International Journal of Research in Orthopaedics
Singh J et al. Int J Res Orthop. 2025 Jul;11(4):757-762
http://www.ijoro.org

Original Research Article

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20251796

Association of serum metallic ion levels in patients with total joint arthroplasty with their adverse effects: a comparative cross-sectional study

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Received: 27 March 2025
Revised: 07 May 2025
Accepted: 29 May 2025

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ABSTRACT

Background: Metallic implants used in joint arthroplasty release ions gradually sometimes resulting in their toxicity. Hence, data regarding exact correlation between serum metallic ion levels and toxicity occurrence is still lacking.
Methods: A total of 90 adult subjects, each with a single total joint arthroplasty (TJA between 1 to 5 years), or without were recruited. The serum levels of Cr, Co, Ni, & Mo in above 2 groups were estimated and correlated with signs and symptoms related to Cr, Co, Ni, & Mo ion toxicity Unpaired Student's t-test, Chi-square test and Pearson correlation coefficient were used to analyses data. A p value<0.05 was considered significant.
Results: The mean serum levels of Cr (21.53±7448 µg/l vs. 19.03±0.3372 µg/l; p=0.0026), Ni (9.643±0.2486 µg/l vs. 9.303±0.2729 µg/l; p=0.83), Co (5.482±0.20 µg/l vs. 5.573±0.21 µg/l; p=0.76), and Mo (5.573±0.2159 µg/l vs. 5.290±0.2208 µg/l; p=0.36) in subjects with implants were higher than in subjects without implants. Five subjects reported six adverse effects (AE) specifically numbness in hands (4), fatigue (1), and bone pain (1), which showed no significant association or correlation with the mean serum levels of the metallic ions.
Conclusion: Results showed increased mean serum chromium levels post one year of implant surgery, while mean serum levels of Co, Ni, and Mo did not demonstrate any significant elevation. No correlation between serum levels of Cr, Co, Ni, and Mo, duration of implant, and observed AE was seen. Causality assessment between reported AE and metal ions (Cr, Co, Ni, and Mo) levels was “possible."

Keywords: Joint arthroplasty, Metal on metal implants, Serum metal ions, Materiovigilance

INTRODUCTION

The prevalence of total hip and knee replacement has increased proportionately with advancement of age, which corresponded to 2.5 million individuals had undergone total hip replacements and 4.7 million with total knee replacement in the United States in 2010.[1] Orthopaedic implants are composed of metals (stainless steel, cobalt, chromium and titanium alloys), non-metals (ceramics, polyethylene,) and bone cement (calcium phosphate, glass polyalkenoate and poly methyl meth acrylate) and are applied to restores mobility of joint.[2,4] The success of any implant depends on its accurate shape, size, and near normal mechanical function, biocompatibility, chemical stability and safety as many of them remain in the body throughout the life span. Generally, metal implants are designed to be inert, but once implanted inside the body the metal ions can leach to cause adverse outcomes.[2] Hip arthroplasties with metal-on-metal implant led to increased whole blood levels of chromium (Cr) and cobalt (Co), and is increasing concern for their possible toxic effects such as local tissue toxicity, inflammation, bone loss, impaired renal function, immune modulation, hypersensitivity, chromosomal damage, malignant cellular transformation, pseudotumor and soft tissue necrosis.[3] Further, potential hazards of circulating debris without physical and chemical characterizations remains obscure and cannot be extrapolated to the clinical situation. Most of the metal ions leached from implants have been recognized as potential carcinogens.[4] Hence, this study was undertaken to estimate the levels of serum chromium (Cr), nickel (Ni), cobalt (Co) and molybdenum (Mo) in patients undergone total joint arthroplasty in last one to five years and their correlation with observed adverse effects if any.

