ISSN 2218-5836 (online)

World Journal of *Orthopedics*

World J Orthop 2024 August 18; 15(8): 683-827

Published by Baishideng Publishing Group Inc

World Journal of Orthopedics

Contents

Monthly Volume 15 Number 8 August 18, 2024

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Orthopedics

Monthly Volume 15 Number 8 August 18, 2024

Contents

World Journal of Orthopedics

Monthly Volume 15 Number 8 August 18, 2024

Contents

NAME OF JOURNAL
World Journal of Orthopedics

ISSN
ISSN 2218-5836 (online)

LAUNCH DATE
November 18, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Massimiliano Leigheb, Xiao-Jian Ye

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF
Xin Gu

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/2218-5836/editorialboard.htm

PUBLICATION DATE
August 18, 2024

PUBLISHING PARTNER
The Minimally Invasive Spine Surgery Research Center Of Shanghai Jiaotong University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shtrhospital.com/zkjs/info_29.aspx?itemid=647

World Journal of Orthopedics

Submit a Manuscript: https://www.f6publishing.com

World J Orthop 2024 August 18; 15(8): 773-782

DOI: 10.5312/wjo.v15.i8.773

ISSN 2218-5836 (online)

ORIGINAL ARTICLE

Prospective Study

Blood metal concentrations and cardiac structure and function in total joint arthroplasty patients

Peter C Brennan, Stephanie M Peterson, Thomas J O'Byrne, Mariana L Laporta, Cody C Wyles, Paul J Jannetto, Garvan C Kane, Maria Vassilaki, Hilal Maradit Kremers

Specialty type: Orthopedics

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Cheng TH

Received: February 9, 2024

Revised: July 19, 2024

Accepted: July 29, 2024

Published online: August 18, 2024

Processing time: 185 Days and 15.5 Hours

Peter C Brennan, Cody C Wyles, Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN 55905, United States

Stephanie M Peterson, Thomas J O'Byrne, Maria Vassilaki, Hilal Maradit Kremers, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN 55905, United States

Mariana L Laporta, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Paul J Jannetto, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, United States

Garvan C Kane, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Hilal Maradit Kremers, MD, Professor, Department of Quantitative Health Sciences, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. maradit@mayo.edu

Abstract

BACKGROUND

There is concern regarding potential long-term cardiotoxicity with systemic distribution of metals in total joint arthroplasty (TJA) patients.

AIM

To determine the association of commonly used implant metals with echocardiographic measures in TJA patients.

METHODS

The study comprised 110 TJA patients who had a recent history of high chromium, cobalt or titanium concentrations. Patients underwent two-dimensional, three-dimensional, Doppler and speckle-strain transthoracic echocardiography and a blood draw to measure metal concentrations. Age and sex-adjusted linear and logistic regression models were used to examine the association of metal concentrations (exposure) with echocardiographic measures (outcome).

RESULTS

Higher cobalt concentrations were associated with increased left ventricular end-

diastolic volume (estimate 5.09; 95%CI: 0.02-10.17) as well as left atrial and right ventricular dilation, particularly in men but no changes in cardiac function. Higher titanium concentrations were associated with a reduction in left ventricle global longitudinal strain (estimate 0.38; 95%CI: 0.70 to 0.06) and cardiac index (estimate 0.08; 95%CI, -0.15 to -0.01).

CONCLUSION
Elevated cobalt and titanium concentrations may be associated with structural and functional cardiac changes in some patients. Longitudinal studies are warranted to better understand the systemic effects of metals in TJA patients.

Key Words: Total joint arthroplasty; Metal-on-metal; Cardiotoxicity; Heart failure; Echocardiography; Cobalt

Core Tip: This study evaluated echocardiographic measures in 110 prospectively recruited total joint arthroplasty patients who had a recent history of elevated metal concentrations. Elevated cobalt and titanium concentrations were positively associated with some structural and functional cardiac changes.

Citation: Brennan PC, Peterson SM, O'Byrne TJ, Laporta ML, Wyles CC, Jannetto PJ, Kane GC, Vassilaki M, Maradit Kremers H. Blood metal concentrations and cardiac structure and function in total joint arthroplasty patients. *World J Orthop* 2024; 15(8): 773-782
URL: https://www.wjgnet.com/2218-5836/full/v15/i8/773.htm
DOI: https://dx.doi.org/10.5312/wjo.v15.i8.773

INTRODUCTION

Total joint arthroplasty (TJA) is one of the most common surgical procedures in the United States and is expected to increase further in the coming years with a projected yearly incidence of nearly 5 million total hip arthroplasty (THA) and total knee arthroplasties (TKA) by the year 2040[1]. More than 7 million Americans are currently living with at least one TJA[2].

