The ototoxic potential of cobalt from metal-on-metal hip implants: a pilot study on the patient-reported auditory, vestibular, and general neurological outcome

Laura Leyssens[a,*] , Bart Vinck[a ,b] , Catherine Van Der Straeten[c] , Ingeborg Dhooge [d], Floris L. Wuyts[e], and Leen K. Maes[a]

[a] Department of Rehabilitation Sciences, Faculty of Medicine and Health Sciences, University of Ghent, Ghent, Belgium

[b] Department of Speech-Language Pathology and Audiology, University of Pretoria, Pretoria, South Africa

[c] Health Innovation and Research Institute, Ghent University Hospital, Ghent, Belgium

[d] Department of Ear Nose Throat, Ghent University Hospital, Ghent, Belgium

[e] Lab for Equilibrium Investigations and Aerospace, University of Antwerp, Antwerp, Belgium

*Contact Laura Leyssens. Email: Laura.Leyssens@UGent.be Mail: Department of Rehabilitation Sciences, University of Ghent, University Hospital Ghent, Corneel Heymanslaan 10, Ghent, 9000, Belgium

Abstract

Objective This study aimed to systematically investigate the ototoxic potential of cobalt in patients with a metal-on-metal (MoM) hip implant, using objective auditory and vestibular assessments and a questionnaire. The results of the objective evaluation were published previously, whereas the current study focused on the questionnaire outcome and its relationship to the blood cobalt level.

Design and study sample: Twenty patients (33–65 years) with a primary MoM hip implant and 20 non-implanted control subjects, matched for age, gender, and noise exposure, received a questionnaire to evaluate the presence of several hearing and balance symptoms (part 1) and general neurological issues (part 2).

Results Concerning part 1, the proportion of auditory-related symptoms in general ($p = 0.022$) and tinnitus ($p = 0.047$) was significantly higher in the MoM patient group, whereas no group difference was found for hyperacusis, increased listening effort, and decreased speech understanding. Concerning part 2, no significant group differences were detected. Within the MoM patient group, the questionnaire outcome was not significantly different between the low-exposure and high-exposure subgroups according to the blood Co level.

Conclusions In line with our previous study, these results potentially imply Co-induced impairment to the auditory system, despite the lack of a clear dose–response relationship.

Keywords: Metal-on-metal implant, cobalt, ototoxicity, neurotoxicity

Introduction

From the 1990s until the early 2000s, cobalt-chromium (CoCr) metal-on-metal (MoM) bearing surfaces were widely used in hip arthroplasty because of their promising performance concerning durability and stability, and their excellent wear properties (Weber 1996; Jacobs et al. 2009; Neuwirth et al. 2018). The popularity of these devices declined rapidly after recalls from several implant companies since 2011, following reports of unexpectedly high failure and revision rates (Kwon et al. 2012; Fehring, Fehring, and Su 2017; Neuwirth et al. 2018). Today, in most countries, MoM bearing surfaces have been abandoned completely for total hip arthroplasty and are exclusively being applied for resurfacing hip arthroplasty in carefully selected patients (Smith et al. 2012; Matharu et al. 2015; Neuwirth et al. 2018).

Various side effects have been associated with MoM hip implants, mostly due to malpositioned components resulting in increased wear and production of Co and Cr metal ions (Langton et al. 2008; Hart et al. 2009; Kop and Swarts 2009; Hart et al. 2010). Excessive exposure to metal wear debris can provoke local adverse tissue reactions and increased metal ion levels in the systemic blood circulation, which may induce systemic toxicity in rare instances. Cobalt ions are considered to be the principal triggering factors for systemic toxicity, as they are more soluble and susceptible to bind with biomolecules compared to chromium (Hanawa 2004; Van Der Straeten 2013a; Ho et al. 2017).

Gessner et al. (2015) and Bradberry, Wilkinson, and Ferner (2014) reviewed several case reports published in the past 15 years that focused on patients with presumed systemic Co toxicity related to their MoM implant. A wide range of systemic (blood) Co levels was observed among these patients, but the majority showed severely elevated concentrations (>20 µg/l). In general, the existing literature shows conflicting evidence concerning the dose–response relationship between Co exposure from MoM hip implants and systemic toxicity (Paustenbach, Galbraith, and Finley 2014; Gessner et al. 2015; Leyssens et al. 2017, 2020; van Lingen et al. 2014; Ho et al. 2017; Jelsma et al. 2020). The condition of systemic Co toxicity, also known as arthroprosthetic cobaltism (Tower 2010), seems to present as a clinical syndrome with varying endocrine, cardiac, and neurological symptoms (Leyssens et al. 2017). The neurological symptom category includes hearing- and balance-related self-reported symptoms (e.g. hearing loss, tinnitus, imbalance), which appeared to be present in 52% (13/52) of the involved cases according to the systematic review of Gessner et al. (2015). Lower percentages were reported by Bradberry, Wilkinson, and Ferner (2014) (39% or 7/18) and Ho et al. (2017) (26% or 8/31 for tinnitus, 29% or 9/31 for hearing loss), but vestibular-related symptoms were not taken into account in these reports. In a more recent study, hearing loss was reported in 40% (25/62) of the MoM hip implant patients, tinnitus in 31% (19/62), and dizziness in 44% (27/62) (Jelsma et al. 2020). Moreover, another recent study demonstrated that MoM hip implant patients (n = 53) with high blood Co levels (≥20 µg/l) exhibited significantly more balance disturbances and hearing problems than the control group (patients with ceramic-on-ceramic hip implants) (Swiatkowska et al. 2020). Most patients included in the reviews of Gessner et al. (2015) and Bradberry, Wilkinson, and Ferner (2014) ultimately underwent a revision surgery of their MoM implant, which generally resulted in a significant reduction of the blood Co level and partial or even complete disappearance of their symptoms. This may indicate a causal relationship between these symptoms and Co ions released from the implant, but the lack of (pre- and post-operative) objective auditory and vestibular measures requires a cautious interpretation of these findings. Besides MoM hip implant patients, hearing impairment has been observed in an individual occupationally exposed to Co (Meecham and Humphrey 1991). Objective evidence of the toxic potential of cobalt to the hearing and vestibular system is currently limited to animal studies, demonstrating a dose- and time-dependent degeneration of the cochlear sensory (outer) hair cells and the spiral ganglion cells (Apostoli et al. 2013; Li et al. 2015; Roth and Salvi 2016).

Considering the previously mentioned findings from the case and cohort studies, and the recent animal experiments, an extensive assessment of the auditory and vestibular function in patients with a MoM hip implant has recently been performed by our research group. More specifically, 20 patients with a primary MoM hip prosthesis and 20 age- and gender-matched non-implanted controls received an objective auditory and vestibular assessment and completed a questionnaire on auditory, balance, and general neurological symptoms. Additionally, the blood (plasma) Co concentration was determined for all participants. The results of the objective auditory and vestibular evaluation were discussed in a previous article (Leyssens et al. 2020), revealing potential signs of Co-induced damage to the auditory function in the high frequencies (especially 8–16 kHz), with the cochlear outer hair cells (OHC) as possible primary targets. In contrast, the vestibular test results showed no hints of Co-induced impairment. The current investigation aimed to compare the occurrence of self-reported auditory, vestibular, and general neurological symptoms, derived from the previously mentioned questionnaire, in the same patient and control group. Additionally, the authors attempted to explore the impact of the blood Co level on the occurrence of these symptoms in the patient group.

