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Association between statin use and consultation or surgery for osteoarthritis of the hip or knee: a pooled analysis of four cohort studies

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SUMMARY

Objective: Experimental findings and previous observational data have suggested lower risk of osteoarthritis (OA) with statin use but results are inconsistent. Large-scale studies with a clinically important outcome are needed. Thus, we aimed to determine whether statin use is associated with a reduced risk of developing clinically-defined hip or knee OA.

Design: Pooled analysis based on time-to-event analysis of four population-based large cohorts, encompassing in total 132,607 persons aged 57–91 years resident in southern and central Sweden. We studied the association between statin use and time to consultation or surgery for OA of the hip or knee by time-dependent exposure analysis and Cox regression.

Results: During 7.5 years of follow-up, we identified 7468 out- or inpatient treated cases of hip or knee OA. Compared with never use, current use of statins conferred no overall reduction in the risk of OA with an adjusted pooled hazard ratio (HR) of 1.04 (95% confidence intervals [95% CI] 0.99–1.10). We found no dose–response relation between duration of current statin use and the risk of OA, with similar HRs among patients with less than 1 year of use (HR 1.09; 95% CI 0.92–1.32) as in patients with use for 3 years or more (HR 1.05; 0.93–1.16). Results were comparable in those with low, medium and high dose of current statin use, without indications of heterogeneity of study results.

Conclusion: Statin use is not associated with reduced risk of consultation or surgery for OA of the hip or knee.

Introduction

The preventive effect of statin use on osteoarthritis (OA) incidence and progression is potentially important, biologically plausible, but contested. In addition to their cholesterol lowering effects through competitive inhibition of hydroxymethyl-glutaryl-coenzyme A reductase that reduces cholesterol biosynthesis, statins – the most commercially successful drugs in history[1] – are recognized for their anti-inflammatory and immune-modulating effects[2]. On a cellular level, statins inhibit leucocyte-endothelial adhesion, reduce *in vitro* expression and production of inducible nitric oxide synthase, interleukins and matrix metalloproteinases, and interfere with osteoclast function and stimulate osteoblast activity leading to subchondral bone formation through increased production of bone morphogenetic protein-2[3–8]. A reduction by statins of OA development has been reported in animal models of induced OA[5,9–11] but was not confirmed in a spontaneous model[12].

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With an appreciation that OA is partially driven by inflammation, relief of OA symptoms and development by statin use has been suggested[5,13,14]. Moreover, since there exist associations between OA and cardiovascular disease[15], the effect of statins on OA could also be mediated indirectly by preventing atherosclerosis development.

A few prospective observational studies have evaluated whether statins reduce the disability and development of OA. Knee, but not hip, OA progression was reported to be lower in statin users in a longitudinal Dutch study with 6.5 years of follow-up[16]. In contrast, statin use was not associated with OA progression, knee function or pain in US or Australian cohorts[17,18]. Higher statin dose was reported to be related to lower incidence of clinically-relevant OA irrespective of joint site in another cohort study, whereas a low dose conferred a higher risk of OA in the same cardiovascular disease cohort based on the UK General Practice Research Database[19]. Finally, statin users had even higher reported risk for the development of radiographic hip OA in the Study of Osteoporotic Fractures[20] and OA in general identified by diagnosis codes in a US military cohort database[21]. Importantly, without taking into consideration a time-dependent exposure and time-to-event analysis, there exists an evident risk of immortal time bias in pharmacoepidemiological studies of statin use leading to an ostensible protective effect on OA[22]. The results of available cohort studies are thus conflicting, perhaps in part due to a lack of external validation of individual study results, low number of outcomes, limited evaluation of dose–response and time-dependent exposure analysis, and a lack of consistent case definitions.

Given the unclear present evidence we used four large Swedish population-based cohorts with substantial information on important confounders (e.g., BMI) to evaluate the risk of consultation or surgery for OA of the hip or knee in statin users compared with non-users of statins.

Methods

Study cohorts

The Malmö Diet and Cancer Study (MDCS)

The MDCS includes 30,447 men born 1923–1945 and women born in 1923–1950 from the general population of Malmö, Sweden[23–27]. Participants attended baseline examinations between 1991 and 1996 with sampling of peripheral venous blood and ascertainment of clinical characteristics and were included in the present study[23–27].

