Cardiac function may be compromised in patients with elevated blood cobalt levels secondary to metal-on-metal hip implants: A pilot study using a novel echocardiography measurement.

Abstract

Aims

Elevated blood cobalt secondary to metal-on-metal (MoM) hip arthroplasties is a suggested risk factor for developing cardiovascular complications including cardiomyopathy. Clinical studies assessing patients with MoM hips using left ventricular ejection fraction (LVEF) have found conflicting evidence of cobalt-induced cardiomyopathy. Global longitudinal strain (GLS) is an echocardiography measurement known to be more sensitive than LVEF at diagnosing early cardiomyopathies. The extent of cardiovascular injury, as measured by GLS, in patients with elevated blood cobalt levels has not previously been examined.

Methods

Sixteen patients with documented blood cobalt ion levels above 13µg/l (13ppb, 221nmol/l) were identified from a regional arthroplasty database. They were matched with eight patients awaiting hip arthroplasty. All patients underwent echocardiography, including GLS, investigating potential signs of cardiomyopathy.

Results

Patients with MoM hip arthroplasties had a mean blood cobalt level of 29µg/l (495nmol/l) compared to 0.01µg/l (0.2nmol/l) in the control group. GLS was significantly reduced in 7 patients with MoM hip arthroplasties compared to 6 without (-15.5% v -18%, (MoM v control) p= 0.025). Pearson correlation demonstrated that GLS significantly correlated with blood cobalt level (r= 0.8521, p=0.0002). However, there was no difference or correlation in other echocardiography measurements including LVEF (64.3% v 63.7% (MoM v control) p=0.845).

Conclusions

This study supports the hypothesis that patients with very elevated blood cobalt above 13µg/l in the presence of a MoM hip implant may have impaired cardiac function compared to a control group of patients awaiting hip arthroplasty. It is the first study to use the more sensitive parameter, GLS, to assess for any cardiac contractile dysfunction in patients with a MoM hip implant and a normal LVEF Larger studies should be performed to determine the potential of GLS as a predictor of cardiac complications in patients with MoM arthroplasties.

Introduction

Metal-on-metal (MoM) hip arthroplasties are known to have higher failure rates than metal-on-polyethylene (MoP) or ceramic-on-ceramic (CoC) total hip arthroplasties (THA)[1]. As a consequence MoM hip implants accounted for less than 1% of hip arthroplasties performed in the United Kingdom last year[2], down from 20% at their peak in 2005[3]. When MoM hips fail they release cobalt and chromium ions into the local tissues and the blood stream. Metal ions can cause significant destruction of local tissue around the hip leading to significant pain and loss of function and a requirement for revision of the MoM prosthesis[4]. Elevated levels of circulating cobalt ions have been linked with a wide range of systemic complications including neurological, endocrine and cardiovascular symptoms[5, 6].

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Cobalt is a widespread trace metal which can be acutely cytotoxic in larger doses[7]. Cobalt induced cardiomyopathy presents as a dilated cardiomyopathy similar to idiopathic, non-ischaemic cardiomyopathy and is diagnosed by demonstration of biventricular dilatation and systolic dysfunction in the presence of elevated blood or tissue cobalt[8]. This dysfunction is reversible as seen by subsequent normalisation of cardiac structure and function when cobalt levels normalise[9].

Case reports have documented MoM patients presenting with cardiovascular complications including cardiomyopathy[10]. However, clinical and laboratory research has found conflicting evidence. Some reports document reduced cardiac ejection fraction (EF) and increased cardiac complications in MoM patients compared to non-MoM implants[11-13]. Other studies have failed to demonstrate negative cardiac effects in patients with elevated blood cobalt levels or across populations of MoM hip patients[14 - 18].

Due to the high rate of failure of MoM hip implants, a screening system using blood cobalt and chromium ion levels is used to assess the performance of MoM hip arthroplasties and identify which patients need further investigation[19]. Higher metal ion levels in the blood reflect a poorly functioning MoM implant with an increased risk of complication and the Medicines and Healthcare products Regulatory Agency (MHRA) guidance recommends using whole blood ion levels of 7ppb (7µg/l, 119nmol/l) as a screening tool for failing MoM arthroplasties[19- 21].

