Concordance between laboratories in metal ion testing in patients with metal-on-metal hip implants

Raghav Saini, MBBS, MS
Pam Railton, MSc
Jessica Boyd, PhD
Hossein Sadrzadeh, PhD
James N. Powell, MD

Accepted Feb. 15, 2018; Published online Oct. 1, 2018

Correspondence to:
J. Powell
Cumming School of Medicine
University of Calgary
3134 Hospital Drive NW
Calgary AB T2N 4N1
jnpowellemail@yahoo.ca

DOI: 10.1503/cjs.015717

Background: Testing of whole blood or serum metal ion levels has become an important part of assessing and monitoring the performance of metal-on-metal bearings, both in hip resurfacing arthroplasty and in total hip replacement. The aim of this study was to determine the concordance between 2 laboratories testing cobalt and chromium ion levels in patients with metal-on-metal bearings.

Methods: Serum and whole blood samples from patients who had undergone metal-on-metal resurfacing or large-diameter total hip arthroplasty were tested for cobalt and chromium ions in laboratory A (a recognized laboratory) and laboratory B (tasked with testing clinical specimens). Laboratory A performed cobalt and chromium testing on whole blood, and laboratory B performed cobalt testing on whole blood and chromium testing on serum.

Results: Samples from 104 patients were tested. Laboratory B reported lower whole blood cobalt levels than laboratory A. Furthermore, laboratory A reported that all patients had elevated whole blood cobalt ion levels compared to the normal reference values for the laboratory, whereas laboratory B reported that 46 patients (44.2%) had whole blood cobalt ion levels within the normal reference range for the laboratory.

Conclusion: This comparative study highlights the importance of using a single laboratory for metal ion testing, as values generated from different laboratories may not be directly comparable. With recent literature suggesting that whole blood cobalt levels as low as 1 ppb may be a predictor of adverse reactions to metal debris, accurate clinical measurement needs to be increasingly exact.

Contexte : Le dosage sanguin ou sérique d'ions métalliques est devenu une étape importante de l'évaluation et du suivi des prothèses à couple de frottement métal–métal utilisées en arthroplastie de resurfaçage ou totale de la hanche. La présente étude visait à évaluer la concordance entre les résultats de 2 laboratoires pour le dosage du cobalt et du chrome chez des patients porteurs de ces prothèses.

Méthodes : Des prélèvements de sérum et de sang entier de patients porteurs d'une prothèse de resurfaçage ou d'une prothèse totale à grand diamètre de hanche à couple métal–métal ont été expédiés au laboratoire A (un laboratoire reconnu) et au laboratoire B (spécialisé en analyse d'échantillons cliniques) pour le dosage des ions cobalt et chrome. Le laboratoire A a effectué toutes ses analyses sur des prélèvements de sang entier, et le laboratoire B a utilisé le sang entier pour le dosage du cobalt et le sérum pour le dosage du chrome.

Résultats : Les prélèvements de 104 patients ont été analysés. Le laboratoire B a détecté des taux sanguins de cobalt inférieurs à ceux du laboratoire A. De plus, le laboratoire A a indiqué que tous les patients présentaient des taux de cobalt sanguins élevés par rapport à ses valeurs de référence, alors que le laboratoire B a déterminé que le taux de cobalt sanguin de 46 patients (44,2 %) se trouvait dans sa fourchette de valeurs de référence normales.

Conclusion : Cette étude comparative vient souligner l'importance de choisir un seul laboratoire pour le dosage des ions métalliques, car les valeurs générées par des établissements différents pourraient ne pas être directement comparables. Comme des études récentes semblent indiquer que des taux de cobalt sanguins aussi faibles que 1 p. p. milliard pourraient être des prédicteurs de réaction indésirable aux débris métalliques, la précision et l'exactitude des mesures cliniques revêtent une importance croissante.

