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EDITORIAL

Metal ion toxicity

IS IT STILL A PROBLEM IN 2021?

J. A. Skinner,
S. A. Sabah,
A. J. Hart

From Royal National Orthopaedic Hospital, Stanmore, UK

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A total of 1.5 million metal-on-metal hip arthroplasties were enthusiastically implanted by orthopaedic surgeons around the world either side of the turn of the 21st century. However, this enthusiasm quickly soured with the recognition that these implants failed at higher rates than conventional total hip arthroplasties.[1,2] Even patients rewarded with good hip function were not necessarily absolved of problems, and some patients with local adverse reactions to metal debris[3] or raised circulating blood metal ions[4] had few symptoms. A nightmare for patients, surgeons, and regulators ensued. It has been nearly 15 years since the initial Medical Device Alerts from the Medicines and Healthcare products Regulatory Agency (MHRA) relating to component size mismatch,[5,6] and more than ten years since the first national guidelines on clinical follow-up.[7]

Concerns around systemic toxicity have received considerable attention, both in the scientific literature and the wider media. Perhaps most notable is the potential for cardiac toxicity. This had been singled out due to the sometimes dramatic presentation of patients with severe symptoms,[8] and the known association between cobalt and dilated cardiomyopathy in susceptible individuals, first recognized nearly 50 years ago.[9] The review by Jenkinson et al in this month's issue shows that such presentations are serious, but extremely rare – a handful of cases over more than two decades. Their review also highlights the low quality of the majority of the evidence – largely limited to retrospective series and case reports. However, the few prospective, comparative studies deserve to be highlighted. These demonstrate impressive collaborations between orthopaedic surgeons and cardiologists, making use of advanced imaging technologies, barely imaginable a decade ago. Acknowledging the limitations of short-term follow-up and the absence of patients with extreme ion levels, these studies have not identified clinically important associations.[10] Research questions around systemic effects are difficult to study and not amenable to experimental designs. Patients with extreme metal ion levels who choose surveillance over revision are rare.[11] Few patients or surgeons would have equipoise for a randomized controlled trial of surveillance versus revision surgery under these circumstances, and nor should they. The decision to revise the implant is usually straightforward in these cases, though the surgery may be anything but.

Detecting more subtle systemic effects, potentially mediated over longer follow-up periods (perhaps decades) is a greater challenge. So far, the main approaches have been to use routine data sources to understand systemic effects on a population basis. These have returned reassuring results following the investigation of cancer and cardiac disease.[12-14] However, these approaches only identify the tip of the iceberg: patients with the most severe diseases who died or were admitted to hospital with a new diagnosis.[14] In addition, current routine datasets do not yet provide sufficient granularity to fully adjust for baseline differences necessary to eliminate confounding by indication. Patients who underwent hip resurfacing were typically healthier and more active than their peers who received other types of total hip arthroplasty, and this is a potential source of bias that may mask any effect. Blood tests are not yet integrated into routinely collected national datasets, explaining the absence of metal ion measurement from these studies. Linkage of the National Joint Registry (NJR) to primary care records in the future may be able to detect more subtle effects, such as a change in medication use. However, such designs at present entail substantial data attrition, since only a fraction of general practices are enrolled. Like all non-randomized studies, causal inference for any observed systemic effect will be challenging.

Correspondence should be sent to John A. Skinner; email: john.skinner@ucl.ac.uk

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It is likely that mass screening of metal-on-metal hip arthroplasties over the past decade has resulted in earlier identification, and revision of patients with the highest metal ion exposures. While the MHRA 'action level' of 7 ppb has often been a target for criticism, we believe that this is often through misinterpretation of its purpose. The threshold was originally defined from simple outlier methodology and designed to prioritize the clinical evaluation of patients with the most abnormal circulating blood metal ion levels. It was generated at a time when 15% of new hip arthroplasties had metal-on-metal bearings[15] and the burden of patients requiring enhanced follow-up loomed large. Blood metal ion testing has always been an adjunct to, rather than a substitute for, clinical and radiological assessment. Studies investigating 'optimum' cut-offs (often just mathematically) and dichotomizing outcomes or exposures are endemic in current medical research. Screening of metal-on-metal hips is a good example that the 'true' answer may be more complicated. It is testament to this that more recent research has prioritised the perspective of the patient - for example, using validated instruments to record and track symptoms.[11]

Many positives have emerged from our collective response to the high failure rate of metal-on-metal hip arthroplasties and, recently, the Cumberlege Report singled out the NJR as an exemplar registry.[16] This is in part due to its willingness to embrace external validation of its data,[17,18] and to develop robust audit processes and outlier methodology. Programmes to benchmark implant performance and closely monitor the introduction of new devices over the longer-term have emerged, including the Orthopaedic Data Evaluation Panel (ODEP),[19] and UK Beyond Compliance programme.[20] Implant retrieval centres have helped us to understand the mode of failure of hip, knee,[21] spine, and other implants.[22] As usage of metal-on-metal bearings has declined to below 1% over the past decade,[23] there has been recognition of adverse reactions to metal debris from other orthopaedic devices (such as lengthening intramedullary nails) or from sources remote from the bearing surface (for example, the taper junction[24] or stem[25]). New imaging technologies[26] and methods for multidisciplinary team working[27] have kept pace, and the future of surveillance of orthopaedic patients looks bright.

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Author information:
- J. A. Skinner, FRCS(Orth), Consultant Orthopaedic Surgeon, Royal National Orthopaedic Hospital, Stanmore, UK.
- S. A. Sabah, FRCS(Orth) BSc, Orthopaedic Registrar, DPhil Student, Royal National Orthopaedic Hospital, Stanmore, UK; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK.
- A. J. Hart, MD FRCSG(Orth), Professor of Orthopaedics, Royal National Orthopaedic Hospital, Stanmore, UK; University College London, London, UK.

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