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Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports

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- Prosthetic hip-associated cobalt toxicity (PHACT) is caused by elevated blood cobalt concentrations after hip arthroplasty.
- The aim of this study is to determine which symptoms are reported most frequently and in what type of bearing. We also try to determine the blood level of cobalt concentrations associated with toxicological symptoms.
- A systematic review was conducted on the 10th of July according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A methodological quality assessment (risk of bias (RoB)) was performed. Primary outcomes were the reported symptoms of cobalt toxicity and the level of cobalt concentrations in blood. These levels were associated with toxicological symptoms. A total of 7645 references were found of which 67 relevant reports describing 79 patients.
- The two most used bearings in which PHACT was described were metal-on-metal (MoM) bearings (38 cases) and revised (fractured) ceramic-on-ceramic (CoC) bearings where the former ceramic head was replaced by a metal head (32 cases).
- Of all reported symptoms, most were seen in the neurological system, of which 24% were in the sensory system and 19.3% were in central/peripheral system, followed by the cardiovascular (22.1%) system.
- The mean cobalt concentration for MoM-bearings was 123.7 ± 96.8 ppb and 1078.2 ± 1267.5 ppb for the revised fractured CoC-bearings.
- We recommend not to use a metal-based articulation in the revision of a fractured CoC bearing and suggest close follow-up with yearly blood cobalt concentration controls in patients with a MoM bearing or a revised fractured CoC bearing.
- Level of Evidence: Level V, systematic review

Keywords
- hip arthroplasty
- prosthetic hip-associated cobalt toxicity
- cobalt

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Introduction

Exposure to metal ions after hip arthroplasty surgery is a widely reported phenomenon. Multiple studies have shown that an increase in metal ions can result in local soft tissue reactions described as an adverse reaction to metal debris (ARMD) (1, 2, 3, 4). There is also an increasing number of case reports describing systemic reactions in relation to elevated blood cobalt concentrations known as prosthetic hip-associated cobalt toxicity (PHACT) (5, 6).

Increased cobalt concentrations are often seen after implantation of metal-on-metal (MoM) hip bearings (7). This can be due to the release of ions from the metal (cobalt–chromium) surface either directly (corrosion) or

during sliding under load, which may create wear particles (adhesion). Another source of significant metal particle release is the application of a metal component for the revision of a fractured ceramic head and/or a fractured ceramic acetabular liner. In this scenario, massive three-body abrasive wear can be created, as small remaining particles of the fractured ceramic bearing lead to abrasion of the metal surface (8, 9).

The systemic effects of cobalt toxicity are historically well documented from industrial exposure, iatrogenic use of oral cobalt chloride tablets and from the beer industry as a foam stabilizing agent (10, 11, 12). The toxicity of cobalt is related to the unbound (free) form of cobalt (Co^{2+}) and certain patient conditions. Unice *et al*. (13) stated that kidney failure, iron deficiencies, sepsis, malnutrition and use of certain medication increased the toxicity of cobalt at lower concentrations. The systemic complaints in patients with PHACT may lead to a variety of symptoms: neuro-ocular toxicity (e.g. tinnitus, vertigo, deafness, blindness, convulsions, headaches and peripheral neuropathy), cardiotoxicity and thyroid toxicity (14). Nausea, anorexia and unexplained weight loss have also been described (6, 15, 16, 17). Initially, there were concerns that high cobalt and chromium concentrations increased the risk of cancer; however, this was not proven in large comparative studies (18, 19).

It is still unknown which of these systemic symptoms are mostly reported in PHACT and at what blood cobalt concentration toxicity occurs. The present study is a systematic review of the current literature reporting systemic cobalt toxicity symptoms after any type of hip arthroplasty. The aim is to define and present the most reported systemic symptoms related to PHACT and to determine blood cobalt levels associated with toxicity.

Methods

The study protocol of this systematic review on case reports was registered in PROSPERO, the international prospective register of systematic review, with registration number: CRD42020215827.

Criteria for considering studies for this review

Types of studies and participants

Case reports concerning cobalt toxicity after hip arthroplasty were included. Patients with any type of bearing (MoM, CoC, metal-on-polyethylene (MoP) and ceramic-on-polyethylene (CoP)) and any type of hip arthroplasty design (hip resurfacing arthroplasty (HRA), short stem hip arthroplasty, and 'conventional' stemmed total hip arthroplasty, both uncemented and cemented) were included. Articles describing allergic reactions on hip prosthesis and/or cobalt and articles reporting only local problems around the hip such as adverse local tissue reactions (ALTR), ARMD and aseptic lymphocytic vasculitis-associated lesion (ALVAL) were excluded.

Types of interventions

The description of intervention was not necessary for inclusion, as patients may have died from cobalt toxicity before intervention could be initiated. In some cases, a revision arthroplasty or chelation therapy was the intervention of choice of the attending physicians.

Types of outcome measures

Primary outcomes were the reported symptoms of cobalt toxicity and the blood cobalt concentration at which these symptoms were seen. All reported symptoms were counted and divided into nine different categories based on the physiological system related to the occurrence of the symptoms. We followed the categories used in the study of Devlin *et al*., with some minor adjustments (6). Cobalt concentrations in blood were reported in nmol/L, µg/L and parts per billion (ppb). Cobalt concentrations in nmol/L were converted to ppb where 1 nmol/L = 0.059 ppb.