Although the TJA implant designs and materials can vary, most are made of metals including cobalt-chromium alloys, stainless steel, and titanium combined with ceramics and polymers[3]. Chronic exposure to these aforementioned metals can occur as metal containing implants are subjected to repeated mechanical and oxidative stresses that subsequently release metal ions locally and systemically[4]. Locally, metal ions released from both metal-on-metal (MoM) implants and metal-on-polyethylene are associated with adverse local tissue reactions[5,6]. In particular, cobalt was first identified as cardiotoxic in 1967 when Quebec beer drinkers developed acute cardiomyopathy after drinking beer that used cobalt as a foam-stabilizing agent[7]. Considering the history of cobalt-related cardiotoxicity, several studies over the last decade investigated the potential for cardiotoxicity associated with MoM implants with a focus on cobalt-chromium ion release [8-12]. In a postmortem study, cobalt concentration was significantly higher in the myocardial cells of patients who underwent a THA and this was postulated to arise from alterations in cardiac calcium handling[7]. In particular, three echocardiographic studies in THA patients showed higher metal concentrations in patients with MoM implants but no clinically significant associations between increased metal concentrations and cardiac dysfunction[13-15]. Even titanium, a biocompatible inert material, was attributed to osteolysis through the formation of titanium dioxide[16]. Due to the high prevalence of TJA and the potential of metal ions to be distributed systemically, concerns remain regarding the potential for long-term cardiotoxicity stemming from the systemic effects of metal ions[4,7].

With this background, the aim of the current study was to examine the association between three commonly used implant metals (cobalt, chromium, titanium) with echocardiographic measures and cardiac biomarkers in THA and TKA patients regardless of their implant type.

MATERIALS AND METHODS

The study population comprised 110 TJA patients prospectively recruited at a large tertiary care medical center between March 2019 and December 2022. Patients were invited to participate based on having elevated blood metal concentrations of either titanium, cobalt, and/or chromium, as flagged in the electronic medical records (concentrations higher than 1 ng/mL for cobalt and chromium, and higher than 2 ng/mL for titanium) over the previous one-year period and had not undergone a revision procedure since their elevated laboratory measurements.

All patients consented to the use of their medical data for research purposes. The Institutional Review Board approved the study and a listing was maintained on clinicaltrials.gov through the duration of the study. All patients had a previous

surgical history of at least one prior THA, TKA, or hip resurfacing procedure. The surgical history was ascertained through self-report and the institutional Total Joint Registry.

Patients who agreed to participate traveled to a single day of in-person appointments where they underwent a single blood draw to measure metal (cobalt, chromium, titanium) concentrations and troponin, and N-terminal pro b-type natriuretic peptide (NT-proBNP) as general indicators of heart health. The cardiac biomarkers were measured using an electrochemiluminescent immunoassay and the metals assayed using inductively coupled plasma mass spectrometry within an International Organization for Standardization Class-7 Laboratory[17,18]. In the present study, cobalt and chromium were analyzed in whole blood while titanium was analyzed in serum. Due to ordering and lab errors, one patient was missing the chromium level, one patient was missing the NT-proBNP level, and two patients were missing the troponin level.

All patients also underwent comprehensive transthoracic echocardiogram (GE E95, General Electric Healthcare) consisting of two-dimensional (2D), three-dimensional (3D), Doppler and speckle-tracking systolic strain echocardiography on the same day as the blood draw. All patients received an ultrasound enhancement agent (Lumason, Bracco Diagnostics) and underwent enhanced measurement of 2D biplane volumes and unenhanced 3D volumes as recommended. All echocardiograms were performed according to the American Society of Echocardiography guidelines[19] and reviewed by a board-certified cardiologist with echocardiography expertise blinded to the results of metal levels.

Patient characteristics, laboratory values and echocardiographic findings were summarized using descriptive statistics [mean ± SD, median, interquartile range (IQR), count, percentage]. Many patients had "undetectable" metal concentrations (< 1 ng/mL), which were converted to numeric by using the highest numeric under the undetectable (*e.g.* 0.99 ng/mL). Metal measurements were treated as binary (detectable *vs* undetectable) or continuously on a log transformed scale (levels < 1 ng/mL was converted to 0.99 ng/mL). The association of log transformed metal concentrations (exposure) with echocardiographic measures and cardiac biomarkers (outcomes) were examined using age and sex-adjusted linear and logistic regression models. For significant results, β coefficients and odds ratio (OR) estimates from regression models were back-transformed to facilitate interpretation in original scales. All estimates represent the change corresponding to a doubling of the recorded metal level (*e.g.* from 1 ng/mL to 2 ng/mL).

RESULTS

The mean age of the 110 TJA patients was 68.8 (SD: 9.2 years) years, 45 (40.9%) were women and 108 (98.2%) were white (Table 1). Only 4 patients were current smokers and 1 had a previous history of heart failure. A total of 79 (71.8%) patients had a history of THA only, 11 (10.0%) TKA only and 20 (18.2%) patients had both surgeries. Of the 99 patients with at least 1 THA, 52 had a history of MoM implants, 5 had ceramic-on-poly implants and 3 had both MoM and ceramic-on-poly implants (remaining had metal-on-poly implants). The average time since the first THA or TKA surgery was 13.4 (SD: 5.7 years) years. A total of 59 patients (53.6%) had at least one revision for their TJA. Detectable metal concentrations were found for chromium (n = 43, 39.5%), cobalt (n = 51, 46.4%) and titanium (n = 89, 80.9%) (Table 2). Median (IQR) metal concentrations among detectable were 1.9 (1.2 ng/mL, 3.8 ng/mL) ng/mL for chromium, 3.7 (1.9 ng/mL, 6.3 ng/mL) ng/mL for cobalt and 3.0 (2.0 ng/mL, 5.0 ng/mL) ng/mL for titanium.