Testing of whole blood or serum metal ion levels has become an important part of assessing and monitoring the performance of metal-on-metal bearings, both in hip resurfacing arthroplasty and in total hip replacement.[1–6] In most cases, metal ion testing involves testing of cobalt and chromium ion levels. Keegan and colleagues[7] looked at cut-off thresholds that are an indication of potential bearing failure. More recently, Kwon and colleagues[8] recommended a lower threshold of 4 μg/L for further investigation of painless metal-on-metal hip arthroplasty as a part of an orthopedic evaluation and management algorithm.

In addition, cobalt can cause systemic toxicity, which can result in serious consequences like blindness, hearing loss, memory loss and cardiomyopathy; cardiomyopathy has caused death in 2 patients.[9–15] Therefore, accurate measurement of cobalt ion levels in this rare but serious situation is key.

More recently, failure of total hip prostheses as a consequence of trunnion wear has been reported.[16] Fillingham and colleagues[16] underlined the importance of accurate testing of metal ion levels to help establish the likelihood of an adverse metal reaction as a consequence of trunnion wear. They concluded that measurement of the serum cobalt level, with a threshold value of 17 nmol/L (1.0 μg/L), is the best test for identifying the presence of adverse local tissue reactions in patients with a metal-on-polyethylene total hip arthroplasty prosthesis.

Different analytical methods have been used to determine metal ion levels in whole blood or serum. Inductively coupled plasma mass spectrometry (ICPMS) is one of the most sensitive techniques for this purpose: it can detect metal ions at concentrations as low as 1 part per quadrillion.

Several investigators have emphasized the importance of using recognized laboratories to ensure accurate levels.[4–6] Pei and colleagues[4] confirmed the concordance of metal ion testing results between a recognized reference laboratory in London, Ontario, and the Alberta Centre for Toxicology, Calgary, both of which used ICPMS. However, Rahmé and colleagues[5] concluded that there was a clinically significant absolute difference in chromium and cobalt ion levels between 2 laboratories. Vials used for sample collection and the method of sample preparation were different in the 2 laboratories, which might have affected the results.

In an effort to determine the accuracy of testing, we performed an audit comparing the results of a new laboratory (laboratory B) tasked with testing clinical specimens with those of a recognized laboratory (laboratory A), whose results have previously been reported.[4]

Methods

Whole blood and serum samples from consecutive patients who had undergone metal-on-metal hip resurfacing or large-diameter total hip arthroplasty performed by 1 surgeon (J.N.P.) were tested for cobalt and chromium concentrations at both laboratory A and laboratory B. As the study was conducted as an audit, there was an agreement with the laboratory that 100 patients would represent a reasonable sample. The data were collected between June 2015 and June 2017. Specimens were collected in 1 clinical laboratory by a single venipuncture as per Clinical and Laboratory Standards Institute guidelines. Specimen collection was performed as per the specimen requirements provided by each laboratory. Specimens were stored at 2°C–6°C and were shipped to the laboratories on ice.

Laboratory A performed cobalt and chromium testing on whole blood, which was collected in a single 6-mL royal blue top trace element Vacutainer tube containing K2-ethylenediaminetetraacetic acid (EDTA) (Becton, Dickinson and Company). Reference intervals provided for laboratory A were 2.3–7.7 nmol/L (0.12–1.40 μg/L) for whole blood chromium level and 1.9–6.6 nmol/L (0.11–0.39 μg/L) for whole blood cobalt level.

Laboratory B performed cobalt testing on whole blood and chromium testing on serum. Whole blood specimens were collected in a 6-mL Monoject royal blue top tube containing Na_2-EDTA (Covidian [now Medtronic Minimally Invasive Therapies]). Serum specimens were collected in a 6-mL BD royal blue top Vacutainer tube with no additive (Becton, Dickinson and Company). Reference intervals provided by laboratory B were 0.0–10.0 nmol/L (0.0–0.52 μg/L) for serum chromium level and 0–20 nmol/L (0–1.2 μg/L) for whole blood cobalt level.

Both laboratories used laboratory-developed ICPMS methods for cobalt and chromium analyses.

Statistical analysis

We performed data analysis using Microsoft Excel 2013. We graphed and compared correlations between the metal ion results from each set of paired samples using a linear regression line. In addition, we generated Bland–Altman graphs to assess the absolute and percent bias between the 2 laboratories. Because the study was conducted as an audit and patient information was blinded, approval was deemed unnecessary by the institutional ethics review board.