Search methods for identification of studies

The search was performed on July 10, 2020, in PubMed, EMBASE, Cochrane Library/Wiley, CINAHL (EBSCO), Web of Science (Clarivate Analytics) and Trial registers (PROSPERO by one author (JJ). The following (MeSH) search terms were used: 'Hip Prosthesis', 'Arthroplasty', 'Replacement', 'Hip and Cobalt'. The full search strategy and terms can be found in Supplementary data 3 (see section on supplementary materials given at the end of this article). Articles published in Dutch, English, German or Spanish were included. There were no further restrictions for publication type or date. Reference lists of included articles were screened for missing items. In addition, also posters presented at congresses and published abstracts were included. Duplicates were identified by one author (JJ) in RefWorks. All records were independently screened on the title and abstract by two authors (JJ, MGMS) and disagreement was resolved by mutual discussion. Full-text articles were assessed for eligibility by two authors (JRWC, MCK), differences were resolved in a consensus meeting and if necessary, through discussion with another author (JJ).

Data collection and analysis

Data were extracted and stored in a Microsoft Excel 2019 file (Microsoft).The following data of the included studies were extracted: study ID (author, year of online publication), number of patients (*n*), patient characteristics at onset of symptoms (age in years, sex), primary intervention

and indication for the primary procedure, secondary intervention and indication (if applicable), follow-up (in months) since surgery, cobalt ion concentration in any type of amount (e.g. nmol/L, µg/L, ppb) when symptoms were seen, symptoms reported and outcome after treatment, regardless of the type of treatment. All results are presented as total (percentage) or as mean (S.D.).

Quality assessment

The risk of bias (RoB) tool of the Cochrane Handbook for Systematic Reviews of Interventions was used and the Newcastle–Ottawa Scale (NOS) was chosen to assess the quality of the articles (20, 21, 22). This checklist was used to determine quality of non-randomized studies, including case-controlled and cohort studies, in three areas: selection, comparability and the ascertainment of either the exposure or outcome of interest. An assessment scale was available to award stars with a maximum score of 9: 1 for each question in the selection and outcome scale and 2 for the comparability domain (Supplementary data 1) (21). The follow-up as described in question 6 was determined to be at least 3 months in agreement with all authors. A score of less than 5 stars represents a high RoB (23).

In addition, a checklist suggested by Murad *et al*. was also used to obtain RoB (24). This checklist is especially designed for case reports and exists of an eight-item tool categorized in four domains: selection, ascertainment, causality and reporting. It is a modification of the tools by Pierson, Bradford Hills and the NOS (Supplementary data 2) (24). The eight items of the tool were scored yes or no. Like the NOS, the adequate follow-up was determined to be 3 months. Questions 5 and 6 of the questionnaire were not taken into account since they were mostly relevant to cases of adverse drug events. Quality of the articles was defined 'good' when 'yes' was scored ≥4 times, 3–2 times 'yes' was defined 'moderate' and ≤1 time 'yes' as 'poor'. All eligible case reports were included in the review irrespective of their methodological quality.

Results

Our search identified 7645 references of which 3898 were screened after removal of duplicates (Supplementary data 3). A total of 3824 were excluded based on title or abstract, resulting in 74 eligible articles. Of these, a total of 67 were included for analysis after excluding another 7 studies, due to no original case description, retraction and no described toxicity (Fig. 1). The RoB classification according to the NOS checklist resulted in a 98.5% ($n=66$) of low RoB and 1.5% ($n=1$) of high-risk bias of the case reports (see Supplementary data 4). According to the checklist of Murad *et al*., 76.1% ($n=51$) of the studies were classified as having good methodological quality. A full review of the Murad checklist is found in Supplementary data 5.

We identified a total of 79 patients with reported PHACT. Table 1 presents the most important data of all articles and methodological quality assessment score.