Chromium concentrations were not significantly associated with any echocardiographic findings (Table 3). Higher cobalt concentrations were associated with left and right ventricular dilatation. Higher cobalt concentrations were associated with increased left ventricular (LV) volumes as indicated with larger 2D biplane LV end-diastolic (estimate 5.09; 95%CI: 0.02-10.17), equating to a 5%-10% increase in LV volume per doubling in cobalt concentrations, and end-systolic volumes (estimate 3.13; 95%CI: 0.40-5.87) (Figure 1). For instance, patients with cobalt concentrations ≥ 4 ng/mL had an average 22.8 unit (95%CI: 7.4-38.1 P = 0.004) higher LV volumes than those with cobalt concentrations £1 ng/mL after adjusting for age and sex. This association was seen in men but not in women (Figure 2). Men had higher 2D biplane LV end-diastolic (estimate 6.86; 95%CI: 0.06-13.66; P = 0.05) and end-systolic volumes (estimate 4.58; 95%CI: 0.95-8.21; P = 0.01). Higher cobalt concentration was also associated with right ventricle enlargement in men (OR 1.94; 95%CI: 1.12-3.35; P = 0.02) but not in women (OR 0.91; 95%CI: 0.11-7.41; P = 0.93). Left atria were also larger in those with higher cobalt concentrations (estimate 4.16; 95%CI: 0.79-7.53), similarly in men and women. There was no association between cobalt concentrations and LV systolic function.

Higher titanium concentrations were associated with measures of reduced LV systolic function as indicated by a reduction in LV global longitudinal systolic strain (estimate 0.38; 95%CI: -0.70 to -0.06) which is a sensitive measure of left ventricle contraction. For instance, patients with titanium concentrations ≥ 3 ng/mL had an average 1.3 (95%CI: 2.2-0.4, P = 0.005) reduction in LV global longitudinal strain than those with titanium concentrations £1 ng/mL after adjusting for age and sex. LV stroke volume, cardiac output, and cardiac index were similarly lower in patients with high titanium concentrations (Table 3). For instance, the normal range for cardiac index is 2.5-4.2 L/min/m^2. A 0.08 unit decrease in cardiac index equates from 1.9% to 3.2% decrease from normal cardiac function when titanium concentration was doubled (*e.g.* from 1 ng/mL to 2 ng/mL). On the contrary, higher titanium concentrations were associated with better left ventricle diastolic function (OR 0.67; 95%CI: 0.47-0.97) and higher left atrial reservoir strain (OR 1.60; 95%CI: 0.55-2.66). No significant associations were observed between metal concentrations and NT-proBNP and troponin levels.

Table 1 Characteristics of the study population, *n* (%)

Characteristic	Total
Age (years)	
Mean (SD)	68.8 (9.2)
Median (IQR)	69.0 (63.0, 75.0)
Min, Max	44.0, 93.0
Women	45 (40.9)
Race	
Pacific Islander	2 (1.8)
White	108 (98.2)
Smoking history	
Current smoker	4 (3.6)
Previous smoker	36 (32.7)
Never smoker	58 (52.7)
History of heart failure	1 (0.9)
Body mass index (kg/m^2)	
Mean (SD)	30.3 (6.0)
Median (IQR)	30.0 (62.2, 34.3)
Min, Max	18.8, 47.0
Body surface area (m^2)	
Mean (SD)	2.1 (0.3)
Median (IQR)	2.1 (1.9, 2.2)
Min, Max	1.4, 2.7
Systolic blood pressure, mmHg	
Mean (SD)	134.0 (18.9)
Median (IQR)	132.0 (122.0, 144.0)
Min, Max	90.0, 187.0
Diastolic blood pressure, mmHg	
Mean (SD)	77.6 (8.8)
Median (IQR)	78.0 (72.0, 83.0)
Min, Max	60.0, 108.0
TJA history	
Joint	
Hip (total hip arthroplasty)	79 (71.8)
Knee (total knee arthroplasty)	11 (10.0)
Both	20 (18.2)
Revision surgery	59 (53.6)
Years between first TJA surgery and study visit	
Mean (SD)	13.4 (5.7)
Median (IQR)	12 (10.0, 16.0)
Min, Max	2.0, 31.0

IQR: Interquartile range; TJA: Total joint arthroplasty.

Table 2 Metal concentrations by sex, *n* (%)

Metal concentrations (ng/mL)	Total	Men	Women
Detectable chromium,	43 (39.5)	28 (43.8)	15 (33.3)
Mean (SD)	3.8 (4.7)	3.0 (3.5)	5.2 (6.3)
Median (IQR)	1.9 (1.2, 3.8)	1.9 (1.3, 2.9)	2.8 (1.2, 5.8)
Min, max	1.1, 21.4	1.1,18.5	1.2,21.4
Detectable cobalt	51 (46.4)	36 (55.4)	15 (33.3)
Mean (SD)	4.9 (4.3)	5.2 (4.7)	4.1 (3.2)
Median (IQR)	3.7 (1.9, 6.3)	4.1 (2.1, 6.9)	3.2 (1.9, 5.2)
Min, max	1.1, 24.6	1.1, 24.6	1.1, 12
Detectable titanium	89 (80.9)	49 (75.4)	40 (88.9)
Mean (SD)	4.8 (5.1)	4.6 (6.1)	5.1 (3.5)
Median (IQR)	3.0 (2.0, 5.0)	3 (1,5)	4 (3,7)
Min, Max	1.0, 35.0	1,35	1,15

IQR: Interquartile range.

