Use of statins is associated with a lower prevalence of generalised osteoarthritis

Recent reports, from The Netherlands[1] and the UK,[2] suggest that statins have a modifying role in osteoarthritis (OA) using different outcome definitions, specifically radiographic OA in the Rotterdam cohort and general practitioner diagnosis from a national database in the UK study. On the other hand, a large longitudinal study from the USA found that statin use was not associated with improvements in knee pain, function or structural progression over a 4-year period.[3] A separate US longitudinal study in elderly women found that statin use may be associated with an increased risk of developing incident radiographic hip OA.[4] The discrepancies between published studies on statins and OA may be due to methodological factors as has been discussed elsewhere.[5]

Studies of generalised OA suggest the potential role of systemic processes in disease pathogenesis.[6] It has been hypothesised, based on evidence from in vitro studies, that a dysfunction in lipid metabolism may play a role in the pathogenesis of OA.[7]

It is therefore possible that lipid dysregulation may be involved more in generalised polyarticular OA than in single large joint OA. Generalised OA (GOA) refers to the involvement of at least three joints, or a group of joints, for example, the interphalangeal (IP) joints. The nodal type of GOA, characterised by Heberden's and Bouchard's nodes predominates in women and associates with underlying radiographic IP OA.[8] There is no agreed consensus definition for generalised OA, but the presence of IP nodes has been shown to result in a different profile of risk factors for both hip and knee OA.[9]

In order to test if statin use is associated with generalised nodal OA, we used data from the Genetics of OA and Lifestyle (GOAL) study, a large case-control study involving clinically severe OA cases, with full radiographic assessment, recruited from secondary care. [8] We focused on the following eight outcomes: (1) nodal OA defined as Heberden's or Bouchard's nodes affecting two or more rays of both hands; (2) knee OA defined as a Kellgren–Lawrence (K/L) score ≥ 2 at the tibiofemoral compartment of either knee excluding hip OA; (3) radiographic hip OA defined as a K/L ≥ 2 at either hip excluding knee OA; (4) hip and knee OA pelvis K/L ≥ 2 at either hip and tibiofemoral ≥ 2 at either knee; (5) generalised knee OA defined as knee OA in addition to nodal status excluding hip OA; (6) generalised hip OA defined as hip OA in addition to nodal status excluding knee OA; (7) generalised hip and knee OA; (8) any GOA (the sum of 5, 6 and 7 above). Details on X-rays and patient recruitment have been reported elsewhere.[9] The descriptive characteristics of study participants are shown in table 1.

After adjustment for confounders we find no evidence for an association between nodal OA, hip OA or knee OA and use of statins (table 2). However, use of statins is associated with a lower prevalence of the GOA phenotype. This association

Table 1 Descriptive characteristics of study participants

Characteristic	Statin use*			
	No		Yes	
n	2510		661	
Years on statin medication	0		4.28	(3.39)
Age years mean (SD)	65.96	(8.10)	68.8	(6.52)
BMI kg/m^2 mean (SD)	29.10	(5.27)	29.92	(5.19)
Years with joint pain mean (SD)†	8.49	(9.46)	8.55	(9.88)
F (n=1537) % (n)	51.3%	(n=1288)	37.7%	(n=249)
Cardiovascular disease (n=1679) % (n)‡	43.1%	(n=1082)	90.3%	(n=597)
Medication for pain (n=1767) % (n)	54.9%	(n=1378)	58.8%	(n=389)
Ever-smoked: ex-smokers (n=1487) and current smokers (n=429) % (n)	58.0%	(n=1457)	69.4%	(n=459)
Controls (n=805) % (n)	26.7%	(n=669)	20.6%	(n=136)
Nodal OA (n=106) % (n)§	3.3%	(n=83)	3.5%	(n=23)
Knee OA (n=729) % (n)¶	21.8%	(n=546)	27.7%	(n=183)
Hip OA (n=499) % (n)¶	15.9%	(n=399)	15.1%	(n=100)
Hip and knee OA (n=427) % (n)¶	12.7%	(n=318)	16.5%	(n=109)
Generalised knee OA: nodal+knee (n=238)	7.5%	(n=188)	7.6%	(n=50)
Generalised hip OA: nodal+hip (n=142)	4.7%	(n=118)	3.6%	(n=24)
Generalised hip and knee OA: nodal+hip and knee (n=225)	7.5%	(n=189)	5.4%	(n=36)

