MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040208
ISSN 2616-1907 Vol. 4 Num. 2

Progress on Cholesterol Metabolism in Osteoarthritis

Xi Zhang[1], Youhuan Hu[1], Shumei Wang[1,*], Jianghua Xie[2]

[1.] *School of Traditional Chinese Medicine, Chongqing Medical University, Chongqing 400016, China*

[2.] *Dianjiang County Hospital of Traditional Chinese Medicine, Chongqing 408300, China*

[*]*Corresponding Author*

Keywords: Osteoarthritis, Cholesterol, Chondrocytes, Oxidative stress

Abstract: Studies on risk factors of Osteoarthritis (OA) suggest that patients with OA are associated with abnormal lipid metabolism, and hyperlipidemia may also be a risk factor for OA. In this paper, we review the crucial role of metabolic syndrome in the pathology of Osteoarthritis, investigate the relationship between osteoarthritis and TC levels, clarify the association between cholesterol levels and chondrocytes, oxidative stress, and the therapeutic means to alleviate Osteoarthritis by regulating cholesterol levels.

1. Introduction

Osteoarthritis (OA), the most widespread disease in total joint degeneration, is characterized by cartilage destruction, bone redundancy formation, and subchondral bone remodeling[1-3]. According to the literature, approximately 10% of men and 18% of women worldwide suffer from various symptoms of Osteoarthritis. The prevalence of OA will continue to increase with aging.[4, 5].OA is associated with individual and joint-level factors, such as gender, age, obesity, genetics, race, ethnicity, joint injury, joint misalignment, and abnormal joint loading[6]. OA is not only a common disease related to physical stress and age but also a manifestation of “metabolic-related syndrome,” in which multiple risk factors combine to cause the development of Osteoarthritis. OA is not only a physical stress and age-related joint disease but also a manifestation of a “metabolic-related syndrome” in which multiple risk factors contribute to the development and progression of the disease, one of which is the value of TC in the body[7].

2. Epidemiological Epidemiologic Association of Cholesterol Levels with OA

Current epidemiological studies have shown a chronic correlation between serum cholesterol levels and OA, and that elevated serum cholesterol is a risk factor for systemic OA[8-10]. Hart et al. found a significant association between moderately elevated serum cholesterol and Osteoarthritis of the knee in a questionnaire survey of OA risk factors in 1330 women aged forty-five to sixty-four years [8]. In a cross-sectional study of 809 patients with OA-related arthroplasty, Sturmer et al. found that patients with hypercholesterolemia were independently associated with systemic OA[9]. OA also demonstrated in a literature study of 446 patients that there was a significant direct association between hand OA and elevated cholesterol[10]. This association is further supported by data from longitudinal studies, which found in a cohort study of healthy Australian women that the

odds of bone marrow damage increased by 1.84 (95% CI: 1.01, 3.36) with each one mmol/L increase in total Cholesterol, P= 0.048[11]. In conclusion, there is an epidemiological association between cholesterol levels and OA.

3. Cholesterol Accumulates in Osteoarthritic Cartilage

Normal chondrocytes prevent intracellular cholesterol accumulation through an exocytotic system[12]. However, in osteoarthritic chondrocytes, this metabolic function is dysfunctional[13]. Prasad et al. showed that hypercholesterolemia increases the amino acid formation and production of pro-inflammatory arachidonic acids, which promote prostaglandin and leukotriene synthesis. Oxygen free radicals are generated during synthesizing these arachidonic acids, and the increased levels of oxygen free radicals eventually lead to chondrocyte damage[14].In a study related to mobility and chemical components in healthy individuals and OA cartilage, Cillero et al. found the presence of lipid-rich droplets in OA cartilage that accumulate only in the surface areas of OA cartilage, demonstrating that lipid metabolism The importance of altered lipid metabolism in OA pathology was demonstrated by Arai et al. who showed that elevated cholesterol levels in OA chondrocytes lead to reduced membrane fluidity, resulting in a blocked signaling cascade for gene expression related to bone formation[15]. Kostopoulou et al. found that in conducting studies on OA pathogenesis, OA pathology was associated with SRBP-2 (a gene that regulates the gene that regulates cholesterol synthesis and uptake) with a single nucleotide polymorphism. The study also noted that the gene and protein expression levels of SREBP-2 were significantly higher in chondrocytes of OA patients compared to normal subjects. In addition, the expression of HMGCR, the target gene of SREBP-2, was also associated with significantly higher expression in OA patients than in normal chondrocytes[16]. De Munter et al. found that LDL cholesterol also affects the development and progression of OA[17]. A progressive rise in LDL was found to cause synovial activation and promote bone formation in mice fed a high-fat diet for OA experiments[18]. Particular emphasis was placed on the possible involvement of oxidized LDL in synovial inflammation development and cartilage destruction[17]. Not coincidentally, Gierman et al. found in an experimental study in mice that a high-fat diet significantly increased cartilage damage while noting that the formation of this cartilage damage was independent of body weight and also that this experiment demonstrated that this cartilage damage could be alleviated by modulating cholesterol levels, suggesting the importance of cholesterol metabolism levels and osteoarthritic chondrocyte damage[19]. In a later study, the group also found a significant increase in spontaneous cartilage damage in mice fed high-cholesterol food in a hyperlipidemic and atherosclerotic mouse model[20]. These results demonstrate that Cholesterol accumulates in osteoarthritic cartilage, but the mechanisms behind it need more research to explain.

