Curtis O. McMillan, MD
Department of Anaesthesia and Intensive Care
Cork University Hospital, Cork, Ireland
Reprint requests: Curtis O. McMillan, MD, Department of Anaesthesia and Intensive Care, Cork University Hospital, Wilton, Cork, Ireland

Christopher G. Burns, BA, MRes, PhD
Brian D. O'Donnell MD, MSc, MD, FCARCSI
University College Cork, Department of Anaesthesia
Cork University Hospital, Cork, Ireland

George D. Shorten, FFARCSI, FRCA, MD, PhD
Cork University Hospital and University College Cork, Cork, Ireland

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Letter to Editor: Cobalt to Chromium Ratio Is Not a Key Marker for Adverse Local Tissue Reaction in Metal-On-Metal Hips

To the Editor:

We read with great interest the article by Fehring et al [1], who tried to assess if the ratio of cobalt and chrome ions is a surrogate marker for presence or absence of adverse local tissue reaction (ALTR) in metal-on-metal (MoM) hip replacements. They measured both cobalt and chrome ion levels in whole blood in 89 patients who had been revised due to variety of reasons. They conclude that "The cobalt chromium ratio is not a predictive marker for MoM bearing malfunction or ALTRs [adverse local tissue reaction]." We have major concerns regarding this study, and the conclusions the authors have made.

First, we think that patient selection is highly biased or even flawed: it is described in the authors' previous study to which they refer in the current one [2]. Patient selection is defined as follows: "Cases were identified by queries of institutional prospective total joint registries and practice management systems." The number of primary operations, number of patients who have had their blood cobalt and chromium measured, and the total number of revision surgeries performed are not described. Lack of this information results to several problems.

Usually, in statistics, one wishes to investigate a mean (or a median for non-Gaussian variable, as should be done for blood cobalt and chromium) value of a variable or a prevalence of an outcome in a certain population. To achieve this, the very basic statistical approach is to have a sample which is drawn from a target population. Results obtained using the sample may then be applied to the whole target population. The applicability of the results is of course dependable on many variables, but the sample should be as representative of the whole population as possible. When investigating joint replacements, we should always and under every circumstance aim for having the target population as a study sample. This means that the study sample should include all patients operated on with given implant(s) within defined time interval in a disclosed institution. We should be rigorous with this aim because "patients who undergone a joint arthroplasty surgery with specified implant" are a clear and a well-defined target population. For example, when examining risk factors for the colorectal cancer, all living humans belong to the target population, and an investigation involving target population as the study sample is not feasible.

If one investigates a phenomenon or a statistical model, that is, correlation between inclination and wear, one can be satisfied with a well-selected study sample from a certain target population. However, when we are dealing with complications associated to MoM hip replacements, we are interested in those cases which deviate from the phenomenon. These cases are usually those with "optimally seated high wearing cups" or who have "low-wearing implants with pseudotumor." To catch all these outliers, we must have a study sample as described earlier. When a study sample includes all patients operated with a defined implant within certain time interval, one can be sure that all possible confounding factors can be taken into account, such as the natural deviations in the cup orientation or latent within-patient factors (ie, hypersensitivity). This way one can also be sure that the results obtained from such data highlight the "true" prevalence of the adverse phenomenon in a certain population.

It is obvious that, in the study by Fehring et al, the risk for selection bias is very high because aforementioned criterion is not met. There were 82 patients with articular surface replacement (ASR) hip replacements. Were the primary total hip arthroplasties (THAs) of these patients performed at the participating centers? If, let us say, primary ASR THA of 10 patients were performed elsewhere and they were later referred to the authors' center because the patients had problems with their ASR THA, these 10 patients most likely evinced elevated metal ion levels or aggressive pseudotumor in cross-sectional imaging. So, including these cases to the study sample makes it impossible to apply findings of Fehring et al to an unscreened MoM patient populations because prevalence of elevated metal ion levels and pseudotumor is certainly higher in this study sample than in the target population ("true prevalence"). The same aspect applies to the cobalt-chrome ratios because the variability of ratio values or soft tissue destruction is distorted and does not highlight the true variability seen in a population. More problematic situation is present if all patients were referred from elsewhere to the participating centers for revision surgery. In this situation, it is almost certain that, for example, aggressive soft tissue reactions in low-wearing cups are seen much more commonly than the true prevalence of this outcome. The applicability of the results should be the very basis of every study involving joint replacements especially if a possible screening method is investigated.

Even if patients were drawn from a clearly specified target population, one should also make sure that all available revision cases were included. That is the only way one can control for the known variability seen in the manifestation of ALTRs. If only patients with a complaint have undergone a blood metal ion measurement, this again introduces a bias assuming that patients with more aggressive ALTRs are generally more symptomatic. Or if patients with borderline imaging findings have undergone a blood metal ion measurement, reader has limited ability to apply the results reported on his/her own patients. This is especially the situation if included and excluded patients have not been properly reported.

