

Prevalence of subclinical cardiac abnormalities in patients with metal-on-metal hip replacements

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Abstract

Background: Metal-on-metal (MOM) hip prostheses have a higher failure rate than conventional prostheses, and leaching of cobalt and chromium has been linked to cardiomyopathy. We screened MOM subjects to determine if cobalt and chromium cause subclinical cardiac dysfunction.

Methods: A single centre, non-randomised, observational study using echocardiography in 95 patients who had undergone MOM hip prostheses, and 15 age matched controls with non-MOM hip replacement. Serial plasma cobalt and chromium levels were recorded, and data compared by tertiles of cobalt exposure. **Results:** Indexed left ventricular (LV) end-diastolic and end-systolic volumes (EDVi and ESVi) increased with tertile of cobalt (omnibus $p=0.003$ for EDVi and ESVi), as did indexed left atrial (LA) volumes ($p=0.003$). MOM subjects had 25% larger EDVi than controls, 32% larger ESVi (40ml vs. 32ml, and 15ml vs. 11ml, $p=0.003$ for both) and 28% larger indexed LA (23ml vs. 18ml, $p=0.002$). There were no differences in LV systolic or diastolic function, including ejection fraction, tissue velocity and mitral E/e' . Estimated glomerular filtration rate was 18% lower in the highest tertile compared with the lowest ($p=0.01$) and correlated inversely with LA volume ($r=-0.36$, $p<0.001$) and LV EDV ($r=-0.24$, $p=0.02$).

Conclusions: Increasing left ventricular and atrial volumes and declining renal function correlated with prolonged exposure to high cobalt, but cardiac function did not. The association with renal function and chamber size requires further evaluation. Case reports of cardiomyopathy in patients with MOM hips imply that an idiosyncratic process cannot be excluded.

Abstract: 240 words

INTRODUCTION

Large head metal-on-metal (MOM) hip replacements were implanted in more than 1 million patients between 2003 and 2010. They were expected to be more durable than conventional metal on polyethylene components, and to have a lower risk of dislocation. In practice, the failure rates have been significantly higher. The bearing surfaces of these prostheses are made from a cobalt-chrome alloy, which may be released when the two surfaces slide over one another on hip movement. Over time this leads to elevated plasma levels of cobalt and chromium. Some patients may develop a localised inflammatory reaction around the joint, which can lead to pain and reduced mobility. Others remain asymptomatic despite elevated heavy metal levels in the blood. Revision surgery becomes necessary to remove the implant due to local complications, including fluid formation, pseudotumours and bone or soft tissue necrosis.

In recent years, reports have emerged of systemic complications associated with high cobalt and chromium levels in MOM hip patients, including neurological, psychological, renal, endocrine and cardiac disturbances.[1] The Medicines and Healthcare products Regulatory Agency (MHRA) have recently reissued a medical device alert regarding MOM hip prostheses, following an initial alert in 2010.[2] This recommends annual review with symptom questionnaire and blood metal levels, with imaging depending on the findings of these two screening measures. Cobalt and chromium levels of 7 ug/L or above suggest soft tissue reaction and the MHRA recommend that patients with these levels undergo further imaging and investigation. The 2017 update places greater emphasis on the role of MRI and ultrasound in decision making. Cardiac and systemic screening are not addressed in this guidance.

Toxicity leading to cardiomyopathy has previously been confined to case reports.[3-8] Typically, these patients have previously undergone either failed MOM hip replacement or revision

of hip arthroplasty; in patients with asymptomatic MOM hip replacements, reports of cardiac complications are scarcer. A review by Bradberry et al found 18 patients identified between 1950 and 2014 with complications from high cobalt levels derived from hip replacements.[1] Of these, 11 had cardiac features, namely left ventricular dysfunction (64%), pericardial effusion (45%) and left ventricular dilatation (27%), although a non-dilated cardiomyopathy was seen in several patients.