Cardiac function is routinely assessed by echocardiography. Dilated cardiomyopathies, such as cobalt induced cardiomyopathy, are usually diagnosed by the presence of a dilated left ventricle and a reduced left ventricular ejection fraction (LVEF)[22]. LVEF is the most commonly reported functional assessment in the cobalt induced cardiomyopathy literature[10]. Global Longitudinal Strain (GLS) is an echocardiography measurement of myocardial deformation that predominantly reflects the function of sub-endocardial longitudinally oriented fibres and is used as an alternative to LVEF to determine systolic function of the heart[23, 24]. GLS can be more sensitive at picking up cardiac damage in early cardiomyopathies, chronic kidney disease and heart failure but has yet to be investigated in patients with MoM hip arthroplasties[24 - 26].

The hypothesis for this study is that patients with elevated blood cobalt, secondary to MoM hip arthroplasties, will have altered GLS, reflective of contractile function, compared with a control group of patients with no history of metal implants.

Methods

Ethical approval for a total of 30 patients was granted by the Bloomsbury Research Ethics Committee. An information sheet, consent form and data protection protocols were all included in the application to the ethics committee.

Patient characteristics

Sixteen patients were chosen from a regional MoM hip arthroplasty database. Inclusion criteria for the study were patients who should be male, over the age of 50 and with a blood cobalt level >13µg/l. This cobalt level is reflective of an elevated blood cobalt level similar to previously published case reports[10]. The lowest previously reported level of blood cobalt to cause cardiomyopathy was 13µg/l, thus every patient in this study had a blood cobalt level which had caused a documented cardiomyopathy[27]. Patients with a past medical history of cardiac disease and those patients in the database who had undergone revision surgery to remove their MoM arthroplasties were excluded.

A control group comprised male patients over 50 years of age with no past cardiac history who were on the waiting list for a primary THA or hip resurfacing and had no history of metal implants. As MoM resurfacing is currently contra-indicated in women they were excluded from both the study and control groups[28]. Due to pandemic restrictions limiting hospital attendance to essential visits, the

control group was chosen from patients who had pre-existing appointments, limiting the scope for exact matching of patients.

After informed consent was given, all participants in the study provided a thorough cardiac and orthopaedic history which was corroborated by a review of their electronic clinical notes. A physical examination was performed which included heart rate (HR) and blood pressure (BP) measurements. Up to date blood cobalt levels were measured by the hospital laboratory and patients underwent 12 lead electrocardiogram (ECG) assessment by trained cardiac physiologists using a GE Mac 5000 ECG machine (General Electric (GE) Healthcare, Chicago, Illinois, USA).

Echocardiograms measuring LVEF, left ventricular (LV) end diastolic volume (LVEDV), LV end systolic dimension (LVESD), fractional shortening (FS), E/E' ratio, GLS, LV end diastolic dimension (LVEDD) and LV wall thickness were performed using Vivid S70N echo machine (General Electric (GE) Healthcare, Chicago, Illinois, USA) by trained sonographers. Sonographers were blinded.

Statistical analysis.

Power calculations were performed which determined that six patients were the minimum number of patients required in each group. Results were reported as means with standard errors (SEM). An unpaired t-test was used to compare the mean values of echocardiography findings between groups. Pearson correlation was used to determine if there was a relationship between each echocardiography measurement and the blood cobalt level with simple linear regression analysis used to assess the significance of these findings. Analysis was performed using Prism-Graphpad (Graphpad Holdings LLC, California, USA). A p value <0.05 was considered significant.

Results

Patient characteristics

Forty six patients with a blood cobalt level >13µg/l were identified from 2414 MoM hip arthroplasties in 1951 patients in the regional MoM database. Of these, 25 were men, all 25 of whom were over the age of 50. Following a case note review, 20 of these patients were found to have no pre-existing cardiac conditions. These 20 patients were invited to attend research clinics and offered the opportunity to enroll in the study. Nineteen accepted and three patients later withdrew due to difficulties attending for echocardiograms during the Covid-19 pandemic.