Results

Specimens from 104 patients were tested. Laboratory A reported that all patients had elevated whole blood cobalt ion levels compared to the normal reference values for the laboratory, whereas laboratory B reported that 46 patients (44.2%) had whole blood cobalt ion levels within the normal reference range for the laboratory. Laboratory A reported elevated chromium ion levels in all patients, and laboratory B reported elevated chromium ion levels in all but 1 patient (Fig. 1B).

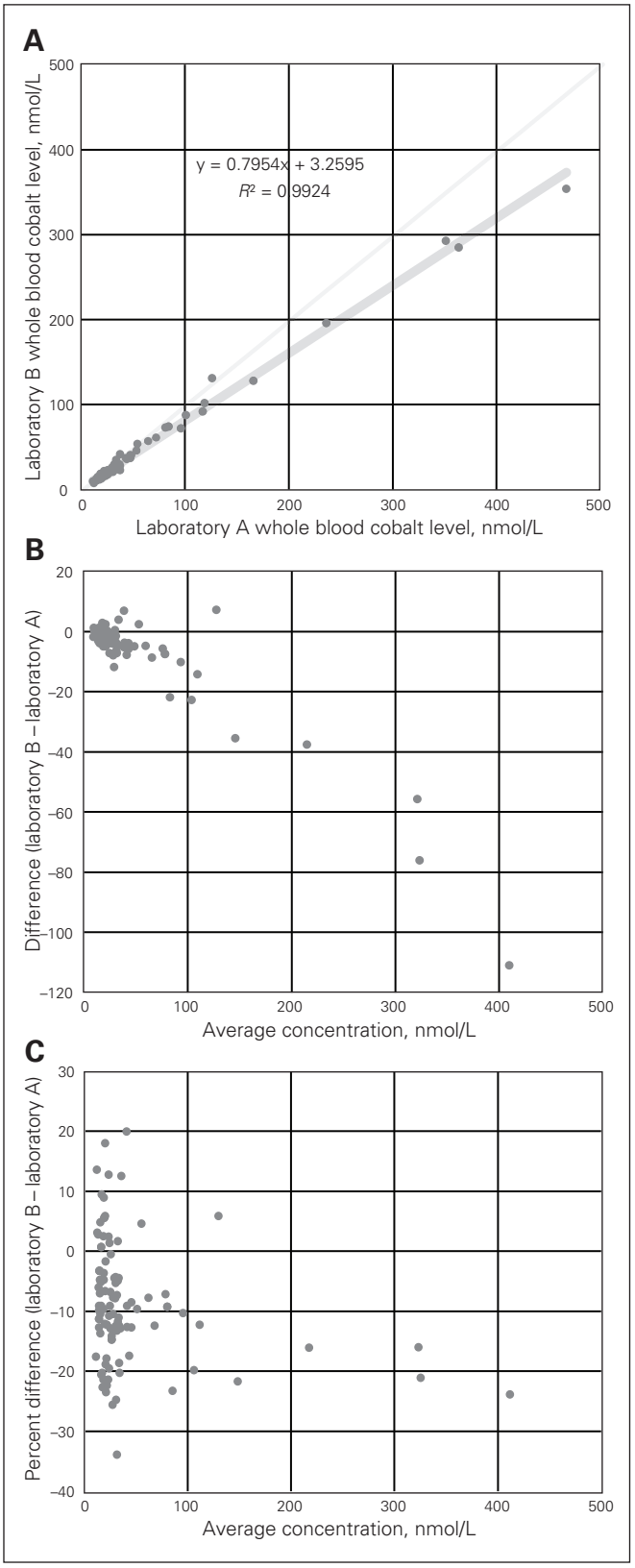

Fig. 1. (A) Comparison of cobalt measurements between laboratory A and laboratory B. (B) Bland–Altman plot of absolute bias between cobalt measurements at laboratory A and laboratory B. (C) Bland–Altman plot of percent bias between cobalt measurements at laboratory A and laboratory B.