One patient at our centre presented to the emergency unit with fulminant cardiac failure having undergone MOM hip replacement in 2007. Despite intensive treatment, she died of multi-organ failure because of severely depressed cardiac function. There is currently no consensus for cardiac screening in patients at risk of this complication. We therefore performed a cross-sectional study of orthopaedic patients who had received MOM hip prostheses to: a) ascertain the prevalence of overt cardiomyopathy and b) evaluate any relationship between subclinical markers of cardiac dysfunction and levels of plasma cobalt and chromium.

METHODS

Setting and study population

This was a single centre, non-randomised, observational study at a tertiary referral centre for orthopaedics and for cardiology in south-east Wales. 1698 patients underwent implantation of one or more MOM prosthesis within the health board. We recruited a sample of 95 patients from an orthopaedic MOM follow-up clinic between 1st July 2014 and 31st December 2015. All subjects with plasma cobalt of 7 ug/L or greater were referred for evaluation. Consecutive subjects with plasma levels between 0 and 7 ug/L were screened during clinic appointments and approached if they met the recruitment criteria. These patients were recruited on a voluntary basis. Exclusion criteria included symptomatic joint dysfunction, previous history of heart failure or prior myocardial

infarction. The study cohort included patients with current MOM prostheses as well as those who had undergone prosthesis removal. We also recruited 15 age-and comorbidity-matched control subjects from general orthopaedic clinics who had undergone hip replacement with non-MOM prostheses according to the same exclusion criteria. A further analysis was performed excluding those subjects who had undergone prosthesis explantation to examine whether the effects of high cobalt persisted after removal of the heavy metal source.

Power calculations were based on longitudinal deformation velocity (first systolic peak) with a mean of the basal septal and basal lateral walls of 7.07 ± 1.65 used as values for normal, healthy subjects. [9] A sample size of 95 MOM patients was decided upon as it would have 80% power to detect a 20% reduction in longitudinal velocity compared with controls, with a sampling ratio of 15 control subjects to 95 patients (non-inferiority margin of 0.25).

For subjects with cobalt and/or chromium >7.0 ug/L at clinic follow-up, the research ethics committee (Wales REC 1) concluded that cardiological evaluation was justified on clinical grounds. A priori approval from the Research Ethics Committee was granted for the inclusion of subjects with cobalt and chromium levels <7.0 ug/L, and for the non-MOM controls in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (14/WA/1236); both of these groups gave written informed consent to participate in this project.

Data were gathered prospectively from clinic appointments, including baseline demographics, height, weight and medication history. Information regarding operative history and serial plasma cobalt and chromium measurements was obtained from the hospital record system. Blood was taken for point plasma cobalt and chromium levels, estimated glomerular filtration rate (eGFR, MDRD) and serum N-terminal pro-B-type Natriuretic Peptide (NTproBNP) levels when patients attended for echocardiography.

Cobalt and chromium analysis

The cobalt and chromium assay used was developed at our laboratory. Five millilitres of venous blood were obtained and processed according to the Trace Elements External Quality Assessment Scheme (TEQAS) as per MHRA guidance. Plasma cobalt and chromium levels were obtained during the cardiology clinic appointment at which echocardiography was also performed. In addition, as most patient had serial measurements, both cobalt and chromium were expressed as total dose exposure by calculating the area under the curve of a graph of time against plasma ion levels. Ion levels at the time of prosthesis implantation were approximated as zero.

Echocardiography

Echocardiography was performed by two experienced, British Society of Echocardiography accredited sonographers and reported by a trained clinician (RK) and research sonographer (RL) who were blinded to each subject's plasma metal levels and medical history. Data were gathered on a Vivid-7 (GE Healthcare) echocardiography machine. Analysis was performed using EchoPAC (Version 13, GE Healthcare). A sample of 10 scans was examined by a second, blinded sonographer with coefficient of variability of 4.5%.

