Lo SCALPELLO (2021) 35:82-86
doi number: 10.36149/0390-5276-217

Chromium and cobalt in blood and serum in the surveillance of metal-on-metal hip implants

Gianluca Scalici[1], Nadia Cirri[2], Irene Bellini[3], Giovanni Benelli[4]

[1] *Neuromusculoskeletal Department Ortopaedics and Traumatology, AOU Careggi-CTO, Florence, Italy;* [2] *RN, Healt Direction, Ospedale "Santo Stefano Prato", Prato, Italy;* [3] *Medical Director, Ospedale "R. Giovannini, Prato, Italy;* [4] *Department of Ortopaedics and Traumatology, Ospedale "Santo Stefano Prato", Prato, Italy*

Summary

Objective. The aim of this study is to evaluate the relationship between serum and whole blood chromium and cobalt levels in a group of patients with metal-on metal total hip arthroplasty (Depuy ASR™). A conversion formula was developed to allow adequate evaluation of patients and correctly interpret the measured value.

Methods. The authors retrospectively reviewed a series of 150 patients and prospectively analysed 64 patients who satisfied inclusion criteria. We collected data by taking simultaneously sample of chromium and cobalt ionemia from blood and serum.

Results. Statistical analyses revealed significant differences between chromium and cobalt values in serum and whole blood (p 0.007), but with a strong positive correlation for both chromium (r 0.927) and cobalt (r 0.935). The authors also calculated a conversion formula to convert whole blood ion levels into serum levels, Cr se = -0.32582 + 1.39018*Cr WB for chromium and Co se = 0.239637 + 0.804279* Co WB, for cobalt.

Conclusions. The difference between serum and blood values of chromium and cobalt is highlighted in a strong positive correlation. The development of the conversion formula allows to better interpret laboratory data and improve care and monitoring of patients.

Key words: total hip arthroplasty, metal-on metal prothesis, serum, blood metal ion

Received: June 15, 2021
Accepted: September 6, 2021

Correspondence
Gianluca Scalici
Neuromusculoskeletal Department Ortopaedics and Traumatology, AOU Careggi- CTO, via Largo Palagi 1, 50100, Florence, Italy
E-mail: gianlucascalici1991@gmail.com

How to cite this article: Scalici G, Cirri N, Bellini I, et al. Chromium and cobalt in blood and serum in the surveillance of metal-on-metal hip implants. Lo Scalpello Journal 2021;35:82-86. https://doi.org/10.36149/0390-5276-217

Introduction

Metal-on metal (MoM) total hip replacements (THR) and resurfacing arthroplasty have been used extensively in elective and post-traumatic hip fractures, restoring mobility and quality of life to thousands of patients. MoM have been used predominantly in young patients, reaching their peak between 2006 and 2008 with over 3000 implants annually. Following the warning of the "Medicine and Healthcare Products Regulatory Agency"(MHRA) in 2010, their use has been gradually reduced and almost completely disappeared in 2019 [1]. This reduction is linked to the high revision rate to which these implants are subjected compared to implants with ceramic or polyethylene coating interface, with 4294 revisions on 22115 total hip replacements with MoM bearing surface and a cumulate percent revision at 10 years ranging from 7.1 to 45% [1]. The main reasons for revision (47.9% of cases) reported in the literature has been described as an adverse reaction to metal debris (ARMD) [2], followed by aseptic loosening (18.3%) and infection (10.8%). The etiopathogenetic mechanism is linked to metallic corrosion, which involves the local and systemic release of chromium and cobalt ions and to wear with the formation of debris [3]. Comparative *in vitro* studies have shown a production of metal debris in the order of 6-834 nm [4], about 20 times smaller than debris of metal-on-polyethylene [5], but numerically greater. Local accumulation of metal debris can lead to T-mediated hypersensitivity reactions [6,7], peri-prosthetic osteolysis [8], joint and periarticular effusions, and chronic inflammatory soft tissue reactions, known as pseudotumors, aseptic lymphocytic vasculitis associated lesions (ALVAL), or adverse local tissue reactions (ALTR) [9]. In addition, debris and metal ions can bind to proteins and cells [10] and can be transported away from joint, increasing the serum, blood and urinary levels of chromium and cobalt [11] with long-term systemic effects with the possible development of polyneuropathy, cardiomyopathy and hypothyroidism [12].

