Strong Association between Smoking and the Risk of Revision in a Cohort Study of Patients with Metal-on-Metal Total Hip Arthroplasty

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ABSTRACT: Thus far the ability to predict who will develop early failure following the insertion of a metal-on-metal (MoM) bearing has been very limited. Our objective was to assess the effect of smoking on failure rates in patients with MoM bearing, compared with patients with ceramic-on-polyethylene (CoP) bearing. From a prospective hospital-based registry we included all primary THAs operated upon between 1/2001 and 12/2011 with MoM or CoP bearings of the same cup design and head size (28 mm). We compared revision rates through 10/2013 classified by smoking status and type of bearing. We included 1,964 patients (median age 71, 57% women), 663 with MoM and 1,301 with CoP bearing. Mean follow-up was 6.9 years (range 1.8–12.8). Revisions were required for 56 THAs. In patients with MoM bearing the adjusted incidence rate of revision among ever-smokers was four times greater than among never-smokers (95% CI 1.4–10.9). Among those with CoP bearing, the rate ratio was only 1.3 (95% CI 0.6–2.5). We found a strong association between smoking and increased failure of MoM THAs. In contrast, the association was weak for patients with CoP bearing. Smoking might be a trigger or an effect amplifier for adverse reactions to metal debris from MoM bearings. © 2014 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res

Keywords: smoking; metal-on-metal hip arthroplasty; revision; metal hypersensitivity; ALTR

To date, the number of metal-on-metal (MoM) bearing hip prostheses implanted world-wide is estimated to be one million.[1] The original rationale was that this bearing surface would result in less implant wear. Recent reports, however, have shown higher failure rates for MoM total hip arthroplasties (THA) compared with other types of bearings.[2,3] Specifically, women receiving the MoM bearing are reported to have a higher risk than men of failure from aseptic loosening and the effects of metal hypersensitivity.[3–5] The reported metal hypersensitivity (delayed type IV lymphocyte dominated-reaction)[6–8] may result in osteolysis, persistent pain, infection, and/or periprosthetic soft tissue reactions, the so-called adverse local tissue reactions (ALTR),[9–14] and ultimately contribute to early failure of the prosthesis. Cases with massive bone and/or soft tissue destruction and with pseudotumor formation around the implants[14–16] have been reported, as well as poorer results after revision for pseudotumors as compared with results after revisions for other causes.[17]

The metals cobalt and nickel, along with chromium and molybdenum, are present in the MoM bearings used in total hip arthroplasties (THA), as well as in hip resurfacing systems.[9] Nickel and cobalt are the two most common metals that produce clinically relevant metal sensitization and allergy.[18] These allergies occur considerably more often in women than in men.[18,19] According to Dotterud and Smith-Sivertsen,[20] the prevalence of allergy to nickel was 27.5% in women compared with 5.1% in men; for cobalt allergies the corresponding prevalence was 4.3% versus 0.9%, respectively. Concomitant sensitization to nickel and cobalt has also been noted to occur frequently.[21]

An important risk factor for both nickel and cobalt sensitization is ear piercing, a practice that is much more frequent in women than in men (82% vs. 17%).[22] Cigarette smoke, which contains traces of cobalt and nickel,[23] has also been associated with an elevated risk of nickel sensitization.[22] Nickel contact allergy was reported to be 18% among female ever-smokers compared with 10% among female never-smokers; among males the comparable figures were 2% among ever-smokers compared with 0% among never-smokers.[24] The association between smoking and nickel sensitization was present in both former and current smokers.[22,24] Whether smoking is a trigger for metal hypersensitivity or adds to the effect of an already present metal hypersensitivity through a negative impact on the immune system is unknown. In either case, one would hypothesize that smoking would be a risk factor for failure of MoM THAs. We conducted the present study to evaluate this hypothesis. Specifically, we assessed the effect of smoking on revision rates in patients with a small head MoM bearing, as well as for patients with a ceramic-on-polyethylene (CoP) bearing, all with the same cup design.

SUBJECTS AND METHODS

Study Design and Study Population

Since March 1996 all patients undergoing THA in the Geneva University Hospitals have been enrolled in a prospective hospital-based registry and followed longitudinally.

Conflict of interest: None.
Ethical approval for the registry (No. CER 05-017 (05-041)) was obtained from the Ethical Committee of the Geneva University Hospitals.
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We included in the study cohort all patients who had undergone primary THA between January 2001 and December 2011 and had received the same uncemented cup (Morscher press-fit cup), a 28 mm head and either a MoM or a CoP bearing. For patients with more than one THA, only the first recorded in the registry was included. We then compared revision rates through October 31, 2013 among these patients, after classifying them by smoking status and type of bearing.