There was good correlation for the results of cobalt ion testing between the 2 laboratories (R^2 = 0.9924) (Fig. 1A). However, a bias toward laboratory A was observed that increased through the concentration range (Fig. 1B). Above 200 nmol/L (11.8 μg/L), the observed percent bias was fairly consistent, around 20% (Fig. 1C).

There was also good correlation for the results of chromium ion testing between the 2 laboratories, with an R^2 of 0.9883, with a bias toward laboratory B (Fig. 2A). A proportional absolute bias was observed for chromium (Fig. 2B), and a percent bias of 60% was observed for values over 175 nmol/L (9.1 μg/L) (Fig. 2C).

Discussion

The importance of monitoring patients who have undergone metal-on-metal hip resurfacing or total hip arthroplasty for chromium and cobalt ions to enable early detection of local tissue adverse reactions and pseudotumour formation is well documented.[1–7] These are important causes of painful hips in such patients and may necessitate revision surgery. Furthermore, acute systemic toxic effects of chromium ions can result in renal, hematological, hepatobiliary and respiratory disorders, and chronic elevated chromium ion levels are known to be allergenic and carcinogenic.[6,15] Similarly, elevated levels of cobalt ions can present with polycythemia, hypothyroidism, cardiomyopathy and neurologic manifestations such as parasthesia, numbness, memory loss, vision loss and hearing loss.[9–15]

Although there was good correlation for the results of both chromium and cobalt ion testing between the 2 laboratories in the current study, the absolute value for both analytes differed substantially at higher concentrations. The 2 laboratories used the same gold standard technique, ICPMS; however, these differences in absolute values for cobalt and chromium reflect differences in calibration between the 2 assays. This is an issue faced by all laboratory assays that are not standardized to a primary reference material and presents a challenge to clinicians in interpreting results produced by different laboratories. This highlights the need to have results generated by 1 laboratory in order to allow for result trending.

A second issue encountered in our study was that, despite the good correlation for cobalt ion testing, 44% of the specimens tested for cobalt by laboratory B were reported as being in the normal reference range. Previous experience with metal ion testing and a review of the literature show that patients with metal-on-metal bearing surfaces have elevated serum or whole blood levels of both chromium and cobalt.[17–20] This suggests that laboratory B's reference interval for cobalt by may have included patients with metal-on-metal hip implants. When clinical decision-making may involve options as complex and challenging as revision hip arthroplasty, it also creates concerns for clinical interpretation when more than 40% of patients fall within the normal