The Malmö Preventive Project (MPP) (reexamination cohort)

The MPP started in the mid-1970s at the Malmö University Hospital[28,29]. Between 1974 and 1992, a total of 33,346 persons were recruited (with a 71% attendance rate). Men were included years 1974–1990 and women 1980–1992. All participants underwent physical examination, and each had blood drawn for measurements of fasting blood glucose and lipid concentrations. Height and weight were measured[30]. Lifestyle factors and medical history was ascertained by questionnaires. Of those participating in the initial screening, 4931 have died, and 551 were lost to follow-up before the re-examination study in the early 2000s. Twenty-five thousand eligible participants were invited to this re-screening visit during 2002–2006, including also a physical examination. Of those invited, 17,284 persons participated in the re-screening and this sample constituted our cohort.

Swedish Mammography Cohort (SMC)

In 1987 through 1990, all women born between 1914 and 1948 and living in Västmanland and Uppsala counties in central Sweden were invited to participate in the SMC[31]. Of the 90,303 women invited, 66,651 (74%) accepted and completed a first self-administered questionnaire regarding diet, alcohol consumption, education, living conditions, body weight and height. In 1997, the 56,030 women who were still alive and still living in the study area received a second questionnaire that was expanded to also include information on smoking status, physical activity and other lifestyle factors; 39,227 (70%) women responded.

Cohort of Swedish Men (COSM)

In 1997, all men who were born between 1918 and 1952 and resided in Västmanland and Örebro counties in central Sweden were invited to participate in the COSM[31]. Of the 100,303 eligible men, 48,850 (49%) accepted and completed the questionnaire regarding diet, alcohol consumption, education, living conditions, body weight and height, physical activity, smoking habits, and other lifestyle factors.

Uniform inclusion and exclusion criteria

For this study we included all study participants from each of the four cohorts who were alive and resident in Sweden by July 1, 2005 (the start of this specific study). We excluded all study participants having had a diagnostic code of knee or hip OA according to the International Classification of Diseases (ICD) classification system in the national Swedish patient register (registered as a main or secondary diagnosis) between Jan 1, 1964 and July 1, 2005. The diagnostic codes were for ICD-10: M16, M17; for ICD-9: 715; for ICD-8: 713; and for ICD-7: 723 (including sub-diagnoses under that coding). All cohort members were linked to the registers since the few individuals who initially reported an incorrect individual personal registration number (<1%) were excluded from the cohorts. The national Swedish patient register was launched in 1964 (psychiatric diagnoses from 1973) but complete coverage did not begin until 1987. Currently, more than 99% of all somatic (including surgery) and psychiatric hospital discharges are registered in the register[32]. All out-patient specialist care is included in the same register since 2001. Both the in-patient and out-patient care is under a legal obligation to provide information to the patient register, with the exception of primary care (GPs). This applies to both private and public health care.

The study, including register linkages, was approved by the regional research ethics review boards at the Karolinska Institutet, Stockholm and Lund University, Lund, Sweden.

Exposure definition

Data on exposure to statins was retrieved from The Swedish Prescribed Drug Register, which includes all prescriptions dispensed in Sweden since July 2005. All drugs are registered using the Anatomical Therapeutic Chemical (ATC) classification system. Measurement units of utilization are prescriptions, Defined Daily Doses and expenditures. The register is complete for the entire population in Sweden (patient identity data are missing for <0.3% of all items).

We defined statin exposure as *any* use of statins registered with ATC codes C10AA01 to C10AA08 from July 1, 2005 until December 31, 2012 in SMC and COSM and until 1 year earlier for the MDCS and MPP cohorts. A person was treated as exposed from the first date of purchase of statins at the pharmacy until the latest purchase date + 90 days (as the drugs are normally dispensed every third month) and as unexposed during remaining time. Current users were analyzed in categories (<1, 1–2, 2–3, >3 years). If no new prescription were collected at the pharmacy 90 days after the previous doses would have been consumed, we regarded this