4. Cholesterol Metabolism and Chondrocytes

Articular cartilage is a 2-4 mm thick, highly differentiated tissue devoid of blood vessels and nerves, whose structural and mechanical properties consist mainly of a dense extracellular matrix whose main component is chondrocytes[21]. Articular cartilage depends on chondrocytes to form and repair itself, and the adequacy of chondrocytes plays a vital role in the effective treatment and tissue regeneration of OA[22]. Cholesterol plays an irreplaceable role as a component of the cell membrane, producing bile acids and steroid hormones that are essential regulators of cellular processes[23]. Cholesterol regulates various cellular processes, including membrane transport and transmembrane signaling. Cholesterol in cell membranes can create a semi-permeable barrier between cellular compartments and control biophysical properties such as membrane fluidity, bending, and permeability[24-27]. In osteoarthritic chondrocytes, synovial fluid, and chondrocytes

store fat and Cholesterol, and excessive cholesterol levels lead to changes in the orientation of cell membrane lipids and changes in the biophysical properties of the membrane[28, 29]. Excessive accumulation of Cholesterol in the cell membrane of chondrocytes leads to the degradation of TGF-β receptors[30, 31]. In addition, changes in cell membrane fluidity regulated by cholesterol levels alter the local adhesion of cells[32]. A study by Arai et al. found that taurodeoxycholic acid could restore the chondrogenic properties of degenerated chondrocytes by indirectly elevating membrane fluidity values through increased intracellular cholesterol values[15]. The results of Wan et al. showed that OA is an in vivo metabolic disorder and that increased cholesterol levels in OA chondrocytes are due to increased Cholesterol. Increased cholesterol levels in OA chondrocytes due to increased cholesterol uptake, increased cholesterol hydroxylases (CH25H and CYP7B1) levels, and a corresponding increase in oxysterol metabolite production[33]. He found that Vaspin inhibited cholesterol efflux from chondrocytes via the miR155/LXRα axis, ultimately leading to the accumulation of fat and the formation of arthritis[34]. In summary, Cholesterol is an essential component of chondrocytes, and cholesterol accumulation within chondrocytes ultimately leads to the development of Osteoarthritis, and regulating cholesterol metabolism within chondrocytes may eliminate the related symptoms of Osteoarthritis.

5. Cholesterol Levels and Oxidative Stress

Overproduced reactive oxygen species (ROS) in chondrocytes can induce stress, and extreme levels of ROS reduce the ability of cellular antioxidant defense systems to scavenge, thus causing oxidative stress and cellular damage, ultimately resulting in the formation of OA[35-37]. Reactive oxygen species are free radicals containing oxygen molecules, so reactive oxygen species have volatile chemical properties and are prone to react with different organisms[38]. In OA chondrocytes, Oxidative stress plays an essential role in the pathogenesis of Osteoarthritis and is corroborated by increased reactive oxygen species production, reduced levels of antioxidant enzymes, and lipid peroxidation products in synovial fluid[39]. High levels of reactive oxygen species prevent extracellular matrix synthesis, and cell migration, reduce growth factor bioavailability, and activate matrix metalloproteinases to promote cartilage destruction and induce chondrocyte death[40]. Li et al. found that Cholesterol induces tendinopathy through the NF-κB signaling pathway activated by reactive oxygen species[42]. Zhang et al. found that high TG, TCHO, and SFA levels induce oxidative stress[42-44]. A study by Wang et al. found that salvianolic acid A effectively reduced severe oxidative stress caused by NAFLD by regulating hepatic pro-inflammatory cytokines and lipid reduction[45].

