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Whole blood titanium metal ion measurement reproducibility of two laboratories



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ABSTRACT

Background: Metal ion blood concentrations evaluation can be useful in monitoring wear and corrosion of orthopedic implants. Elevated metal ion level may help detecting defective hip arthroplasty implants and serve as an indicator for revision surgery. Our objective was to evaluate the reproducibility of titanium metal ion level measurements by two different laboratories.

Methods: Seventy-one whole blood samples were collected from 64 patients with unilateral ceramic-on-ceramic hip arthroplasty. For each patient, two whole blood samples were collected and analyzed in two different laboratories.

Results: For each case, laboratory 1 had significantly higher values than laboratory 2. There was a clinically significant absolute difference between the two laboratories, above the predetermined threshold, for 90% of samples. A mean variation ratio of 410% between the two laboratories was found.

Conclusion: Not all laboratories use the same techniques and calibrations to perform these measurements. Therefore, their results should be interpreted with caution and clinical decision should rely on metal ion trends provided by the same laboratory.

1. Introduction

Total hip replacement (THR) has proven to be a highly effective treatment of degenerative joint disease. Hip replacement implants can be made of different metallic alloys according to their specific properties and the related clinical need. Chromium-cobalt (CrCo) and titanium (Ti) alloys are the most common. Metal ions from these alloys will be systematically released due to the bearing wear, taper junction wear/corrosion or passive surface corrosion. Performance of each implant can be assessed indirectly by measuring systemic ion levels in whole blood [1–4]. High-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) is one of the most sensitive and versatile techniques available for metal ions measurement and most clinicians rely on results obtained with this method [5,6].

Ti is considered a highly biocompatible metal due to its capacity for osseointegration, its resistance to corrosion from body fluids, its modulus of elasticity similar to cortical bone, and its high resistance to failure. But because of its low resistance to scratch and third body wear, Ti is usually not used as a bearing surface. Systemic Ti release mainly comes from implant surface passive corrosion or modular junction wear. Passive corrosion of the exposed surface is a factor influencing the concentration of metal ions in the synovium and bloodstream [7]. Ti release should be directly proportional to the metal area exposed to body fluids and tissues. The real surface exposed to corrosion in grit blasted or plasma sprayed metallic surfaces is difficult to estimate, but the porosity of the surface increases the area exposed to Ti corrosion.

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Large-diameter head (LDH) THR is an attractive option for improving range of motion, avoiding implant impingement, reducing dislocation rates and providing durable bearing surfaces [3,8,9]. However, over the last decade, concerns have arisen regarding metal-on-metal (MoM, CrCo) LDH THR prostheses [10]. CrCo ion release from wear and corrosion at the CrCo femoral head - Ti stem taper junction led to local adverse reactions to metal debris and, in some situations, severe complications [11]. The mechanisms eliciting wear and corrosion are still not completely clear [12]. Direct comparison of different MoM LDH THR designs yields different metal ion levels and revision rates [3]. As an alternative to MoM, CoC LDH THR were introduced in clinical practice. Measuring systemic Ti levels in these patients is an indirect way to assess femoral head-stem modular junction performance (wear and/or corrosion). In a series of 27 cases of CoC LDH THR, after an average of 20 months (min 12, max 46), we found reassuring whole blood Ti level of 2.1 $\mu\text{g/L}$ (min 1.6, max 3.1) [13].

Harmful Ti systemic levels have not yet been determined. Studies have shown that Ti levels associated with well-functioning implants can range from $<1 \mu\text{g/L}$ to $14 \mu\text{g/L}$ and ARMD is not expected with level $<10 \mu\text{g/L}$ [14]. Unlike CoCr, local adverse effects associated with Ti alloy debris have seldom been reported. Swiatkowska et al. assessed the passive corrosion of well-functioning Ti THR implants with CoC bearing (diameter 32 mm) and proposed 2.2 $\mu\text{g/L}$ as the "normal" Ti level [15]. Although the toxicological significance of local and systemic elevations in Ti ions has not been definitively established, monitoring patients concentrations in the blood can be useful in determining the performance of these new CoC LDH modular junctions [13]. Moreover, the evolution over time of Ti ion level is a good way to identify a defective implant [14].