Materials and methods

Participants

Twenty patients implanted with a primary unilateral or bilateral MoM hip prosthesis were matched for age, gender, and noise exposure to twenty non-implanted control subjects. Concerning noise exposure, all participants were asked to describe their history on excessive noise exposure, for which the examiner provided several examples of sources that may produce loud sounds (e.g. heavy motorised vehicles, mechanical/electrical tools, firearms, large music systems) and associated exposure settings (e.g. factories, farms, music festivals/concerts). The participant was identified as (being) excessively exposed to noise when the exposure took/is taking place at least weekly and no consistent hearing protection measures were/are being taken. For these participants, the exposure dose was estimated, based on the frequency (number of hours per week) and duration (number of years) of the exposure. Additionally, the type of exposure (occupational vs. recreational) was inquired, based on whether the exposure took place during professional or leisure activities, regardless of the sound source(s). Both the exposure dose and type were then used for matching purposes with the control group.

The patients were recruited via two orthopaedic surgeons. Specific exclusion criteria were applied for each group and can be consulted in Supplementary Table 1. Furthermore, information about metal allergies, medication and vitamin intake, diabetes, cardiovascular disease/treatment, and occupational exposure to metal compounds was registered by self-report, and the body mass index (BMI) was calculated for all participants.

The study was approved by the Ethics Committee of the Ghent University Hospital and was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. All participants granted written informed consent prior to participation.

Questionnaire

The questionnaire was administered on the same day of the objective auditory and vestibular assessment and the blood collection. Two separate parts can be distinguished within the questionnaire, further specified below.

Part 1: Auditory and vestibular symptoms

Each subject was first asked if they currently experience auditory- and/or vestibular-related problems ("yes-or-no" questions) (Supplementary Table 3), which are later referred to as "general presence/occurrence" of auditory- and/or vestibular-related symptoms. Within the auditory domain, additionally, the presence of the following specific symptoms was inquired with simple closed-ended ("yes-or-no") questions (Supplementary Table 3): (chronic) tinnitus, hyperacusis, decreased speech understanding in noisy environments, decreased speech understanding in quiet environments, and increased listening effort. Within the vestibular domain, the characteristics (e.g. nature, frequency, origin, possible triggers, accompanying otological and/or neurological symptoms, evolution, duration) of eventual symptoms were qualitatively inquired based on the SO STONED mnemonic tool for history taking of a dizzy patient (Wuyts, Van Rompaey, and Maes 2016). For each question concerning the symptom characteristics, a few "example" answer options were given to be selected by the subject, or they could provide their own input.

The MoM patients were specifically instructed to only consider the post-implantation period when completing this part of the questionnaire.

Part 2: General neurological symptoms

Neurological symptoms were inquired using two existing validated tools. The Neurotoxic Symptom Checklist − 60 (NSC-60), developed by the Dutch Organisation for Applied Scientific Research (TNO-MBL, Rijswijk, the Netherlands) (Hooisma and Emmen 1992), has previously been used as an individual screening instrument for persons occupationally exposed to neurotoxic compounds and in a few studies with MoM hip implant patients (Van Der Straeten et al. 2013c; van Lingen et al. 2014; Jelsma et al. 2020). It consists of 60 closed-ended questions with 4 possible answers scored as follows: 1 = never, 2 = rarely, 3 = sometimes and 4 = often. Fifty-

three questions are categorised into the following 9 clusters: cognitive deficits, sleeping disorders, chest symptoms, equilibrium disturbances, sensorimotor symptoms, fatigue, mood and behavioural changes, physical symptoms, and solvent-related symptoms. The 7 remaining questions are personality-related to estimate a person's tendency towards negative responses. Cluster scores were calculated as the arithmetic mean of the answer scores from the individual questions within a given cluster. In addition, the validated Diabetic Neuropathy Symptom (DNS) score (Mao, Wong, and Crawford 2011; Meijer et al. 2002) was used to detect a possible peripheral neuropathy. This tool includes 4 questions answered with "yes" (=1) or "no" (=0), of which the sum was computed as the total DNS score.

Statistical analysis

Statistical analyses were performed using the SPSS software, Version 25.0 (Released 2017, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY). The normality of the data was evaluated both statistically (Shapiro–Wilk test) and graphically (QQ-plots, histograms). For part 1 of the questionnaire (auditory and vestibular symptoms), the general and specific symptom occurrence was compared between groups using Fisher's exact tests (two-tailed), and relative risk (RR) ratios were calculated where possible. Subsequently, the MoM patient group was divided in a low-exposure and high-exposure group according to the local institutional threshold for blood cobalt levels (4 and 5 µg/l for unilateral and bilateral MoM implants, respectively) (Van Der Straeten et al. 2013b). Likewise, Fisher's exact tests were applied to compare these subgroups for general and specific symptom occurrence, and RR ratios were calculated where possible. For part 2 (general neurological symptoms), the NSC-60 cluster and total scores, and the total DNS score were compared between patients and controls applying the independent samples t-test. Additionally, Fisher's exact tests and RR calculations were conducted to compare the occurrence of aberrant NSC-60 cluster and total DNS scores between groups, based on cut-off values accepted in literature (Hooisma and Emmen 1992; Meijer et al. 2002). The same methods were applied to compare MoM patients with low versus high cobalt levels, according to the local institutional threshold (cf. part 1 of the questionnaire).

An alpha level of 0.05 was accepted as a criterion of statistical significance for all analyses.

Results

Participant demographics and cobalt levels

The participant demographics, information on the MoM hip implant and blood cobalt levels can be consulted in Supplementary Table 2.

Table 1 displays the presence of potential confounders and comorbidities in the MoM patient and control group. Diabetes, metal allergies, and occupational exposure to metal compounds were negative for all participants. Two MoM patients reported a cardiovascular treatment (coronary stents, pacemaker) in their history, and hypertension occurred approximately equally in both groups. Vitamin use was more prevalent in the MoM patient group, with the majority taking a multivitamin complex. Likewise, medication use was slightly higher in the MoM patient group, with antihypertensive and anticholesterol drugs most frequently consumed in both groups. Additionally, two MoM patients reported contemporary use of antidepressants, and nonsteroidal anti-inflammatory drugs (NSAIDs) were also only consumed in the MoM patient group. The BMI was statistically compared between MoM patients and controls, revealing no significant group difference.

Table 1. Overview of the presence of potential confounders and comorbidities in the metal-on-metal (MoM) patient versus control group.

Confounder/comorbidity	Subtype/-class	Number of subjects reporting the confounder/comorbidity	
		Control subjects (n = 20)	MoM patients (n = 20)
Diabetes		0	0
Metal allergies		0	0
Occupational exposure to metal compounds		0	0
Cardiovascular treatment/disease	Hypertension	3	2
	Coronary stents	0	2
	Pacemaker	0	1
Vitamin use	Multivitamin complex	1	3
	Vitamin C	0	1
	Vitamin D	0	2
Medication use	Proton pump inhibitors	1	1
	Antidepressants	0	2
	Uric acid reducers	2	1
	Antihypertensive medication	3	2
	• Calcium channel blockers	0	1
	• Beta blockers	0	1
	• Angiotensin II receptor antagonists	3	0
	• Diuretics	1	0
	Anticholesterol medication	1	2
	• Statins	1	2
	• Fibrates	0	1
	NSAIDs	0	2
	• Acetylsalicylic acid	0	1
	• Tenoxicam	0	1
Body mass index (BMI)	Mean (SD)	25,79 (5,29)	26,20 (2,34)

MoM: metal-on-metal; NSAIDs: nonsteroidal anti-inflammatory drugs; SD: standard deviation.