6. Treatment

Regulation of cholesterol levels may be one way to treat OA, the current state of research on the involvement of Cholesterol in the pathogenesis of OA may provide new clues for the treatment of Osteoarthritis. No drug has been found to improve the structural progression of OA significantly. Although cytokine-targeted therapy is an effective treatment for rheumatoid arthritis, anti-IL-1β[46, 47] and anti-tumor necrosis factor[48, 49] have not shown convincing therapeutic effects. Therefore, the current therapies are mainly anti-inflammatory and analgesic[50]. Statins reduce the systemic levels of LDL by decreasing cholesterol biosynthesis. Thus, we can try to use lipid-lowering drugs to alleviate the related symptoms of OA. in research, Gierman et al. found that statins shed the degree of symptoms of cholesterol-induced OA[20]. Statins reduce the development of atherosclerosis by modulating oxidized LDL-mediated pathology[51, 52], and it is theorized that statins play a role in Osteoarthritis. Interestingly, another study showed that statin simvastatin did not affect cartilage destruction in a spontaneous OA model in SRT/Ort mice[53]. Statins effectively

degrade cartilage in OA animal models in some animal studies[54, 55]; however, there are no definitive statin findings for OA[56]. A prospective population-based cohort study in the Netherlands[57] and two studies in the United Kingdom[58,59] showed active influences of statins. In comparison, two studies in the United States did not show positive effects[60, 61].

7. Conclusion

In conclusion, the current study suggests a compelling link between cholesterol metabolism and OA and that dysregulated cholesterol metabolism may contribute to one of the essential pathologies of OA. Further understanding of OA progression and cholesterol metabolism and how to intervene aggressively during this period may lead to new therapeutic strategies for patients with OA.

References

[1] Loeser R F, Goldring SR, Scanzello C R, et al. Osteoarthritis: a disease of the joint as an organ[J]. Arthritis Rheum, 2012,64(6):1697-1707.DOI:10.1002/art.34453.

[2] Moon P M, Beier F. Novel Insights into Osteoarthritis Joint Pathology from Studies in Mice[J]. Curr Rheumatol Rep, 2015,17(8):50.DOI:10.1007/s11926-015-0524-1.

[3] Mandl L A. Osteoarthritis year in review 2018: clinical[J].Osteoarthritis Cartilage, 2019,27(3):359-364.DOI:10.1016/j.joca.2018.11.001.

[4] Wallace I J, Worthington S, Felson D T, et al.Knee osteoarthritis has doubled in prevalence since the mid-20th century[J]. Proc Natl Acad Sci U S A, 2017,114(35):9332-9336.DOI:10.1073/pnas.1703856114.

[5] Hunter D J, Schofield D, Callander E. The personal and socioeconomic impact of Osteoarthritis [J].Nat Rev Rheumatol, 2014,10(7):437-441.DOI:10.1038/nrrheum.2014.44.

[6] Hunter D J, Bierma-Zeinstra S. Osteoarthritis[J].Lancet, 2019,393(10182):1745-1759.DOI:10.1016/S0140-6736(19)30417-9.

[7] Farnaghi S, Crawford R, Xiao Y, et al. Cholesterol metabolism in the pathogenesis of osteoarthritis disease[J]. Int J Rheum Dis, 2017,20(2):131-140.DOI:10.1111/1756-185X.13061.

[8] Hart D J, Doyle D V, Spector T D. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study[J]. J Rheumatol, 1995,22(6):1118-1123.

[9] Sturmer T, Sun Y, Sauerland S, et al. Serum cholesterol and Osteoarthritis. The baseline examination of the Ulm Osteoarthritis Study[J].J Rheumatol, 1998,25(9):1827-1832.

[10] Addimanda O, Mancarella L, Dolzani P, et al. Clinical associations in patients with hand osteoarthritis[J]. Scand J Rheumatol, 2012,41(4):310-313.DOI:10.3109/03009742.2012.656699.

[11] Davies-Tuck M L, Hanna F, Davis SR, et al. Total Cholesterol and triglycerides are associated with developing new bone marrow lesions in asymptomatic middle-aged women - a prospective cohort study[J]. Arthritis Res Ther, 2009,11(6): R181.DOI:10.1186/ar2873.