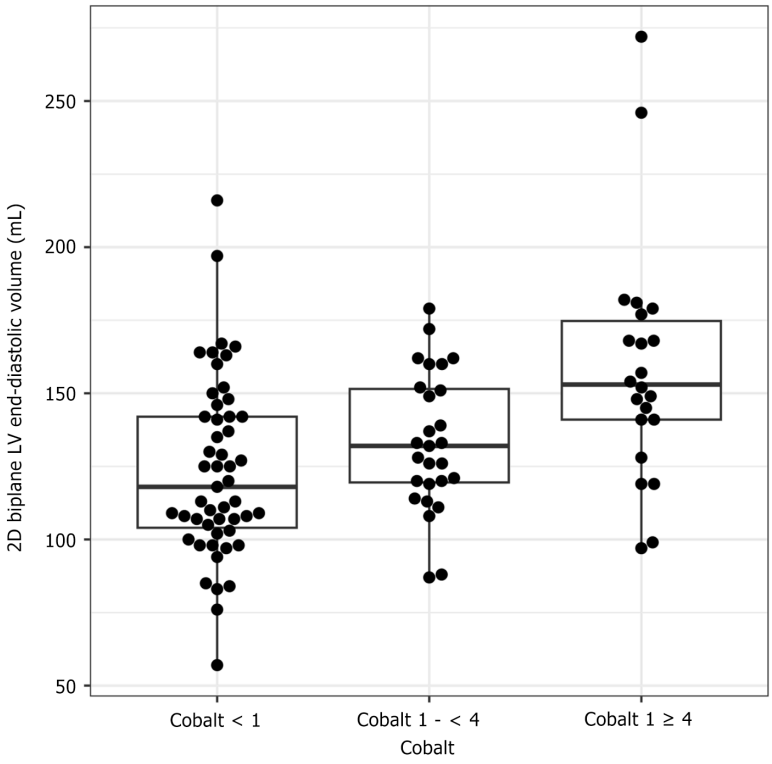

Figure 1 Distribution of two-dimensional biplane left ventricle end-diastolic volume by cobalt concentrations. 2D: Two-dimensional; LV: Left ventricle.

DISCUSSION

There is concern regarding the systemic effects of increased metal concentrations in TJA patients. However, evidence has been limited to anecdotal case reports or large registry-based studies with limited data on clinical findings or echocardiographic abnormalities. In this study, we investigated the association of systemic chromium, cobalt, and titanium concentrations with echocardiographic measures of cardiac structure and function and cardiac labs troponin and NT-proBNP. Overall, we found that cobalt was associated with both left and right ventricular dilation in men and titanium was associated with significant changes in LV systolic function (*i.e.*, cardiac index in Table 3). No significant associations were observed for chromium.

Table 3 Association of metal concentrations with echocardiographic parameters

	Measure available	Mean (SD); Median (interquartile range)	Regression estimates (95%CI)[1]		
Measure (unit)			**Chromium**	**Cobalt**	**Titanium**
LV size and systolic function					
2D Biplane LV end-diastolic volume (mL)	100	134.04 (34.14); 129.5 (109, 153)	1.20 (-5.23 to 7.64)	5.09 (0.02-10.17)[a]	-3.67 (-8.55 to 1.22)
3D LV end-diastolic volume (mL)	95	130.38 (32.14); 126 (110, 147)	0.95 (-4.59 to 6.50)	4.09 (-0.57 to 8.74)[a]	-1.69 (-6.35 to 2.96)
2D Biplane LV end-systolic volume (mL)	99	50.76 (18.22); 48 (38, 60)	0.44 (-3.05 to 3.92)	3.13 (0.40-5.87)	-1.53 (-4.20 to 1.14)
3D LV end-systolic volume (mL)	94	49.24 (14.2); 48 (38, 57)	0.44 (-1.86 to 2.75)	1.46 (-0.50 to 3.42)	-1.16 (-3.09 to 0.76)
3D LV ejection fraction	94	62.12 (4.34); 62 (60, 65)	-0.10 (-0.88 to 0.68)	-0.51 (-1.17 to 0.15)	0.07 (-0.59 to 0.73)
LV global longitudinal strain	108	-19.74 (2.12); -20 (-21, -19)	-0.15 (-0.55 to 0.26)	-0.27 (-0.60 to 0.07)	-0.38 (-0.70 to 0.06)[b]
LV stroke volume (mL)	108	94.5 (17.22)/91 (82.5, 105)	-0.28 (-3.43 to 2.87)	1.59 (-0.99 to 4.16)	-2.69 (-5.24 to 0.15)[b]
LV cardiac output (l/minute)	109	6.12 (1.3); 5.84 (5.22, 6.8)	-0.01 (-0.35 to 0.16)	0.01 (-0.20 to 0.22)	-0.20 (-0.40 to 0.004)[a]
LV cardiac index (l/minute/m^2)	108	2.92 (0.4)/2.82 (2.68,3.16)	0.01 (-0.08 to 0.09)	0.01 (-0.06 to 0.07)	-0.08 (-0.15 to -0.01)[b]
LV diastolic function					
LV diastolic function (normal/abnormal)	110	Normal 42 (38.2)	Reference	Reference	Reference
		Abnormal 68 (61.8)	1.21 (0.78-1.87)	1.14 (0.80-1.62)	0.67 (0.47-0.97)[b]
Medial E/e' ratio	106	10.76 (3.7)/10 (8.3,12.5)	-0.38 (-1.02 to 0.27)	-0.05 (-0.60 to 0.49)	0.18 (-0.34 to 0.70)
LA biplane vol index (mL/m^2)	107	31.32 (9.02); 30 (25, 37)	1.26 (-1.36 to 3.86)	2.72 (0.60-4.84)[b]	-0.24 (-2.3 to 1.82)
LA reservoir strain	105	29.9 (6.9); 29.5 (26.2, 33.9)	0.002 (-1.38 to 1.39)	0.083 (-1.06 to 1.22)	1.602 (0.55-2.66)[c]
Right heart parameters					
RV systolic pressure (mmHg)	80	28.34 (5.34); 28 (23.5, 32)	-0.41 (-1.54 to 0.73)	-0.22 (-1.19 to 0.75)	-0.28 (-1.15 to 0.58)
RV size (normal/enlarged)	110	Normal 99 (90)	Reference	Reference	Reference
		Abnormal 11 (10)	1.66 (0.91-3.05)	1.80 (1.08-2.99)[b]	1.22 (0.74-2.01)
RV basal diameter (mm)	53	40.48 (6.3); 41 (36, 46)	0.37 (-1.18 to 1.92)	1.17 (-0.18 to 2.51)[a]	-0.17 (-1.42 to 1.08)
Tricuspid annular plane systolic excursion (mm)	91	23.58 (3.7); 23 (21, 26)	-0.34 (-1.21 to 0.53)	0.11 (-0.61 to 0.83)	0.17 (-0.50 to 0.84)
RV Basal Lateral Systolic Strain	34	-25.06 (4.88); -26 (-29, -24)	1.19 (-0.64 to 3.01)	0.40 (-1.50 to 2.29)	-0.59 (-2.12 to 0.94)
Other parameters					
Mid ascending thoracic aortic diameter (mm)	82	35.9 (4.08); 36 (33, 38)	0.16 (-0.65 to 0.98)	0.43 (-0.27 to 1.13)	-0.71 (-1.38 to -0.05)[b]
N terminal pro b-type natriuretic peptide (pg/mL)	109	153.4 (269.3); 85 (42, 138)	-20.47 (-72.32 to 31.38)	10.01 (-32.78 to 52.80)	13.41 (-27.74 to 54.55)
Troponin (ng/mL)	108	13.4 (11.3); 11 (7, 15)	-0.97 (-2.94 to 0.99)	-0.85 (-2.47 to 0.77)	0.22 (-1.34 to 1.78)