As described above, our institution applied threshold values for the interpretation of Co levels in patients with a MoM hip implant: 4 µg/l and 5 µg/l is considered a “safe upper limit” for unilateral and bilateral MoM hip implants, respectively (Van Der Straeten et al. 2013b). In our cohort, 5 (25%) patients exceeded this threshold, with Co levels ranging between 6.3 and 29.4 µg/l.

Part 1: Auditory and vestibular symptoms

Corresponding to our previous article (Leyssens et al. 2020), one control subject was excluded for this part of the questionnaire because of a clinically relevant asymmetry between both ears.

Table 2 contains the output of the group comparisons and the RR values for the general presence of auditory and vestibular symptoms, as well as for specific auditory- and vestibular-related symptoms. The proportion of auditory-related symptoms was found to be higher in the MoM patient group for most symptoms. More specifically, the general presence of auditory-related symptoms ($p = 0.022$) and tinnitus ($p = 0.047$) was significantly higher compared to the control group. The group difference for hyperacusis was not found statistically significant ($p = 0.065$), despite a 30% higher proportion in the MoM patient group. According to the most notable RR ratios, the MoM patients exhibited an increased risk of developing general auditory-related symptoms (185%), hyperacusis (280%), and decreased speech understanding in noisy environments (122%).

Light-headedness (n = 2) and instability (n = 1) were the only vestibular-related symptoms reported in the current sample (MoM patient group), with varying symptom characteristics. For all 3 patients, the exact starting point of their symptoms was unclear, but specific triggering or aggravating factors could be identified (e.g. fast head movements, fatigue, stress, alcohol use, bending forward or backward). The patients experiencing light-headedness both reported that the symptom is continuously present and accompanied by otological symptoms (e.g. tinnitus, hyperacusis, aural fullness, hearing loss), but they described the evolution differently ("ups and downs" vs. "status quo"). For the patient experiencing instability, the symptom occurs in very short (seconds) episodes typically triggered by fast head movements, and rather occasionally.

Table 2. Relative Risk (RR) values and Fisher's exact test results for auditory- and vestibular-related symptoms in the metal-on-metal (MoM) patient versus control group.

Symptom	Proportion of subjects reporting the symptom		RR value [95% CI]	*p* Value Fisher's exact test
	Control subjects (*n* = 19)	MoM patients (*n* = 20)		
Auditory-related symptoms (general presence)	21.1%	60.0%	2.850 [1.112, 7.306]	0.022*
Tinnitus	0.0%	25.0%	n/a	0.047*
Hyperacusis	10.5%	40.0%	3.800 [0.922, 15.667]	0.065
Decreased speech understanding in noisy environments	15.8%	35.0%	2.217 [0.669, 7.344]	0.273
Decreased speech understanding in quiet environments	0.0%	15.0%	n/a	0.231
Increased listening effort	5.3%	5.0%	0.950 [0.064, 14.132]	1.000
Vestibular-related symptoms (general presence)	0.0%	15.0%		0.231
Light-headedness	0.0%	10.0%	n/a	0.487
Instability	0.0%	5.0%	n/a	1.000

CI: confidence interval; MoM: metal-on-metal; RR: relative risk; n/a: RR calculation not applicable due to proportion of 0% in one group.

*Significant difference ($p < 0.05$).

Table 3 represents the auditory and vestibular symptom occurrence in the low-exposure and high-exposure subgroups (according to the blood Co level) of the MoM patients. None of the proportions were significantly different between the low-exposure (Co level < 4 or 5 µg/l) and high-exposure group (Co level ≥ 4 or 5 µg/l) according to the auditory and vestibular outcome, and the group with the highest proportions was variable. More specifically, tinnitus and hyperacusis were more prevalent in the low-exposure group, whereas increased listening effort, instability, and decreased speech understanding in noisy and quiet environments were more frequently reported in the high-exposure group. The most notable RR values were observed for decreased speech understanding in noisy and quiet environments, reflecting a 110% and 460% higher risk of developing these symptoms in the high-exposure group, respectively. The remaining symptoms (general presence of auditory-related and vestibular-related symptoms, light-headedness) did not show remarkable differences between both exposure groups.

Table 3. Relative Risk (RR) values and Fisher's exact test results for auditory- and vestibular-related symptoms in metal-on-metal (MoM) patients with Co levels below versus above the institutional threshold (4 and 5 µg/l for unilateral and bilateral MoM hip implants, respectively).

Symptom	Proportion of subjects reporting the symptom		RR value [95% CI]	*p* Value Fisher's exact test
	[Co] < 4/5 µg/l (*n* = 14[a])	[Co] ≥ 4/5 µg/l (*n* = 5)		
Auditory-related symptoms (general presence)	64.3%	60.0%	0.933 [0.413, 2.109]	1.000
Tinnitus	35.7%	0.0%	n/a	0.257
Hyperacusis	50.0%	20.0%	0.400 [0.064, 2.493]	0.338
Decreased speech understanding in noisy environments	28.6%	60.0%	2.100 [0.703, 6.275]	0.305
Decreased speech understanding in quiet environments	7.1%	40.0%	5.600 [0.638, 49.166]	0.155
Increased listening effort	0.0%	20.0%	n/a	0.263
Vestibular-related symptoms (general presence)	14.3%	20.0%	1.400 [0.159, 12.292]	1.000
Light-headedness	14.3%	0.0%	n/a	1.000
Instability	0.0%	20.0%		0.263

CI: confidence interval; MoM: metal-on-metal; RR: relative risk; [Co]: plasma Cobalt concentration; n/a: RR calculation not applicable due to proportion of 0% in one group.

[a]The cobalt concentration of one patient could not be determined due to a miscommunication in the lab.

Table 4. Relative Risk (RR) values and Fisher's exact test results for aberrant NSC-60 cluster and total DNS scores in the metal-on-metal (MoM) patient versus control group.

Score type/cluster [cut-off value[a]]	Proportion of subjects with aberrant scores		RR value [95% CI]	*p* Value Fisher's exact test
	Control subjects (*n* = 20)	MoM patients (*n* = 20)		
NSC-60				
Cognitive deficits [2.9]	10%	5%	0.500 [0.049, 5.083]	1.000
Sleeping disorders [2.7]	5%	30%	6.000 [0.793, 45.422]	0.091
Chest symptoms [2.1]	0%	10%	n/a	0.487
Equilibrium disturbances [2.0]	0%	10%	n/a	0.487
Sensorimotor symptoms [2.8]	0%	0%	n/a	n/a
Fatigue [3.1]	0%	5%	n/a	1.000
Mood and behavioural changes [2.7]	0%	20%	n/a	0.106
Physical symptoms [2.5]	5%	0%	n/a	1.000
Solvent-related symptoms [2.6]	0%	5%	n/a	1.000
Personality [2.9]	10%	0%	n/a	0.487
DNS				
Total score [1.0]	15%	15%	1.000 [0.229, 4.373]	1.000

CI: confidence interval; DNS: Diabetic Neuropathy Symptom; MoM: metal-on-metal; n/a: RR calculation not applicable due to 0% proportion in one group OR Fisher's exact test not applicable due to 0% proportion in both groups; NSC-60: Neurotoxic Symptom Checklist 60; RR: relative risk.