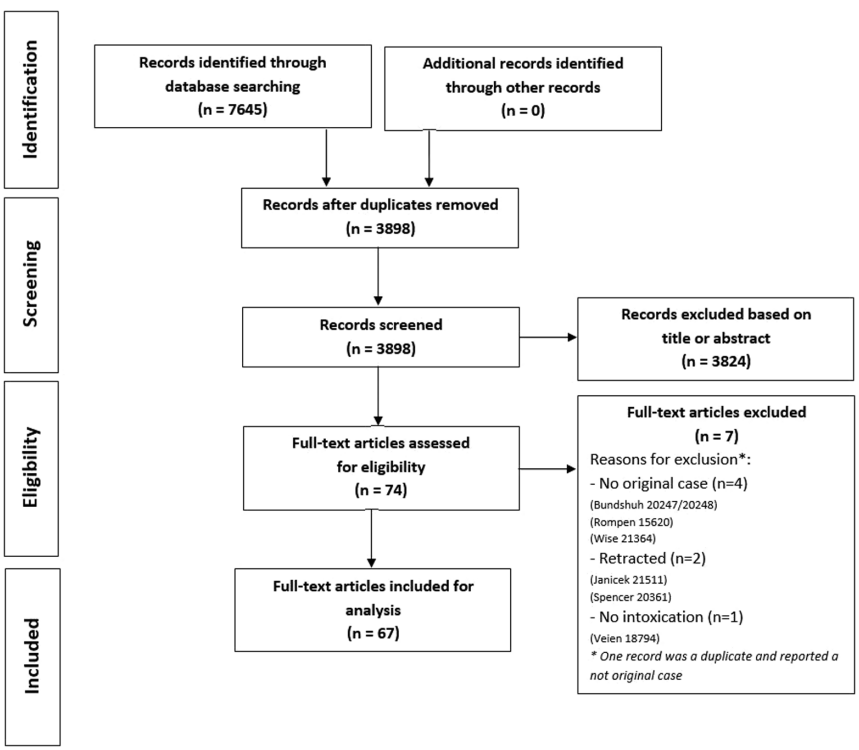

Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart.

Table 1 Most important details of the reviewed articles and quality assessment score results. For a complete overview see Supplementary data 2.

Reference	Patients, *n*	Major reported systemic symptoms (classified)	Cobalt in ppb (sample)	Primary intervention	Secondary intervention	Indication revision	Quality score	
							NOS	Murad
Allen *et al.* (32)	1	Cardiovascular	287.6 (S)	MoM	CoP	Systemic symptoms	Low	Good
Apel *et al.* (33)	1	Neurological (sensory and C/P), cardiovascular	355 (S)	CoC	MoC	Fracture CoC implant	Low	Good
Austin *et al.* (34)	1	Neurological (sensory), cardiovascular	1351.4 (WB)	-	-	Systemic symptoms	Low	Good
Balbouzis *et al.* (35)	1	Cardiovascular	22.2 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Bartholomeu *et al.* (36)	1	Neurological (sensory)	-	-	-	Systemic symptoms	Low	Good
Biglia *et al.* (37)	1	Metal/psychosocial	14 (WB)	CoC	MoM	Fracture CoC implant	Low	Good
Bonilla & Bhimaray (38)	1	Cardiovascular (shock)	100 (WB)		-	Systemic symptoms	Low	Good
Briani *et al.* (39)	1	Neurological (C/P)	14.3 (WB)	CoC	-	Systemic symptoms	Low	Good
Charette *et al.* (40)	1	Cardiovascular	156 (S)	MoM bilateral	CoP	Systemic symptoms	Low	Good
Choi *et al.* (41)	2	Cardiovascular, neurological (sensory)	489.5 (S)	CoP	MoP	Fracture CoC implant	Low	Good
		Cardiovascular	111.9 (S)	CoC bilateral	CoM	Fracture CoC implant		
Citak *et al.* (42)	1	Cardiovascular, neurological (sensory)	-	CoC	MoP	Fracture CoC implant	Low	Poor
Czekaj *et al.* (43)	1	Neurological (sensory and C/P)	206 (WB)	MoM	CoP	Systemic symptoms	Low	Good
Dahms *et al.* (44)	1	Neurological (sensory), cardiovascular	885 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Davies & Chareonthaitawee (45)	1	Neurological (sensory), cardiovascular	953 (S)	CoC	MoP	Fracture CoC implant	Low	Poor
Dolliana & Nüesch (46)	1	Neurological (sensory), gastroenterology	819.2 (WB)	CoC	MoM	Fracture CoC implant	Low	Moderate
Enseleit *et al.* (47)	1	Neurological (sensory), Cardiovascular	-	Bilateral	-	Systemic symptoms	Low	Poor
Sánchez & Cardona (48)	1	Neurological (sensory and C/P), cardiovascular	1036 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Fox (2016) (29)	1	Neurological (sensory and C/P), cardiovascular	817 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Garcia *et al.* (49)	1	Neurological (sensory and C/P), Cardiovascular	1000 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Gautam *et al.* (50)	1	Cardiovascular	373 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Giampreti *et al.* (51)	1	Neurological (C/P)	352.6 (S)	MoM	CoP	Hip pain	Low	Moderate
Giampreti *et al.* (52)	4	Neurological (sensory and C/P), cardiovascular	50 -352.6 (WB)	MoM	-	Systemic symptoms	Low	Moderate
Gilbert *et al.* (53)	1	Cardiovascular	1085 (S)	CoC bilateral	MoP	Fracture CoC implant	Low	Good
Goel & Hoskote (54)	1	Cardiovascular (shock)	25 (S)	MoM bilateral		Systemic symptoms	Low	Moderate
Grant *et al.* (55)	1	Neurological (sensory and C/P)	2148(P)	CoC	MoM	Fracture CoC implant	Low	Good
Griffiths *et al.* (56)	1	Neurological (sensory and C/P), cardiovascular	2006 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Grillo *et al.* (57)	1	Neurological (sensory), cardiovascular	107.8 (S)	CoC	MoM	Fracture CoC implant	Low	Good
Grosso *et al.* (58)	1	Neurological (sensory)	1076 (WB)	CoC	MoM	Fracture CoC implant	Low	Poor
Guevara *et al.* (59)	1	Neurological (sensory), cardiovascular	-	-	-	Systemic symptoms	Low	Poor
Harris *et al.* (60)	1	Neurological (sensory and C/P), cardiovascular	788.1 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Ho *et al.* (61)	1	Neurological (sensory and C/P), cardiovascular	799 (S)	CoC	-	Systemic symptoms	Low	Moderate
Ikeda *et al.* (62)	1	Neurological (C/P)	400 (WB)	CoC bilateral	MoP	Fracture CoC implant	Low	Good
Jones *et al.* (25)	7	Not classified		McKee hip	Girdlestone	Recurrent dislocations	Low	Good
		Not classified		McKee hip	MoP	Possible fracture		
		Not classified		McKee hip	MoP	Persistent pain		
		Skin/hair		McKee hip bilateral	Girdlestone	Protrusion acetabulum		
		Not classified		McKee hip	None described	Hip pain		
		Not classified		McKee hip	Recemented prosthesis	-		
		Not classified		McKee hip	MoP	Recurrent dislocations		
Kao & Bunning (63)	1	Neurological (C/P)	20 (WB)	Bilateral MoP	-	Systemic symptoms	Low	Moderate
Kim *et al.* (64)	1	Neurological (sensory and C/P), cardiovascular	397.8 (WB)	CoP bilateral	MoP	Fracture CoP implant	Low	Good
Lapena Motilva *et al.* (65)	1	Neurological (sensory and C/P)	892.8 (WB)	-	-	Systemic symptoms	Low	Good
Lecoanet *et al.* (66)	1	Neurological (sensory and C/P), cardiovascular	1463.7 (S)	CoC	MoP	Fracture CoC implant	Low	Good