In 2014, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) developed guidelines for monitoring MoM [13] based on patients' clinical evaluation, blood and serum values of chromium (Cr) and cobalt (Co) and radiological diagnostics. Measurements of metal ions and their interpretation have become fundamental [14]. Various matrices, such as whole blood (WB), serum (Se) and urine, can be used. Analyses in whole blood or serum is preferable, since urine requires a 24h collection and the levels seem to be more variable due to variations in hydration, serum creatinine and renal function [15]. Concerning the preferential measurement in Se or WB, no consensus has emerged regarding the superiority of one method over another. However, serum values are a slightly more accurate source of information, since they do not include chromium and cobalt intracellular ions, especially within red blood cells (RBC). The use of the same matrix (Se or WB) in the comparison of consecutive ionic values in the same patient or in different patients is essential since these values are not interchangeable and their correlation is still under study and evaluation [16].

The aim of our study is to evaluate serum and blood values of chromium and cobalt with double sampling on the same day in a group of patients. A conversion equation was also evaluated to calculate serum ion levels from whole blood, allowing blood values to be converted into serum levels and vice versa.

Materials and methods

Study was approved by the International Review Board. The authors retrospectively analyzed a series of 150 patients with MoM prostheses, already in follow-up since 2012 at our hospital (single regional reference center). A prospective study was conducted between March 2019 and March 2020, following 64 patients in a controlled study. All patients were subjected to Cr and Co ionemia sampling on whole blood and serum at the same time, and all subsequent blood sampling was carried out in the same manner.

Patients with MoM Depuy ASR™ and ASR™XL acetabular system implanted at our center from 2005 to 2010 were included in the study (64 patients), with at least 10 years of follow-up and not subjected to revision of the implant. The exclusion criteria concerned 86 patients implanted with MoM implants with a follow-up less than 10 years, with incomplete radiological or clinical documentation, or who had already carried out an implant revision. In addition, patients with serum and blood cobalt values lower than 0.5 µg/L were excluded from the study.

Clinical and demographic data of patients (gender, age, years of implantation, blood and serum values of chromium and cobalt) were prospectively collected in clinical records.

Blood samples were collected using non-metallic needles, discarding the first 5 ml of blood to avoid contamination, and collecting the next 5 ml in tubes containing 6 ml of ethylenediaminetetraacetic acid (EDTA). After collection, the blood tube with the coagulation activator was set aside for about 30 minutes and centrifuged at about 3600 rpm for 10 minutes, prior to storage at a maximum of 4°C and sent to two different laboratories for analysis. The level of chromium and cobalt ions in blood was determined using the ICP/MS Perkin Elmer DRCII spectrophotometric apparatus with cyclonic chamber under laminar flow. Measurements of serum values were carried out by inductively coupled plasma mass spectrometry, icap Q (ICP/MS, Thermo Fischer Scientific, USA) with Cetac ASX520 (Cetac Technologies), PFA cyclonic spraying chamber and quartz injector with diameter 2.5 mm.

Descriptive statistics were obtained by reporting average, median and interquartile ranges (IQR) for continuous variables and frequencies and proportions for discrete variables, as appropriate. The continuous variables were analyzed with the Wilcoxon sign range test (Wilcoxon signed - Rank Test) based on their non-normal distribution for serum and blood values of chromium and cobalt, respectively. The normal distribution of variables was tested by the Kolmonorov-Smirnov test. The correlation between serum and blood values of chromium and cobalt was analyzed by the correlation coefficient for Spearman ranks, based on the abnormal distribution of values.

The elaboration of the equation "serum metal level = $\alpha + \beta *$ metal level in whole blood" was obtained by simple linear regression with an adapted model having 85.88% of the variability in serum metal. Statistical significance was set as $p < 0.005$. All tests were two-tailed. The analysis was developed using SPSS v.24 (IBM SPSS Statistics for Mac, Armonk, NY, IBM Corp).