Second, Fehring et al include only patients who have been revised. This research frame is problematic as we highlight in the Figure. If we studied a correlation between inclination and whole blood metal ion levels and we would only include patients who have been revised, it is likely that we would not observe any significant correlation assuming that elevated metal ion levels have a major role in clinical decision making. Similarly,

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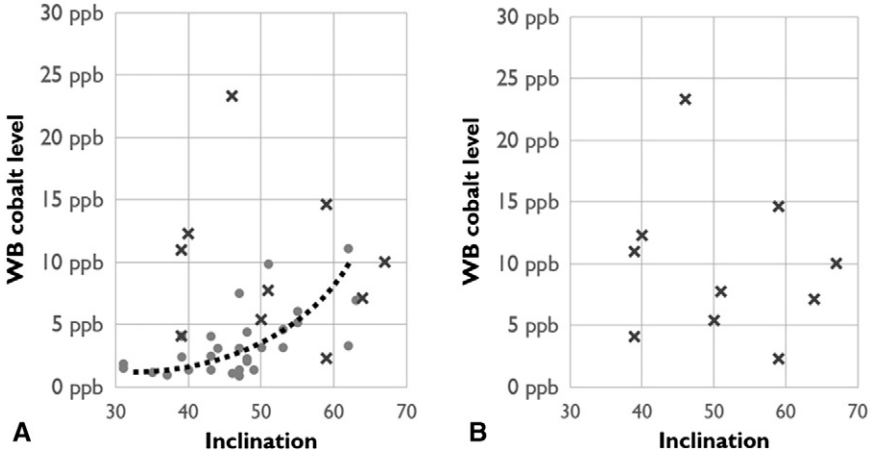

Figure. (A) Scatter plot of inclination vs cobalt ion level in whole blood. Dotted line described the "phenomenon" or a statistical model, which is this example is exponential correlation between inclination and metal ion level. Case with cross sign indicates a revision surgery. (B) If only revision cases were selected, the observed phenomenon is not seen.

concluding that Co/Cr ratio is not predictive for ALTR based on Co/Cr ratios from highly selected sample (revised patients) includes a high risk of a false-negative result. Indeed, severity of soft tissue destruction can only be assessed in revision surgery, but the possible confounding effect should be kept in mind when in interpretation of the results.

Third, Fehring et al conclude "The cobalt-chromium ratio is not a predictive marker for MoM bearing malfunction or ALTRs." To justify this statement, the authors should at least report the Co-Cr ratio in nonrevised patients. In our opinion, this conclusion cannot be drawn based on this study. How can one draw any conclusions of a certain marker if no controls are included? Predictability is always a matter of controls vs cases dealing with a certain continuous variable.

Fourth, Fehring et al report and compare mean values for both cobalt and chrome levels. So, they assume normal distribution of the blood metal ion levels. We find this highly unusual because cobalt and chrome levels are usually highly skewed to the right. Logarithmic transformation is usually required for metal ion levels to meet the assumptions of normality. We would call for the results of a normality test (ie, Kolmogorov-Smirnov test) for the cobalt and chrome levels to justify the comparison of means, not the least them being the basis of their results and analysis.

Finally, we would like to mention that the problem of flawed patient selection is not an issue solely in this study. Numerous studies which are used as evidence for national guidelines regarding the management of patient with MoM hip replacements are plagued with flawed patient selection. There is a clear need for studies analyzing these issues in true target populations with MoM hip replacements.

Aleksi R.P. Reito, MD, PhD*
Olli S. Lainiala, MD
Antti P. Eskelinen, MD, PhD
Coxa Hospital for Joint Replacement, Tampere, Finland
*Reprint requests: Aleksi Reito, MD, PhD, Biokatu 6b, 33520 Tampere Tampere, Finland
E-mail addresses: aleksi.reito@fimnet.fi, lainiala.olli.s@student.uta.fi, antti.eskelinen@fimnet.fi

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In Reply

We appreciate the thoughtfulness of the detailed peer review of our article by Drs Matharu and Pandit. We share their frustration that, currently, there is no diagnostic biomarker readily available to assist the treating surgeon when evaluating a metal-on-metal patient. Rather the diagnostic workup is complex and similar to the diagnostic workup of periprosthetic infection where multiple diagnostic and clinical clues must be considered. We had hoped that we could use the cobalt-chromium ratio in an algorithm that already includes ion levels, magnetic resonance imaging, clinical symptoms, cup design, and cup position. Unfortunately, this is not currently the case.

In specific response to some of their criticism, the responders raise some concern in their Introduction that we should have studied whether the ratio is predictive in patients with and without adverse local tissue reaction (ALTR). Because the classification system that we used included grade 0 and grade I that is no ALTR or minimal staining neither of which have significant ALTRs, I believe that we did have a comparator.

In the Methods section, the responders were particularly critical of the published grading system that we used stating that it was subjective and not validated by intraobserver or interobserver reliability. This grading scale which was published in our original article was based on a project that was started in 2010. At the time, there was no intraoperative clinical grading scale available. There was only a histologic grading scale of ALVAL by Campbell et al. Because this manuscript is based on our previous work published in 2012 on patients operated in 2010 and 2011, it was impossible to go back in a retrospective manner and validate this through intraobserver or interobserver reliability tests. We do, however, feel that this simple observational grading scale most likely accurately describes the pathology encountered.

In the Results section, the responders were critical of how we compared those with and without ALTR and wanted us to describe the median and interquartile range. We agree that median and interquartile range would have been appropriate to report.

In the Discussion, we disagree with the responders' statement that our Discussion was of limited use. We feel that readers need to

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