Leikin *et al.* (67)	1	Neurological (sensory and C/P)	1096.5 (S)	CoC	MoM	Fracture CoC implant	Low	Poor
Machado *et al.* (68)	1	Cardiovascular	13.6 (P)	MoM	-	Systemic symptoms	Low	Poor
Mao *et al.* (69)	2	Neurological (sensory and C/P)	24.2 (S)	MoM	CoP	Systemic symptoms	Low	Good
		Neurological (sensory and C/P)	15.2 (S)	MoM	CoP	Systemic symptoms		
Marcus & Woodkotch (70)	1	Neurological (sensory and C/P)	-	MoM	MoP	Systemic symptoms	Low	Moderate
Martin *et al.* (71)	1	Cardiovascular	192 (S)	MoM bilateral	Bilateral CoP	Systemic symptoms	Low	Good
Moniz *et al.* (72)	1	Cardiovascular	169 (S)	MoM	CoP	Systemic symptoms	Low	Good
Mosier *et al.* (73)	1	Cardiovascular	189 (S)	MoM bilateral	Dual mobility CoP	Systemic symptoms	Low	Good
Ng *et al.* (74)	1	Neurological (sensory and C/P)	44.7 (S)	MoM bilateral	-	Systemic symptoms	Low	Good
Nogar & Bells (75)	1	Neurological (C/P), cardiovascular	208 (S)	MoM	-	Systemic symptoms	Low	Good
Oldenburg *et al.* (26)	1	Neurological (sensory and C/P), cardiovascular	625 (S)	CoP	MoP	Fracture CoP implant	Low	Good
Payen *et al.* (76)	1	Cardiovascular (shock)	267.2 (WB)	MoM bilateral	-	Systemic symptoms	Low	Good
Pelayo-de Tomas *et al.* (77)	1	Neurological (sensory and C/P), cardiovascular	651.2 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Pelclova *et al.* (78)	1	Neurological (sensory and C/P)	506 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Peters *et al.* (79)	1	Neurological (sensory and C/P)	596.5 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Reich *et al.* (80)	1	Neurological (C/P)	10.1 (S)	Revision MoM	2nd revision MoP	Acetabular osteolysis	Low	Good
Reid *et al.* (81)	1	Cardiovascular	-	MoM	Unstable	Systemic symptoms	Low	Good
Rizzetti *et al.* (27)	1	Neurological (sensory and C/P)	549 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Sanches Dalmau *et al.* (82)	1	Neurological (sensory and C/P)	259 (P)	MoP bilateral	Chelationtherapy	Systemic symptoms	High	Poor
Sanz Perez *et al.* (83)	1	Cardiovascular (shock)	652 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Shapiro *et al.* (84)	1	Neurological (C/P)	39 (S)	MoM	CoP	Systemic symptoms	Low	Good
Sotos & Tower (85)	1	Neurological (sensory and C/P)	122 (S)	MoM	CoP	Systemic symptoms	Low	Good
Steens *et al.* (28)	1	Neurological (sensory and C/P)	-	CoC	CoM	Chronic pain	Low	Good
Tilney *et al.* (86)	1	Cardiovascular	246.3(WB)	MoM	-	Systemic symptoms	Low	Good
Tower (87)	1	Neurological (sensory and C/P)	74 (S)	MoM	-	Systemic symptoms	Low	Poor
Tower (88)	2	Neurological (sensory and C/P)	122 (S)	MoM	-	Systemic symptoms	Low	Good
		cardiovascular	23 (S)	MoM	-	Systemic symptoms		
Vasukutty *et al.* (89)	1	Cardiovascular	44.9 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Woelber *et al.* (90)	1	Neurological (sensory and C/P)	116 (S)	MoM bilateral	BilateralCoP	Systemic symptoms	Low	Good
Wong & Nixon (91)	1	Skin/hair	57.1 (S)	MoM	ToP	Systemic symptoms	Low	Good
Zeynalov *et al.* (92)	1	Metal/psychosocial	1.6 (S)	MoM	CoM	Systemic symptoms	Low	Good
Zywiel *et al.* (93)	1	Cardiovascular	6521 (WB)	CoC	MoP	Fracture CoC implant	Low	Good

C/P, central and peripheral; CoC, ceramic-on-ceramic; CoP, ceramic-on-polyethylene; MoM, metal-on-metal; MoP, metal-on-polyethylene; NOS, Newcastle–Ottawa Scale; P, plasma; ppb, parts per billion; S, serum; ToP, titanium-on-polyethylene; WB, whole blood.