Results

The study group included 64 patients considered eligible and a mean age at the time of the study of 74 years (IQR, 71-77 years) and a median age of 76 years (DS 11); 36 patients were male (56.25%) and 28 female (43.75%). The average of years since the primary prosthesis was 11 years (IQR 10-11 years) and 10 median years (DS 1). The median of serum cobalt was 6.08 μg/L (DS 8.46), serum chromium 3.67 μg/L (DS 5.31), blood cobalt 7.2 μg/L (DS 9.83) and blood chromium 2.9 μg/L (DS 3.5). Data are shown in Table I.

After evaluation with Kolmonorov-Smirnov test and verified non-parametric distribution of the analyzed data, univariate analysis was carried out based on the Wilcoxon Sign Rank test which showed a significant difference between serum and blood chromium values with a p-value of 0.007 and thus allowing to reject the null hypothesis. A similar calculation was made to analyze the significant difference between serum and blood cobalt values; a p-value of 0.007 was obtained.

The correlation coefficient analysis, carried out using the correlation coefficient for Spearman ranks indicated by "r", was carried out considering as "x" the value on blood and "y" the value on serum. It was calculated according to the following formula, considering both chromium and cobalt values previously converted into ranks:

$$r = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2 \sum_i (y_i - \bar{y})^2}}$$

Measured a value of r = 0.927 (p 0.001) for chromium and r = 0.935 (p 0.001) for cobalt and being both values of "r" remarkably close to +1, it can be deduced that the blood and serum measurements of the two metals are positively correlated to one another.

Linear regression analysis according to a simple linear model Y = α+ β*X, with serum chromium (Cr se) as a dependent variable and blood chromium (Cr WB) as an independent variable, showed the following conversion formula: Cr se= -0.32582 + 1.39018*Cr WB with p value < 0.05 (R- 85.8834%) (Fig. 1). Using analogous analysis, with dependent variable the serum cobalt (Co se) and independent variable the blood cobalt (Co WB), following conversion formula has been obtained: Co se = 0.239637 + 0.804279* Co WB with p value < 0.05 (R-87.3728%) (Fig. 2).

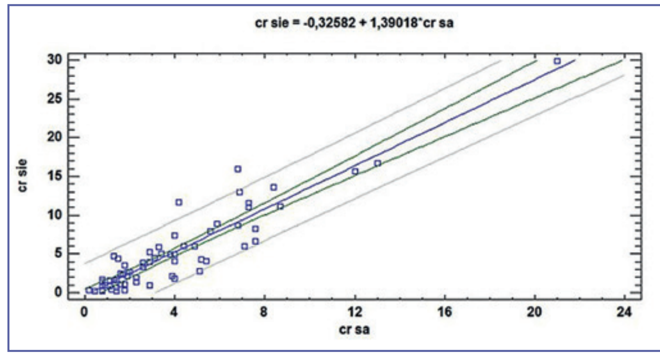

Figure 1. Conversion formula for blood chromium into serum on simple linear regression model.

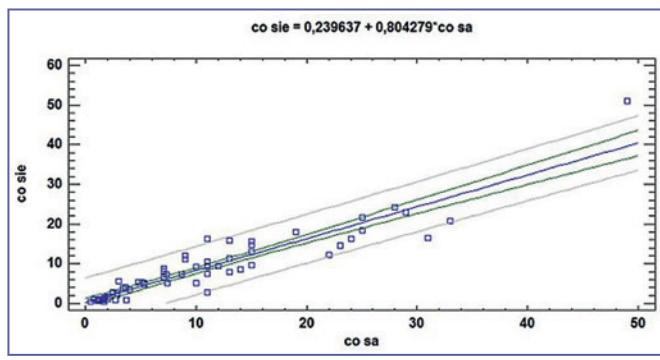

Figure 2. Conversion formula for blood cobalt to serum based on simple linear regression model.

Table I. Table on clinical patient data.

Clinical data of 64 patients		
Gender, n (%)	Male	36 (56.25%)
	Females	28 (43.75%)
Average age of patients (IQR)		74 (71-77)
Years from primary replacement (median, DS)		10 (DS 1)
Serum cobalt values (median, DS)		6.08 ųg/L (DS 8.46)
Serum chromium values (median, DS)		3.67 ųg/L (DS 5.31)
Blood cobalt values (median, DS)		7.2 ųg/L (DS 9.83)
Blood chromium (median, DS) values		2.9 ųg/L (DS 3.5)

Discussion

The assessment of metal ion levels is becoming increasingly important in the evaluation of MoM implants as an indicator of the mechanical failure of the implant and possible tissue and systemic damage, as reported by the literature and MHRA in 2010 [14,17]. The analysis of analytical data should be accompanied by clinical evaluation of patients, medical history and radiological imaging, using hematic or serum ionemia as a central element [13].