[a]According to Hooisma and Emmen (1992) and Meijer et al. (2002)

Part 2: General neurological symptoms

The independent samples t-test did not reveal significant group differences for the NSC-60 cluster and total scores, nor for the total DNS score. In addition to a group comparison of the exact scores, the proportion of subjects with aberrant scores according to accepted cut-off values was determined in each group. The output of this analysis can be consulted in Table 4 and, likewise, no significant group differences were detected. However, the RR ratio for the NSC-60 cluster "sleeping disorders" reflected a 500% higher risk of having sleeping disorders for MoM patients versus controls.

Analogous to the analysis of part 1 (auditory and vestibular symptoms, Table 3), the MoM patient group was subdivided in a low- and high-exposure group based on the blood Co level. Table 5 contains the proportions of subjects with aberrant NSC-60 and DNS scores in the low- versus high-exposure group. Despite the proportion of subjects with aberrant scores being higher in the low-exposure group than the high-exposure group for some clusters (e.g. sleeping disorders, mood and behavioural changes), the proportions were not found significantly different. RR ratios could only be calculated for the NSC-60 cluster "equilibrium disturbances" and for the total DNS score, reflecting a 180% and 40% higher risk for aberrant scores in the high- versus low-exposure group, respectively.

Table 5. Relative Risk (RR) values and Fisher's exact test results for aberrant NSC-60 cluster and total DNS scores in metal-on-metal (MoM) patients with Co levels below versus above the institutional threshold (4 and 5 µg/l for unilateral and bilateral MoM hip implants, respectively).

Score type [cut-off value[b]]	Proportion of subjects with aberrant scores		RR value [95% CI]	*p* Value Fisher's exact test
	[Co] < 4/5 µg/l (*n* = 14[a])	[Co] ≥ 4/5 µg/l (*n* = 5)		
NSC-60				
Cognitive deficits [2.9]	7.1%	0.0%	n/a	1.000
Sleeping disorders [2.7]	42.9%	0.0%	n/a	0.128
Chest symptoms [2.1]	14.3%	0.0%	n/a	1.000
Equilibrium disturbances [2.0]	7.1%	20.0%	2.800 [0.213, 36.836]	0.468
Sensorimotor symptoms [2.8]	0.0%	0.0%	n/a	n/a
Fatigue [3.1]	7.1%	0.0%	n/a	1.000
Mood and behavioural changes [2.7]	28.6%	0.0%	n/a	0.530
Physical symptoms [2.5]	0.0%	0.0%	n/a	n/a
Solvent-related symptoms [2.6]	7.1%	0.0%	n/a	1.000
Personality [2.9]	0.0%	0.0%	n/a	n/a
DNS				
Total score [1.0]	14.3%	20.0%	1.400 [0.159, 12.292]	1.000

CI: confidence interval; DNS: Diabetic Neuropathy Symptom; [Co]: plasma Cobalt concentration; MoM: metal-on-metal; n/a: RR calculation not applicable due to 0% proportion in one group OR Fisher's exact test not applicable due to 0% proportion in both groups; NSC-60: Neurotoxic Symptom Checklist 60; RR: relative risk.

[a]The cobalt concentration of one patient could not be determined due to a miscommunication in the lab.

[b]According to Hooisma and Emmen (1992) and Meijer et al. (2002).

Discussion

In this study, the ototoxic potential of cobalt ions released from metal-on-metal hip implants was investigated, using objective auditory and vestibular assessments as well as a questionnaire. The findings from the objective

evaluation were extensively discussed in our recently published article (Leyssens et al. 2020), whereas the patient-reported (questionnaire) data were the main focus of the current pilot study.

Part 1: Auditory and vestibular symptoms

Overall, considerably more auditory-related symptoms were reported in the MoM patient group compared to the control group (Table 2), with the most remarkable group differences for tinnitus, hyperacusis, and decreased speech understanding in noisy environments. Tinnitus is often generated by peripheral cochlear damage due to presbyacusis, noise-induced or chemicals-induced hearing loss, among other otological, infectious, or neurological aetiologies (Lockwood, Salvi, and Burkard 2002; Keppler, Degeest, and Dhooge 2017). As the patient and control group in the current study were matched for age and noise exposure, the observed group difference for tinnitus is unlikely to be attributed to these factors. Tinnitus has been anecdotally reported in several cases of systemic cobaltism from MoM hip implants, in whom revision surgery mostly resulted in partial or complete alleviation of the symptom (Bradberry, Wilkinson, and Ferner 2014; Gessner et al. 2015). The 25% occurrence in our MoM patient group also corresponds to the percentages reported in the cohorts studies of Ho et al. (2017) (26%) and Jelsma et al. (2020) (31%). Additionally, previous studies in the context of chemicals-induced ototoxicity, especially concerning cisplatin chemotherapy, reported a tinnitus prevalence ranging between 10% and 39% (Bokemeyer et al. 1998; Fossa˚ et al. 2003; Biro et al. 2005; Rybak and Whitworth 2005; Arora et al. 2009; Dille et al. 2010; Frisina et al. 2016), which well encompasses the proportion found in the current study. According to a comprehensive guide on pharmaceuticals inducing ototoxicity or auditory- and vestibular-related symptoms (Cianfrone et al. 2011), some of the medications consumed in the current study population (antidepressants, calcium channel blockers, tenoxicam and angiotensin II receptor antagonists) are classified as “potentially tinnitus-generating”. However, it is unlikely that this impacted the current findings on the occurrence of tinnitus, since the group differences in intake of these medications can be considered cancelled out (Table 1): antidepressants, calcium channel blockers, and tenoxicam were only consumed in the patient group (respectively 2 to 0, 1 to 0, and 1 to 0), whereas the use of angiotensin II receptor antagonists was only reported in the control group (3 to 0).

To the authors’ knowledge, hyperacusis has not yet been cited in relation to systemic Co toxicity from MoM hip implants. However, it has been regularly mentioned in reports on chemicals-induced ototoxicity (Shellack and Naude 2013), but the authors are not aware of available prevalence data in the literature. Nevertheless, there is evidence for a strong overlap in presence between tinnitus and hyperacusis; approximately 10–80% of hyperacusis patients also suffer from tinnitus (Tyler et al. 2014). Moreover, the underlying pathological mechanisms of these disorders are believed to be highly similar (Pienkowski et al. 2014).

Similar to hyperacusis, decreased speech understanding in noisy environments has not been previously reported by MoM hip implant patients. However, occurrence rates of “hearing loss” have been described in several case series and cohort studies (Bradberry, Wilkinson, and Ferner 2014; Gessner et al. 2015; Ho et al. 2017; Jelsma et al. 2020), in which decreased speech understanding in noise may be indirectly incorporated. Furthermore, it is often regarded as the first symptom in case of chemicals-induced hearing loss (Rybak et al. 2007; Lanvers-Kaminsky et al. 2017; Campbell and Le Prell 2018), but this is also associated with other aetiologies of sensorineural hearing loss (e.g. aging, noise exposure).