Two-dimensional, M-mode, pulse wave and continuous wave Doppler and tissue Doppler measurements were taken in accordance with British Society of Echocardiography guidelines. The average value for consecutive three beats was used for calculating echocardiographic parameters. Five beats were used where the subject was in atrial fibrillation or had frequent ectopy. Ectopic and post-ectopic beats were excluded from analysis. Left ventricular and left atrial volumes were measured using Simpson's biplane method of discs with end-diastolic and end-systolic frames used in the apical four-chamber and apical two-chamber views. Ejection fraction was calculated from left ventricular volume measurements. Strain was measured using speckle tracking of the left ventricle

by measuring the peak early systolic strain. Global longitudinal strain was calculated as the average of six myocardial segments.

Data analysis

Statistical analysis was performed using SPSS (version 23, IBM). Normally distributed data were expressed using mean \pm standard deviation (SD), non-normally distributed data as median \pm interquartile range and qualitative data as number and percentage. Analysis was performed using the one-way ANOVA for parametric non-ordinal data and the Jonckheere-Terpstra test for all ordinal data; this is a non-parametric test used to determine whether there is a statistically significant trend between an ordinal independent variable and a continuous or ordinal dependent variable. Correlations were assessed using Pearson's correlation coefficient. Qualitative data were compared using Chi-squared homogeneity test, or Fischer's Exact Test (using the Freeman-Halton extension) where observed counts were less than 5. Where data were missing, analysis was conducted for those entries that were present; where data were absent for more than 20% of subjects, data was marked as being incomplete. .

RESULTS

Data were obtained on 95 MOM hip patients (median age: 74.4yrs, 53% male) and 15 controls (median age: 74.6yrs, 40% male) with non-MOM hip prostheses All patients meeting the inclusion and exclusion criteria who had high ion levels agreed to participate, but of the low plasma ion group, 17 declined follow-up. 4 non-MOM subjects were unsuitable due to pre-existing heart problems. MOM prosthesis types included Anthology (Smith and Nephew) – 52, ASR (De Puy) – 26, Corail/Pinnacle (De Puy) – 9, Cormet (Corin) – 14, Profemur (Wright) – 8 and Trilogy (Zimmer) – 2. In three subjects, the prosthesis model was not available from clinical notes. 114 MOM prostheses

were used across 95 patients. 19 had received bilateral MOM hips. 18 patients had undergone subsequent prosthesis removal, with a median time of 42 days since removal (mean 611 days). MOM patients were divided into tertiles according to plasma cobalt levels taken at the echocardiography clinic to examine more closely a dose-response relationship between heavy metal levels and cardiac findings. Cobalt was chosen as excess of cobalt has historically been demonstrated to cause cardiomyopathy whereas chromium has not been causally linked to cardiac problems.[10] Baseline characteristics are shown in Table 1. MOM subjects had undergone a mean of 5.2 plasma metal measurements between implantation and study end, the earliest of which was in October 2009.

There was a strong correlation between plasma cobalt and chromium levels ($r=0.78$, $p<0.001$), but only a weak correlation between clinic cobalt and cumulative cobalt levels ($r=0.31$, $p=0.001$). Clinic and cumulative chromium levels were also weakly related ($r=0.38$, $p<0.001$). Plasma cobalt was not correlated with age ($r=-0.09$, $p=0.92$). Calcium channel blocker use tended towards being more common than expected in patients compared with controls ($p=0.07$). There was no other difference in medication use or comorbidity. Median eGFR decreased with increasing tertile of cobalt although no correlation was seen between eGFR and cobalt level ($r=-0.14$, $p=0.14$), or chromium level ($r=-0.10$, $p=0.28$). Cumulative cobalt and chromium were not related to eGFR ($r=-0.04$, $p=0.71$ and $r=-0.05$, $p=0.58$, respectively). There was no difference or correlation between serum NTproBNP measurements between groups ($r=0.03$, $p=0.74$ for cobalt, $r=-0.001$, $p=0.99$ for chromium).