METHODS

A comparative cross-sectional study was conducted during November 2022 to January 2024 at Departments of Pharmacology and Orthopaedics, Lady Hardinge Medical College and associated Smt. Sucheta Kriplani Hospital, New Delhi on 90 adults each requiring unilateral total knee or hip replacement surgery and individuals who had undergone arthroplasty in last one to five years. Those patients with history of any implant removal or prior occupational exposure to chromium, cobalt, nickel or molybdenum such as stainless-steel welding, refinery of nickel processing plants, metal mining industry were considered in exclusion criteria. Adult patients irrespective of gender with total joint arthroplasties who have completed a postoperative period between 1 to 5 years were included in the inclusion criteria.[5]

The study was conducted after obtaining informed written consent from all the individuals. The study proposal was approved by the Institutional Ethics Committee for Human Research numbered LHMC/IEC/2022/PG Thesis/140 dated 27/09/2022. The patient's demographic profile and medical history including monitored for suspected adverse effects such as anaemia, renal dysfunction, bone pain, dermatitis, breathing difficulty, hearing loss, vision loss, forgetfulness, numbness or tingling sensation in feet or hands, muscle weakness or fatigue, loose stools, cardiac failure and unsuspected adverse effects. The causality assessment of observed adverse effects was done using WHO causality assessment scale.[6]

Venous blood sample (6 ml) was withdrawn under aseptic conditions pre-operatively from 90 adults requiring unilateral total knee or hip joint replacement surgery and from another 90 individuals who had undergone such arthroplasty in last one to five years. Half of the sample was used to estimate complete blood count (CBC), routine biochemical (LFT, KFT, serum calcium and vitamin D) investigations.

Whereas from rest of the sample, serum was separated to estimate serum Co, Cr, Ni and Mo levels using Inductively coupled plasma mass spectrometry method using single quadruple pole Q series equipment.[7] To examine the association between serum levels of metal ions and observed adverse effects, the data from both groups were divided into two categories: serum metal ion levels within the normal range and those above the normal range. Correlation analyses were also performed to assess the relationship between the duration of total joint arthroplasties and observed adverse effects.

The data were transformed, coded, and entered into Microsoft Excel (2016). Statistical analyses were performed using GraphPad Prism free trial software (version 8.0). Serum metal ion levels were expressed as Mean ± SEM. Comparisons of serum metal ion levels between subjects without implants and those with implants were conducted using an unpaired Student's t-test. The association of each serum metal ion level with observed adverse effects following total joint arthroplasties was assessed using the Chi-Square Test of Association.

Correlations between the duration of total joint arthroplasties and observed adverse effects were analysed using Pearson's correlation coefficient. A p value of < 0.05 was considered statistically significant for comparison within a 95% confidence interval.

RESULTS

All 90 enrolled participants each with and without implants, completed the study. Subjects in both the implant (66%) and non-implant (81%) group were predominantly male. The proportion of males and females in each group were statistically comparable (p=0.68). The overall mean ages of subjects in both groups were also comparable (51.78±1.54 years vs. 52.41±1.54 years; p>0.5).

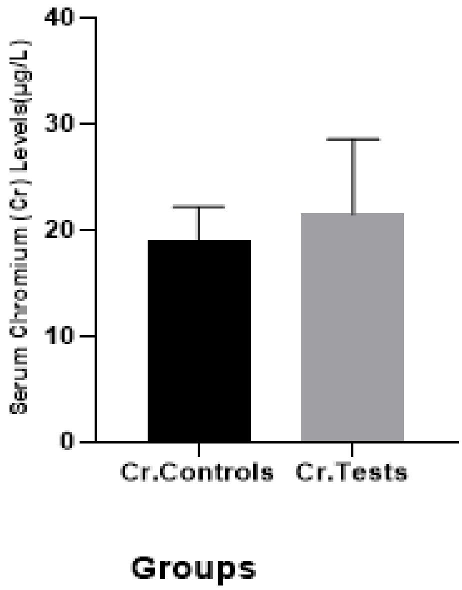

Figure 1: Comparison of mean serum Cr levels in pt's (with implant), (n=90) and subjects (no implants), (n=90).

p=0.0026.