Key Variables

Of the 2,033 patients meeting our entry criteria, 1,964 (96.6%) had information on smoking status which was abstracted from the anesthesiology record at the time of the THA surgery. We classified patients as either ever- or never-smokers as of the time of their primary THA. Ever-smokers were further divided into current and former smokers. The outcome of interest was all-cause revision, defined as the change or removal of one or all prosthetic components. Causes of revision were assessed by the operating surgeon according to the following categories: aseptic loosening, infection, dislocation, periprosthetic fracture, impingement, early implant migration, and other. The presence of ALTR was recorded based on the intraoperative findings and/or the histology report. The spectrum of ALTR comprises metallosis, granulomatous inflammation, necrosis, and aseptic lymphocyte-dominated vasculitis-associated lesions, perioperative findings include pseudotumors appearing as a necrotic tissue mass.

We had information on the following potential confounders: (1) age at operation; (2) BMI at operation (continuous and dichotomized at 30 kg/m^2); (3) American Society of Anesthesiology (ASA) score (1–2 vs. 3–4); (4) presence of diabetes; (5) diagnosis of osteoarthritis (primary vs. secondary osteoarthritis); (6) Charnley disability grade (AB vs. C)[25]; (7) statin use at the time of operation; (8) type of stem (cemented vs. uncemented); and (9) cup inclination angle (continuous and dichotomized at 45°).

Implant-Related Information

The Morscher press-fit cup (Zimmer Ltd., Winterthur, Switzerland) used for acetabular replacement has shown very good mid- and long-term survival rates.[26] It is an uncemented, non-modular, titanium-mesh monoblock component. The bearing surface was either a ceramic-on-polyethylene with a standard ultra-high molecular weight polyethylene (UHMWPE) insert or a metal-on-metal insert consisting of high-carbon, wrought-forged cobalt–chromium (CoCrMo) alloy (Metasul®, Zimmer Ltd.). Choice of bearing surface was left to the surgeon. The acetabular component was used together with either a cemented stem (Müller straight stem or Virtec stem, both CoNiCrMo alloy, Zimmer, Winterthur, Switzerland) or an uncemented stem (CLS Spotorno or Wagner Cone, both titanium aluminum alloy, Zimmer Ltd.). The procedures were performed in an ultra-clean air laminar flow operating room by different surgeons. With use of a cemented stem, Gentamycin-loaded bone cement was employed, and cementing was performed using a third generation technique with pulsed lavage and an intramedullary plug.

Data Collection

Information about baseline characteristics and the surgical intervention, including implant- and technique-related details, was routinely documented by the orthopedic surgeon on specifically designed data collection forms. Information about co-morbidities was retrieved from the anesthesia record and discharge summary. Cup inclination was measured on immediate postoperative radiographs by an independent orthopedic surgeon blinded to the patients' exposure status and outcome. Nearly all revisions (96%) were performed at the Geneva University Hospital as this is the only public hospital for the canton of Geneva, and the health care system required patients with public insurance to be treated at the public institution of their canton of residence. In rare cases patients received a revision at other institutions. Information on these procedures was obtained during regular follow-up visits or from telephone interviews for those who were unable or unwilling to come to the hospital. Information on change of residence and death was obtained from the population registry.

Statistical Analysis

We measured the incidence rates of all-cause revision in two sub-cohorts: (1) patients with MoM bearing; and (2) patients with CoP bearing. We calculated person-time at risk for revision as the length of the interval between date of surgery for primary THA and the date of revision, death, or end of follow-up (March 31, 2013 or date of change of residence in case the patient moved out of the area). We adjusted for confounding by estimating the propensity that each patient was an ever-smoker at the time of arthroplasty, using a multiple logistic regression model. This propensity score served as a summary confounder score, which was then controlled using stratification. The logistic model predicted smoking status as a function of sex, type of bearing, age (continuous), BMI (continuous), ASA score, presence of diabetes, preoperative statin use, Charnley disability grade, diagnosis, type of stem and cup inclination angle (continuous), all recorded at baseline. We included in the model product terms between sex and bearing, age and bearing, sex and age, sex and BMI, BMI and bearing, sex and ASA, ASA and bearing, sex and diagnosis, diagnosis and bearing, sex and stem type; stem type and bearing, sex and cup inclination, and cup inclination and bearing. Patients whose propensity score was lower than the 2.5 percentile of the score distribution of ever-smokers were excluded, as were patients whose propensity score was greater than the 97.5 percentile of the distribution of never-smokers, thus "trimming" the study distributions to include the overlapping ranges of the distributions for ever- and never-smokers and excluding the non-overlapping ranges and outliers.[27] After trimming, we stratified patients by decile of propensity score and calculated summary incidence rate ratios (IRR) using the Mantel–Haenszel method applied to cohort data with person-time denominators.[28]

