The cobalt to chromium ratio "may be" a key marker for adverse local tissue reactions in metal-on-metal hips

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We read the recent paper by Fehring *et al*. with interest [1]. The authors conclude the "Cobalt to Chromium Ratio Is Not a Key Marker for ALTR in Metal on Metal Hips." The study aimed to determine whether the cobalt-to-chromium ratio predicts adverse local tissue reactions (ALTRs) in metal-on-metal (MoM) total hip arthroplasty patients. This paper is both timely and relevant given difficulties currently experienced with managing MoM patients [2,3]. In their concluding remarks Fehring *et al*. state their work has helped "bring clarity to the use of this ratio as a diagnostic tool." However, we feel this paper only confuses an already complex issue. The paper has numerous important limitations that we consider have not been adequately addressed during peer review, nor have the authors appropriately acknowledged these limitations. We have subsequently discussed these limitations in the sections they were encountered within the paper.

Introduction

Whilst the authors summarise the background to the problem reasonably well, they cite their own unpublished work regarding the natural history of cystic lesions around MoM hips (reference 4 in their paper) rather than using established data [4,5]. We also have concerns regarding the study aim in light of the work presented. Although the authors state their aim was to determine whether the cobalt-to-chromium ratio was "a predictor for periarticular ALTRs," their four-point tissue grading scale and the statistics used suggest they have actually assessed whether the cobalt-to-chromium ratio predicts the severity of ALTR's. To determine whether the ratio predicts ALTRs requires two patient groups, one with and one without ALTR at revision arthroplasty.

Patients and Methods

The methods section is quite short, even for an abbreviated follow-up report. It is frustrating to have to repeatedly refer to the 2012 methods [6], but what is more concerning is that neither paper reports fundamental demographic and baseline data required for all clinical papers [1,6]. This includes: age, gender, primary hip diagnosis, femoral head diameter, cup position, and renal function at blood sampling. We feel the lack of such important data poses significant limitations regarding the conclusions drawn.

It is acknowledged that Fehring *et al*. have detailed the implant designs, and the earlier report clearly excluded patients with bilateral MoM hip bearings. However, given blood metal ion levels are affected by MoM implant design and modularity [7,8], it would have been preferable to exclude the 7 patients with different designs and focus on the 82 patients with DePuy ASR hips.

Another significant limitation not acknowledged by Fehring *et al*. is the intra-operative tissue grading scale used. This four-point scale was devised by the authors with little detail provided in either paper [1,6]. The grading was performed by one author retrospectively reviewing operative notes, although it is not clear how many surgeons performed the revision procedures. This assessment is subjective, which itself relies on the equally subjective ability of different surgeons to accurately document the presence or absence of revision findings such as metallosis and tissue necrosis. Furthermore there was no attempt in either study to assess the intra-observer and inter-observer reliability [1,6], which we would expect as a minimum when attempting to introduce a potentially subjective grading system. It is also not clear: (1) how the authors dealt with patients with revision features from more than one category (for example, metallosis and necrosis), (2) how lesion consistency was dealt with

given that solid pseudotumours have poor outcomes following revision [9], and (3) why the grading system did not incorporate histopathological findings from revision which are important in assessing ALTRs [10,11].

Results

This section is very similar to the initial paper [6]. The only new data presented by Fehring *et al*. is the mean (and range) cobalt-to-chromium ratio for the same 89 patients reported on in 2012, and the finding that no correlation existed between this ratio and tissue grade.

The metal ion data presented is unlikely to be normally distributed, but the authors provide the mean and range for cobalt and chromium. Previous studies have shown blood metal ion distributions to be non-parametric due to the presence of extreme outliers, therefore the median and inter-quartile range are preferable when describing this data [7,12]. The variation in mean blood cobalt and chromium reported between the tissue grades may be explained by a few extreme outliers. To answer the originally posed question of whether the cobalt-to-chromium ratio is predictive of ALTRs, the authors could have assessed the ratio in patients without evidence of ALTR (grade 0; n=23) and those with ALTR (grades 1 to 3; n=66). This may have resulted in a different conclusion regarding the role of the cobalt-to-chromium ratio.

Discussion

The discussion is of limited use. The only real mention of their data in the context of the literature is “The average ratio of 2.2 is similar to the average cobalt chromium ratio of 2.96 noted in the current study.” The rest of the discussion relates to the variability in alloy composition, ion solubility, and ion excretion, with these also mentioned in the abstract.

However, none of this relates to the present work by Fehring *et al*. but is instead their interpretation of previous literature. This distinction has not been made very clear but should be given they are using these interpretations to conclude the cobalt-to-chromium ratio has no role in identifying ALTRs. In addition, the authors state in the discussion they were hopeful the cobalt-to-chromium ratio would simplify the diagnosis of ALTR. We find this difficult to understand given in the same patient cohort the cobalt and chromium separately were not useful [6], therefore why would the ratio devised from the same data be helpful? Using similar logic one could question why the chromium-to-cobalt ratio was not assessed?

Although we have highlighted a number of limitations not recognised by the authors, Fehring *et al*. did acknowledge the power of the study was low at 26%, with 80% representing acceptable power. It is therefore surprising that the authors have subsequently concluded so definitely that the cobalt-to-chromium ratio is not a key marker for ALTR in such a hugely underpowered study. A further limitation not acknowledged by the authors is that any findings only apply to patients with the implants studied, the majority of which were those with the highest failure rates [13].

Conclusions

Given the significant limitations described we feel the only acceptable conclusion from the data presented by Fehring *et al*. is that the cobalt-to-chromium ratio "may be" a key marker for ALTR in MoM hip patients. Well-designed studies involving large patient cohorts are needed before the cobalt-to-chromium ratio can be recommended or dismissed as a marker for ALTR.

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