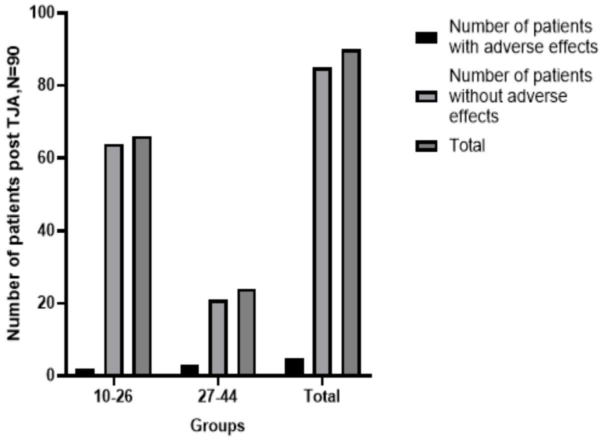

Figure 2: Association between mean srum levels of chromium (Cr), (n=90) and adverse effects, (n=5).

(p=0.55).

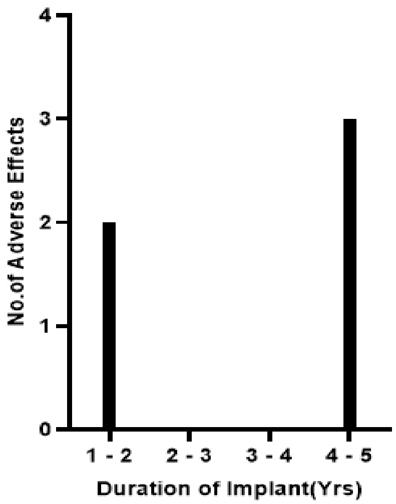

Figure 3: Correlation of adverse effects with post implant duration.

Correlation coefficient r=0.3162, p=0.6667.

All the subjects in both groups had serum chromium levels exceeded the normal physiological limit of ≤ 1.4 µg/l. The mean chromium level for all the 90 subjects with implants was 21.86±0.82 µg/l. Of these, 67 subjects had mildly elevated levels, ranging from 10 to 26 µg/l, with a mean serum chromium level of 17.88±0.35 µg/l. The remaining 23 subjects with implants had moderately elevated levels, ranging from 27 to 40.1 µg/l, with a mean concentration of 32.19±0.84 µg/l.

In contrast, all the 90 subjects without implants had mean chromium levels of 19.03±0.33 µg/l. The mean serum chromium levels in subjects with post-arthroplasty were significantly higher than those in the subjects without implants, with a mean difference of 2.49±0.81 (21.86±0.82 µg/l vs. 19.03±0.33 µg/l; p=0.0026) (Table 1, Figure 1). The mean serum nickel level in subjects without implants was 9.3±0.27 µg/l (ranging from 1.1 to 15.7 µg/l), while the mean serum nickel level in subjects with implants was slightly higher at 9.43±0.24 µg/l (ranging from 3.4 to 14.99 µg/l). The mean difference between these two groups (0.07±0.36 µg/l) was statistically insignificant (9.3±0.27 µg/l vs. 9.43±0.24 µg/l; p=0.83). All subjects with implants had serum nickel levels above the normal physiological limit of less than 0.3 µg/l (Table 1).

A total of 14 subjects with implants had serum cobalt levels within normal physiological limits (1-3.5 µg/l), while the remaining subjects had levels above this range. The mean serum cobalt level in subjects with implants was 5.48±0.20 µg/l (ranging from 1 to 9.2 µg/l), while the mean serum cobalt level in subjects without implants was numerically higher (5.57±0.21 µg/l, p=0.76) (Table 1). The mean serum molybdenum level in subjects with implants was 5.57±0.22 µg/l (ranging from 1 to 9.2 µg/l), while subjects without implants had slightly lower levels (5.29±0.22 µg/l; p=0.36).

Only one subject with an implant had serum molybdenum levels within the normal physiological limits (0.28-1.17 µg/l). No subjects without having implant had serum molybdenum levels within normal physiological limits (Table 1). In this study, none of the subjects without implant, experienced any AEs. Five subjects with implants reported six adverse events (AEs): numbness of the hands (4), fatigue (1), and bone pain (1). All five subjects with implants who experienced these AEs had serum chromium levels ranging from 10 to 40.1 µg/l, nickel levels between 1.0 to 16 µg/l, and molybdenum levels 1.1 to 9.2 µg/l. (Table 2, Figure 2). All the five subjects with implant who experienced AE had serum Cr, Ni and Mo above normal physiological limits.