Interestingly, the higher prevalence of these auditory-related symptoms in the MoM patients corresponds to the findings from the objective auditory outcome parameters (Leyssens et al. 2020). The MoM patients exhibited significantly reduced DPOAE (Distortion Product Otoacoustic Emission) amplitudes at 8 kHz and increased audiometric thresholds in the extended high frequencies (11.2–16 kHz), which mirrors the typical damage pattern observed in cases of chemicals-induced ototoxicity (Rybak and Whitworth 2005; Rybak et al. 2007; Xie, Talaska, and Schacht 2011; Brock et al. 2012; Lanvers-Kaminsky et al. 2017; Brooks and Knight 2018; Campbell and Le Prell 2018). Consequently, both the objective and the patient-reported auditory outcome in our cohort could imply cobalt-induced damage to the auditory system in a few patients. At the individual level, however, the association between these objective outcome measures and the previously mentioned patient-reported symptoms is less straightforward, as normal hearing subjects may present with such symptoms as well. Previous investigation has

indicated that not the hair cells, but the synapses between the hair cells and adjacent cochlear nerve terminals are affected first in the aging, noise-exposed, or ototoxin-exposed ear (Liberman et al. 2016; Liberman and Kujawa 2017). This condition, labelled “cochlear synaptopathy”, is believed to provoke symptoms like impaired speech understanding in noise, tinnitus, and hyperacusis, without apparent aberrations on audiometry or even OAE (Otoacoustic Emission) measurements (Liberman et al. 2016; Song et al. 2018). Moreover, this condition has already been mentioned as a plausible damage pathway in the context of cobalt ototoxicity (Roth and Salvi 2016).

In contrast to the auditory-related symptoms, no notable group differences were detected for the vestibular-related symptoms (Table 2). Moreover, the 3 MoM patients reporting vestibular-related symptoms could not recall when the symptoms exactly started, so the onset might have been before the implantation. Likewise, the objective vestibular outcome in our cohort did not reveal potential cobalt-induced damage to the vestibular system (Leyssens et al. 2020). However, the relatively small sample size and large inter-subject variability of most vestibular outcome parameters may have hampered the detection of potential subtle Co-triggered effects. If cobalt would exhibit any vestibulotoxic potential, it is hypothesised that the accompanying symptoms would go unnoticed by patients as well as clinicians, as the damage is expected to progress slowly and manifest in both ears. Based on the findings in the context of chemicals-induced vestibulotoxicity, this degradation process typically results in rather vague symptoms like oscillopsia, postural instability, and chronic disequilibrium (Black and Pesznecker 1993; Ward et al. 2013; van de Berg, van Tilburg, and Kingma 2015; Lucieer et al. 2016; Van Hecke et al. 2017), which the patient/clinician might relate to the hip prosthesis itself rather than the inner ear. Moreover, a peripheral vestibular impairment is often compensated and, consequently, obscured by sensory substitution mechanisms involving the visual and somatosensory system (van de Berg, van Tilburg, and Kingma 2015).

Based on the previously mentioned classification of pharmaceuticals according to their ototoxic potential (Cianfrone et al. 2011), the majority of the medications reported in Table 1 are solely classified as “potentially vertigo-generating”. Although the overall medication intake was slightly higher in the MoM patient group, this is not expected to have impacted our findings, as the proportion of vestibular-related symptoms was also not significantly higher in this group. The only drug in the current sample classified as “potentially otologically harmful or ototoxic” (Cianfrone et al. 2011) was acetylsalicylic acid, which was consumed by one MoM patient (Table 1). As this patient only reported vestibular-related symptoms, the influence on the present findings for both the auditory- and vestibular-related symptoms is thought to be negligible.

Within the MoM patient group, comparison of the low- and high-exposure group did not suggest an impact of the blood Co level on the occurrence of auditory and vestibular symptoms (Table 3). The RR values for decreased speech understanding in noisy and quiet environments suggested a higher risk for developing these symptoms when exposed to higher Co levels, but the difference was not statistically significant. Moreover, the unequal and small sample size of the low- and high-exposure group further restricts in-depth interpretation of the results. Despite these shortcomings, the lack of a discernible dose–response relationship was not a surprise and was also observed for the objective auditory and vestibular assessments in the Leyssens et al. (2020) investigation. In the literature, the Co levels from MoM patients presenting signs of systemic toxicity are widely variable (Gessner et al. 2015), and two recent studies found no correlation between the blood Co level and the previously described toxicity symptoms (e.g. cardiovascular, endocrine, and neurological) nor the outcome from corresponding clinical or diagnostic examinations (van Lingen et al. 2014; Ho et al. 2017). In contrast, Jelsma et al. (2020) detected a significantly higher proportion of ocular, auditory, and vestibular symptoms in patients with higher Co levels when applying 3 different threshold values (120 nmol/l or 7 µg/l, 170 nmol/l or 10 µg/l, 220 nmol/l or 13 µg/l). However, a significant age difference was observed between the low- and high-exposure group for the 7 and 10 µg/l thresholds, which may have contributed to these findings. In summary, patient-specific factors (medical history) are thought to complicate the dose–response relationship and manipulate the individual susceptibility for and clinical presentation of systemic Co toxicity (Catalani et al. 2012; Paustenbach et al. 2013; Van Der Straeten et al. 2013c; Paustenbach, Galbraith, and Finley 2014; Gessner et al. 2015; Zywiel et al. 2016; Facchin et al. 2017; Leyssens et al. 2017). A few authors have proposed a biological basis for this

concept, which suggests that certain “disease states” (e.g. renal failure, iron deficiency, sepsis) can increase the individual susceptibility to develop systemic toxicity by provoking a shift in the balance of protein-bound versus free Co2+ ions in the blood circulation. More details on this mechanism can be consulted elsewhere (Paustenbach, Galbraith, and Finley 2014; Leyssens et al. 2017).

Part 2: General neurological symptoms

The group comparison of the NSC-60 and DNS scores yielded no significant group differences when treated as continuous variables, nor as dichotomous variables (normal vs. aberrant, respecting cluster-specific cut-off values) (Table 4). However, the difference in the proportion of sleeping disorders (NSC-60 cluster) was large (25%) between MoM patients and controls, and accordingly, the RR ratio suggested a considerably elevated risk of developing this symptom in the MoM patient group. On the other hand, the 95% confidence interval (CI) of the RR was very wide, which restricts the confidence of this conclusion. Nevertheless, sleeping disorders have been previously reported in several case reports of MoM patients with presumed systemic Co toxicity. In the systematic review of Gessner et al. (2015), this symptom was allocated to the “constitutional” symptom category, which includes symptoms that can affect various body systems and represented the most frequently reported symptoms among the included case reports. Although this finding apparently supports our results, we must emphasise that sleeping disorders may be the consequence of other underlying conditions not controlled for in the current study (e.g. psychiatric disorders, chronic pain). In contrast to our findings, Swiatkowska et al. (2020) revealed significantly worse scores for most NSC-60 clusters (including total score) and the total DNS in their cohort of MoM hip implant patients compared to a control group of patients with ceramic-on-ceramic implants. The fact that the authors only included MoM patients with a history of markedly elevated Co levels (≥20 µg/l) may explain the inconsistency with our findings. Moreover, their MoM patient group showed a significantly higher tendency to over-report symptoms, which they acknowledged as a potential confounder.

In the current study, no significant group differences were detected for the “personality” cluster score, so an equal tendency towards negative responses could be presumed in both groups. Consequently, the results are unlikely to be confounded by the personality factor.

Corresponding to the findings from the auditory and vestibular part of the questionnaire, none of the NSC-60 or DNS scores indicated an impact of the blood Co level in the MoM patient group (Table 5). Although not significantly different, the proportion differences seemed to consistently indicate more aberrant scores in the low-exposure group. However, as mentioned earlier, the small and unequal sample size may have contributed to this counter-intuitive result. Accordingly, the RR ratio of the “equilibrium disturbances” cluster score suggested an increased risk for occurrence of this symptom with higher blood Co levels, but the proportions did not differ significantly between both groups.