*Study participants underwent a home visit[9] and the research nurse reviewed medications and repeat prescriptions from participants. Participants were classified as being on statin medication if they were taking any of the following medications: pravastatin, rosuvastatin, simvastatin, atorvastatin or fluvastatin. No information on dose was available.
†For patients with only knee OA (nodal or not) this is the years with knee pain; for patients with hip OA, the years with hip pain; for patients with both knee and hip OA, this is the largest of years with hip or knee pain; controls are not included, for asymptomatic cases it is 0.
‡Comorbidities were evaluated by nurse-applied questionnaire. A participant is considered to have cardiovascular disease if they replied yes to the question 'have you been diagnosed by your general practitioner or a specialist to have heart disease or hypertension'.
§The presence of Heberden's and Bouchard's nodes was assessed by a nurse. The nodal phenotype was defined as Heberden's and/or Bouchard's nodes that affected at least two rays of each hand.
¶Hip OA was defined as Kellgren–Lawrence at the pelvis (K/L $\geq$2) knee OA cases (K/L $\geq$2)=1617 controls.
BMI, Body Mass Index; OA, osteoarthritis.

Table 2 Association between statin use and prevalence of OA phenotypes in the GOAL study

	Adjusted for age, sex, BMI			Adjusted for additional covariates		
	OR*	95% CI	p Value	OR†	95% CI	p Value
Nodal OA	1.11	(0.59 to 2.09)	0.74	1.04	(0.53 to 2.05)	0.91
Hip OA	0.98	(0.70 to 1.38)	0.93	1.00	(0.68 to 1.48)	0.99
Knee OA	1.32	(0.99 to 1.75)	0.06	1.27	(0.91 to 1.77)	0.15
Knee and hip OA	1.04	(0.75 to 1.43)	0.83	0.92	(0.63 to 1.34)	0.66
Generalised hip OA	0.85	(0.52 to 1.38)	0.51	0.80	(0.47 to 1.35)	0.40
Generalised knee OA	0.91	(0.59 to 1.41)	0.67	0.79	(0.46 to 1.35)	0.40
Generalised knee and hip OA	0.66	(0.42 to 1.01)	0.06	0.63	(0.38 to 1.04)	0.07
All generalised OA	**0.75**	**(0.59 to 0.94)**	**0.012**	**0.76‡**	**(0.59 to 0.97)**	**0.028**

*OR=OR for association between statin use and OA. Association was assessed by logistic regression, with hip OA, knee OA or generalised OA being the outcome variables, statin use (yes/no) the independent variable, and including age, sex and Body Mass Index (BMI), as covariates.
†Further adjustment for a diagnosis of hypertenstion or any form of cardiovascular comorbidity, smoking (never smoked=0, ex-smoker=1, current smoker=2) and use of pain medication was also performed.
‡Additional adjustment for stroke, kidney disease, type 2 diabetes, and years with pain at the target joint OR=0.77 (0.60 to 0.99) p<0.048.
GOAL, genetics of OA and lifestyle; OA, osteoarthritis.
Bold font indicates a statistically significant (p<0.05) result.

remains statistically significant after further adjustment for a diagnosis of various comorbidities (table 2).

The present study has a number of limitations: its cross-sectional nature, a hospital-based case control design, and the lack of statin dose information. Nonetheless, our data provide further evidence supporting that statin use may affect OA although in our case only a specific OA phenotype (ie, generalised nodal OA). Given the lack of structure-modifying drugs,[10] it would be much welcome news if statins were proved to reduce OA risk or progression even if this was only on a subset of patients. Further studies primarily designed to address this question are warranted.

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