In our study, a significant difference was found between blood and serum values of chromium and cobalt after a double sampling carried out simultaneously in patients. Concerning the serum-blood difference for a given metal, slightly lower serum values with an average difference of 1.72 μg/L were found for cobalt; in the case of chromium, the serum values found were higher with an average difference of 1.19 μg/L, in accordance with literature results [18]. The slight deviation from the literature can be attributed to the different sampling and processing systems [19]. Although the superiority of one method over the other has not been demonstrated and both can be used in clinical practice [16], serum values are more precise as they are not influenced by the intracellular ionic portion. Daniel et al. [11] noted that many laboratories continue to prefer whole blood measurements to avoid contamination and sample abnormalities during centrifugation and separation of serum from blood. Analysis of the correlation coefficient showed a high positive correlation index for both chromium and cobalt. Although the blood and serum values measured in a single patient are significantly different, they are low or high in a consensual way giving a representative measurement of the values of metal ions in the patient and increasing the predictive value.

The verification of the conversion formula to extrapolate from whole blood the levels of metal ions in serum is attractive for obvious reasons as reported by Smolders et al. [18]. Although they are not interchangeable values, conversion and possible adjustment from one parameter to another is possible with high levels of statistical accuracy. The wide range of serum and blood values of chromium and cobalt in our study allowed to greatly increase the predictive value of the conversion formula, becoming particularly useful and effective for a range of Cr WB values between 0.2 and 12 µg/L and Co WB 0.5 and 33 µg/L. The levels can also be estimated with a low prediction error given the wide range of values considered, i.e. less than 1.38 µg/L for chromium and 1.95 µg/L for cobalt.

A conversion formula between serum and blood measurements is reported in the literature [18], but it shows a more limited range of metal ions with a predictive error margin of about 1 µg/L, which is high for a limited range of values.

Our study highlights the importance of standardizing the analytical methods and predictive value of metal ion screening in the evaluation and follow-up of patients with MoM implants in accordance with medical alerts [17], but also it allows comparison and interpretation of serum and blood measurements of chromium and cobalt ions in a wide range of use, which is not present in the existing literature. The wide range of values recorded on a homogeneous group of patients for prosthetic implants (Depuy ASR™ Hip System) highlights the close relationship between the level of metal ions and implant malfunction. In 2017, the MHRA established that for all patients with whole blood metal ion values > 7 µg/L (equivalent to 119 nmol/L for cobalt and 134.5 nmol/L for chromium) a close follow-up with clinical evaluation and radiological imaging with magnetic resonance imaging with metal artifact suppression sequences (MARS-RM) is indicated [20]. In these patients, the development of tissue reactions or ARMD-type reactions should be considered likely [20].

High levels of serum or blood Cr and Co ions can be found in patients carrying mechanical heart valves, orthodontic implants, intake of food equivalents or environmental/professional sources, becoming confusing factors in the interpretation of data. Given the enormous variability of the prosthetic design, technical specifications and fabrication of the implant and the reactive and inflammatory response of the patient, it is always necessary to carry out second-level radiological investigations (MRI with metal suppression sequence, MARS- MRI or CT) and clinical examination before indicating a review surgery.

The limits of our study are linked to the limited number of 64 patients, a sample of patients in significant reduction for the increase of revised implants with metal-polyethylene, ceramic- ceramic or ceramic-polyethylene and for the general aging of the population analyzed. Our results have also been influenced by being collected by a single regional reference center, both positively and negatively. The process of collection and analysis of the results has been revised and analyzed through collegial methods and the analytical path was constant and methodical during the duration of the study.

Conclusions

The Authors highlight that significant positive correlation of serum and blood values for chromium and cobalt. The development of a conversion formula for the blood and serum values of the two metals allows to better interpret laboratory data and improve the care and monitoring of patients.

Informed consent/compliance with ethical standards

All procedures described in the study involving human beings have been implemented in accordance with the ethical standards established by the Helsinki Declaration of 1975 and subsequent amendments. Informed consent was obtained from all patients included in the study. The study was approved by our Ethics Review Committee.