The objective of this study was to evaluate the reproducibility of whole blood metal Ti ion levels drawn for a same patient at the same time but analyzed in two different laboratories. The aim was to see if there was a difference between the laboratories that may be of clinical significance and that could lead to misinterpretation in the results.

2. Material & methods

2.1. Study population

From September 2011 to April 2014, we collected 71 whole blood samples from 64 patients with unilateral LDH THR CoC (7 patients had samples collected at two different evaluations). For the purpose of the present study, patients were eligible when at least two tubes of whole blood collected at the same time were available with a minimum of 1 year after THR implantation. Exclusion criteria were the presence of Ti implants, such as other joint arthroplasties, internal fixation devices, dental devices or renal insufficiency. Implants were the CLS-Spotorno femoral stem (Zimmer) and Maxera acetabular component (Zimmer). The CLS-Spotorno Ti uncemented stem has a grit-blasted surface and is made of Ti-6Al-7Nb alloy. It has a 12/14 trunnion with an angle of $5^{\circ}38'$. The Maxera cup shell is made of Ti-6Al-4V alloy with a pure Ti plasma sprayed surface for secondary fixation. The ceramic liner is inserted during manufacture, and the component is implanted as monoblock. Delta ceramic femoral heads (manufactured by Ceram Tec (GmbH) but distributed by Zimmer) of 36–48 mm diameter were implanted according to acetabular component diameter. Femoral head had a Ti adapter sleeve (Ti-6Al-4V, Ceram Tec) described as a 12/14 taper with an angle of $5^{\circ}43'$, systematically present for heads with a 44 mm and above diameter and optional for smaller diameters. The outside of the Ti taper adapter sleeve and the inside of the ceramic head are 16/18 tapers (Ceram Tec). All femoral heads were impacted with 3 hammer blows on a clean and dry trunnion.

2.2. Sample collection

Two samples of 5 mL blood were collected in BD Vacutainer® Royal Blue plastic tubes (reference 368381, Plastic K2EDTA. 10.8 mg) by the same research nurse with a 23 gauge stainless steel Butterfly needle (Reference 367292, BD Insyte, BD Medical, UT, USA). Patients were excluded from further analysis if the sampling protocol was unsuccessful. Samples were kept in a refrigerator at 4°C for analysis in two different laboratories. Different laboratories measured whole blood Ti ion levels.

2.2.1. Laboratory 1 analysis, ICP-MS

The concentrations of Ti, Cr and Co ions in whole blood samples were measured with a single quadrupole ICP-MS Elan DRCII from PerkinElmer. The detection limits were 0.1 $\mu\text{g/L}$ for Cr and 0.035 $\mu\text{g/L}$ for Co. Blood samples were diluted in diluent containing 0.5% (v/v) NH_4OH and 0.1% (v/v) octylphenol ethoxylate. External calibration curves were prepared by diluting human blood in diluent and spiking with different volumes of 1 mg L^{-1} multi-elements standard solution (SCP Science, PlasmaCal ICP-MS Verification Standard 1, 5% HNO_3 , #141-110-011) in order to emulate 0, 4, 20, 80, and 200 $\mu\text{g/L}$ in the standards solutions. The internal standard for calibration standards and blood samples was Yttrium 89 for ^{59}Co (standard mode with correction equation) and Indium 115 for ^{53}Cr (DRC mode with ammonia as reaction gas). Commercial blood reference materials were used as controls to verify the results. Average usual imprecision was 5% (CV = 5%).

2.2.2. Laboratory 2 analysis, HR-ICP-MS

The concentrations of Ti, Cr and Co ions in the whole blood samples were measured in an Element 2 High Resolution, Sector-Field, Inductively Coupled Plasma Mass Spectrophotometer (Thermo Fisher Scientific GmbH, Bremen, Germany). The detection limits were 0.1 $\mu\text{g/L}$ for Cr and 0.02 $\mu\text{g/L}$ for Co. The blood samples were exposed to concentrated nitric acid to digest protein and concentrated hydrogen peroxide to digest lipids. After dilution with water and internal standard Yttrium 89, the final sample was introduced into the instrument and compared against aqueous standards with commercial blood controls to verify the results. Average usual imprecision was 10% (CV = 10%).

