but not rosuvastatin (RR=1.18; 95%CI: 1.12-1.24) was associated with a reduced risk of developing knee pain [24].

However, in a West-European study among 336 knee OA patients (from placebo arm of SEKOIA trial), statin use in 71 of them was associated with radiological worsening (JSN ≥ 0.5 mm) of the tibio-femoral joint over 3 years, regardless of other potential confounding factors (obesity, type 2 DM, hypertension, disease duration, symptom intensity and radiological severity) [16]. Campion *et al*. further described aggravated knee pain in a 42-year-old insulin-dependent diabe-

tes mellitus (DM) patient following an increment of simvastatin dose from 10 mg to 40 mg/day that was reversed after resuming the lower statin dose (10 mg /day) [19].

A pooled analysis of four population-based large cohorts with a total of 132,607 Swedish people aged between 57 and 91 years, who were having statin therapy for a mean of 7.5 years, also conferred no overall OA-knee risk reduction in terms of consulting physicians and / or surgery [20]. A retrospective cohort study was done on patients enrolled in a regional military healthcare system between 2003 and 2012 [23]. A total of 6728 statin users could be compared with 6728 non-users. It appeared that non-traumatic arthropathies were higher in the statin-users (59.8% *versus* 56.0%) and also in those with trauma-related joint disorders, dislocations, sprains and strains (31.9% in statin users and 29.8% in nonusers). There was no difference between statin users and non-users who underwent rehabilitation [23]. In a cohort of 13.906 middle-aged and older Chinese people, hyperlipidemia was associated with knee pain (OR 1.34, 1.23-1.45) and clinical knee OA (1.34, 1.15-1.55), those with hyperlipidemia who consumed lipid-lowering drugs, had the highest risks of knee pain (1.40, 1.26-1.56) and clinical KOA (1.45, 1.21-1.75) [26].

A recent RCT with 60 postmenopausal Polish women with knee-OA and hypercholesterolemia was randomly divided into treatment- and control groups [25]. Thirty patients who fell in the treatment group received simvastatin (20-40 mg/day) for about 1 year and, the other 30 patients were in the control group, without statin. Both groups were on dietary restrictions on silicon and calcium. Serum was tested for calcium and silicon, in the statin group, serum calcium decreased, and silicon increased. A significant positive correlation between plasma silicon and simvastatin levels (r = 0.3) was found. It could be due to inactive silicon dioxide with simvastatin. Some suggest simvastatin-mediated increased serum silicon, influencing joint metabolism, may link with OA-knee pathophysiology, a possible therapeutic target for the disorder [25]. Statin further improves BMLs score in radiographic OA knee. In a longitudinal analysis, Mahajer *et al*. described the effect of statin on MRI-based BMLs in HN-positive generalized OA cases. MRI KOA scores were used to define BMLs before and after the statin intervention. HN-positive participants compared with HN-negative participants or those HN-positive patients with baseline moderate/severe BMLs were associated with lower odds of both BML score worsening (odds ratio, 95% confidence interval: 0.62, 0.39-0.98) and an increased number of affected subregions (0.54, 0.33-0.88) [7].

3.2. Preclinical Studies

3.2.1. In vitro Culture of Human Articular Cartilage Tissue in Statin-Rich Media

Human OA articular cartilage-derived chondrocytes treated *in vitro* with statin-rich (simvastatin and atorvastatin) media reversed the pro-inflammatory cytokine (IL-1β) mediated effects on damaged cartilage, and the effects were statin dose-dependent: reduced expression of mRNA of MMP-3, 13; increased expression of mRNA of AGC and COL2a1 proteins [27, 28]. Commercially derived chondrocytes of cryopreserved normal articular cartilage stimulated with IL-1β yielded increased mRNA-MMP-3 and MMP-9, the effect was significantly reversed by dose-dependent pravastatin treatment (p = 0.002 for MMP-3, and p= 0.001 for MMP-9); however, the overall reduction of MMP enzyme activity was non-significant (p = 0.07) [11].