[1]Estimates from age and sex-adjusted linear regression models indicate the β coefficients as the mean change in echocardiographic measures or cardiac markers per log-unit increase in metal concentrations. Odds ratio estimates from age and sex-adjusted logistic regression models indicate the odds of

abnormal findings per log-unit increase in metal concentrations.
[a]$0.05 \leq P < 0.1$;
[b]$0.01 \leq P < 0.05$;
[c]$P < 0.01$. LA: left atrium; LV: Left ventricular; RV: right ventricle.

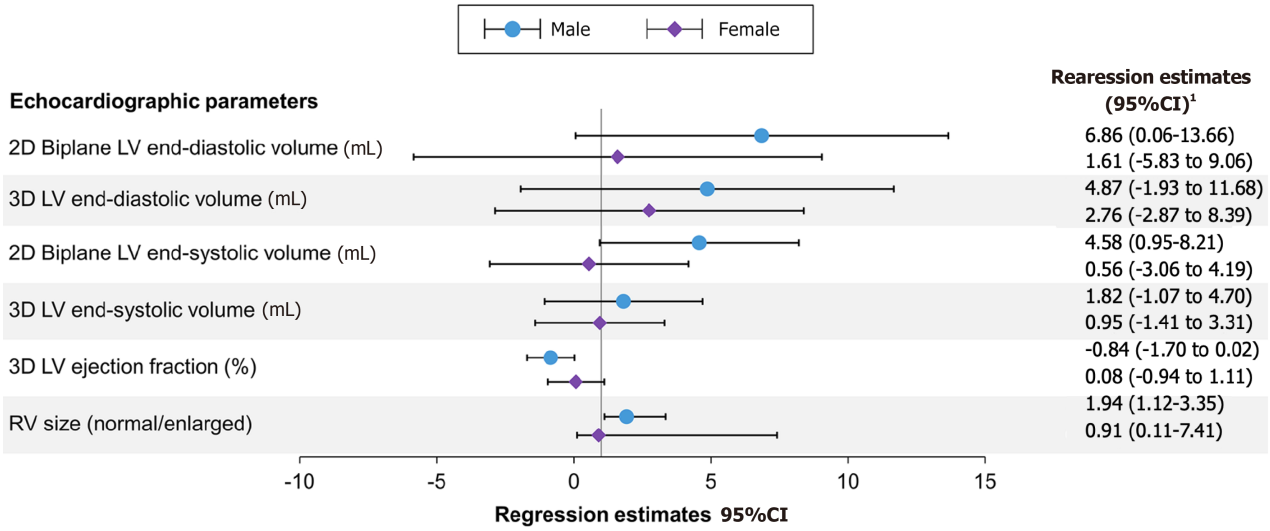

Figure 2 Forest plot of linear and logistic regression estimates 95%CI for the association between cobalt concentrations and echocardiographic parameters by sex. [1]Regression coefficients 95%CI retained from linear regression analyses, except the estimates for the right ventricle size (normal/enlarged) that is the odds ratio 95%CI retained from logistic regression analyses. LV: Left ventricle; RV: Right ventricle; 2D: Two-dimensional; 3D: Three-dimensional.