Results of echocardiography are given in Table 2. Left ventricular end-diastolic and end-systolic volumes, both as absolute values and when indexed for body size, increased with tertile of plasma cobalt (Figure 1). Left atrial size also increased with tertile of cobalt, whereas right ventricular sizes were similar. There was no difference in markers of left and right ventricular

systolic function, including longitudinal deformation velocity, ejection fraction; LVOT VTI; MAPSE; TAPSE; or strain in the basal septal and basal lateral segments. Diastolic parameters were also similar. These included mitral E and A waves; E/A ratio; mitral E deceleration time; isovolumic relaxation time; and medial and lateral e' velocity on tissue Doppler. Measurement of global longitudinal strain was possible in 76 subjects (67%); it was unrelated to cobalt exposure.

All MOM patients were also compared with controls (Tables 1 and 2). Left atrial volume was 31% greater in patients than controls and LAVI was 25% greater ($p=0.002$). EDV was 32% greater, indexed EDV 25%, ESV 41% and indexed ESV 32% greater in patients compared with controls ($p\leq 0.002$ for all). Posterior wall thickness was reduced in patients versus controls (mean difference 1.1mm, $p=0.01$).

42 patients had clinic cobalt levels less than the MHRA cut-off of 7 ug/L for device dysfunction and 53 had plasma levels more than 7 ug/L. Using this cut-off, EDVi was greater in those with high cobalt levels (37.0 ml/m² vs. 40.0 ml/m², $p=0.03$), but ESVi (13.7 vs. 15.0, $p=0.30$) and LAVi (20.6 ml/m² vs. 23.3 ml/m², $p=0.68$) were similar. However, eGFR remained lower in the group with the highest cobalt levels (mean rank 66.3 vs. 43.9, $p<0.001$). There was no difference in systolic or diastolic parameters (Vs 4.7 cm/s vs. 4.4 cm/s, $p=$; EF 63% vs 63%, $p=0.82$; e' 7.6 cm/s vs. 7.5 cm/s, $p=0.78$; E/e' 9.3 vs. 9.3, $p=0.78$)

There was a weak inverse correlation between eGFR and left atrial volume ($r=-0.39$, $p<0.001$ Figure 2). A weak inverse correlation was seen between eGFR and left ventricular end-diastolic volume ($r=-0.24$, $p=0.02$, Figure 2), with a similar correlation that approached significance between eGFR and end-systolic volume ($r=-0.20$, $p=0.06$).

The analyses were repeated excluding subjects who had undergone prosthesis removal. There remained a positive association between tertile of clinic cobalt and left ventricular and left atrial chamber size: (mean \pm SD) EDVi: T1 38.7 ± 6.8 ml/m², T2 37.7 ± 7.7 , T3 42.1 ± 9.1 , $p=0.003$; ESVi: T1 14.3 ± 4.1 , T2 13.7 ± 4.3 , T3 16.1 ± 3.8 , $p=0.003$; LAVi: T1 21.2 ± 7.9 , T2 20.3 ± 5.3 , T3 26.5 ± 8.7 , $p=0.003$. A negative association was seen with eGFR (Median T1: 86.1 ± 18.9 μ mol/L, T2 83.9 ± 21.3 , T3 70.7 ± 23.3 , $p=0.007$). There was no difference in longitudinal deformation velocity ($p=0.22$), global longitudinal strain ($p=0.38$), ejection fraction ($p=0.14$) or diastolic parameters (mitral valve E/A ($p=0.34$) and DT ($p=0.07$), and tissue Doppler indices (e' $p=0.11$; E/e' $p=0.92$, IVRT $p=0.67$). Calcium channel blocker use was more common in the highest tertile of cobalt exposure ($p=0.02$), but all other demographics were similar.--

DISCUSSION

We found that increased exposure to cobalt was associated with increased heart size. Despite this, we observed no difference in sensitive markers of systolic or diastolic left ventricular function, or in right ventricular size.