Table 1
Implants specifications.

N	64
Mean acetabular component size	53.9 (48–64; 3.55)
Head Size (N (%))	3 (5%)
36	26 (41%)
40	22 (34%)
44	13 (20%)
48	
Head with Ti sleeve (yes: no)	35 : 29

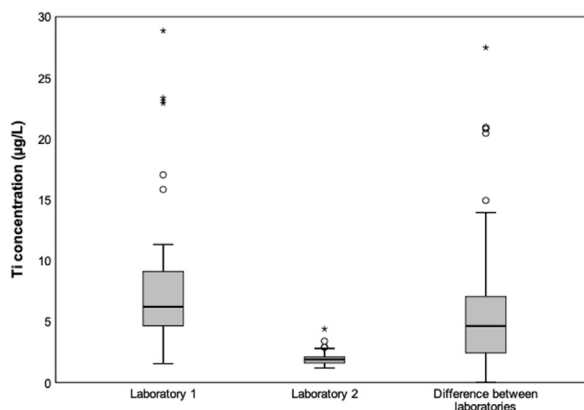


Fig. 1. Box plot of the concentration of titanium metal ions in the two laboratories and the difference between laboratories (laboratory 1 minus 2). Horizontal bars define the quartiles, with the second and third quartiles contained in the boxes. Circles represent outliers, defined as values that are 1,5 to 3 times higher than the values of the third quartile. Data identified with stars are extreme outliers, defined as values that are at least three times higher than the values of the third quartile.

Table 2
Mean concentrations of Ti ions for laboratory 1 and 2 and mean differences (laboratory 1 – laboratory 2).

Ions	Lab	N	Mean (min-max)	Standard deviation	p-value
Titanium Concentration	1	71	7.70 (1.56–28.86)	5.19	< 0.001
In µg/L	2		1.95 (1.20–4.40)	0.51	
Difference of concentration	2–1	71	5.76 (0.0–27.47)	5.16	< 0.001

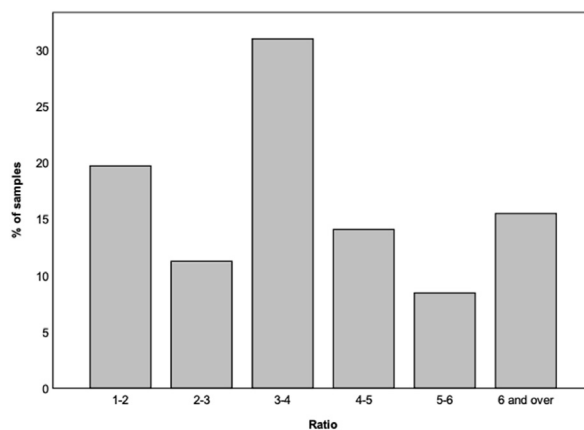


Fig. 2. Diagram showing the percentage of cases for different concentration ratios between laboratories (laboratory 1 divided by laboratory 2).

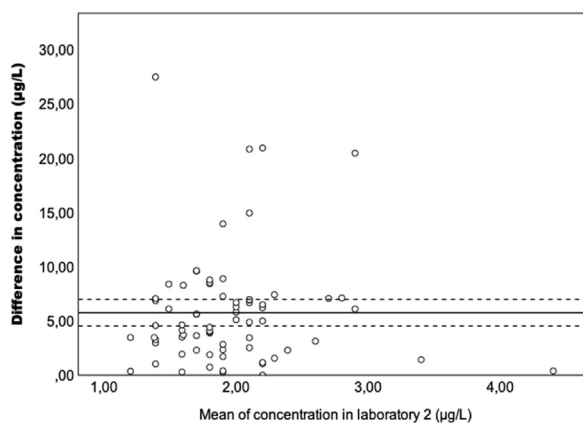


Fig. 3. Bland-Altman plot between titanium concentrations obtained in two different laboratories based on mean concentration in laboratory 2. The solid line indicates the mean difference (or bias); the dotted lines indicate the 95% CI of the mean difference between laboratories.