[12] Cillero-Pastor B, Eijkel G, Kiss A, et al. Time-of-flight secondary ion mass spectrometry-based molecular distribution distinguishing healthy and osteoarthritic human cartilage[J]. Anal Chem, 2012,84(21):8909-8916. DOI:10.1021/ac301853q.

[13] Tsezou A, Iliopoulos D, Malizos K N, et al. Impaired expression of genes regulating cholesterol efflux in human osteoarthritic chondrocytes[J]. J Orthop Res, 2010,28(8):1033-1039.DOI:10.1002/jor.21084.

[14] Prasad K, Lee P. Suppression of oxidative stress as a mechanism of reduction of hypercholesterolemic atherosclerosis by aspirin[J]. J Cardiovasc Pharmacol Ther, 2003,8(1):61-69.DOI:10.1177/107424840300800i109.

[15] Arai Y, Choi B, Kim B J, et al. Tauroursodeoxycholic acid (TUDCA) counters Osteoarthritis by regulating intracellular cholesterol levels and membrane fluidity of degenerated chondrocytes[J]. Biomater Sci, 2019,7(8):3178-3189.DOI:10.1039/c9bm00426b.

[16] Kostopoulou F, Gkretsi V, Malizos K N, et al. Central role of SREBP-2 in the pathogenesis of Osteoarthritis [J].PLoS One, 2012,7(5):e35753.DOI:10.1371/journal.pone.0035753.

[17] De Munter W, van der Kraan P M, van den Berg WB, et al. High systemic levels of low-density lipoprotein cholesterol fuel the flames in inflammatory Osteoarthritis?[J]. Rheumatology (Oxford), 2016,55(1):16-24.DOI:10.1093/rheumatology/kev270.

[18] De Munter W, Blom A B, Helsen M M, et al. Cholesterol accumulation caused by low-density lipoprotein receptor deficiency or a cholesterol-rich diet results in ectopic bone formation during experimental Osteoarthritis [J].Arthritis Res Ther, 2013,15(6): R178.DOI:10.1186/ar4367.

[19] German L M, van der Ham F, Koudijs A, et al.Metabolic stress-induced inflammation plays a significant role in