The full overview is shown in Supplementary data 6. A total of 46 (58.2%) patients were male and 27 (34.2%) were female. Sex was not mentioned in six patients. The mean age at primary surgery was 53.2 ± 14.2 years. The main known reason for primary surgery was osteoarthritis ($n = 28$; 35.4%); however, in most reports, the primary indication was unknown ($n = 36$; 45.6%). Table 2 presents the demographic data of the entire group.

PHACT related to type of bearing

The two most used bearings in the primary surgery were MoM ($n = 38$; 48.0%) and CoC ($n = 32$; 40.5%). Also, MoP ($n = 2$; 2.5%) and CoP ($n = 2$; 2.5%) were reported; in five cases (6.5%), no primary bearing was reported.

In 38 (48.0%) patients, the PHACT symptoms occurred after primary surgery; of which, in 34 (89.5%) after a primary MoM bearing. The mean time between the primary surgery and onset of symptoms was 2.1 (range: 0–13) years. A total of 41 (52.0%) patients developed PHACT symptoms after they had revision surgery. Especially, revision of a (fractured) CoC bearing for a MoP ($n = 21$) or MoM bearing ($n = 6$) caused the onset of cobalt toxicity symptoms. In this group, the mean time of developing PHACT was 8.8 (range: 4–15) years after the primary surgery and 2.4 (range: 0–9) years after the revision surgery (Table 3).

Table 2 **Demographics of all patients** ($n = 79$). **Data are presented as mean ± S.D. or as** n (%).

Demographics	Values
Primary surgery	
Mean age at primary surgery	53.2 ± 14.2
Indications for primary surgery	
Primary osteoarthritis	28 (35.4%)
Avascular necrosis	9 (11.4%)
Fracture	3 (3.8%)
Dysplasia	2 (2.5%)
Hip pain	1 (1.3%)
Unknown	36 (45.6%)
Male/female	46/27 (58.2%/34.2%)
Primary bearing	
MoM	38 (48%)
CoC	32 (40.5%)
MoP	2 (2.5%)
CoP	2 (2.5%)
Unknown	5 (6.5%)
Revision surgery	
Mean age at revision surgery	58.6 ± 11.1
Indication for revision surgery	
Systemic symptoms	38 (48.1%)
Fracture CoC	31 (39.2%)
(chronic) Pain	4 (5.1%)
Recurrent dislocations	2 (2.5%)
Protrusion acetabulum	1 (1.3%)
Fracture	1 (1.3%)
Osteolysis	1 (1.3%)
Unknown	1 (1.3%)
Male/female	26/15 (63.4%/36.6%)
Cobalt toxicity	
Mean age at onset of symptoms	59.0 ± 11.5
Primary PHACT complaints	38 (48%)
Revision PHACT complaints	41 (52%)
Mean cobalt toxicity level in ppb	572 ± 962.1
Mean follow-up time in months	12.7 ± 14.2

CoC, ceramic-on-ceramic; CoP, ceramic-on-polyethylene; MoM, metal-on-metal; MoP, metal-on-polyethylene; PHACT, prosthetic hip-associated cobalt toxicity; ppb, parts per billion.

PHACT related systemic symptoms

A total of 321 symptoms were scored and divided into nine different categories: neurological, cardiovascular, gastroenterology, musculoskeletal, skin/hair, thyroid, mental/psychosocial and others. The neurological symptoms were subcategorized in central/peripheral and sensory. Some patients had more than one reported symptom during the first presentation. All documented symptoms were considered and scored as possible PHACT. Table 4 shows all the different symptoms in the nine different categories.

The most identified symptoms were neurological related. Since most symptoms were especially related to the sensory system, we divided them into sensory system ($n = 77$; 24.0%) and central/peripheral-related symptoms ($n = 62$; 19.3%) .

Hearing impairment/loss and visual impairment/retinal dysfunction were the most mentioned problems in the sensory system, with a total of 34 (44.2%) and 25 (32.5%), respectively. Within the 79 described patients, hearing impairment/loss encounters for a total of 43.0% and visual impairment/retinal dysfunction for 31.6%. In the central/peripheral group, the most described symptoms were cognitive, memory, or concentration problems ($n = 16$; 12.6%) and paresthesia/anesthesia ($n = 13$; 16.5%).