The sixteen patients who enrolled were assessed for medical comorbidities, type of implant and length of time from surgery. Eight patients had a hip resurfacing arthroplasty and eight had a THA. The average time from insertion of implant to completion of the study was fifteen years. Seven out of the sixteen patients had no past medical history, seven had a history of non-cardiac conditions and two developed a cardiac condition between being invited to partake in the study and undergoing echocardiogram. One of these patients had developed hypertension and the other atrial fibrillation. Both patients' conditions were adequately controlled with appropriate medication **(Table 1a)**. The control group had no history of cardiac conditions. All members of both groups were non-smokers.

The mean blood cobalt level in the study group was 29µg/l compared to 0.01µg/l in the control group ($p=0.0002$). Seven of the eight patients in the control group had an undetectable cobalt level and the final patient had a blood cobalt of 0.1µg/l **(Table 1b)**. The mean blood cobalt level for the 1905 patients excluded from the study due to levels below 13µg/l was 1.76µg/l (range 0.05µg/l to 12.73µg/l).

Cardiovascular parameters

There was no statistically significant difference between the two groups for either HR or BP. The mean HR was 80 bpm for the study group compared to 78bpm for the control group (p=0.717, SEM±7.55). The mean systolic BP was 143mmHg for the study group compared to 152mmHg for the control group (p=0.165, SEM±7.013) and the mean diastolic BP was 81mmHg for the study group compared to 88mmHg for the control group (p=0.179, SEM) **(Table 1)**.

ECG analysis showed 50% of the study group have normal sinus rhythm compared to 62.5% of the control group. In of the study group 20% had 1st degree heart block compared to none of the control group whereas 30% of the control group had sinus rhythm with premature ventricular complexes compared to 12.5% of the study group.

All sixteen patients in the study group and all eight in the control group underwent echocardiograms. Unfortunately, due to the pandemic the intended standardised echocardiogram protocol was not followed in all cases There was no statistically significant difference between the two groups for LVEDV, LVESD, FS, E/E' ratio, LVEDD and LV wall thickness **(Figure 1)**. There was no statistically significant difference between the mean LVEF in the study and control groups. Mean LVEF for the cobalt study group was 64.3% compared to 63.7% for the control group (p=0.8453, SEM ±3.239) and the difference between the means was 0.6% (95% CI -7.5 to 6.2)**(Figure 2)**. Ten patients in the study group and all eight patients in the control group had LVEF measured. There was no statistically significant correlation between these measurements and blood cobalt level **(Table 2)**.

GLS was available for seven patients in the study group and six in the control group. Due to the pandemic, five patients had their echocardiograms performed in departments which do not measure GLS and for the other four patients the sonographer documented that they were unable to measure GLS due to image quality related to patient body habitus. The mean GLS was significantly reduced in the cobalt study group with a mean value of -15.5% compared to -18% in the control group (p=0.0254 SEM ±0.9427). The difference between the two groups was 2.4% (95% CI 0.4 to 4.5) **(Figure 3a).** The Pearson correlation for GLS and blood cobalt in the study population was r 0.7799 (95% CI 0.06505 to 0.9658, p=0.0386) and simple linear regression analysis demonstrated a significant slope (p=0.0386) (**Figure 3b**). When a Pearson correlation was performed for every patient who had a GLS result available from both groups, a statistically significant correlation of GLS with cobalt level was also observed (**Figure 3c).** Pearson correlation of r=0.8521 (95% CI 0.5675 to 0.9548, p=0.0002) and simple linear regression demonstrated a significant slope (p=0.0002).

Six of the seven patients in the study group and all six patients in the control group who had GLS successfully measured had no comorbidities. The remaining patient in the study group to have GLS measured had type 2 diabetes mellitus and then developed atrial fibrillation between enrollment in the study and having their echocardiogram. Their GLS was -16%, if this result is removed from the analysis the mean value of the study group is -15.4% compared to -18% in the control group (p=0.0335, 95% CI 0.2405 to 4.793) and the result is still statistically significant.