Table 1: The mean serum levels of the individuals with and without arthroplasty.

Metal ions	No. of subjects	Mean serum levels of the individuals (µg/l)		Mean difference	P value
		With arthroplasty	Without arthroplasty		
Chromium	90	21.86±0.82	19.03 ± 0.33	2.49±0.81	0.0026
	67	17.88±0.35			
	23	32.19±0.84			
Nickel	90	9.43±0.24	9.3±0.27	0.07±0.36	0.83
Cobalt	90	5.48±0.20	5.57±0.21	0.09±0.30	0.76
Molybdenum	90	5.57±0.22	5.29±0.22	0.28±0.30	0.36

Table 2: The segregation of observed adverse events as per serum metal ions level (µg/l), with their causality assessment.

Metal ions (normal physiological limit)	Serum ions level (µg/l)	Adverse event (number)	Causality assessment
Chromium (≤1.4 µg/l)	≤1.4	Nil	
	>1.4	Fatigue (1), numbness in hands (4), bone pain (1)	Possible
Nickel (≤0.3 µg/l)	≤ 0.3	Nil	
	>0.3	Numbness in hands (4), fatigue (1), bone pain (1)	Possible
Cobalt (1-3.5 µg/l)	≤3.5	Fatigue (1)	Possible
	>3.5	Numbness in hands (4), bone pain (1)	
Molybdenum (0.28-1.17 µg/l)	≤ 1.17	Nil	
	>1.17	Fatigue (1), numbness in hands (4), bone pain (1)	Possible

Table 3: The correlation of duration since arthroplasty and occurrence of observed adverse effect.

Duration post arthroplasty (in years)	Adverse event (AE)	No. of individuals experience AE	r value (P value)
1 to 2	Numbness in hands fatigue	2	0.316 (0.66)
>2 to 3	None	0	
>3 to 4	None	0	
>4 to 5	Numbness in hands bone pain	3	

Whereas, one subject who experienced fatigue (1) had serum cobalt levels with in normal physiological limits (1-3.5 µg/l), while five subjects with serum cobalt levels between 3.6 and 9.2 µg/l experienced numbness in the hands (4) and bone pain (1) (Table 2). Causality assessment of these events in relation to serum Cr, Ni, Co and Mo ion levels, using the WHO causality assessment scale, indicated a "possible" association (Table 2). However, there was no significant association between the serum levels of the aforementioned metallic ions and the observed six AEs. The mean duration of arthroplasty for all subjects was 2.57±0.16 years (ranging from 1 to 5 years). No correlation was found between the post arthroplasty duration and the occurrence of the observed adverse effects concerning all the studied metal ions (r=0.316; p=0.66) (Table 3, Figure 3).

DISCUSSION

Metal on metal implants made up of cobalt, chromium, nickel, molybdenum and carbon have high strength, and temperature and wear resistance characteristic with a survival rate above 95% for 10 years.[8] All metal implants and metal-on-metal bearings corroded to release of metal ions viz. cobalt and chromium in blood.[8] The released metallic ions has been associated with signs and symptoms of systemic toxicity including carcinogenicity and mutagenicity in both humans and in animal models.[9] In our study, subjects with both with and without implant were dominated by male population with a mean age was 51.78±1.54 and 52.4±1.54 years respectively. On the contrary, in England, women aged between 75–79 years underwent hip arthroplasty.[10] Though, Hawker estimated impending need for arthroplasty greater among women (44.9 per 1000) than men (20.8 per 1000) due to the higher prevalence of severe hip and knee arthritis in women causing greater arthritis pain, and disability with regards to performing daily activities.[11] The perceived gender disparity in the rate of arthroplasty might also be due to the socioeconomic factors posing greater barrier to access to health care for women than for men whereas on the other hand, Karlson found no difference between men and women in their willingness to undergo arthroplasty, as reasons for refusing arthroplasty by both men and women, were similar except men considered arthroplasty as too risky.[11,12]