The second most reported complaints were grouped in the cardiovascular origin. We found 71 suspected cobalt-induced cardiovascular complaints after primary and/or revision hip surgery. The described cardiovascular symptoms divers from dyspnea ($n = 25$; 31.6%), cardiomyopathy ($n = 12$; 15.2%), heart failure ($n = 10$; 12.7%) to cardiogenic shock ($n = 4$; 5.1%) (Table 3).

Another systemic problem, often related to cobalt toxicity, is hypothyroidism or thyroid dysfunction. We found nine patients (11.4%) with proven thyroid abnormalities. A total of 17 (21.5%) patients described fatigue and nine had thyroid dysfunction. Of these nine patients, only three patients had also proven thyroid dysfunction, whereas in all other patients, the cause of fatigue had not been investigated or described.

A total of 32 (40.5%) patients were recorded with hip pain as one of the symptoms. Despite this being no systemic complaint, we felt obligated to describe this symptom as it is most likely related to the (early) failure of the hip prosthesis.

In all patients who received treatment for the symptoms, by either removing the prosthesis or by medication, the symptoms reduced considerably.

Table 3 Demographics of all bearings (n = 79). Data are presented as mean ± SD. or as n (%).

Variable	Primary bearing		
	MoM	CoC	Others
n	38	32	9*
Primary surgery			
Mean age at primary surgery in years	56.2 ± 14.9	50.5 ± 13.1	54.4 ± 19.9
Indications for primary surgery (%)			
Primary osteoarthritis	16 (42.1%)	11 (34.4%)	3 (33.3%)
Avascular necrosis	2 (5.3%)	4 (12.5%)	1 (11.1%)
Fracture	3 (7.9%)	1 (3.1%)	0 (0%)
Dysplasia	2 (5.3%)	0 (0%)	0 (0%)
Hip pain	0 (0%)	1 (3.1%)	0 (0%)
Unknown	15 (39%.5)	15 (46.9%)	5 (55.6%)
Male/female (%)	20/13 (52.6%/34.2%)	20/12 (62.5%/37.5%)	6/2 (66.7%/22.2%)
Primary PHACT complaints (%)	34 (89.5%)	1 (3.1%)	3 (33.3%)
Revision PHACT complaints (%)	4 (10.5%)	31 (96.9%)	6 (66.7%)
Cobalt toxicity level in ppb	123.7 ± 96.8	1.078.2 ± 1.267.5	379.4 ± 369.3
Mean age at onset of symptoms in years	58.3 ± 12.9	59.3 ± 10.9	58.5 ± 11.5
Mean time in years at onset of symptoms after primary surgery (range)	2.1 (0–13)	8.8 (4–15)	4.1 (2–12)
Revision surgery			
Mean age at revision surgery in years	60.7 ± 11.2	56.9 ± 11.4	58.5 ± 8.8
Indication for revision surgery (%)			
Systemic symptoms	29 (76.3%)	1 (3.1%)	2 (22.2%)
Fracture CoC	0 (0%)	29(90.6%)	2 (22.2%)
(Chronic) pain	3 (7.9%)	1 (3.1%)	0 (0%)
Recurrent dislocations	2 (5.3%)	0 (0%)	0 (0%)
Protrusion acetabulum	1 (2.6%)	0 (0%)	0 (0%)
Fracture	1 (2.6%)	0 (0%)	0 (0%)
Osteolysis	1 (2.6%)	0 (0%)	0 (0%)
Unknown	1 (2.6%)	1 (3.1%)	5 (55.6%)
Bearing after revision (%)			
MoM	0 (0%)	6 (18.8%)	0 (0%)
CoC	0 (0%)	0 (0%)	0 (0%)
MoP	5 (13.2%)	21 (65.6%)	2 (22.2%)
CoP	12 (31.6%)	0 (0%)	0 (0%)
ToP	1 (2.6%)	0 (0%)	0 (0%)
CoM/MoC	1 (2.6%)	3 (9.4%)	0 (0%)
Girdlestone	2 (5.3%)	0 (0%)	0 (0%)
Not suitable	16 (42.1%)	0 (0%)	0 (0%)
Unknown	1 (2.6)	2 (6.25)	6 (66.7%)
Mean follow-up time in months	13 ± 12.2	11 ± 13.5	15 ± 25.3

*MoP: 2; CoP: 2; unknown: 7.
CoC, ceramic-on-ceramic; CoM, ceramic-on-metal; CoP, ceramic-on-polyethylene; MoC, metal-on-ceramic; MoM, metal-on-metal; MoP, metal-on-polyethylene; PHACT, prosthetic hip-associated cobalt toxicity; ppb, parts per billion; ToP, titanium-on-polyethylene.

PHACT and blood cobalt concentrations

The mean cobalt concentration in blood at which the systemic symptoms were related was 572.0 ± 962.2 ppb for the total group. However, these concentrations differ greatly between the different bearings. The mean cobalt toxicity level for specific MoM, revised CoC, and other bearings were respectively 123.7 ± 96.8, 1078.2 ± 1267.5 and 379.4 ± 369.3 ppb. Table 5 described the mean cobalt concentration between the MoM and revised CoC bearings and three major systemic symptoms: neurological, central/peripheral and sensory and cardiovascular. There was no noticeable difference between the cobalt toxicity concentrations and the developed symptoms in the two bearings. After revision of the MoM bearing or a second revision of the earlier fractured CoC bearing, cobalt concentrations decreased in almost all reported patients.