the development of Osteoarthritis in mice[J]. Arthritis Rheum, 2012,64(4):1172-1181.DOI:10.1002/art.33443.
*[20] German L M, Kuhnast S, Koudijs A, et al. Osteoarthritis development is induced by increased dietary Cholesterol and can be inhibited by atorvastatin in APOE*3Leiden.CETP mice--a translational model for atherosclerosis[J].Ann Rheum Dis, 2014,73(5):921-927.DOI:10.1136/annrheumdis-2013-203248.*
[21] Sophia F A, Bedi A, Rodeo S A. The basic science of articular cartilage: structure, composition, and function[J]. Sports Health, 2009,1(6):461-468.DOI:10.1177/1941738109350438.
[22] Dreier R. Hypertrophic differentiation of chondrocytes in Osteoarthritis: the developmental aspect of degenerative joint disorders[J].Arthritis Res Ther, 2010,12(5):216.DOI:10.1186/ar3117.
[23] Tabas I. Consequences of cellular cholesterol accumulation: basic concepts and physiological implications[J]. J Clin Invest, 2002,110(7):905-911.DOI:10.1172/JCI16452.
[24] Yang S T, Kreutzberger A, Lee J, et al. The role of Cholesterol in membrane fusion[J]. Chem Phys Lipids, 2016,199:136-143.DOI:10.1016/j.chemphyslip.2016.05.003.
[25] Holthuis J C, Menon A K. Lipid landscapes and pipelines in membrane homeostasis[J].Nature, 2014,510(7503):48-57.DOI:10.1038/nature13474.
[26] Evans E, Rawicz W. Entropy-driven tension and bending elasticity in condensed-fluid membranes[J].Phys Rev Lett, 1990,64(17):2094-2097.DOI:10.1103/PhysRevLett.64.2094.
[27] Pan J, Tristram-Nagle S, Nagle J F. Effect of Cholesterol on structural and mechanical properties of membranes depends on lipid chain saturation[J].Phys Rev E Stat Nonlin Soft Matter Phys, 2009,80(2 Pt 1):21931.DOI:10.1103/PhysRevE.80.021931.
[28] Ikonen E. Cellular cholesterol trafficking and compartmentalization[J].Nat Rev Mol Cell Biol, 2008,9(2):125-138.DOI:10.1038/nrm2336.
[29] Kwik J, Boyle S, Fooksman D, et al. Membrane cholesterol, lateral mobility, and the phosphatidylinositol 4,5-bisphosphate-dependent organization of cell actin[J]. Proc Natl Acad Sci U S A, 2003,100(24):13964-13969.DOI:10.1073/pnas.2336102100.
[30] Chen C L, Chen C Y, Chen Y P, et al. Betulinic acid enhances TGF-beta signaling by altering TGF-beta receptors partitioning between lipid-raft/caveolae and non-caveolae membrane microdomains in mink lung epithelial cells[J].J Biomed Sci, 2016,23:30.DOI:10.1186/s12929-016-0229-4.
[31] Chen C L, Liu I H, Fliesler S J, et al. Cholesterol suppresses cellular TGF-beta responsiveness: implications in atherogenesis[J].J Cell Sci, 2007,120(Pt 20):3509-3521.DOI:10.1242/jcs.006916.
[32] Gopalakrishna P, Chaubey S K, Manogaran P S, et al. Modulation of alpha5beta1 integrin functions by the phospholipid and cholesterol contents of cell membranes[J].J Cell Biochem, 2000,77(4):517-528.
[33] Choi W S, Lee G, Song W H, et al. The CH25H-CYP7B1-RORalpha axis of cholesterol metabolism regulates Osteoarthritis [J].Nature, 2019,566(7743):254-258.DOI:10.1038/s41586-019-0920-1.
[34] He H, Lu M, Shi H, et al. Vaspin regulated cartilage cholesterol metabolism through miR155/LXRalpha and participated in the occurrence of Osteoarthritis in rats[J].Life Sci, 2021,269:119096.DOI:10.1016/j.lfs.2021.119096.
[35] Bolduc J A, Collins J A, Loeser R F. Reactive oxygen species, aging and articular cartilage homeostasis[J]. Free Radic Biol Med, 2019,132:73-82.DOI:10.1016/j.freeradbiomed.2018.08.038.
[36] Lepetsos P, Papavassiliou A G.ROS/oxidative stress signaling in Osteoarthritis [J].Biochim Biophys Acta, 2016,1862(4):576-591.DOI:10.1016/j.bbadis.2016.01.003.
[37] Altindag O, Erel O, Aksoy N, et al. Increased oxidative stress and its relation with collagen metabolism in knee osteoarthritis[J]. Rheumatol Int, 2007,27(4):339-344.DOI:10.1007/s00296-006-0247-8.
[38] Adam-Vizi V, Chinopoulos C. Bioenergetics and the formation of mitochondrial reactive oxygen species[J].Trends Pharmacol Sci, 2006,27(12):639-645.DOI:10.1016/j.tips.2006.10.005.
[39] Ersoy Y, Ozerol E, Baysal O, et al. Serum nitrate and nitrite levels in patients with rheumatoid arthritis, ankylosing spondylitis, and Osteoarthritis [J].Ann Rheum Dis, 2002,61(1):76-78.DOI:10.1136/ard.61.1.76.
[40] Li J, Dong S.The Signaling Pathways Involved in Chondrocyte Differentiation and Hypertrophic Differentiation[J].Stem Cells Int, 2016,2016:2470351.DOI:10.1155/2016/2470351.
[41] Li K, Deng G, Deng Y, et al.High Cholesterol inhibits tendon-related gene expressions in tendon-derived stem cells through reactive oxygen species-activated nuclear factor-kappaB signaling[J].J Cell Physiol, 2019,234(10):18017-18028.DOI:10.1002/jcp.28433.
[42] Day C P, James O F. Steatohepatitis: a tale of two "hits"?[J].Gastroenterology, 1998,114(4):842-845.DOI:10.1016/s0016-5085(98)70599-2.
[43] Musso G, Gambino R, Cassader M. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD)[J].Prog Lipid Res, 2009,48(1):1-26.DOI:10.1016/j.plipres.2008.08.001.
[44] Zhang X, Shen J, Man K, et al.CXCL10 plays a key role as an inflammatory mediator and a non-invasive biomarker of non-alcoholic steatohepatitis[J]. J Hepatol, 2014,61(6):1365-1375.DOI:10.1016/j.jhep.2014.07.006.
[45] Ding C, Zhao Y, Shi X, et al.New insights into salvianolic acid A action: Regulation of the TXNIP/NLRP3 and TXNIP/ChREBP pathways ameliorates HFD-induced NAFLD in rats[J].Sci Rep,