2.3. Clinical significance

Although we do not know the toxic level of Ti, we defined in a previous study that a variation in concentration above 1 µg/L for Ti could be clinically significant (23). This threshold was established based on the average concentrations of Ti varying between 1 and 3 µg/L in blood when implants work well (Table 3). In the event of a malfunction or clinical problem, the concentration of these ions usually increases dramatically from 2 to 20 µg/L. The significant change limit (SCL) is a decision-making tool that helps distinguish day-to-day changes in results that are caused by the inherent variability of the analytical procedure from changes that are caused by modification in the patient's physiology and pathology. The detection limit of the HR-ICP-MS is approximately 3 times the background noise of the samples. The limit of quantification, which determines more precisely the sensitivity and accuracy of the device, is approximately 10 times the background noise. The limit of quantification is therefore 3.33 times the limit of detection. An approximation of the SCL is three times the usual imprecision observed in the laboratory (SCL = 15% and 30% for laboratory 1 and laboratory 2 respectively). Using the SCL tool, a difference of 0.45–0.9 µg/L could be considered clinically significant. Therefore, according to the authors, a variation in concentration of less than 1 µg/L between results would have no consequences on clinical evaluation and follow up.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA). All patients with paired results were included in the study. Continuous values were presented as an average \pm standard deviation with minimum and maximum values. Differences between pairs of samples were analyzed by a Wilcoxon signed rank test with a confidence interval of 95% to assess the non-normal distribution of the results. Correlations between laboratories' results were analyzed by a Spearman correlation test with a confidence interval of 95%. Statistical significance was set at 0.05.

2.5. Ethical considerations

The Scientific Committee and the Ethics Committee of our center approved the research project. The study was explained to patients and informed consent was obtained.

3. Results

We analyzed 71 pairs of whole blood samples from 64 patients. Patient's mean age at time of surgery was 54 years old (range 33–73; SD 9.2), 26 men and 38 women. The mean follow-up at the time of the blood collection was 68 months (range 12–89; SD 24.0). Implant specifications are shown in Table 1.

The distributions of Ti concentrations from the two laboratories are shown in Fig. 1 and Table 2. No distinction was done for the direction of the difference in Ti concentration (minus or positive) since 100% of results from laboratory 1 were higher than laboratory 2. The concentrations obtained from laboratory 1 are significantly different from those of laboratory 2. The average ratio between laboratories (#1 divided by #2) is 4.10 (range 1–20.76). The percentages of cases according to the ratio between laboratory 1 and 2 are shown in Fig. 2. In 69% of cases the difference was above 300%, and in 39% above 500%. Ninety percent (64/71) of paired samples had an absolute difference above the predetermined threshold of 1 µg/L.

No statistical correlation was found between the two laboratories ($\rho = 0.165$; $p = 0.170$). The Bland and Altman graph, shown in Fig. 3, established that the confidence interval of the difference in the Ti measures is over the predetermined clinical significance threshold.

Table 3
Ti level reported in the literature.