Discussion

The present review shows that PHACT is mostly seen in primary MoM and after revision of a (fractured) CoC bearings for an MoP or MoM articulation. PHACT is a relevant and serious complication with severe systemic symptoms in the neurological, cardiovascular and thyroid system.

It was only after the recall of several MoM prostheses in 2010 that PHACT was increasingly associated with this type of bearing (6, 15). Before that, only Jones *et al*. described several cases with cobalt-induced systemic issues in the McKee hip (firstgeneration MoM). In this case series (seven cases), the most frequently mentioned symptom was hip pain and there was increased concentrations of cobalt ions in urine and joint fluid (25). Three other reports before 2010 by Oldenburg *et al*., Rizzetti *et al*. and Steens

Table 4 **All systemic symptoms** ($n = 321$; 100.0%) **reported in 79 patients. Data are presented as** *n* (%).

Symptoms	Patients
Neurological	
Central and peripheral	62 (19.3)
Cognitive/memory/concentration	16 (20.3)
Paresthesiaanesthesia	13 (16.5)
(Poly)neuropathy	8 (10.1)
Proprioception loss/difficulty walking	7 (8.9)
Headache	4 (5.1)
Hyposthenia/asthenia	3 (3.8)
Spasm/musclecramps	3 (3.8)
Lower motor neuron syndromes	2 (2.5)
Axonopathy	1 (1.3)
Bulbarpalsy	1 (1.3)
Convulsions	1 (1.3)
Neuropaticpain	1 (1.3)
Parkinson	1 (1.3)
Tremors	1 (1.3)
Sensory*	77 (24.0)
Hearing impairment/loss	34 (43.0)
Visual impairment/retinaldysfunction	25 (31.6)
Dysgeusia/metallic taste	9 (11.4)
Tinnitus	5 (6.3)
Vertigo	2 (2.5)
Loss of smell/anosmia	1 (1.3)
Opticnervearthrophy	1 (1.3)
Cardiovascular	71 (22.1)
Dyspnoe/apnoe/orthopnea	25 (31.6)
(Peri)cardiomyopathie	12 (15.2)
Heart failure	10 (12.7)
Tachycardia	5 (6.3)
Cardiogenic shock	4 (5.1)
Exertionalchest tightness/pain	4 (5.1)
Oedema	4 (5.1)
Pericarditis	2 (2.5)
Hypertension	2 (2.5)
Syncope	2 (2.5)
Pericardial effusion	1 (1.3)
Gastroenterology	12 (3.7)
Diarrhea	3 (3.8)
Nausea	3 (3.8)
Vomiting	3 (3.8)
Anorexia	2 (2.5)
Liver failure	1 (1.3)
Musculoskeletal	5 (1.6)
Arthromyalgia	1 (1.3)
Decreasedmusclemass	1 (1.3)
Polyarthralgia	1 (1.3)
Polymyalgia	1 (1.3)
General stiffness	1 (1.3)
Skin/hair	8 (2.5)
Rash/dermatitis/sarcoid-like	6 (7.6)
Diaphoresis	1 (1.3)
Hair loss	1 (1.3)
Thyroid	9 (2.8)
Hypothyroidism/thyroiddysfunction	9 (11.4)
Mental/pschosocial	25 (7.8)
Fatigue	17 (21.5)
Depression	4 (5.1)
Anxious	2 (2.5)
Insomnia	2 (2.5)
Other	20 (6.2)
Weight loss	7 (8.9)
Weakness	4 (5.1)
Fever	2 (2.5)
Malaise	2 (2.5)
Polydipsia	2 (2.5)
Multi-organ failure	1 (1.3)
Polycythemia	1 (1.3)
Uncontrolled diabetes	1 (1.3)

*Visual, auditory, gustatory olfactory, somatosensory and vestibular.

et al. showed cobalt-related problems in revised ceramic bearings (26, 27, 28).

In primary MoM implants, the bearing surfaces can release metal particles through corrosion and adhesion (induced by wear). After revision of a (fractured) CoC bearing to a metal containing articulation (e.g. MoP or MoM), potentially remaining small ceramic particles in the soft tissue and joint space can cause massive abrasion on the metal surface through three-body wear. All mechanisms of particle release may contribute not only to local adverse reactions but also to potential systemic cobalt toxicity (8, 9, 29).

Limitations

There are some limitations that should be mentioned. Since there are no comparative studies, the present review consists mainly of case reports. Therefore, a publication bias is not ruled out and case reports are considered low-quality research. To minimize these limitations, we have assessed the articles on quality by two different methods as guidance for a systematic review methodology publication. As suggested by the Cochrane Handbook, we used the NOS to determine the RoB and assess the quality (22). Since this questionnaire is not entirely consistent with the assessment of case reports, we also used the checklist suggested by Murad *et al*. (24). A second major limitation is the lack of controlled comparison studies, no clear reported patient histories and a wide range of blood cobalt ion concentrations. Because of that, a direct relationship between the presented symptoms and elevated cobalt concentrations can not be proven. Some of the reported symptoms can also occur independent ofm cobalt toxicity and might relate to common health issues or are associated with age. However, we were able to describe and present as adequately as possible the most reported symptoms associated with cobalt toxicity and high probability.

