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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 evaluate if cobalt and chromium are related to 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 (40 ml vs. 32 ml, and 15 ml vs. 11 ml, $p = 0.003$ for both) and 28% larger indexed LA (23 ml vs. 18 ml, $p = 0.002$). 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: No correlations between sensitive measures of systolic or diastolic cardiac function or serum cobalt/chromium levels were observed in this study. However, there was a relationship between increasing left ventricular and left atrial volumes and declining renal function with high cobalt levels which requires further evaluation in MOM patients.

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1. Introduction

Large head metal-on-metal (MOM) hip replacements were implanted in >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) reissued a medical device alert in 2017 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 μg/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 screenings are not addressed in this guidance.

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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 systolic dysfunction (64%), pericardial effusion (45%) and left ventricular dilatation (27%), although a non-dilated cardiomyopathy was seen in several patients.

Conflicting evidence has been published regarding the risk of cardiac complications in the MOM hip population [9–12]. There is currently no consensus for cardiac screening in patients who are being monitored for their prostheses. 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.

2. Methods

2.1. 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 our region. 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 μg/l or greater were referred for evaluation. Consecutive subjects with plasma levels between 0 and 7 μg/l were screened during clinic appointments and approached if they met the recruitment criteria. Exclusion criteria included symptomatic joint dysfunction or history of heart failure prior to recruitment (diagnosis of heart failure on clinical records or pre-existing echocardiographic evidence of reduced left ventricular ejection fraction). The study cohort comprised 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), an accepted measure of sub-clinical cardiac dysfunction [13], with a mean of the basal septal and basal lateral walls of 7.07 ± 1.65 used as values for normal, healthy subjects [14]. A sample size of 95 MOM patients was used 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 μg/l at clinic follow-up, the hospital ethical committee 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 μg/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.

2.2. Cobalt and chromium analysis

The cobalt and chromium assay used was developed at our laboratory. Five millilitres of venous blood were obtained using a 21-gauge needle connected to sodium heparin trace element vacutainers (Vacuette®, Greiner Bio-One GmbH, Austria). The vacutainer was centrifuged within four hours of venepuncture and the plasma separated and stored at 4 °C pending analysis. Cobalt (Co) and chromium (Cr) were measured using an Agilent 7700x inductively-coupled plasma mass spectrometer (Agilent Technologies, Berkshire, UK). Isotopes 59 and 52 were measured for Co and Cr respectively using Helium gas for interference correction. The laboratory participates in the Trace Elements External Quality Assessment Scheme (TEQAS) as per MHRA guidance.

2.3. 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% for left ventricular volume measurements.

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.

2.4. Data analysis

Statistical analysis was performed using SPSS (version 23, IBM). Normally distributed data were expressed using mean ± standard deviation (SD), non-normally distributed data as median ± 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 <5. Where data were missing, analysis was conducted for those entries that were present; where data were absent for >20% of subjects, data was marked as being incomplete.

3. Results

Data were obtained on 95 MOM hip patients (median age: 74.4 yrs, 53% male) and 15 controls (median age: 74.6 yrs, 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, 3 declined follow-up. 2 non-MOM subjects were unsuitable due to pre-existing heart failure. MOM prosthesis types included Anthology (Smith and Nephew) – 52 (46%), ASR (De Puy) – 26 (23%), Corail/Pinnacle (De Puy) – 9 (8%), Cormet (Corin) – 14 (12%), Profemur (Wright) – 8 (7%) and Trilogy (Zimmer) – 2 (2%). 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 any dose-response relationship between heavy metal levels and cardiac findings. Cobalt level at the time of echocardiography was chosen as our primary comparator as excess of cobalt has historically been demonstrated to cause cardiomyopathy whereas chromium has not been causally linked to cardiac problems [15]. Baseline characteristics are shown in Table 1.

There was a strong correlation between plasma cobalt and chromium levels ($r = 0.78$, $p < 0.001$). 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 ($r = -0.10$, $p = 0.28$). 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 (Fig. 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;

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