Authors	Savarino	Nam	Vendittoli	Vendittoli	Zeng	Hutt	Barry	Barlow	Deny
Years	2008	2015	2009	2009	2015	2016	2017	2017	2018
Fu months	124	12	12	12	48	12	12	12	12
Hip THR	replacement	THR	THR	THR	Resurfacing	THR	THR	THR	THR
Acetabular cup	Ti	Ti	Ti grit-blasted with a macro-textured	CoCr with Ti plasma spray	Ti	CoCr with Ti plasma spray	Ti alloy with Ti plasma sprayed Ceramic	Ti	Ti
Acetabular bearing	Ceramic	Cross linked polyethylene liner	CoCr28 mm liner in polyethylene sandwich	CoCr monoblock	Cobalt-chrome-molybdenum Ceramic	CoCr monoblock	Ceramic	Ceramic / Polyethylene	Ceramic
Femoral head	Ceramic (28-mm)	Ceramic (32–40 mm)	CoCr alloy (28 mm)	CoCr alloy		CoCr with Ti adaptor sleeve	Ceramic	CoCr / Ceramic	Ceramic
Stem	CoCr (n = 11) or Ti (n = 5)	Ti with Porous coating	Ti with grit-blasted surface	–	Ti	Ti	Ti	CoCr / Ti	Ti
Measurement method	Graphite furnace atomic absorption spectrometer	HR-SF-ICP-MS	HR-ICP-MS	HR-ICP-MS	HR-ICP-MS	HR-ICP-MS	HR-ICP-MS	Quantitative ICP-MS	HR-ICP-MS
Medium	Serum	Whole blood	Whole blood	Whole blood	Whole blood	Whole blood	Whole blood	Serum	Whole blood
Detection Limit	2.9 µg/L	NA	0.2 µg/L	0.2 µg/L	NA	0.2 µg/L	0.1 µg/L	10 µg/L	0.1 µg/L
Mean Ti	concentration	3.4 µg/L	2.2 µg/L	1.8 µg/L	3.1 µg/L	2.1 µg/L	3.0 µg/L	1.59–1.98 µg/L	0–2.45 µg/L
Potential Ti sources	Passive corrosion of the acetabular component and femoral stems (5/16) and wear of the Ti-Cer modular junction	Passive corrosion of the acetabular component and femoral stem and wear of the Ti-Cer modular junction	Passive corrosion of the femoral stem and acetabular component and wear of the Ti-CoCr modular junction	Passive corrosion of the acetabular component's plasma spray Ti	Corrosion and wear tapers	Passive corrosion of the acetabular component and femoral stem and wear of the Ti-Ti modular junction	Passive corrosion	Fretting and corrosion	Passive corrosion

4. Discussion

Review of the literature suggest that most THR studies use HR-ICP-MS to measure Ti concentration in whole blood and that level varies approximately from 1 to 3 $\mu\text{g/mL}$ (Table 3). Several complications related to Cr and Co release were linked to local adverse reactions to metal debris (ARMD), pseudotumor, osteolysis, and systemic problems [16–19]. Although Ti implants have been used in orthopedics for several decades with excellent clinical results, concerns still exists regarding their safety and monitoring systemic concentrations can be useful in determining the implant performance. The objective of our study was to evaluate the reproducibility of Ti ion levels values measured by two laboratories. The multiplication of sampling centers to facilitate patient access to blood samples makes it not uncommon for samples from the same patient to be analyzed by different laboratories. In addition, inter-laboratories reproducibility for metal ions measurements is essential to allow data comparison at a time when clinically significant levels are not defined and to ensure that surgeons can safely use results originating from different laboratories. Our study showed significant higher Ti level measured by one laboratory compared to the other one. Moreover, 90% of paired samples had a difference above 1 $\mu\text{g/L}$ and 69% had more than 300% difference.

HR-ICP-MS is use in many studies (Table 3) and has already been proven to be the gold standard method in metal ion analysis even though some laboratories still use Atomic Absorption Spectrometry (AAS) [5,6,20]. In our study, both laboratories were equipped with ICP-MS instruments, with the difference being that laboratory 1 used an ICP-TripleQ MS and laboratory 2 used a high resolution ICP-MS. A high-resolution device allows discarding some spectral interference common with an ICP-MS analysis technology. Polyatomic interferences are known to occur in analysis by ICP-MS. However, when an analysis is directed to trace or ultratrace concentrations of metals, possible interferences that appeared to be insignificant or nonexistent can have an important impact on the validity of the analysis [21]. This instrument can provide up to 10,000 mass resolution, which equates to resolving peaks separated by just 0.005 mass unit while the ICP-TripleQ MS have a resolution of one mass unit [22]. This means that HR-ICP-MS could differentiate a mass of 47 from a 47.005 while the IPC-TripleQ MS could differentiate a mass of 47 from a mass 48 but not from a mass 47.5. However not all subjects have the same interferences which could explain why the differences between the two laboratories are not systematic.

Other variables can be taken into account for explaining the differences between the results of the two laboratories such as sample contamination, stability of the sample over time as well as the sampling protocol and the method itself. Moreover, the sample preparation prior to analysis is very different for both laboratories. Laboratory 1 proceeds through a simple dilution of the blood sample with a basic diluent combined with a matrix matched calibration while the procedure of laboratory 2 involves digestion of the samples and an aqueous calibration in order to minimize matrix effect. This main difference in sample preparation could explain the variations in Ti levels observed between the two laboratories. A standardized sample preparation seems preferable to allow comparison between published research data and moreover when threshold values are proposed to differentiate a well-functioning implant from a defective one.