Besides case reports and registry-based studies, three previous studies are similar to ours and examined the correlation between metal concentrations and echocardiographic findings. Prentice *et al*[15] compared 35 MoM hip resurfacing patients with 35 matched asymptomatic THA patients with conventional implants. Patients with MoM implants had higher systemic cobalt and chromium concentrations (1.75 μg/L *vs* 0.38 μg/L and 1.27 μg/L *vs* < 0.30 μg/L for chromium), but relatively minor differences in cardiac ejection fraction and LV end-diastolic diameter.

In another study, 90 THA patients were split into three groups based on bearing type and blood metal concentrations, and cardiac function was evaluated using both cardiac magnetic resonance imaging and echocardiography[13]. There was no evidence for an association between metal concentrations and cardiac structure or function. Despite the large sample size similar to ours and 3 groups of THA patients with a wide spectrum of chromium and cobalt concentrations, linear associations between metal concentrations and LV structural measures were not reported. Splitting patients into 3 separate groups may have resulted in loss of power. Finally, 75 THA patients with the same modular implants (49 MoM bearings) were evaluated at two visits for cobalt, chromium, and titanium concentrations and an echocardiogram at the second visit[14]. Cobalt and chromium concentrations were higher in MoM patients, but titanium concentrations and cobalt-chromium ratios were not different between groups. Cobalt and chromium concentrations increased between time-points in the MoM patients with significantly lower global longitudinal strain than compared with the non-MoM group. Cobalt concentrations were associated with tricuspid annular plane systolic excursion, an indicator of right ventricular function. We similarly observed several associations between cobalt and titanium concentrations and cardiac function measures. Consistent with the previous study, we found an association between cobalt and right ventricular size as well as an association with LV volume, not described in earlier studies.

Cobalt and chromium concentrations were undetectable in about half of our patients and were not associated with echocardiographic differences in women. Yet, a relationship between LV dilation was found with cobalt concentrations in men. Furthermore, a doubling of cobalt levels in men was associated with a 1.9-fold increase in the prevalence if right ventricular enlargement. Prior studies have suggested a link between cobalt deposition and cardiac toxicity potentially related to intracellular calcium mishandling[7]. Here a tendency for abnormal ventricular dilation is a well-recognized finding that precedes the development of heart failure[20].

Titanium was the most commonly elevated metal in our study and was associated with several measures of decreased LV systolic function but not diastolic function. Better measurement of small concentrations in cobalt and chromium may allow detection of associations between these metals and heart function measures. Compared with cobalt and chromium, relatively little is known about the potential systemic effects of titanium. Evidence to date comes only from laboratory studies. For example, in an experimental laboratory study in hypertensive rats, intra-tracheal administration of titanium resulted in irreversible hemodynamic impairment and cardiac structural damage[21].

Our findings should be interpreted considering potential limitations. Due to the small sample size, we were unable to perform subgroup analyses by number of surgeries, surgery/implant types, potential reasons for high metal ions (*e.g.* trunnionosis) or among subgroups of patients such as those with smoking history, other lifestyle factors or selected

comorbidities like heart failure. Adverse cardiac effects of high metal concentrations may vary in different ethnic and racial groups. With mostly Caucasian white patients, the generalizability our findings is limited. Our power calculations prior to the study indicated that with a sample size of 100 patients, the linear regression test of correlation = 0 (P = 0.05 two-sided) between the cardiac outcomes and metal concentrations would have 80% power to detect a correlation of 0.27 (with a corresponding r-square of 0.073). The main exposure variable in this study was the metal concentrations which were examined as a log-transformed continues exposure variable. Dichotomizing or categorization of continuous exposure variables for analysis is inefficient and misleading[22,23]. Importantly, we examined cross-sectional associations and observed some significant correlations with cobalt and titanium concentrations, but the magnitude was small. Therefore, these significant findings should be interpreted with caution and bearing in mind the evidence from other lines of research. Ideally, information on longitudinal changes in systemic metal concentrations and cardiac measures would be needed to further interpret causal implications of these cross-sectional findings. Furthermore, in addition to TJA implants, other environmental exposures, such as dental implants and food additives, nutritional status or alcohol intake can contribute to higher systemic levels[24,25]. Strengths include the use of 3D and speckle-tracking echocardiography, which provide much more sensitive markers of cardiac dysfunction than the traditional 2D echocardiography.

CONCLUSION

In conclusion, elevated cobalt and titanium concentrations may be associated with structural and functional cardiac changes in some patients. Given the high prevalence of TJA and limited evidence on the potential long-term cardiotoxicity of metal implants, more research is warranted to better understand how the systemic distribution of metal ions may affect cardiac function and the temporal relationship and quantitative thresholds for metal concentrations and cardiac pathology.

FOOTNOTES

Author contributions: Maradit Kremers H has full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis, study supervision, obtained funding; Brennan PC, Vassilaki M, and Maradit Kremers H took responsibility for study concept and design, and drafting of the manuscript; O'Byrne TJ and Peterson SM took responsibility for statistical analysis; Brennan PC and Maradit Kremers H took responsibility for administrative, technical, or material support; all authors took responsibility for acquisition, analysis, interpretation of data, critical revision of the manuscript for important intellectual content, and have read and approved the final manuscript.