3.2.2. Animal Studies

Animal studies involved oral and IA statin intervention of spontaneous (un-physiologic loading) and induced (chemical or surgical) degenerated articular cartilage of OA-knee models of rabbit, rat, mouse, and bovine [8-10, 29-36]. Animal studies yielded statin-mediated chondro-protective effects [8-10, 30-36]. Statin caused suppression of MMP activity in articular cartilage; statin prevented cartilage degeneration by inhibiting the Wnt/β-catenin signaling pathway in chondrocytes, minimized articular synovial inflammation, and catabolic-stress induced aging of cartilage [11, 30, 33-36].

The Frizzled (FRZB) gene family encodes trans-membrane proteins serving as receptors for the Wnt family glycoprotein ligands. Wnt and FRZB stimulate signaling pathways integral to disease development, including OA. In an association analysis with the sample from the population-based cohort, the R324G but not the R200W variant of the FRZB gene was seen to be involved in generalized OA phenotypes [37]. In the animal OA-knee model simvastatin caused Wnt (Wnt is a portmanteau of int and Wg oncogenes and stands for "Wingless-related integration site) / β-catenin signaling pathway dependent chondrocyte dedifferentiation inhibition and cartilage degeneration. Another preclinical study with human OA articular cartilage-derived chondrocytes treated *in vitro* simvastatin-rich media reversed the interleukin (IL-1β) mediated effects on degenerated cartilage (reduced expression of mRNA of MMP-3, 13; increased expression of mRNA of aggrecan and collagen2a1 proteins) [6].

Statin (atorvastatin and simvastatin) interventions in OA-knee models unveiled positive outcomes based on biochemical and cartilage histopathology examinations [29, 32-35]. The biochemistry panel involved increased lipid peroxidation, superoxide, protein carbonyl, SOX9, AGC, BMP2, reduced expression of COL1, α-smooth muscle actin, MMP-3, glutathione, and total thiol levels, decreased activity of catalase, and glutathione-*S*-transferase [29, 32-33].

The histopathological classifications of Pelletier and of Mankin were used respectively for macroscopic and microscopic articular cartilage morphology [29]. With electron microscopy, a homogenous cartilage was demonstrated with regular collagen fibrils, proteoglycans, and chondrocytes rich with granulous regular endoplasmic reticulum, similar to healthy cartilage chondrocytes [29]. The Osteoarthritis Research Society International (OARSI) histopathology assessment system scores were also used to classify articular cartilage tissue degeneration, based on six grades (1-6, measures in depth cartilage degeneration) and four stages

(measures horizontal extent of cartilage involvement) (Tables **1-3**) [34, 35].

In a study, thirty-two mature ACL transected rabbit OA-knees received weekly IA mevastatin injections for six weeks; the histopathology of the articular cartilage unveiled thin synovial tissue due to reduced sub-synovial infiltration of CD68+monocyte lineage cells with reduced mRNA expressions of MCP-1, IL-1β, MMP-3, 13, compared with untreated controls [30]. Reduced mRNA expressions of MCP-1, IL-1β, MMP-3, and MMP-13 were more predominant in synovial tissues than in articular cartilage [30]. Another study of Bovine articular chondrocytes treated in simvastatin-rich media revealed changes in phenotype and morphology of chondrocytes by increasing SOX9 mRNA and protein expression [32]. In an *in vivo* study with the STR/OrtCrlj mouse spontaneous OA-knee model, statin therapy prevented catabolic stress-induced articular cartilage aging in OA [36]. In the same mouse model, the induced OA knee cartilage treated with statin *in vitro* inhibition of IL-1β-mediated production of MMP- 1, 13 was found, and cellular senescence (β-galactosidase activity) and accelerated production of cartilage matrix proteoglycans in chondrocytes [36].