Discussion

This study is the first specifically designed to clarify the correlation between elevated (>13µg/l) blood cobalt ions and cardiomyopathy in a population of asymptomatic British patients. This is the first study to use GLS to demonstrate early cardiac changes in patients with elevated blood cobalt ions secondary to metal on metal hip arthroplasties. Elevated cobalt at levels over 250µg/l have been shown to be a risk factor for developing systemic complications[29] and published case reports document cardiac transplantation and death in patients with severely elevated blood cobalt ions[10]. However, it had previously been unclear whether asymptomatic patients with elevated levels of

blood cobalt ions below this threshold were developing cardiac complications; previous research has found conflicting evidence as to whether MoM hips cause cardiac complications such as cardiomyopathy[11-17]. This study is the first in the literature to use the additional and more sensitive parameter GLS to assess for any cardiac contractile dysfunction in patients with a MoM hip implant and a normal ejection fraction.

No previous studies have directly compared patients who have elevated blood cobalt levels secondary to MoM hip implants with patients awaiting such implants. Instead patients with hip arthroplasties have been used as control groups. These control groups have been categorised as either MoM hips and low blood cobalt[30] or non-MoM hip implants[11-18]. In the current study the absence of previous hip arthroplasty in the control group has ensured the absence of confounding factors, such as metal ions from trunnion wear. This ensures that any effects on cardiac function can be attributed to circulating levels of cobalt originating from the MoM implant. Registry data from previous studies has shown various outcomes ranging from a slight increase in cardiac complications[13], to slightly better cardiac function in MoM patients[31], to no difference between MoM and non-MoM patients[17, 18]. While these studies involve a large number of patients and can provide reassurance that MoM implants are safe for the vast majority of patients, population-based studies are designed to demonstrate epidemiological trends. Registry data does not pick up small subsets of a population such as the patients in this study which were selected from the highest 2% blood cobalt levels from a regional database. Registries cannot specifically address whether patients with blood cobalt ion levels above 13µg/l have higher rates of cardiac damage than patients without hip implants. Previous studies addressing this more specific question have shown variable outcomes including echocardiography changes[11] and increased hospitalisation with heart failure e in MoM patients[12] or no differences compared to the chosen control groups[14-16].

For the first time we have used GLS to assess for cardiac contractile dysfunction in patients with a MoM hip implant where ejection fraction is normal. GLS is a measure of LV function and can pick up subtle changes in cardiac contractile function that are not evident using other routine echocardiogram parameters[32]. GLS is considered normal below -17% and the risk of cardiac disease has been shown to increase on a continuous scale where less risk correlates with a more negative value[24, 33]. GLS does not change with advancing age[34]**.** In the present study GLS was the only echocardiography parameter which showed a significant difference between groups, with the study group having an impaired GLS of -15.5% compared to -18% in the control group**.** When patients from both groups had their results combined a statistically significant correlation between blood cobalt level and GLS was found and this was confirmed with linear regression analysis. GLS predicts cardiovascular morbidity and mortality in the general population as demonstrated in a study of 1296 men in Copenhagen, Denmark. Men with a GLS similar to our study group (> -15.8%) had 5 times the risk of developing heart failure and 2 times the risk of cardiovascular death over an 11 year period than men with a normal GLS in keeping with our control group (< -18%)[35]. There were no other statistically significant differences in echocardiography measurements, physiological measurements or ECG results between the two groups. This demonstrates the effect that impaired cardiac function, as measured by GLS, has on patient morbidity and mortality. This is an example of heart failure with normal ejection fraction, sometimes also known as heart failure with preserved ejection fraction (HFpEF), a condition where patients presenting with the symptoms of heart failure have a normal ejection fraction which is often under diagnosed leading to deteriorating cardiac function[36, 37]. Importantly, and highly relevant to the current study, patients with HFpEF and normal LVEF often present with significantly impaired GLS measurements. These findings demonstrate that patients with impaired GLS are developing silent cardiac damage before they become symptomatic. This is the first study to demonstrate a potential for patients with MoM hip implants to develop HFpEF as

measured by GLS. Thus the findings of this study are relevant despite registry studies analysing large numbers of patients not demonstrating a link between having a MoM implant and developing cardiovascular disease[17, 18].