In a previous study, we reported the reproducibility of 46 Cr and Co samples analyzed by two different laboratories (Laboratory 2 of the present study versus another one). One laboratory had higher results and a clinically significant absolute difference above the predetermined threshold was found for 35% of Cr samples and 38% of Co samples [23]. Saini et al. also found significant differences when comparing Cr and Co samples from 104 patients tested by two laboratories. One laboratory reported lower whole blood cobalt levels [24].

We also reported the reproducibility of Cr, Co and Ti samples analyzed by the same laboratory (Laboratory 2 of the present study) [25]. The laboratory did blind analyses of 78 pairs of whole blood samples taken at the same time from the same patients. The absolute difference between the two samples was greater than the limit of quantification of the HR-ICP-MS device for Cr, Co and Ti (0.84 versus 0.35 $\mu\text{g/L}$ for Cr, 0.74 versus 0.07 for Co, and 0.88 versus 0.70 $\mu\text{g/L}$ for Ti). For Ti, the intra lab difference (Lab 2) was much smaller than the inter lab difference found in the present study (1.95 versus 7.70 $\mu\text{g/L}$).

Measuring systemic metal ions is linked to important inter laboratory reproducibility. As shown in our study, the variation between laboratories may be very high (mean ratio 410%) and the risk of misinterpretation is significant. Systemic effects of metal ions can occur in a variety of ways and it is often impossible to determine their consequences. So the poor reliability of metal ion measurement should be taken into account when assessing a patient with suspected clinical problem related to elevated systemic metal ions. Our study demonstrates that patient results must whenever possible be compared to results from the same laboratory to avoid the risk of misinterpreting inter-laboratory variations. Moreover, it is important to base our clinical decision on a metal ion unfavorable trend over a certain period and not on a simple elevated measure. In addition, out of clinical context, absolute values are less meaningful. We recommend that the same laboratory make metal measurements, and moreover, in presence of doubtful results, clinician should not hesitate to send further samples to a second laboratory using a different method.

5. Conclusion

Ions metal blood screening is a common way of detecting mal-functioning orthopedic implants. However, all laboratories do not use the same technologies or calibrations to do these measurements. Different laboratories leading to a significant risk of misinterpretation can measure clinically significant level difference. Therefore, clinical decision should not rely on a single measurement made by one laboratory.

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CRediT authorship contribution statement

Janie Barry: Methodology, Data curation, Formal analysis. **David Eichler:** Data curation, Writing - original draft, Writing - review & editing. **Robert Robitaille:** Conceptualization, Methodology, Writing - original draft. **Pascal-André Vendittoli:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.plabm.2020.e00167>.