PHACT related to type of bearing

The present review showed PHACT in 38 patients with an MoM bearing; of which, 34 (89.5%) were detected within 2.1 (range: 0–13) years after the primary surgery. This is

Table 5 **The total number of the three most presented systemic symptoms in relation with the cobalt toxicity level in the two most reported bearings** (MoM and CoC).

Major systemic symptoms	Bearing type and cobalt Level (ppb)			
	MoM, *n*	Cobalt, mean ± S.D.	CoC, *n*	Cobalt, mean ± S.D.
Neurological C/P	17	127.2 ± 110.9	16	889.1 ± 574.9
Neurological sensory	13	119.4 ± 98.7	19	1000.1 ± 517.9
Cardiovascular	16	169.0 ± 100.2	19	778.4 ± 504.4

C/P, central and peripheral; CoC, ceramic-on-ceramic; MoM, metal-on-metal; ppb, parts per billion.

in contrast with the 32 described revised CoC bearings. In these bearings, only 1 (3.1%) patient had PHACT related complications after primary surgery, whereas 31 (96.9%) patients experienced PHACT within 2.4 (range: 0–9) years after revision surgery. In 29 (93.5%) of these revision cases, the indication was a fractured CoC-bearing plus, all the bearings used in the revision surgery contained at least one metal component (Table 3).

PHACT-related systemic symptoms

The three most affected systems in patients with cobalt toxicity are in the sensory, neurological and cardiovascular systems. The neurotoxic effects of cobalt have already been well established in multiple animal studies (12, 27, 30). In addition, some case series describe the neurotoxicity in patients after the treatment with cobalt for anemia. Not only tinnitus and deafness but also paresthesia and ataxia seem to be associated with the use of cobalt (12).

All reviewed reports presume a direct relationship with increased blood cobalt concentrations. Within the sensory system, a total of 77 symptoms were described; of which, the most involved were hearing ($n = 34$; 44.2%) and visual impairment/loss. Most of these symptoms diminished after revision of the prosthesis and a decrease in blood cobalt concentrations was seen. The neurological problems contain mainly cognitive, memory and concentration dysfunction ($n = 16$; 25.8%), as well as paresthesia/anesthesia ($n = 13$; 21.0%). Patients with these symptoms also improved after explanting or revision of the hip prosthesis.

The second most reposted complaints were grouped in the cardiovascular origin ($n = 71$; 22.1%). Of these, dyspnea/apnea/orthopnea ($n = 25$; 31.6%), cardiomyopathy ($n = 12$; 15.2%), heart failure ($n = 10$; 12.7%) and cardiogenic shock ($n = 4$; 5.6%) were most described. The four patients with a cardiogenic shock showed cobalt concentrations from 25 to 652 ppb; however, a clear dose–response effect of the cobalt in these cases could not be established. Of these four patients, one died due to the cardiogenic shock, one needed heart transplantation and two others clinically recovered after explanting the hip prosthesis.

Thyroid dysfunction in relation to cobalt toxicity is also well described in the literature (31) and proven in nine reported patients (11.4%). Another symptom, often mentioned in relation to thyroid dysfunction, is fatigue. A total of 17 patients reported fatigue; of which, only 3 had proven thyroid dysfunction. In all other cases, there was no thyroid dysfunction described. If we combine the 2 different groups, a total of 23 patients (29.11%) may have cobalt-related thyroid issues. This will make the thyroid dysfunction a third major affected systemic system; however, we could not prove this.

PHACT and blood cobalt concentrations

Most published reports provide a toxicity level of cobalt concentration in their cases; however, this concentration divers between all patients and different bearings. The cobalt levels associated with systemic toxicity were considerably higher in patients with revised CoC bearings when compared to patients with a primary MoM bearing (mean of 1078.2 and 123.7 ppb, respectively see Table 5). Our assumption is that corrosion- and adhesion-related metal exposition in MoM bearings is more gradual and slower than the massive release of cobalt-containing metal wear through three-body-related abrasion in fractured CoC bearings, which have been revised with metal-containing components. Another possible explanation is the awareness of local and systemic problems of the metal ions in MoM bearings. As a result, clinicians are more likely to link sudden or unexplained systemic issues to the hip prosthesis.

Unfortunately, we found no controlled studies to definitively link the systemic clinical findings with the elevated blood cobalt concentrations and we were unable to determine a safe upper limit threshold for cobalt toxicity.

Conclusion

Since many MoM bearings are still *in situ*, we can expect more PHACT cases. This systematic review showed that wide blood cobalt concentrations are observed in the onset of systemic symptoms linked to serum cobalt levels. It was not possible to provide a clear threshold level for cobalt-related toxicity from this analysis.

Nevertheless, clinicians should be aware that patients with an MoM or revised CoC bearing are at risk for developing systemic problems. Especially, new-onset systemic diseases related to neurological, both central/peripheral and sensory, and cardiovascular-related symptoms could be provoked by elevated cobalt concentrations. We also recommend not to use a metal-based articulation in the revision of a fractured ceramic bearing and suggest keeping a close follow-up with yearly blood cobalt concentration controls in patients with an MoM or revised fractured CoC bearing.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EOR-21-0098.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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