RESULTS

Our study cohort comprised 1,964 patients (median age 71 years, 57% women), of whom 663 had MoM bearing prostheses (34%) and 1,301 had a CoP bearing. Seven hundred thirty-four patients (37%) were ever-smokers, 430 men (51%) and 304 women (27%). Comparison of baseline characteristics (Table 1) revealed that ever-smokers in both groups were younger and more likely to be male than never-smokers. They also had a higher proportion of ASA scores 3–4

Table 1. Baseline Characteristics of Patients With Metal-on-Metal and Ceramic-on-Polyethylene Bearing Total Hip Arthroplasties According to Smoking Status

	Metal-on-Metal		Ceramic-on-Polyethylene	
	Ever-Smoker ($n = 284$)	Never-Smoker ($n = 379$)	Ever-Smoker ($n = 450$)	Never-Smoker ($n = 851$)
Women (%)	102 (35.9)	199 (52.5)	202 (44.9)	610 (71.7)
Men (%)	182 (64.1)	180 (47.5)	248 (55.1)	241 (28.3)
Age, median, IQR	60 (53; 67)	65 (60; 73)	72 (66; 78)	75 (69; 81)
BMI, median, IQR	26.7 (23.5; 30.1)	26.5 (23.7; 30.1)	26.5 (24.1; 29.9)	26.4 (23.5; 29.7)
Obese (%)	74 (26.1)	95 (25.1)	111 (24.7)	201 (23.6)
ASA 3–4 (%)	46 (16.2)	55 (14.5)	169 (37.6)	209 (24.6)
Diabetes (%)	24 (8.5)	30 (7.9)	72 (16.0)	87 (10.2)
Preoperative statin use (%)	53 (18.7)	56 (14.8)	84 (18.7)	149 (17.5)
Charnley grade C (%)	82 (28.9)	91 (24.0)	196 (43.6)	291 (34.2)
Diagnosis (%)				
Primary OA	185 (65.1)	307 (81.0)	358 (79.6)	749 (88.0)
Secondary OA	99 (34.9)	72 (19.0)	92 (20.4)	102 (12.0)
Type of stem (%)				
Cemented	189 (66.5)	317 (83.6)	432 (96.0)	813 (95.5)
Uncemented	95 (33.5)	62 (16.4)	18 (4.0)	38 (4.5)
Cup inclination median, IQR	40 (36; 44)	39 (35; 43)	39 (35.5; 43.6)	39.8 (35.7; 43.5)
Cup inclination, >45° (%)	57 (20.1)	54 (14.2)	76 (16.9)	147 (17.3)

and Charnley disability grade C, and were more likely to have secondary arthritis as an indication for surgery. MoM THAs were mainly developed to improve prosthesis longevity in young and active patients. This intent is reflected by the higher proportion of men in this group, their substantially younger age as compared with the CoP group (63 years vs. 74 years), the lower proportion of ASA scores 3–4, Charnley disability grade 3 and diabetes, as well as more secondary osteoarthritis and a much higher use of uncemented stems. No substantial difference was seen in median BMI and median cup inclination angle except for a higher proportion of cup inclination >45° in ever-smoking compared with never-smoking patients with a MoM bearing.

The mean follow-up period was 6.9 years (range 1.8–12.8 years). During the follow-up, 56 of the 1,964 THAs were revised. In patients with a MoM bearing there were 18 revisions occurring in 2,061 person-years of follow-up among ever-smokers (crude rate = 8.7 revisions per 1,000 person-years) and 4 revisions in 2,727 person-years among never-smokers (crude rate = 1.5 revisions per 1,000 person-years), giving a crude rate ratio for those with a MoM bearing of 6.0 (95% CI 2.0–17.6). This crude estimate was reduced to 4.0 (95% CI 1.4–10.9) after trimming the non-overlapping tails of the propensity score distributions and stratifying the remaining data by propensity score decile (Table 2). In patients with a CoP bearing there were 16 revisions occurring in 2,934 person-years among ever-smokers (crude rate = 5.5 revisions per 1,000 person-years) and 18 revisions occurring in 5,866 person-years among never-smokers (crude rate = 3.1 revisions per 1,000 person-years). The crude rate ratio for ever-smoking patients with a CoP bearing compared with never-smoking patients receiving a CoP bearing was 1.8 (95% CI 0.9–3.5), which became 1.3 (95% CI 0.6–2.5) after trimming and stratification by propensity score decile. The adjusted rate ratios were similar for women and men (Table 2). Stratifying MoM ever-smokers into current and former smokers revealed that rates were similar, and if anything greater for former smokers (9 revisions occurring in 845 person-years, for a crude rate of 10.6 revisions per 1,000 person-years) than for current smokers (9 revisions in 1,215 person-years for a crude rate of 7.4 revisions per 1,000 person-years). Comparing former smokers with never-smokers, the crude rate ratio was 7.3 (95% CI 2.2–23.6) and the adjusted rate ratio was 4.8 (95% CI 1.7–13.8). Comparing current smokers with never-smokers, the crude rate ratio was 5.1 (95% CI 1.6–16.4) and the adjusted rate ratio was 2.8 (95% CI 0.9–9.3).