In present study, mean serum chromium levels in subjects with post arthroplasty were significantly higher (p=0.0026). This finding is in accordance with the observations of Leutzner, in which the patients with unilateral or bilateral knee arthroplasty had higher levels of serum chromium after one year of surgery.[13] Moreover, the patients with hip arthroplasty also had raised serum chromium levels.[9] The reason for raised serum chromium level could be due to corrosion of implant. The release of metal ions which was more in knee arthroplasty than hip arthroplasty due to its larger surface area though we did not analyses their levels separately.[14] Henning et al reported that the serum concentrations of nickel were slightly elevated in patients with post hip arthroplasty of duration exceeding one year.[15] On the contrary, in our study, the serum nickel levels in post joint arthroplasty were insignificantly raised (p=0.83).

Interestingly, the serum nickel levels of all subjects in both groups were above normal physiological limits. The reason for higher serum levels of nickel in control in our study could be due to their exposure to nickel through consumption of chocolate, coffee, legumes, and contaminated water in the general population.[15] In addition, dust emissions from factories, coal combustion, waste incineration, cigarette smoking and body piercings with high nickel-releasing items or jewellery.[16,17,19] The seasonal trends of higher levels of nickel in November and March compared to June and August as reported from Korean study could be another confounding factor in our study affecting nickel concentrations.[18]

Our study showed no significant increase in the serum cobalt levels in subjects with metallic implants post one year of joint arthroplasty as compared to the subjects without implants. Since the subjects included in this study had a post-arthroplasty duration exceeding one year but less than five years, the release of Co due to corrosion of the implant led to its increased urinary excretion within 24 hours, attaining peak levels at six months followed by its decreased excretion.[18] In this study, post arthroplasty serum molybdenum levels were only numerically elevated as compared to those in without implant. These findings were in concordance with a study conducted on post implant patients in which no increase in serum molybdenum level was seen.[8]

In our results, raised serum levels of Cr, Ni and Mo above normal physiological limits in post arthroplasty individuals led to the observed adverse events in some patients (Table 2). However, there was no significant association of adverse effects with the metal ion concentrations. Additionally, correlation analysis between duration of implant and appearance of these adverse events did not show any significance (Table 3). Similar evidence was found in some earlier studies which observed that despite the release of these metallic ions from implants and their accumulation in the nearby tissues, subjects had no signs & symptoms of metal ion toxicity.[20] Further, Hall reported that even after 7 years of arthroplasty, the release and accumulation of metal ions from implant could not substantiate a correlation between duration of implant and appearance of adverse events.[21]

The post arthroplasty mean duration in our study was 2.57±0.16, years. In a previous study done on post knee arthroplasty patients with duration more than one-year, no clinical symptoms of cobalt, chromium & nickel ions toxicity were observed.[22] Supporting literature was also found in a study by Weissinger which concluded that after two years of joint arthroplasty, there was no significant association between serum cobalt levels and clinically observed adverse effects.[23] Similar findings were reported by Heisse that despite accumulation of molybdenum in RBCs and macrophages, no clinically observed adverse effects and symptoms of metal ion toxicity were seen even after more than one year of joint arthroplasty.[24]

One limitation of our study might be that the surface area of the implant was not considered while estimating the mean serum metal ion levels. Further studies are warranted to substantiate our findings and also include a greater number of test subjects post five years of joint arthroplasty.

CONCLUSION

The results of our study showed that only mean serum chromium levels increase significantly after one year of implant surgery while mean serum levels of nickel, cobalt and molybdenum either showed a non-significant increase or remained unchanged as compared to control group subjects. Hence, the mean serum levels of Ni, Co and Mo did not show any change. There was no association and correlation between serum levels, duration of implant and observed adverse effects. The causality assessment of all the adverse effects (numbness in hand, fatigue and bone pain) reported in this study was possible.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Singh J, Rehan HS, Arora T, Kalra M, Gupta LK, Das M, et al. Association of serum metallic ion levels in patients with total joint arthroplasty with their adverse effects: a comparative cross-sectional study. Int J Res Orthop 2025;11:757-62.