There have been over 1 million MoM hip arthroplasties implanted worldwide and large numbers remain in situ[38]. The blood cobalt levels of patients included in this study are in keeping with the levels of patients who had cardiac complications in the case reports. Despite this, these blood cobalt levels are not excessively high and are likely to be replicated in MoM patients worldwide. Hip resurfacing remains the best clinical option for young, active, male patients and they are provided with a full list of potential complications as part of the pre-operative consent process. This list could now include potential cardiac complications such as HFpEF if blood cobalt ion levels are above 13µg/l. A more detailed cardiac assessment prior to surgery, including echocardiography, may be considered in order to detect any underlying cardiac condition that could be exacerbated by elevated blood cobalt.

This study has demonstrated that patients with blood cobalt levels above 13µg/l can have impaired cardiac function as assessed by GLS even when a normal ejection fraction has been recorded. While the blood cobalt levels reported in this study are elevated (mean 29µg/l) they are not as high as most of the patients with cobalt-induced-cardiomyopathy identified in the case reports (mean 326µg/l)[10]. This demonstrates that cardiac damage may be occurring at lower blood cobalt levels than previously reported. The MHRA cut off, above which patients with MoM hips require further investigation is 7µg/l. Future clinical guidance may wish to consider whether patients with blood cobalt levels above 13µg/l should have cardiac function assessed by an echocardiogram and, whether this should include GLS. Currently revision of MoM implants occurs if the patient is symptomatic or significant soft tissue destruction is evident[19]. Going forward, and taking the results from the current study into consideration, it would seem reasonable to consider monitoring cardiovascular function in asymptomatic patients where elevated blood cobalt may impact upon cardiac output. A pilot study such as this does not provide enough evidence to recommend using GLS to determine when revision arthroplasty is performed.

The number of patients in this study was limited due to restrictions placed on the NHS by the Covid-19 Pandemic. Echocardiography had to be performed across different locations rather than only at the central unit where a standardised echocardiography protocol would have been followed. Patients withdrew from the study due to self-isolation requirements or a reluctance to travel. The body habitus of some patients also limited the numbers of patients who were able to have GLS performed. One of the seven patients who had GLS measured developed atrial fibrillation (AF) during the study, before their echocardiogram. AF has been shown to cause a worse GLS[39]. If their results are removed from the study it does not affect the significance of either the comparison between groups or correlation of GLS with cobalt. Despite the small numbers of patients, the difference between GLS in the two populations is statistically significant, as is the correlation between cobalt level and GLS. Going forward, it will be important for research to focus on developing an additional cardiovascular biomarker assay to include as part of patient monitoring where GLS might not be possible.

The small number of patients included in this study limits the findings to those of a pilot study. To corroborate the findings, larger numbers of patients from multiple centres should be enrolled. This would increase the likelihood of identifying statistically significant differences across other echocardiography measurements, as well as providing confirmation of the potential importance of GLS and increase the significance of the results reported here. In future, there should be strict standardisation of echocardiogram measurements as had originally been planned for this study. If

the findings of this study are replicated in multicentre studies with a larger number of patients then cardiac function may become part of the decision making algorithm for revision surgery.

Further studies should include patients with cobalt levels as low as 7µg/l in line with current MHRA guidance. Analysis of this extended population could be performed to determine a cut off value for blood cobalt above which patients are at increased risk of developing cardiomyopathy. Echocardiography could be performed before and after revision surgery to assess if cardiac function improves following removal of MoM implant.