During the follow-up period, of the 663 patients in the MoM group 53 died and 44 moved out of the area. Of the 1,301 patients in the CoP group 270 died and 59 moved out of the area. Mean follow-up times were similar between ever- and never-smokers in the MoM (7.2 years vs. 7.2 years) and CoP group (6.5 years vs. 6.9 years). In the MoM group the mean time between primary THA and revision substantially differed in ever-smokers as compared with never-smokers (60 months vs. 7 months, mean difference 53 months, 95% CI 30; 75), and it was similar between ever-and never-smokers of the CoP group (44 months vs. 36 months, mean difference 8 months, 95% CI −39; 21). Among ever-smokers of the MoM group, 5 of the 18 revisions (28%) were early revisions (performed

Table 2. Incidence Rates of Revision According to Smoking Status and Bearing Surface (All Patients and Stratified by Sex)

	Metal-on-Metal		Ceramic-on-Polyethylene	
	Ever-Smoker ($n = 284$)	Never-Smoker ($n = 379$)	Ever-Smoker ($n = 450$)	Never-Smoker ($n = 851$)
All				
Revision cases	18	4	16	18
Person-years	2,061	2,727	2,934	5,866
Incidence rate (cases/1,000 P-yrs)	8.7	1.5	5.5	3.1
Crude IRR (95% CI)	6.0 (2.0; 17.6)		1.8 (0.9; 3.5)	
IRR MH (95% CI)	4.0 (1.4; 10.9)		1.3 (0.6; 2.5)	
Women				
Revision cases	9	2	7	11
Person-years	768	1,438	1,313	4,206
Incidence rate (cases/1,000 P-yrs)	11.7	1.4	5.3	2.6
Crude IRR (95% CI)	8.4 (1.8; 39.0)		2.0 (0.8; 5.3)	
IRR MH (95% CI)	4.7 (1.2; 17.9)		1.3 (0.6; 3.0)	
Men				
Revision cases	9	2	9	7
Person-years	1,293	1,288	1,621	1,660
Incidence rate (cases/1,000 P-yrs)	7.0	1.6	5.6	4.2
Crude IRR (95% CI)	4.5 (1.0; 20.7)		1.3 (0.5; 3.5)	
IRR MH (95% CI)	4.6 (0.7; 29.4)		1.1 (0.4; 3.5)	

within the first 2 years), whereas among never-smokers all four revisions (100%) were early revisions. The causes of revision are summarized in Table 3. An adverse local tissue reaction (ALTR) was detected intraoperatively and/or at the histological examination in six patients, all were ever-smokers with a MoM bearing.

DISCUSSION

We found a strong association between smoking and increased failure of MoM hip arthroplasties, with a similar value for both sexes. In contrast, the association was weak among both sexes with a CoP bearing of the same cup design and head size.

The literature on smoking and the risk of revision after THA overall is sparse consisting of a small number of studies as concluded in a recent systematic review.[29] The review reported an unadjusted relative risk for reoperation or revision of 1.4 (95% CI 0.6–2.1) comparing current smokers with never-smokers and of 1.2 (95% CI 0.8; 1.6) comparing former smokers with never-smokers, similar to our results in the CoP group. Moreover, another study evaluating one specific cup design found an increased risk of early failure

Table 3. Causes of Revision According to Smoking Status and Bearing Surface

	Metal-on-Metal		Ceramic-on-Polyethylene	
	Ever-Smoker ($n = 284$)	Never-Smoker ($n = 379$)	Ever-Smoker ($n = 450$)	Never-Smoker ($n = 851$)
Revision, *n*	18	4	16	18
Causes				
Aseptic loosening	3	0	3	3
Infection	5	1	2	8
Dislocation	2	1	7	3
Periprosthetic fracture	2	0	0	0
Impingement	3	0	1	1
Early implant migration	0	1	2	1
Other[a]	3	1	1	2
Intraoperative/histological				
Adverse local tissue reaction	6	0	0	0

[a]Other (according to table columns): three patients with pain and presence of pseudotumor diagnosed on MRI; one patient with instability; one patient with persistent pain and suspicion of infection (not confirmed); one patient with persistent pain, and one patient with persistent pain and suspicion of infection (not confirmed).

among current (10%) and former smokers (10%) compared with never-smokers (3%).[30] There have been no studies examining the influence of smoking on hip arthroplasty failure depending on the type of bearing surface.