Supported by The National Institutes of Health, No. R01HL147155 and No. R01AG060920.

Institutional review board statement: All patients consented to the use of their medical data for research purposes. The Institutional Review Board approved the study and a listing was maintained on clinicaltrials.gov through the duration of the study. All patients had a previous surgical history of at least one prior THA, TKA, or hip resurfacing procedure. The surgical history was ascertained through self-report and the institutional Total Joint Registry.

Clinical trial registration statement: The clinical trial is registered with ClinicalTrials.gov, using identifier NCT04166539.

Informed consent statement: All study participants provided written consent prior to study enrollment.

Conflict-of-interest statement: Dr. Jannetto reported receiving consultant fees from Roche Diagnostics and Thermo Fisher Scientific and serving on the AACC Board of Directors. Dr. Kane reported royalties for an echocardiography textbook. The Echo Manual. Wolters Kluwer. Dr. Maradit Kremers reported receiving grants from the National Institutes of Health during the conduct of the study. Dr. Vassilaki reported receiving grants from the National Institutes of Health during the conduct of the study, receiving grants from F. Hoffmann-La Roche Ltd, St. Anne's University Hospital Brno/International Clinical Research Center (Czech Republic/EU), and Biogen and consultant fees from F. Hoffmann-La Roche Ltd outside the submitted work, and being a stockholder in Abbott Laboratories, Johnson and Johnson, Medtronic, Amgen, AbbVie and Merck. She serves on the editorial board for Journal of Alzheimer's Disease. The other authors report no potential competing interests.

Data sharing statement: I take full responsibility for the data, the analyses and interpretation, and the conduct of the research; I have full access to all of the data; I have the right to publish any and all data separate and apart from any sponsor.

CONSORT 2010 statement: This manuscript was checked and revised according to the CONSORT 2010.