A related laboratory project is concurrently looking at the viability of novel biomarkers for cobalt induced cardiomyopathy. Future research could include analysing cardiac biomarkers along with echocardiography data to assess cardiac health in this population of patients. Cardiac biomarkers could be investigated to determine if they can provide an earlier indication of cobalt induced cardiomyopathy.

This study supports the hypothesis that patients with elevated blood cobalt above 13µg/l in the presence of a MoM hip implant may have impaired cardiac function compared to a control group of patients awaiting hip arthroplasty. This is a pilot study with a small number of patients, however, it presents a novel finding which deserves further inquiry and investigation. HFpEF is a condition which has been shown to cause morbidity and mortality in large numbers of patients with a similar GLS to the group investigated in this study. Larger studies should be performed to corroborate these findings and determine the potential of GLS as a predictor of cardiac complications in patients with MoM arthroplasties and elevated blood cobalt ions above 13µg/l.

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Blood cobalt (µg/l)	**Age (Years)**	**Implant**	**Year of surgery**	**Medical history**	**Heart rate (bpm)**	**Blood pressure (mmHg)**
26	71	THA	2007	AF, T2DM	92	140/82
41	61	Resurfacing	2009	Gastric reflux	77	124/71
27	66	Resurfacing	2008	Nil	77	150/101
20	59	THA	2008	Nil	90	157/76
19	68	THA	2008	Nil	78	145/78
22	71	Resurfacing	2004	Nil	70	150/92
17	74	THA	2006	Gout	72	162/89
18	74	THA	2007	Hypertension	79	140/77
25	76	THA	2004	Hiatus Hernia	79	160/102
17	71	THA	2008	Vascular Ulcers	61	135/80
28	83	Resurfacing	2006	Nil	94	124/70
18	67	THA	2008	Diverticulitis	77	143/80
17	68	Resurfacing	2008	AML Prostate cancer	71	148/77
29	82	Resurfacing	2001	Nil	80	123/84
84	61	Resurfacing	2014	Nil	92	140/82
54	69	Resurfacing	2004	Hypercholesterolaemia	77	124/71

Table 1a Patient characteristics of study group

Blood cobalt (µg/l)	Age	Medical history	**Heart rate (bpm)**	**Blood pressure (mmHg)**
0.0	65	Nil	64	133/89
0.0	77	Sleep Apnoea	93	140/70
0.0	60	Nil	60	174/100
0.1	60	Ulcerative colitis	128	161/97
0.0	57	Hypertension	71	154/82
0.0	60	Nil	60	153/90
0.0	64	Hypertension	77	148/88
0.0	52	Gout	68	136/90

Table 1b Patient characteristics of the control group

	Study Group mean	Control Group mean	Standard error of the mean	Mean P value	Pearson Correlation with blood cobalt	Correlation P value
Age (Years)	70	61	±2.922	0.005	r -0.33	0.217
Heart rate (bpm)	80	78	±7.55	0.717	r -0.41	0.188
Systolic blood pressure (mmHg)	143	152	±7.013	0.165	r -0.41	0.206
Diastolic blood pressure (mmHg)	81	88	±4.819	0.179	r -0.24	0.470
Blood cobalt (µg/l)	29	0.01	±6.348	0.0002*		
GLS (%)	-15.5	-18	±0.943	0.025*	r 0.78	0.039**
LVEF (%)	64.3	63.7	±3.239	0.845	r -0.39	0.109
LV end diastolic volume (ml)	100.8	122.7	±13.99	0.137	r 0.46	0.180
LV end systolic dimension (cm)	2.8	3.0	±0.237	0.398	r -0.33	0.245
Fractional shortening (%)	40.8	40.1	±4.526	0.881	r -0.16	0.555
E/e' ratio	7.8	7.8	±0.802	0.965	r -0.42	0.121
LV end diastolic dimension (cm)	4.7	5.0	±0.220	0.180	r 0.14	0.623
Wall thickness (cm)	1.1	1.0	±0.079	0.221	r -0.05	0.865

Table 2 Echocardiogram measurements. * significant differences between study and control group in blood cobalt levels and GLS. ** significant correlation between study group and blood cobalt level.