Several case reports describe patients who presented with dilated cardiomyopathy. Typically, the pathophysiology of adverse cardiac remodelling involves initial damage to the myocardium which then results in dilatation due to changes in wall tension. In our study, subjects did not have evidence of myocardial dysfunction, suggesting that dilatation may precede the loss of myocardial function. The mechanism for this remains obscure. Prentice et al compared 35 subjects with MOM resurfacing hip replacements with 35 age and sex-matched controls with non-MOM hip prostheses.[11] They found a 6% increase in left ventricular end-diastolic diameter and a 7% decrease in ejection fraction. End-systolic diameter and wall thickness were similar between the groups. These results corroborate our findings, although we did not find a statistically significant difference in ejection fraction. There was no difference in the prevalence of comorbidities between

patients and controls, or between different tertiles of cobalt, implying that these conditions are not causally linked with development of cardiac changes.

No subjects in this study had enlarged left ventricular volumes. The chamber size recorded in this study is unusually small, with the mean for control subjects being below the normal range. All measurements of left ventricular and atrial volumes were conducted by the same researcher. Measurements for 10 randomly-chosen scans were repeated by a second blinded operator and were in agreement with the first measurements with low inter-observer variability (4.5%). The trend in chamber size was consistent across the patient and control groups, suggesting that the chamber size effect is consistent and are still interpretable as a comparison between controls and the three patient groups.

Gillam et al recently found an association between large head ASR prostheses and hospitalisation for heart failure in males. The study found no such links with metal-on-metal prostheses in females or with other types of prosthesis. This was a population study and did not investigate markers of cardiac function, however it suggests that there may be more widespread links between MOM hip replacements and occult cardiomyopathy. The study population was marginally older than in this cohort (median 79 years), and had high levels of comorbidities, with 55% of them having 4 or more comorbidities.

No difference in cardiac chamber size was seen between groups when using the standard MHRA cut-off of 7 µg/L. This raises the possibility that the effects of cobalt on visceral organs are evident at lower or higher plasma ion levels, and that 7 µg/L is not a sensitive cut-off for detecting the difference between these two groups. Given that the effect found in this study is seen across three different measures of cardiac chamber size, it seems unlikely that the results are down to probability, but this remains possible. Berber et al recently looked at the effects of cobalt plasma levels on cardiac magnetic resonance imaging as well as multiple echocardiography parameters and found no evidence of an effect on cardiac function or chamber size when stratifying groups

according to whether they fell above or below the MHRA's cut-off. [12] The MHRA guidelines were developed to indicate the likelihood of joint dysfunction, rather than visceral complications. In their case series, Bradberry et al note that cardiac complications were only evident in those subjects with the highest cobalt concentrations. [1]

Estimated glomerular filtration rate (eGFR) decreased in our cohort with increasing cobalt exposure. This may be due to reduced excretion of cobalt in subjects with reduced renal function; alternatively, it could be that deposition of heavy metals in the renal parenchyma causes reduction in renal function. In a study of subjects with end-stage renal disease, it was found that plasma chromium and cobalt levels were elevated compared with controls.[13] It is therefore possible that renal dysfunction is the index event which triggers accumulation of cobalt and chromium in these patients. eGFR was moderately correlated with left atrial size and weakly with left ventricular end-diastolic volume, suggesting that the volume increase may be related to activation of the renin-angiotensin-aldosterone system rather than cardiotoxicity. This is supported by the increased numbers of subjects on calcium channel blockers in the third tertile, implying treated hypertension which may be related to renal disease. There is a non-significant trend towards more patients with atrial fibrillation in the higher tertiles of cobalt compared with controls. It may be that the control group is too small to identify a true difference between these groups as the numbers are small. Atrial fibrillation is correlated with increased left atrial size and our results would therefore suggest that it is aetiologically possible that this condition is associated with increasing plasma cobalt. This has not previously been identified in the literature.