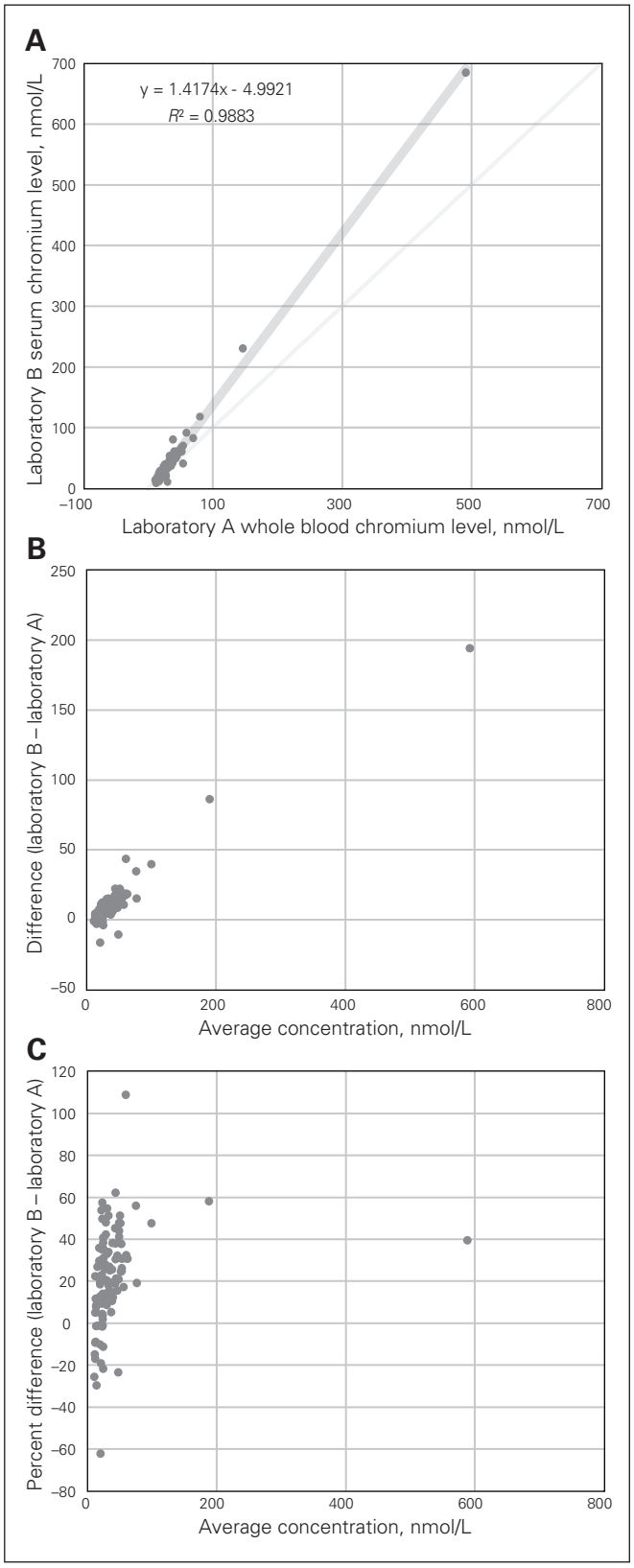

Fig. 2. (A) Comparison of chromium measurements between laboratory A and laboratory B. (B) Bland–Altman plot of absolute bias between chromium measurements at laboratory A and laboratory B. (C) Bland–Altman plot of percent bias between chromium measurements at laboratory A and laboratory B.

reference interval. These issues with laboratory B lead us to conclude that changing testing to laboratory B could cause confusion when interpreting results, making it extremely difficult for clinicians involved in making treatment decisions.

Strengths and limitations

One of the strengths of our study is that it involved prospectively collected data. In addition, samples were collected in similar EDTA vials for whole blood analysis, and the method of sample preparation before analysis was similar for the 2 laboratories. Both laboratories validated the stability of samples used for analysis. These similarities strengthen our findings. One factor that could have a bearing on correlation of the chromium results is that laboratory A used whole blood samples, whereas laboratory B used serum samples. Smoulders and colleagues[21] compared whole blood and serum chromium levels and reported that serum results were higher than whole blood results, similar to our findings.

Conclusion

Clinicians usually encounter challenging scenarios when choosing options such as revision surgery for patients with metal-on-metal hip resurfacing and total hip arthroplasty, especially when patients have nonpainful hips and raised levels of metal ions. Accuracy and reliability of laboratory testing are very important for absolute metal ions results to be accurate. In such situations, it is critical for treating clinicians who are relying on metal ion values to be aware that there are substantial differences between laboratories. The use of laboratories with good accuracy and reproducibility is important for clinical decision-making. Given the results of the current study, we no longer send specimens to laboratory B for metal ion testing. We also recommend that, until there is reliable standardization between laboratories, patients be followed using results generated by a single laboratory.

Affiliations: From the Cumming School of Medicine, University of Calgary, Calgary, Alta. (Powell, Saini, Boyd, Railton); and Calgary Laboratory Services, Calgary, Alta. (Sadrzadeh).

Competing interests: None declared.

Contributors: J. Powell, J. Boyd, P. Railton and H. Sadrzadeh designed the study. J. Powell and P. Railton acquired the data, which J. Powell, R. Saini, J. Boyd and H. Sadrzadeh analyzed. J. Powell, R. Saini, J. Boyd and P. Railton wrote the article, which all authors reviewed and approved for publication.

References

1. Billi F, Campbell P. Nanotoxicology of metal wear particles in total joint arthroplasty: a review of current concepts. *J Appl Biomater Biomech* 2010;8:1-6.
2. Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br* 2008;90:847-51.