As mentioned earlier, the existing literature indicates that the dose–response relationship for systemic Co toxicity is not clear-cut due to the impact of patient-specific factors, which remain to be further elucidated. In the study of van Lingen et al. (2014), the NSC-60 and DNS questionnaire was administered in a much larger cohort of MoM patients, enabling additional stratification of blood Co levels (i.e. 0–2, 2–4, 4–10, and 10–20 µg/l) and thus more confidence in estimating a possible dose–response relationship. In line with our findings, these authors could not withhold an effect of the blood Co level on the patient-reported symptoms.

Limitations

This study has several limitations requiring to be mentioned. Firstly, the relatively low sample size limits the power and conclusive strength of the findings and led to wide 95% confidence intervals of the RR ratios. Secondly, since participation to the study took place on a voluntary basis, a selection bias was possible. As such, patients with previous or contemporary hearing and/or balance problems might have been more eager to participate. However, the patients from these orthopaedic surgeons are accustomed to a strict follow-up protocol (i.e. monitoring of Co levels) and most of them have already been enrolled in scientific projects in the past. Moreover, the recruitment process was random to a large extent; patients were contacted only based on criteria regarding their age (≤65 years) and prosthesis type (total/resurfacing MoM). Additionally, both the patients and

control subjects had no knowledge of their blood Co level nor the outcome from the objective auditory and vestibular assessment prior to completion of the questionnaire. Thirdly, the authors had no access to the complete medical history of the participants, so certain confounding comorbidities might have been missed (e.g. smoking status). Nevertheless, several potential confounders were inquired and controlled for (e.g. cardiovascular disease/treatment, medication and vitamin use, BMI, diabetes, metal allergies, occupational exposure to metal compounds). Two patients reported contemporary use of antidepressants, which might suggest an underlying psychiatric or psychologic disorder. However, as the scores of the "personality" cluster (NSC-60) did not differ significantly between groups, the effect on our results is assumed to be negligible. Furthermore, the vitamin use was considerably higher in the MoM patient group (Table 1). Although none of the participants reported intake of vitamin B12, of which cobalt is the main metal constituent, multivitamin complexes may contain B12 as well. However, no major impact on our results is predicted, since a normal daily dose (2.4 µg per day) of vitamin B12 is not expected to pose significant health hazards (Paustenbach et al. 2013; Leyssens et al. 2017). Lastly, none of the questionnaire parts are specifically designed or validated for (systemic) cobalt toxicity, so their sensitivity in detecting Co-induced toxicity symptoms is uncertain. The NSC-60 was originally developed for the evaluation of metal toxicity symptoms in solvent-exposed workers, which is a completely different exposure setting. Nevertheless, it has been used before in a few studies with MoM hip implant patients (Van Der Straeten et al. 2013c; van Lingen et al. 2014; Jelsma et al. 2020).

Conclusion

Despite the limited power of these preliminary findings, the patient-reported (questionnaire-based) outcome may reflect potential signs of cobalt-induced toxic injury to the auditory system. Interestingly, these results are in line with the findings from the objective auditory assessment (high-frequency audiometry, otoacoustic emissions), described in our previous work (Leyssens et al. 2020). The specific auditory-related symptoms found to be more prevalent in our MoM patient group (i.e. tinnitus, hyperacusis, decreased speech understanding in noise) have previously been identified as key symptoms in the context of chemicals-induced ototoxicity. Consequently, clinicians in both the ear-nose-throat and orthopaedic field should be attentive for such symptoms and eventually provide appropriate referral (e.g. neurologist, mutual referral between ENT and orthopaedic specialists). As the patient-reported symptomatic image of auditory sensorial degradation induced by ototoxic agents, noise, and age is essentially the same, objective screening methods are indispensable for monitoring purposes. Although no Co-induced vestibulotoxic manifestations were detected in our sample, the necessity for objective screening also applies for the vestibular system, as vestibulotoxic damage typically results in rather vague symptoms. In contrast to the auditory-related findings, no convincing hints of (general) neurotoxicity were detected in the current study. Finally, none of the investigated patient-reported outcome parameters were influenced by the blood Co level in the MoM patient group, which corresponds to the results from the objective auditory and vestibular assessment (Leyssens et al. 2020) and other recent studies (van Lingen et al. 2014; Ho et al. 2017) regarding the dose–response relationship.

Acknowledgements

The authors thank Dr. Koen De Smet and Bart De Roest from the ANCA hip clinic (Ghent, Sint-Martens-Latem) for the assistance in the recruitment of patients with a metal-on-metal hip implant.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

L.L. has received funding from the Special Research Fund of Ghent University (BOF) [grant no. BOF15/DOC/330] and is currently receiving funding from the Research Foundation Flanders (FWO) [grant no. FWO/17/ASP/143], as a predoctoral research fellow.

References

Apostoli, P., S. Catalani, A. Zaghini, A. Mariotti, P. L. Poliani, V. Vielmi, F. Semeraro, et al. 2013. "High Doses of Cobalt Induce Optic and Auditory Neuropathy." *Experimental and Toxicologic Pathology: Official Journal of the Gesellschaft fur Toxikologische Pathologie* 65 (6): 719–727.

Arora, R., J. S. Thakur, R. Azad, N. K. Mohindroo, D. R. Sharma, and R. K. Seam. 2009. "Cisplatin-Based Chemotherapy: Add High-Frequency Audiometry in the Regimen." Indian Journal of Cancer 46 (4): 311–317.

Biro, K., L. Noszek, P. Prekopp, K. Nagyiványi, L. Géczi, I. Gaudi, and I. Bodrogi. 2005. "Characteristics and Risk Factors of Cisplatin Induced Ototoxicity in Testicular Cancer Patients, Detected by Distortion Product Otoacustic Emmision (DPOAE)." *Journal of Clinical Oncology* 23 (16 suppl): 4578–4578.

Black, F. O., and S. C. Pesznecker. 1993. "Vestibular Ototoxicity. Clinical Considerations." *Otolaryngologic Clinics of North America* 26 (5): 713–736.

Bokemeyer, C., C. C. Berger, J. T. Hartmann, C. Kollmannsberger, H. J. Schmoll, M. A. Kuczyk, and L. Kanz. 1998. "Analysis of Risk Factors for Cisplatin-Induced Ototoxicity in Patients with Testicular Cancer*." British Journal of Cancer* 77 (8): 1355–1362.

Bradberry, S. M., J. M. Wilkinson, and R. E. Ferner. 2014. "Systemic Toxicity Related to Metal Hip Prostheses." *Clinical Toxicology (Philadelphia, Pa.)* 52 (8): 837–847.

Brock, P. R., K. R. Knight, D. R. Freyer, K. C. M. Campbell, P. S. Steyger, B. W. Blakley, S. R. Rassekh, et al. 2012. "Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale*." Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 30 (19): 2408–2417.

Brooks, B., and K. Knight. 2018. "Ototoxicity Monitoring in Children Treated with Platinum Chemotherapy." *International Journal of Audiology* 57 (sup4): S34–S68.

Campbell, K. C., and C. G. Le Prell. 2018. "Drug-Induced Ototoxicity: Diagnosis and Monitoring*." Drug Safety* 41 (5): 451–464..

Catalani, S., M. C. Rizzetti, A. Padovani, and P. Apostoli. 2012. "Neurotoxicity of Cobalt." *Human & Experimental Toxicology* 31 (5): 421–437.

Cianfrone, G., D. Pentangelo, F. Cianfrone, F. Mazzei, R. Turchetta, M. P. Orlando, and G. Altissimi. 2011. "Pharmacological Drugs Inducing Ototoxicity, Vestibular Symptoms and Tinnitus: A Reasoned and Updated Guide." *European Review for Medical and Pharmacological Sciences* 15 (6): 601–636.