Country of origin: United States

ORCID number: Hilal Maradit Kremers 0000-0003-3882-602X.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Singh JA**, Yu S, Chen L, Cleveland JD. Rates of Total Joint Replacement in the United States: Future Projections to 2020-2040 Using the National Inpatient Sample. *J Rheumatol* 2019; **46**: 1134-1140 [PMID: 30988126 DOI: 10.3899/jrheum.170990]
2 **Maradit Kremers H**, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA, Jiranek WA, Berry DJ. Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am* 2015; **97**: 1386-1397 [PMID: 26333733 DOI: 10.2106/JBJS.N.01141]
3 **Merola M**, Affatato S. Materials for Hip Prostheses: A Review of Wear and Loading Considerations. *Materials (Basel)* 2019; **12**: 495 [PMID: 30764574 DOI: 10.3390/ma12030495]
4 **Cheung AC**, Banerjee S, Cherian JJ, Wong F, Butany J, Gilbert C, Overgaard C, Syed K, Zywiel MG, Jacobs JJ, Mont MA. Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition Part 1 - history, mechanism, measurements, and pathophysiology. *Bone Joint J* 2016; **98** -B: 6-13 [PMID: 26733509 DOI: 10.1302/0301-620X.98B1.36374]
5 **Sutphen SA**, MacLaughlin LH, Madsen AA, Russell JH, McShane MA. Prevalence of Pseudotumor in Patients After Metal-On-Metal Hip Arthroplasty Evaluated with Metal Ion Analysis and MARS-MRI. *J Arthroplasty* 2016; **31**: 260-263 [PMID: 26253484 DOI: 10.1016/j.arth.2015.07.011]
6 **Daniel J**, Holland J, Quigley L, Sprague S, Bhandari M. Pseudotumors associated with total hip arthroplasty. *J Bone Joint Surg Am* 2012; **94**: 86-93 [PMID: 22218386 DOI: 10.2106/JBJS.J.01612]
7 **Wyles CC**, Wright TC, Bois MC, Amin MS, Fayyaz A, Jenkins SM, Wyles SP, Day PL, Murray DL, Trousdale RT, Anavekar NS, Edwards WD, Maleszewski JJ. Myocardial Cobalt Levels Are Elevated in the Setting of Total Hip Arthroplasty. *J Bone Joint Surg Am* 2017; **99**: e118 [PMID: 29135673 DOI: 10.2106/JBJS.17.00159]
8 **Lassalle M**, Colas S, Rudnichi A, Zureik M, Dray-Spira R. Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases. *Clin Orthop Relat Res* 2018; **476**: 1441-1451 [PMID: 29698302 DOI: 10.1097/01.blo.0000533617.64678.69]
9 **Sabah SA**, Moon JC, Jenkins-Jones S, Morgan CL, Currie CJ, Wilkinson JM, Porter M, Captur G, Henckel J, Chaturvedi N, Kay P, Skinner JA, Hart AJ, Manisty C. The risk of cardiac failure following metal-on-metal hip arthroplasty. *Bone Joint J* 2018; **100** -B: 20-27 [PMID: 29305446 DOI: 10.1302/0301-620X.100B1.BJJ-2017-1065.R1]
10 **Gillam MH**, Pratt NL, Inacio MC, Roughead EE, Shakib S, Nicholls SJ, Graves SE. Heart failure after conventional metal-on-metal hip replacements. *Acta Orthop* 2017; **88**: 2-9 [PMID: 27759468 DOI: 10.1080/17453674.2016.1246276]
11 **Goodnough LH**, Bala A, Huddleston J III, Goodman SB, Maloney WJ, Amanatullah DF. Metal-on-metal total hip arthroplasty is not associated with cardiac disease. *Bone Joint J* 2018; **100-B**: 28-32 [PMID: 29305447 DOI: 10.1302/0301-620X.100B1.BJJ-2017-0366.R1]
12 **Deere K**, Matharu GS, Ben-Shlomo Y, Wilkinson JM, Blom AW, Sayers A, Whitehouse MR. The risk of all-cause mortality, heart outcomes, cancer, and neurodegenerative disorders with cobalt-chrome-containing total hip arthroplasty implants : an analysis of the National Joint Registry. *Bone Joint J* 2022; **104** -B: 359-367 [PMID: 35227088 DOI: 10.1302/0301-620X.104B3.BJJ-2021-0397.R1]
13 **Berber R**, Abdel-Gadir A, Rosmini S, Captur G, Nordin S, Culotta V, Palla L, Kellman P, Lloyd GW, Skinner JA, Moon JC, Manisty C, Hart AJ. Assessing for Cardiotoxicity from Metal-on-Metal Hip Implants with Advanced Multimodality Imaging Techniques. *J Bone Joint Surg Am* 2017; **99**: 1827-1835 [PMID: 29088037 DOI: 10.2106/JBJS.16.00743]
14 **Darrith B**, Rahman TM, Ananthasubramaniam K, Culvern C, Jacobs JJ, Silverton CD. Echocardiographic Changes in the Context of Metal-on-Metal Versus Nonmetal-on-Metal Total Hip Arthroplasty. *J Arthroplasty* 2020; **35**: 3230-3236 [PMID: 32665157 DOI: 10.1016/j.arth.2020.06.020]
15 **Prentice JR**, Clark MJ, Hoggard N, Morton AC, Tooth C, Paley MN, Stockley I, Hadjivassiliou M, Wilkinson JM. Metal-on-metal hip prostheses and systemic health: a cross-sectional association study 8 years after implantation. *PLoS One* 2013; **8**: e66186 [PMID: 23762480 DOI: 10.1371/journal.pone.0066186]
16 **Yao JJ**, Lewallen EA, Trousdale WH, Xu W, Thaler R, Salib CG, Reina N, Abdel MP, Lewallen DG, van Wijnen AJ. Local Cellular Responses to Titanium Dioxide from Orthopedic Implants. *Biores Open Access* 2017; **6**: 94-103 [PMID: 29034133 DOI: 10.1089/biores.2017.0017]
17 **Day PL**, Eckdahl SJ, Maleszewski JJ, Wright TC, Murray DL. Establishing human heart chromium, cobalt and vanadium concentrations by inductively coupled plasma mass spectrometry. *J Trace Elem Med Biol* 2017; **41**: 60-65 [PMID: 28347464 DOI: 10.1016/j.jtemb.2017.02.009]
18 **Yao JJ**, Lewallen EA, Thaler R, Dudakovic A, Wermers M, Day P, Eckdahl S, Jannetto P, Bornhorst JA, Larson AN, Abdel MP, Lewallen DG, van Wijnen AJ. Challenges in the Measurement and Interpretation of Serum Titanium Concentrations. *Biol Trace Elem Res* 2020; **196**: 20-26 [PMID: 31696354 DOI: 10.1007/s12011-019-01891-4]
19 **Lang RM**, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1-39 [PMID: 25559473 DOI: 10.1016/j.echo.2014.10.003]
20 **Goldberg LR**, Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. *Circulation* 2006; **113**: 2851-2860 [PMID: 16785351 DOI: 10.1161/CIRCULATIONAHA.105.600437]
21 **Rossi S**, Savi M, Mazzola M, Pinelli S, Alinovi R, Gennaccaro L, Pagliaro A, Meraviglia V, Galetti M, Lozano-Garcia O, Rossini A, Frati C, Falco A, Quaini F, Bocchi L, Stilli D, Lucas S, Goldoni M, Macchi E, Mutti A, Miragoli M. Subchronic exposure to titanium dioxide nanoparticles modifies cardiac structure and performance in spontaneously hypertensive rats. *Part Fibre Toxicol* 2019; **16**: 25 [PMID: 31234877 DOI: 10.1186/s12989-019-0311-7]
22 **Senn S**. Dichotomania: an obsessive compulsive disorder that is badly affecting the quality of analysis of pharmaceutical trials. 2005; 13.

Available from: https://www.semanticscholar.org/paper/Dichotomania%3A-An-Obsessive-Compulsive-Disorder-that-Senn/8c390cb90465ad1f08b86cee52474859e4dffd77

23 **van Smeden M**. A Very Short List of Common Pitfalls in Research Design, Data Analysis, and Reporting. *PRiMER* 2022; **6**: 26 [PMID: 36119906 DOI: 10.22454/PRiMER.2022.511416]

24 **Kim KT**, Eo MY, Nguyen TTH, Kim SM. General review of titanium toxicity. *Int J Implant Dent* 2019; **5**: 10 [PMID: 30854575 DOI: 10.1186/s40729-019-0162-x]

25 **Zhou Z**, Shi Q, Wang J, Chen X, Hao Y, Zhang Y, Wang X. The unfavorable role of titanium particles released from dental implants. *Nanotheranostics* 2021; **5**: 321-332 [PMID: 33732603 DOI: 10.7150/ntno.56401]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com