It is well recognised that cobalt is deposited within the myocardium when present in high levels.[14] Animal studies demonstrated that contractility of cardiac myocytes is reduced in the presence of high cobalt concentrations.[15] The presence of a pericardial effusion is frequently noted in cobalt-related cardiomyopathy. This is likely to be the cardiac equivalent of the para-joint

effusions seen with affected MOM joints and is a sign of generalised inflammation and tissue oedema. A series of patients presenting with cobalt related cardiomyopathy was reported in 1967 in subjects without MOM hips who drank beer with cobalt added to stabilise the bubbles in the foam.[10] The clinical picture was of a non-dilated cardiomyopathy associated with pericardial effusion that regressed after the additive cobalt was removed from the beer. At that time, cobalt was also given to subjects with anaemia, due to its stimulatory effect on erythropoiesis. There were no reports of cardiomyopathy in the anaemic subjects, suggesting the presence of an additional aetiological factor in the development of cardiomyopathy.

Typical histological findings in affected heart tissue in case reports include interstitial oedema, myocyte hypertrophy, increased lipofuscin, vacuolation and interstitial fibrosis although these findings are not specific to cobalt toxicity and may be found in many causes of cardiomyopathy, including dilated, hypertensive and restrictive subtypes.[16] Abnormal mitochondrial appearance is a common, but non-specific finding and tends to be seen in heavy metal poisoning. Nonetheless, the presence of ventricular dysfunction and high plasma cobalt levels, especially in the presence of pericardial effusion and polycythaemia, should suggest the diagnosis.

MOM hip prostheses are no longer being implanted, and many subjects with high metal ion levels have had their devices explanted. The overall population impact of this phenomenon is therefore declining. However, individuals remain with the potential for systemic complications and clinicians should therefore be aware of the presentation.

Study limitations

This study was observational and collected limited data on frailty, nutritional status and alcohol consumption. Further studies investigating the link between cobalt and idiosyncratic

cardiomyopathy could investigate these cofactors to look for underlying predisposition to development of cardiac symptoms. Biopsies of the myocardium to correlate myocardial heavy metal deposition with cardiac findings on echocardiography were not investigated in this study, although the index case was shown to have elevated myocardial cobalt and chromium levels at autopsy. Confirmation of the link between chamber dilatation and elevated plasma cobalt and chromium levels would be aided by corroboration with histological findings in subclinical groups.

The study was adequately powered to detect differences in systolic function. However, analyses were carried out on a number of parameters and therefore may have been subject to multiplicity. Other studies have used similar sample sizes, but confirmation of the effects would ideally be corroborated by larger studies.

CONCLUSIONS

Left ventricular and atrial volumes increase with increased plasma cobalt. However, no evidence of systolic or diastolic cardiac dysfunction related to prolonged exposure to high plasma metal ions was found in this study.

In view of multiple case reports of fulminant cardiomyopathy in subjects with MOM hip prostheses, an idiosyncratic process cannot be excluded. Despite declining patient numbers with MOM prostheses and high metal ion levels, clinicians should be aware of the potential for cardiac complications and investigate accordingly.

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FIGURE LEGENDS

Figure 1: Effect of increasing tertile of cumulative plasma cobalt levels on: (top panel, left to right) left ventricular EDV indexed for body surface area (BSA), ESV indexed for BSA; (middle) left atrial volume indexed for body size and estimated glomerular filtration rate; (bottom panel) ejection fraction and mean septal and lateral basal systolic Doppler velocities; p values for given pairwise comparisons. Mean values given unless otherwise stated. LV = left ventricular.

Figure 2: Correlation between estimated glomerular filtration rate and (from top) cumulative cobalt exposure, left ventricular end-diastolic volume and left atrial volume.