Dille, M. F., D. Konrad-Martin, F. Gallun, W. J. Helt, J. S. Gordon, K. M. Reavis, G. W. Bratt, and S. A. Fausti. 2010. "Tinnitus Onset Rates from Chemotherapeutic Agents and Ototoxic Antibiotics: Results of a Large Prospective Study." *Journal of the American Academy of Audiology* 21 (6): 409–417.

Facchin, F., S. Catalani, E. Bianconi, D. De Pasquale, S. Stea, A. Toni, S. Canaider, and A. Beraudi. 2017. "Albumin as Marker for Susceptibility to Metal Ions in Metal-on-Metal Hip Prosthesis Patients." *Human & Experimental Toxicology* 36 (4): 319–319.

Fehring, K. A., T. K. Fehring, and E. P. Su. 2017. “Complications of Metal-on-Metal Bearings.” In *Complications after Primary Total Hip Arthroplasty*, edited by M. P. Abdel and C. J. Della Valle, 151–160. Cham, Switzerland: Springer.

Fosså, S. D., Ronald de Wit, J. T. Roberts, P. M. Wilkinson, P. H. M. de Mulder, G. M. Mead, P. Cook, et al., Medical Research Council Testicular Cancer Study Group TE20. 2003. “Quality of Life in Good Prognosis Patients with Metastatic Germ Cell Cancer: A Prospective Study of the European Organization for Research and Treatment of Cancer Genitourinary Group/Medical Research Council Testicular Cancer Study Group (30941/TE20).” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 21 (6): 1107–1118.

Frisina, R. D., H. E. Wheeler, S. D. Fossa, S. L. Kerns, C. Fung, H. D. Sesso, P. O. Monahan, et al. 2016. “Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus after Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer.” *Journal of Clinical Oncology* 34 (23): 2712–2720.

Gessner, B. D., T. Steck, E. Woelber, and S. S. Tower. 2015. “A Systematic Review of Systemic Cobaltism after Wear or Corrosion of Chrome-Cobalt Hip Implants.” Journal of Patient Safety 15 (2): 97–104.

Hanawa, T. 2004. “Metal Ion Release from Metal Implants*.” Materials Science & Engineering C – Biomimetic and Supramolecular Systems* 24 (6-8): 745–752.

Hart, A. J., A. Sandison, P. Quinn, B. Sampson, K. D. Atkinson, J. A. Skinner, A. Goode, J. J. Powell, and J. F. W. Mosselmans. 2009. “Microfocus Study of Metal Distribution and Speciation in Tissue Extracted from Revised Metal on Metal Hip Implants.” In *14th International Conference on X-Ray Absorption Fine Structure (XAFS14),* edited by J. P. C. Ser, 012208. IOP Publishing.

Hart, A. J., P. D. Quinn, B. Sampson, A. Sandison, K. D. Atkinson, J. A. Skinner, J. J. Powell, and J. F. W. Mosselmans. 2010. “The Chemical Form of Metallic Debris in Tissues Surrounding Metal-on-Metal Hips with Unexplained Failure.” *Acta Biomaterialia* 6 (11): 4439–4446.

Ho, J. H., J. B. Leikin, P. I. Dargan, J. R. H. Archer, D. M. Wood, and J. Brent. 2017. “Metal-on-Metal Hip Joint Prostheses: A Retrospective Case Series Investigating the Association of Systemic Toxicity with Serum Cobalt and Chromium Concentrations.” *Journal of Medical Toxicology : official Journal of the American College of Medical Toxicology* 13 (4): 321–328.

Hooisma, J., and H. Emmen. 1992. *Defining the Normal Data of the Neurotoxicity Symptom Checklist (NSC-60).* Amsterdam: Stichting Arbouw.

Jacobs, J. J., R. M. Urban, N. J. Hallab, A. K. Skipor, A. Fischer, and M. A. Wimmer. 2009. “Metal-on-Metal Bearing Surfaces.” *Journal of the American Academy Orthopaedic Surgeons* 17 (2): 69–76.

Jelsma, J., M. Schotanus, H. Kleinveld, B. Grimm, and I. Heyligers. 2020. “Self-Reported Systemic Complaints in Patients with Metal-on-Metal Hip Arthroplasty.” *Journal of Orthopaedics* 18: 213–217.

Keppler, H., S. Degeest, and I. Dhooge. 2017. “The Relationship Between Tinnitus Pitch and Parameters of Audiometry and Distortion Product Otoacoustic Emissions.” *The Journal of Laryngology and Otology* 131 (11): 1017–1025.

Kop, A. M., and E. Swarts. 2009. “Corrosion of a Hip Stem with a Modular Neck Taper Junction: A Retrieval Study of 16 Cases.” *The Journal of Arthroplasty* 24 (7): 1019–1023.

Kwon, Y.-M., J. J. Jacobs, S. J. MacDonald, H. G. Potter, T. K. Fehring, and A. V. Lombardi. 2012. “Evidence-Based Understanding of Management Perils for Metal-on-Metal Hip Arthroplasty Patients.” *The Journal of Arthroplasty* 27 (8 Suppl): 20–25.

Langton, D., S. Jameson, T. Joyce, J. Webb, and A. V. F. Nargol. 2008. “The Effect of Component Size and Orientation on the Concentrations of Metal Ions after Resurfacing Arthroplasty of the Hip.” *The Journal of Bone and Joint Surgery. Britisch* 90-B (9): 1143–1151.

Lanvers-Kaminsky, C., A. Zehnhoff-Dinnesen, R. Parfitt, and G. Ciarimboli. 2017. “Drug-Induced Ototoxicity: Mechanisms, Pharmacogenetics, and Protective Strategies.” *Clinical Pharmacology and Therapeutics* 101 (4): 491–500.

Leyssens, L., B. Vinck, C. Van Der Straeten, F. Wuyts, and L. Maes. 2017. “Cobalt Toxicity in Humans—A Review of the Potential Sources and Systemic Health Effects.” *Toxicology* 387: 43–56.

Leyssens, L.,. B. Vinck, C. Van Der Straeten, K. De Smet, I. Dhooge, F. L. Wuyts, H. Keppler, et al. 2020. “The Ototoxic Potential of Cobalt from Metal-on-Metal Hip Implants: Objective Auditory and Vestibular Outcome.” *Ear and Hearing* 41 (1): 217–230.

Li, P., D. Ding, R. Salvi, and J. A. Roth. 2015. “Cobalt-Induced Ototoxicity in Rat Postnatal Cochlear Organotypic Cultures.” *Neurotoxicity Research* 28 (3): 209–221.

Liberman, M. C., and S. G. Kujawa. 2017. “Cochlear Synaptopathy in Acquired Sensorineural Hearing Loss: Manifestations and Mechanisms.” *Hearing Research* 349: 138–147.

Liberman, M. C., M. J. Epstein, S. S. Cleveland, H. Wang, and S. F. Maison. 2016. “Toward a Differential Diagnosis of Hidden Hearing Loss in Humans.” *PLoS One* 11 (9): e0162726.

Lockwood, A. H., R. J. Salvi, and R. F. Burkard. 2002. “Tinnitus.” *The New England Journal of Medicine* 347 (12): 904–910.

Lucieer, F., P. Vonk, N. Guinand, R. Stokroos, H. Kingma, and R. van de Berg. 2016. “Bilateral Vestibular Hypofunction: Insights in Etiologies, Clinical Subtypes, and Diagnostics.” *Frontiers in Neurology* 7: 26.