3.2.3. Statin Dose in Preclinical Versus Clinical Research

In preclinical research, statin doses and routes of statin treatment varied. In a preclinical study with IA statin, for example, 0.4 mg/kg of 40 mg atorvastatin in 100 mL saline once a week for three weeks was chondroprotective in rabbits [8]. IA SIM (10 µg/mL) coated collagen satisfactorily healed ACL graft-bone lesions [9]. IA injection of 0.4 mg/ml/kg saline atorvastatin weekly for three weeks seemed to protect cartilage in induced OA in New Zealand rabbits [29]. Oral atorvastatin (3, 10, and 30 mg/kg) for 20 days [34] and SIM (20 mg/kg per day for eight weeks) also healed damaged cartilage in induced OA [35]. SIM-treated rabbit [10], human and bovine [32], and mouse chondrocytes [36] regenerated articular cartilage with a doses (50 µM), (0.2, 1.0, 5.0 and 10.0 µM), and (1.0 or 10.0 µM), respectively. Besides, Pravastatin (1, 5, and 10 µM [11], and Mevastatin (1, 10, 50 µM [30] proved chondrocyte differentiation with matrix synthesis. However, that was not the case for the clinical study. Irrespective of doses, duration, and treatment route, statin outcomes on articular chondrocytes were promising in preclinical research. However, that was not the case in clinical study. The chondroprotective effect of statin in clinical OA knee is yet to be conclusive. In clinical research, no statin dose was tested for the treatment of KOA. All clinical research tested how clinical, radiographic phenotypes varied among statin recipients in an association. A prospective, longitudinal study is required to see how statin formulations (oral, IA) work in clinical OA.

4. DISCUSSION

In many studies, an association has been found between OA and dyslipidemia [38, 39]; generalized OA is less prevalent among statin users [13, 25, 38]. A systematic review and meta-analysis of 48 cross-sectional-, cohort-, and case-control studies demonstrated a greater risk of overall OA (OR 1.98, 95% CI 1.43 to 2.75, p=0.0001), knee OA (OR 2.27, 95% CI 1.33 to 3.89, p=0.003), and hand OA (OR 2.12, 95% CI 1.46 to 3.07, p=0.0001) risks with dyslipidemia [38]. Another systematic review of nine human studies (four cohorts, three case-control- and two cross-sectional studies) also depicted an increased risk of OA with dyslipidemia based on a meta-analysis of the case-control and cross-sectional studies, but such a risk was not found in meta-analysis of the cohort studies (RR = 1.00; 95%CI = 0.85-1.14) [39]; hence further study was recommended [39]. No test for funnel plot asymmetry was carried out due to the limited number of included studies (less than 10). Nevertheless, Begg's and Egger's tests failed to identify substantial publication bias.

In a clinical study, one-unit increase in triglyceride was seen associated with an increased risk of clinical knee OA prevalence and knee OA onset [26], so it was suggested that lipid-lowering agents might have a beneficial effect on OA-knee. The Genetics of OA and Lifestyle (GOAL) study involving clinically severe knee-, hip-, and nodal OA cases with full radiographic assessments, recruited from secondary care, documented a link between statin use and lower prevalence of generalized nodal OA, defined as: 'involvement of at least three joints or a group of joints, such as interphalangeal joints' [13]. Nodal OA involves Heberden's or Bouchard's nodes affecting two or more rays of both hands, being more common in women and associated with interphalangeal OA [40].

Our review shows that most preclinical studies have promising statin-mediated outcomes in OA treatment [8-10, 11, 27-36], but clinical studies show varying results (Table **1**). Clinical study outcomes regarding the effectiveness of statins in OA knee are conflicting and inconclusive: some documented improved clinical and radio-imaging outcomes [13, 15, 17, 20, 22, 24], others depicted the opposite results (Table **1**) [16, 19, 21, 23, 26]. The discrepancy with the findings in clinical studies may be explained by the fact that people with knee OA tend to be more overweight and tend to have DM with co-existing hyperlipidemia. Pathological changes of spontaneous cartilage degeneration in clinical OA and induced animal OA models could also contribute to animal and human study outcomes discrepancies. However, further research should be done addressing the association.