2016,6:28734.DOI:10.1038/srep28734.
[46] Caron J P, Fernandes J C, Martel-Pelletier J, et al. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental Osteoarthritis. Suppression of collagenase-1 expression[J].Arthritis Rheum, 1996,39(9):1535-1544.DOI:10.1002/art.1780390914.
[47] Dougados M, Emery P, Lemmel E M, et al. Efficacy and safety of leflunomide and predisposing factors for treatment response in patients with active rheumatoid arthritis: RELIEF 6-month data[J].J Rheumatol, 2003,30(12):2572-2579.
[48] Grunke M, Schulze-Koops H. Successful treatment of inflammatory knee osteoarthritis with tumour necrosis factor blockade[J].Ann Rheum Dis, 2006,65(4):555-556.DOI:10.1136/ard.2006.053272.
[49] Magnano M D, Chakravarty E F, Broudy C, et al. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory Osteoarthritis of the hands[J]. J Rheumatol, 2007,34(6):1323-1327.
[50] Hochberg M C, Altman R D, April K T, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in Osteoarthritis of the hand, hip, and knee[J].Arthritis Care Res (Hoboken), 2012,64(4):465-474.DOI:10.1002/acr.21596.
[51] Dje N P, Riediger F, Vardarova K, et al. Statins control oxidized LDL-mediated histone modifications and gene expression in cultured human endothelial cells[J]. Arterioscler Thromb Vasc Biol, 2009,29(3):380-386.DOI:10.1161/ATVBAHA.108.178319.
[52] Maki-Petaja K M, Booth A D, Hall F C, et al. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis[J].J Am Coll Cardiol, 2007,50(9):852-858.DOI:10.1016/j.jacc.2007.04.076.
[53] Wei W, Clockaerts S, Bastiaansen-Jenniskens Y M, et al. Statins and fibrates do not affect development of spontaneous cartilage damage in STR/Ort mice[J].Osteoarthritis Cartilage, 2014,22(2):293-301.DOI:10.1016/j.joca.2013.11.009.
[54] Akasaki Y, Matsuda S, Nakayama K, et al. Mevastatin reduces cartilage degradation in rabbit experimental osteoarthritis through inhibition of synovial inflammation[J].Osteoarthritis Cartilage, 2009,17(2):235-243.DOI:10.1016/j.joca.2008.06.012.
[55] Aktas E, Sener E, Gocun P U. Mechanically induced experimental knee osteoarthritis benefits from anti-inflammatory and immunomodulatory properties of simvastatin via inhibition of matrix metalloproteinase-3[J].J Orthop Traumatol, 2011,12(3):145-151.DOI:10.1007/s10195-011-0154-y.
[56] Conaghan P G.The effects of statins on Osteoarthritis structural progression: another glimpse of the Holy Grail?[J]. Ann Rheum Dis, 2012,71(5):633-634.DOI:10.1136/annrheumdis-2011-201135.
[57] Clockaerts S, Van Osch G J, Bastiaansen-Jenniskens Y M, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study[J].Ann Rheum Dis, 2012,71(5):642-647.DOI:10.1136/annrheumdis-2011-200092.
[58] Kadam U T, Blagojevic M, Belcher J. Statin use and clinical osteoarthritis in the general population: a longitudinal study[J].J Gen Intern Med, 2013,28(7):943-949.DOI:10.1007/s11606-013-2382-8.
[59] Valdes A M, Zhang W, Muir K, et al. Use of statins is associated with a lower prevalence of generalised Osteoarthritis [J].Ann Rheum Dis, 2014,73(5):943-945.DOI:10.1136/annrheumdis-2013-204382.
[60] Beattie M S, Lane N E, Hung Y Y, et al. Association of statin use and development and progression of hip osteoarthritis in elderly women[J].J Rheumatol, 2005,32(1):106-110.
[61] Riddle D L, Moxley G, Dumenci L. Associations between statin use and changes in pain, function and structural progression: a longitudinal study of persons with knee osteoarthritis[J].Ann Rheum Dis, 2013,72(2):196-203.DOI:10.1136/annrheumdis-2012-202159.