Mao, X., A. A. Wong, and R. W. Crawford. 2011. “Cobalt Toxicity–An Emerging Clinical Problem in Patients with Metal-on-Metal Hip Prostheses?” *Medical Journal of Australia* 194 (12): 649–651.

Matharu, G. S., H. G. Pandit, D. W. Murray, and R. B. C. Treacy. 2015. “The Future Role of Metal-on-Metal Hip Resurfacing.” International Orthopaedics 39 (10): 2031–2036.

Meecham, H. M., and P. Humphrey. 1991. “Industrial Exposure to Cobalt Causing Optic Atrophy and Nerve Deafness: A Case Report.” *Journal of Neurology, Neurosurgery, and Psychiatry* 54 (4): 374–375.

Meijer, J. W. G., A. J. Smit, E. V. Sonderen, J. W. Groothoff, W. H. Eisma, and T. P. Links. 2002. “Symptom Scoring Systems to Diagnose Distal Polyneuropathy in Diabetes: The Diabetic Neuropathy Symptom Score.” *Diabetic Medicine : A Journal of the British Diabetic Association* 19 (11): 962–965.

Neuwirth, A. L., B. S. Ashley, W. M. Hardaker, and N. P. Sheth. 2018. “Metal-on-Metal Hip Implants: Progress and Problems.” In *Biomedical Applications of Metals*, edited by M. Rai, A. P. Ingle, S. Medici, 73–93. Cham: Springer International Publishing.

Paustenbach, D. J., B. E. Tvermoes, K. M. Unice, B. L. Finley, and B. D. Kerger. 2013. “A Review of the Health Hazards Posed by Cobalt.” Critical Reviews in Toxicology 43 (4): 316–362.

Paustenbach, D. J., D. A. Galbraith, and B. L. Finley. 2014. “Interpreting Cobalt Blood Concentrations in Hip Implant Patients.” *Clinical Toxicology (Philadelphia, Pa.)* 52 (2): 98–112.

Pienkowski, M., R. S. Tyler, E. R. Roncancio, H. J. Jun, T. Brozoski, N. Dauman, C. B. Coelho, et al. 2014. “A Review of Hyperacusis and Future Directions: Part II. Measurement, Mechanisms, and Treatment.” *American Journal of Audiology* 23 (4): 420–436.

Roth, J. A., and R. Salvi. 2016. “Ototoxicity of Divalent Metals.” *Neurotoxicity Research* 30 (2): 268–282.

Rybak, L. P., and C. A. Whitworth. 2005. “Ototoxicity: Therapeutic Opportunities.” *Drug Discovery Today* 10 (19): 1313–1321.

Rybak, L. P., C. A. Whitworth, D. Mukherjea, and V. Ramkumar. 2007. “Mechanisms of Cisplatin-Induced Ototoxicity and Prevention.” *Hearing Research* 226 (1-2): 157–167.

Shellack, N., and A. Naude. 2013. “An Overview of Pharmacotherapy-Induced Ototoxicity.” *South African Family Practice* 55 (4): 357–365.

Smith, A. J., P. Dieppe, P. W. Howard, and A. W. Blom. 2012. “Failure Rates of Metal-on-Metal Hip Resurfacings: Analysis of Data from the National Joint Registry for England and Wales.” *The Lancet* 380 (9855): 1759–1766.

Song, K., S. A. Shin, D. S. Chang, and H. Y. Lee. 2018. “Audiometric Profiles in Patients with Normal Hearing and Bilateral or Unilateral Tinnitus.” *Otology & Neurotology* 39 (6): e416–e421.

Swiatkowska, I., J. Henckel, S. A. Sabah, and A. J. Hart. 2020. “Self-Reported Neurotoxic Symptoms in Hip Arthroplasty Patients with Highly Elevated Blood Cobalt: A Case-Control Study.” *Journal of Patient Safety.* Advance online publication.

Tower, S. 2010. “Arthroprosthetic Cobaltism: Identification of the At-Risk Patient.” *Alaska Medicine* 52: 28–32.

Tyler, R. S., M. Pienkowski, E. R. Roncancio, H. J. Jun, T. Brozoski, N. Dauman, N. Dauman, et al. 2014. “A Review of Hyperacusis and Future Directions: Part I. Definitions and Manifestations.” *American Journal of Audiology* 23 (4): 402–419.

van de Berg, R., M. van Tilburg, and H. Kingma. 2015. “Bilateral Vestibular Hypofunction: Challenges in Establishing the Diagnosis in Adults.” ORL; *Journal for Oto-Rhino-Laryngology and Its Related Specialties* 77 (4): 197–218.

Van Der Straeten, C. 2013a. The Genesis and Aftermath of Metal Ions and Particles in Metal-on-Metal Hip Arthroplasty [dissertation]. Ghent, Belgium: Department of Orthopaedics and Traumatology, Ghent University.

Van Der Straeten, C., D. Van Quickenborne, S. Pennynck, K. De Smet, and J. Victor. 2013c. “Systemic Toxicity of Metal Ions in a Metal-on-Metal Hip Arthroplasty Population.” *Bone & Joint Journal Orthopaedics Proceedings Supplemen*t 95 (Supp34): 187.

Van Der Straeten, C., G. Grammatopoulos, H. S. Gill, A. Calistri, P. Campbell, and K. A. De Smet. 2013b. “The 2012 Otto Aufranc Award: The Interpretation of Metal Ion Levels in Unilateral and Bilateral Hip Resurfacing.” *Clinical Orthopaedics and Related Research*® 471 (2): 377–385.

Van Hecke, R., V. Van Rompaey, F. L. Wuyts, L. Leyssens, and L. Maes. 2017. “Systemic Aminoglycosides-Induced Vestibulotoxicity in Humans.” *Ear and Hearing* 38 (6): 653–662.

van Lingen, C. P., H. B. Ettema, C. Van Der Straeten, B. J. Kollen, and C. C. Verheyen. 2014. “Self-Reported Neurological Clinical Manifestations of Metal Toxicity in Metal-on-Metal Hip Arthroplasty.” Hip International: *The Journal of Clinical and Experimental Research on Hip Pathology and Therapy* 24 (6): 568–574.

Ward, B. K., Y. Agrawal, H. J. Hoffman, J. P. Carey, and C. C. Della Santina. 2013. “Prevalence and Impact of Bilateral Vestibular Hypofunction: Results from the 2008 US National Health Interview Survey.” *JAMA Otolaryngology- Head & Neck Surgery* 139 (8): 803–810.

Weber, B. G. 1996. “Experience with the Metasul Total Hip Bearing System.” *Clinical Orthopaedics and Related Research* 329: S69–S77.

Wuyts, F. L., V. Van Rompaey, and L. K. Maes. 2016. ““SO STONED”: Common Sense Approach of the Dizzy Patient*.” Frontiers in Surgery* 3: 32.

Xie, J., A. E. Talaska, and J. Schacht. 2011. “New Developments in Aminoglycoside Therapy and Ototoxicity.” *Hearing Research* 281 (1-2): 28–37.

Zywiel, M. G., J. J. Cherian, S. Banerjee, A. C. Cheung, F. Wong, J. Butany, C. Gilbert, et al. 2016. “Systemic Cobalt Toxicity from Total Hip Arthroplasties Review of a Rare Condition Part 2. Measurement, Risk Factors, and Step-Wise Approach to Treatment.” *The Bone & Joint Journal* 98-B (1): 14–20.