3. Visuri TI, Pukkala E, Pulkkinen P, et al. Cancer incidence and causes of death among total hip replacement patients: a review based on Nordic cohorts with a special emphasis on metal-on-metal bearings. *Proc Inst Mech Eng H* 2006;220:399-407.
4. Pei KL, Kinniburgh DW, Butlin L, et al. An ORS-ICP-MS method for monitoring trace levels of cobalt and chromium in whole blood samples from hip arthroplasty patients with metal-on-metal prostheses. *Clin Biochem* 2012;45:806-10.
5. Rahmé M, Lavigne M, Barry J, et al. Whole blood metal ion measurement reproducibility between different laboratories. *J Arthroplasty* 2014;29:2214-8.
6. Zywiel MG, Cherian JJ, Banerjee S, et al. Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition — Part 2. Measurement, risk factors, and step-wise approach to treatment. *Bone Joint J* 2016;98-B:14-20.
7. Keegan GM, Learmonth LD, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient. *J Bone Joint Surg Br* 2007;89:567-73.
8. Kwon YM, Jacobs JJ, MacDonald SJ, et al. Evidence-based understanding of management perils for metal-on-metal hip arthroplasty patients. *J Arthroplasty* 2012;27(8 Suppl):20-5.
9. Pelayo-de Tomás JM, Novoa-Parra C, Gómez-Barbero P. Cobalt toxicity after revision total hip replacement due to fracture of a ceramic head. *Rev Esp Cir Ortop Traumatol* 2017;61:203-7.
10. Fox KA, Phillips TM, Yanta JH, et al. Fatal cobalt toxicity after total hip arthroplasty revision for fractured ceramic components. *Clin Toxicol (Phila)* 2016;54:874-7.
11. Gilbert CJ, Cheung A, Butany J, et al. Hip pain and heart failure: the missing link. *Can J Cardiol* 2013;29:639.e1-2.
12. Harris A, Johnson J, Mansuripur PK, et al. Cobalt toxicity after revision to a metal-on-polyethylene total hip arthroplasty for fracture of ceramic acetabular component. *Arthroplast Today* 2015;1:89-91.
13. Rizzetti MC, Liberini P, Zarattini G, et al. Loss of sight and sound. Could it be the hip? *Lancet* 2009;373:1052.
14. Apel W, Stark D, Stark A, et al. Cobalt–chromium toxic retinopathy case study. *Doc Ophthalmol* 2013;126:69-78.
15. Green B, Griffiths E, Almond S. Neuropsychiatric symptoms following metal-on-metal implant failure with cobalt and chromium toxicity. *BMC Psychiatry* 2017;17:33.
16. Fillingham YA, Della Valle CJ, Bohl DD, et al. Serum metal levels for diagnosis of adverse local tissue reactions secondary to corrosion in metal-on-polyethylene total hip arthroplasty. *J Arthroplasty* 2017;32:S272-7.
17. Lhotka C, Szekeres T, Steffan I, et al. Four-year study of cobalt and chromium blood levels in patients managed with two different metal-on-metal total hip replacements. *J Orthop Res* 2003;21:189-95.
18. Daniel J, Ziaee H, Pradhan C, et al. Six-year results of a prospective study of metal ion levels in young patients with metal-on-metal hip resurfacings. *J Bone Joint Surg Br* 2009;91:176-9.
19. Imanishi T, Hasegawa M, Sudo A. Serum metal ion levels after second-generation metal-on-metal total hip arthroplasty. *Arch Orthop Trauma Surg* 2010;130:1447-50.
20. Jacobs JJ, Skipor AK, Doorn PF, et al. Cobalt and chromium concentrations in patients with metal on metal total hip replacements. *Clin Orthop Relat Res* 1996;329(Suppl):S256-63.
21. Smolders JM, Bisseling P, Hol A, et al. Metal ion interpretation in resurfacing versus conventional hip arthroplasty and in whole blood versus serum. How should we interpret metal ion data. *Hip Int* 2011; 21:587-95.