Human and animal Right

This study does not require the inclusion of any statement concerning studies in humans and animals.

Acknowledgement

None.

Funding

None.

Conflict of interest

All Authors declare that they have no conflict of interest to declare. The Authors have not received any support from Organizations for the article sent.

Author contributions

The Authors contributed equally to the work.

References

1 AOANJRR. Annual 2020. Aust Orthop Assoc Natl Jt Replace Regist 2020 Annu Rep:219-289.

2 Scholes SC, Hunt BJ, Richardson VM, et al. Explant analysis of the Biomet Magnum/ReCap metal-on-metal hip joint. Bone Jt Res 2017;6:113-122. https://doi.org/10.1302/2046-3758.62.BJR-2016-0130.R2

3 Meek RMD, Afolaranmi GA, Tettey J, et al. Release of chromium from orthopaedic arthroplasties. Open Orthop J 2008;2:10-18. https://doi.org/10.2174/1874325000802010010

4 Doom PR, Campbell PA, Worrall J, et al. Metal wear particle characterization from metal on metal V total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. J Biomed Mater Res 1998;42:103-111. https://doi.org/10.1002/(sici)1097-4636(199810)42:1<103::aid-jbm13>3.0.co;2-m

5 Amstutz HC, Campbell P, McKellop H, et al. Metal on metal total hip replacement workshop consensus document. Clin Orthop Relat Res 1996:297-303. https://doi.org/10.1097/00003086-199608001-00027

6 Hallab NJ, Mikecz K, Vermes C, et al. Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. J Biomed Mater Res 2001;56:427-436. https://doi.org/10.1002/1097-4636(20010905)56:3<427::AID-JBM1112>3.0.CO;2-E

7 Willert H-G, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. J Bone Jt Surg-Am 2005;87:28-36. https://doi.org/10.2106/00004623-200501000-00006

8 Park YS, Moon YW, Lim SJ, et al. Early osteolysis following second-generation metal-on-metal hip replacement. J Bone Jt Surg - Ser A 2005;87:1515-1521. https://doi.org/10.2106/JBJS.D.02641

9 Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. J Bone Jt Surg - Ser B 2008;90:847-851. https://doi.org/10.1302/0301-620X.90B7.20213

10 Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. Clin Orthop Relat Res 1996329(Suppl):S233-S243. https://doi.org/10.1097/00003086-199608001-00020

11 Daniel J, Ziaee H, Pynsent PB, et al. The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. J Bone Jt Surg - Ser B 2007;89:736-741.https://doi.org/10.1302/0301-620X.89B6

12 Ikeda T, Takahashi K, Kabata T, et al. Polyneuropathy caused by cobalt-chromium metallosis after total hip replacement. Musc Nerve 2010;42:140-143. https://doi.org/10.1002/mus.21638

13 Epstein M, Emri I, Hartemann P, et al. Scientific Committee on Emerging and Newly Identified Health Risks SCENIHR opinion on the safety of metal-on-metal joint replacements with a particular focus on hip implants, 2014.

14 Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? Clin Orthop Relat Res 2005;177-181. https://doi.org/10.1097/01.blo.0000166901.84323.5d

15 Band TJ. Materials and metallurgy. Mod Hip Resurfacing 2009:43-63. https://doi.org/10.1007/978-1-84800-088-9_2

16 Malek IA, Rogers J, King AC, et al. The interchangeability of plasma and whole blood metal ion measurement in the monitoring of metal on metal hips. Arthritis 2015:1-7. https://doi.org/10.1155/2015/216785

17 Medicines and Healthcare products Regulatory Agency. Medical Device Alert, All metal-on-metal (MoM) hip replacements, 2010. Distribution 1-4.

18 Smolders JMH, 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;21:587-595. https://doi.org/10.5301/HIP.2011.8643

19 Estey MP, Diamandis EP, Van Straeten C Der, et al. Cobalt and chromium measurement in patients with metal hip prostheses. Clin Chem 2013;59:880-886. https://doi.org/10.1373/clinchem.2012.193037

20 Agency Medicines and Healthcare Products Regulatory. Medical Device Alert (MDA/2017/018). MHRA, 2017. Database 1-7.