References

- [1] P.A. Vendittoli, et al., Metal Ion release with large-diameter metal-on-metal hip arthroplasty, *J. Arthroplasty* 26 (2) (2011) 282–288.
- [2] P.A. Vendittoli, et al., Modular junction may be more problematic than bearing wear in metal-on-metal total hip arthroplasty, *Hip Int.* 29 (3) (2019) 262–269.
- [3] J. Hutt, et al., Comparison of whole-blood metal ion levels among four types of large-head, metal-on-metal total hip arthroplasty implants: a concise follow-up, at five years, of a previous report, *J. Bone Joint Surg. Am.* 98 (4) (2016) 257–266.
- [4] P.E. Ridon, et al., Long-term comparative study of large-diameter metal-on-metal bearings: resurfacing versus total arthroplasty with large-diameter Durom bearing, *Orthop. Traumatol. Surg. Res.* 105 (5) (2019) 943–948.
- [5] E.E. Brouwers, et al., The application of inductively coupled plasma mass spectrometry in clinical pharmacological oncology research, *Mass Spectrom. Rev.* 27 (2008) 67–100.
- [6] J.E. Sonke, V.J. Salters, Capillary electrophoresis-high resolution sector field inductively coupled plasma mass spectrometry, *J. Chromatogr. A* 1159 (1–2) (2007) 63–74.
- [7] Y. Yan, A. Neville, D. Dowson, Understanding the role of corrosion in the degradation of metal-on-metal implants, *Proc. Inst. Mech. Eng. H* 220 (2) (2006) 173–181.
- [8] W.G. Blakeney, et al., Excellent results of large-diameter ceramic-on-ceramic bearings in total hip arthroplasty: is Squeaking Related to Head Size, *Bone Joint Lett. J* 100-B (11) (2018) 1434–1441.
- [9] S.M. McDonnell, et al., The incidence of noise generation arising from the large-diameter Delta Motion ceramic total hip bearing, *Bone Joint Lett. J* 95-B (2) (2013) 160–165.
- [10] A. Carli, et al., Adverse soft-tissue reactions around non-metal-on-metal total hip arthroplasty - a systematic review of the literature, *Bull. NYU Hosp. Jt. Dis.* 69 (Suppl 1) (2011) S47–S51.
- [11] J.T. Munro, et al., High complication rate after revision of large-head metal-on-metal total hip arthroplasty, *Clin. Orthop. Relat. Res.* 472 (2) (2014) 523–528.
- [12] K. Osman, et al., Corrosion at the head-neck interface of current designs of modular femoral components: essential questions and answers relating to corrosion in modular head-neck junctions, *Bone Joint Lett. J* 98-B (5) (2016) 579–584.
- [13] A. Deny, et al., Effect of sleeved ceramic femoral heads on titanium ion release, *Hip Int.* 28 (2) (2018) 139–144.
- [14] I. Swiatkowska, N. Martin, A.J. Hart, Blood titanium level as a biomarker of orthopaedic implant wear, *J. Trace Elem. Med. Biol.* 53 (2019) 120–128.
- [15] I. Swiatkowska, et al., Blood and plasma titanium levels associated with well-functioning hip implants, *J. Trace Elem. Med. Biol.* 57 (2019) 9–17.
- [16] B.D. Gessner, et al., A systematic review of systemic cobaltism after wear or corrosion of chrome-cobalt hip implants, *J. Patient Saf.* 15 (2) (2019) 97–104.
- [17] G.S. Matharu, et al., No threshold exists for recommending revision surgery in metal-on-metal hip arthroplasty patients with adverse reactions to metal debris: a retrospective cohort study of 346 revisions, *J. Arthroplasty* 34 (7) (2019) 1483–1491.
- [18] K.L. Urish, et al., Trunnion corrosion in total hip arthroplasty-basic concepts, *Orthop. Clin. N. Am.* 50 (3) (2019) 281–288.
- [19] S.C. Kim, et al., Fourth-generation ceramic-on-ceramic THA results in improvements in midterm outcomes compared to third-generation THA but does not resolve noise problems: a cohort study of a single-hip system, *BMC Musculoskel. Disord.* 20 (1) (2019) 263.
- [20] C. Delaunay, et al., Metal-on-metal bearings total hip arthroplasty: the cobalt and chromium ions release concern, *Orthop. Traumatol. Surg. Res.* 96 (8) (2010) 894–904.
- [21] C.P. Case, et al., Development of a routine method for the determination of trace metals in whole blood by magnetic sector inductively coupled plasma mass spectrometry with particular relevance to patients with total hip and knee arthroplasty, *Clin. Chem.* 47 (2) (2001) 275–280.
- [22] ThermoFisher Triple, Quadrupole ICP-MS or high resolution ICP-MS? *Which Instrument is right for me?* [cited 2019; Available from: <https://assets.thermofisher.com/TFS-Assets/CMD/Specification-Sheets/SN-43402-ICP-MS-Triple-Quadrupole-High-Resolution-SN43402-EN.pdf>, 2017.
- [23] M. Rahme, et al., Whole blood metal ion measurement reproducibility between different laboratories, *J. Arthroplasty* 29 (11) (2014) 2214–2218.
- [24] R. Saini, et al., Concordance between laboratories in metal ion testing in patients with metal-on-metal hip implants, *Can. J. Surg.* 62 (1) (2019) 9–13.
- [25] J. Barry, M. Lavigne, P.A. Vendittoli, Evaluation of the method for analyzing chromium, cobalt and titanium ion levels in the blood following hip replacement with a metal-on-metal prosthesis, *J. Anal. Toxicol.* 37 (2) (2013) 90–96.