Overall, animal studies depicted chondroprotective effects of statins in degenerated cartilage with chondrocytes rich with collagen, proteoglycans, and granulus regular endoplasmic reticulum [29]. Beneficial effects were also seen in studies using chondrocytes rich in SOX9 gene-related protein, MCP-1, AGC, BMP2, COL2a1, and α-smooth muscle actin. There were reduced levels of IL-1β, MMP-1, 3, β-catenin (Tables **2** and **3**) [8-10, 11, 27-36]. Both *in vivo* and *in vitro* animal studies and preclinical *in vitro* studies with human degenerated cartilage demonstrated statin-mediated chondroprotective effects.

Eymard *et al*. showed that statin use in 71 knee OA patients was associated with worsening, but this was not an

RCT and the indication of the treatment was not the OA but other disorders, often connected with OA [16]. Based on previous human observational studies, outcomes of statin interventions in OA treatments are inconclusive; we are yet to have an RCT to test the efficacy of oral statin in human OA treatment. A study of the effect of statin treatment in patients with knee OA still seems to be indicated. IA statin therapy outcomes in animal models are encouraging. We could try to translate preclinical study outcomes in human OA, and a prospective phase-II clinical trial to test the effectiveness of IA statin in human OA seems feasible.

KOA is the most common OA variety with modifiable and non-modifiable risk factors. Preclinical and clinical study regarding KOA treatment is available so that we can compare any new outcome from the observational and experimental research. Clinical KOA symptom improves with IA steroid; we can test whether the same approach works for the IA-statin. In some KOA, oral statin may be contraindicated or lead to adverse musculoskeletal outcomes. However, IA-statin may be free from fatigue, myalgia, nocturnal muscle cramping, and rhabdomyolysis [2, 41].

Limitation of the evidence included: preclinical studies included in the review tested whether statin induced cartilage regeneration. None of the clinical studies tested statin's cartilage regeneration potential; instead, they observed and analyzed the changes in joint complaints, radiological joint space narrowing, surgical consultation, or joint replacement required among statin users. Clinical studies included in the review were of low-quality evidence.

Limitation of the review process: the review is based on articles found on two databases; more search engines could have helped find more articles regarding the study problems.

Study strengths: the synthesis includes both clinical and preclinical data. Selected clinical research satisfied the CASP.

CONCLUSION

At this stage, there is no argument yet to recommend oral statin to treat patients with osteoarthritis. As preclinical studies are promising and the findings of clinical studies are conflicting, an RCT testing the efficacy of oral statins in patients with OA knees was never done and still seems justified. A phase-II clinical trial with knee osteoarthritis could also test the efficacy of intra-articular statin. Researchers should further address barriers and ways to overcome them to translate preclinical study outcomes into clinical research.

KEY MESSAGES

1. Statin appears useful in articular cartilage regeneration of animal OA knee.
2. *In vitro* analysis of knee osteoarthritis cartilage resected surgically treated in statin-rich media depicted chondroprotective effects.
3. Effects of statin in human OA knee are inconclusive: some shows positive, others showed adverse outcomes.
4. A randomized controlled trial testing the efficacy of statin (oral or intra-articular) in OA knee is yet to perform and should be done.
5. Further study could be planned to explore the discrepancy of statin outcomes between preclinical and clinical osteoarthritis research

LIST OF ABBREVIATIONS

AEs	=	Adverse Effects
AGC	=	Agreecan
COL2a	=	Collagen 2a
IL-1β	=	Interleukin-1beta
KL	=	Kellgren Lawrence
KOA	=	Knee OA
LDL	=	Low-Density Lipoprotein
MMP	=	Matrix Metalloproteinases
MRI	=	Magnetic Resonance Imaging
OA	=	Osteoarthritis
OARSI	=	Osteoarthritis Research Society International
PCR	=	Polymerase Chain Reaction
RCT	=	Randomized Controlled Trial
ROA	=	Radiographic OA
TFJ	=	Tibiofemoral Joint
WOMAC	=	Western Ontario and McMaster Universities Arthritis Index

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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