Thus far the ability to predict who will develop a hypersensitivity reaction following the insertion of a MoM bearing has been limited.[31] The situation is complicated by the fact that the periprosthetic soft tissue reactions are often clinically "silent" and only reliably detectable on MRI.[32] Our findings identify smoking as a potentially strong risk factor for revision for patients receiving a MoM bearing, but not for those receiving a CoP bearing. In addition, the six patients in our study showing adverse local tissue reactions were ever-smokers. This interaction between smoking and MoM bearing could be related to metal hypersensitivity. In patients with a MoM bearing, metal hypersensitivity was found to be mediated by nickel, rather than cobalt or chromium,[33] and nickel is present in cigarette smoke, as evidenced by higher concentrations of nickel in the urine of smokers.[34] On the other hand Thyssen et al.[22] contended that smoking alone probably plays a minor role with respect to nickel sensitization given that about 50% of men in their study were smokers but only 1% had nickel sensitization. Thus, a combined effect of an already existing metal allergy and a smoking habit might be more plausible. Smoking affects both the innate and the adaptive immune response,[35] and has also been associated with an increased risk of autoimmune diseases.[36] Stämpfli and Anderson[35] stated that "These adverse effects on the immune system not only occur in active smokers…, and may persist for decades after exposure has ended." Cigarette smoke was found to be associated with increased local T-helper 17 cell production.[37,38] T-helper 17 cells, a CD4 helper T-cell subset, produce Interleukin-17 (IL-17), which plays an important pathogenic role in allergy, asthma, and several autoimmune diseases such as rheumatoid arthritis and psoriasis and is considered a promising therapeutic target in autoimmune diseases.[39,40] IL-17 has been reported to amplify inflammation and cause tissue destruction.[41,42] A recent study[43] reported that nickel-allergic patients with a painful MoM THA showed a different immunologic response from nickel allergic patients with THA who were free of symptoms. In symptomatic patients the response was predominantly of the IL-17 type. No study to date has elucidated the effects of metal debris and smoking on local IL-17 production and metal hypersensitivity-related prosthesis failure.

LIMITATIONS

Information regarding a pre-existing metal hypersensitivity was not available. Thus, we were unable to assess directly the influence of metal allergy on prosthesis failure. Another limitation was possible misclassification of smoking status for some patients. Any such misclassification, however, must be unrelated to the study outcome and therefore leading to an underestimate of smoking effect, because smoking status was assessed by the anesthesiologist before the intervention. Information on the amount of smoking was not systematically available. However, we reported separate incidence rates for current and former smokers. The fact that the results did not substantially differ between current and former smokers in the MoM group is in accordance with the study by Lombardi et al.[30] and with the finding that the association between smoking and increased risk of nickel sensitization was present in both former and current smokers.[22,24]

The wide confidence intervals for both the crude and adjusted estimates reflect the fact that overall there were relatively few revisions in our study population, but even so the increase in revision rate among smokers with a MoM bearing is striking. Owing to the schedule for obtaining information on those revisions performed outside the study hospital, some patients receiving their arthroplasty between 2008 and 2011 may have had a revision outside the hospital without this information being reported to us. Given the low proportion of revisions performed elsewhere and the much lower risk of revision in the first years after surgery, presumably few revisions were missed in this way.

The adverse effect of smoking was observed in small head MoM bearings and during a limited follow-up time. The effect could differ with large head MoM bearings and a longer follow-up period. Also, we did not have direct measures of patient activity, which is known to influence the risk of revisions due to aseptic loosening. We did, however, adjust for age, sex, Charnley disability grade and ASA score, which have been shown to correlate well with patient activity.[44]

CONCLUSION

In summary, we found a strong association between smoking and the increased failure of MoM bearing hip arthroplasties. This association was not evident with ceramic-on-polyethylene bearing hip arthroplasties of the same cup design and head size. This finding may shed light on a mechanism for early failure of metal-on-metal hip arthroplasties, and improve the possibilities for identifying patients at increased risk.

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financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.
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