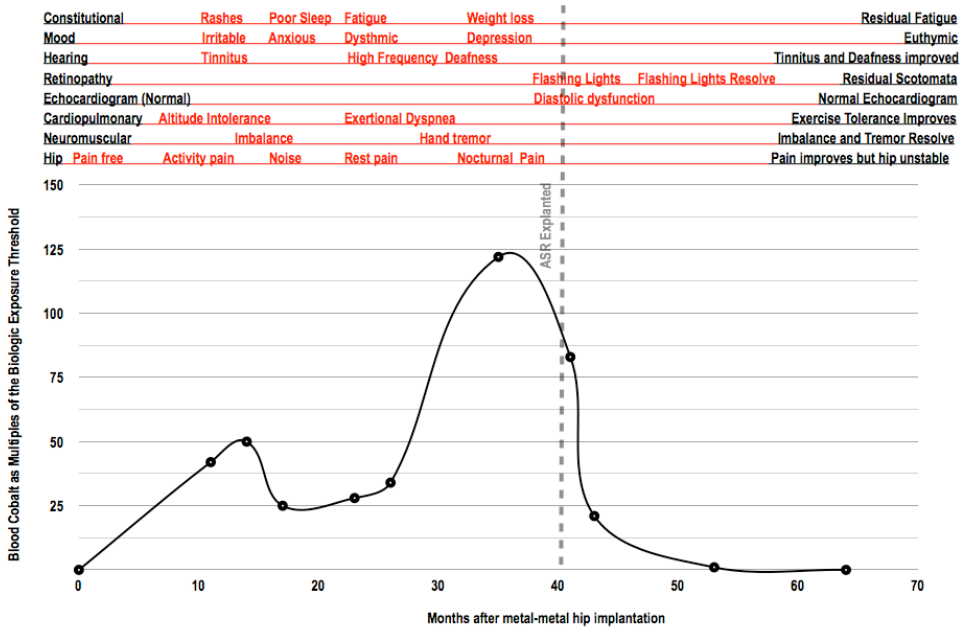
Introduction

Systemic cobalt poisoning from excessive wear of a hip implant was first reported in 2001. The male patient presented with profound peripheral neuropathy, a metal laden pericardial effusion, and immune thyroiditis in 1997. Notable elevations of cobalt and chromium were detected in the patient's blood and urine. The patient had no symptoms at his prosthetic hip but the chrome-cobalt femoral head was out-of-round on radiographs. A Metal-on-Ceramic Wear Mechanism (MoCWM) explained the patient's extreme cobaltemia. Ceramic bits from the broken primary femoral head embedded in the revision plastic socket liner and severely abraded the revision chrome-cobalt alloy femoral head.[1]

Nine years later we reported the first two cases of ArthroProsthetic Cobaltism (APC) from a Metal-on-Metal Wear Mechanism (MoMWM). The articular surfaces of a Metal-on-Metal Hip Replacement (MoMHR) are wrought or forged of chrome-cobalt alloy.[2] Our patients' ASR (DePuy) hips wore excessively resulting in notable cobaltemia. Both men developed disordered mood and cognition, audio-vestibular dysfunction, rashes, and symptomatic cardiomyopathies. The more severely cobaltemic and involved patient developed retinopathy. His Blood Cobalt Level ([BCo]) peaked at 122BET (122 times the Biologic Exposure Threshold [BET] of 1 mcg/L) and 600 times the mean [BCo] of subjects without hip replacements.[2 3 4 5] The ASR hips were exchanged for Ceramic-on-Plastic (CoP) implants after 3.5 years because of progressive hip pain and noise, the periprosthetic tissues were stained by metal debris (metallosis) and wear of the explant of the index patient was 2 orders of magnitude above that predicted by the ASR's designers.[6] Both men's mood and cognition improved over months as their [BCo] declined. Their cardiomyopathies, rashes, audio-vestibular and optic impairments largely resolved over three years.[7] An author of this paper (ST) was the index case and he wrote that report. The second subject was the only patient that ST implanted with an ASR hip. The surgeon's [BCo] during his ASR implantation and recovery, and the chronology of the development and resolution of his constitutional, dermatological, psychological, neurological, and cardiac cobaltism manifestations are depicted in Figure 1.[7] His *JBJS* report was accompanied by a commentary commissioned by the Presidential Line of the American Academy of Orthopedic Surgeons (AAOS) that concluded:[3 8] "The report is unusual because of the rarity of the occurrence of metal-induced systemic complications in patients with total hip replacement and the fact that the author was one of the patients. As millions of patients worldwide have undergone total hip replacement, these cases represent rare events indeed."

Figure 1: Illustration of the clinical course of the index case of APC from a MoMWM



The FDA in January of 2013 proposed that MoMHR marketed in the US under the 510(k) exemption be removed from the market unless industry submits evidence to the FDA that these devices are safe and efficacious to the standard of a Pre Market Approved (PMA) implant. The FDA listed five references to justify this proposed rule that will remove most all MoMHR from the American market. ST's JBJS case

report was the second reference and the only one addressing cobaltism.[9] An approximate half million Americans are implanted with MoMHR, about 100,000 of these implantations occurred during the three years between the first publication of the Alaskan cases and the FDA's proposed rule change.[2]

The spectrum and epidemiology of APC is important because about one million resurfacing or stemmed MoMHR were implanted over the past decade, predominately in the US and the UK.[10] [11] The safety and efficacy of the MoMHR and regulatory processes that allowed their use has come under scrutiny because they are failing and requiring revision surgery at much higher rates than historical or contemporary Metal-on-Plastic Hip Replacements (MoPHR) due to Adverse Reactions to Metallic Debris (ARMD).[12] [13] ARMD may by asymptomatic and results in masses at the hip (solid and cystic pseudo-tumors) and hip tissue inflammation or necrosis resulting in damage to ligaments, tendons, muscles, nerves, vessels and bone.[14] [15] Hundreds of thousands of patients fitted with MoMHR will come to premature revision surgery because of ARMD and they are younger than patients requiring revision of MoPHR. Revision surgery for ARMD is complication prone because of periprosthetic tissue loss, repeated operations may be required, and the function of the salvaged arthroplasty is often suboptimal.[15] Patients requiring ARMD related revision of MoMHR have mean [BCo] > 20 BET.[16] [17] [18]

Annual [BCo] monitoring for most patients fitted with MoMHR, at the discretion of the patient's medical provider, is recommended by the British MHRA because cobaltemic patients are known to be at increased risk for ARMD, may be asymptomatic, and are at risk for progressive periprosthetic tissue damage that might complicate eventual revision surgery.[19] The Australian NPS also recommends annual review of general, mental, neurologic, and cardiac health is indicated and an annual [BCo].[20] The FDA and the NIH mention that patients implanted with MoMHR are at risk for ARMD, cobaltemia, and cobaltism but fall short of recommending systematic annual screening of MoMHR implantees for cobaltemia and the manifestations of cobaltism.[18] [21]

American, British, and European surgeons who are continuing to perform resurfacing MoMHR, and developed and promoted stemmed and resurfacing MoMHR in partnership with industry are involved in developing guidelines, supported by American and European Orthopedic organizations, for monitoring the patients fitted with MoMHR.[22] [23] [24] [25] [26] These recommendations recognize the utility of [BCo] to indicate MoMHR implantees with hip symptoms for cross sectional imaging to assess for ARMD and proscribe further stemmed MoMHR implantations. Patients fitted with still popular, resurfacing, MoMHR are at risk for periprosthetic tissue damage, notable cobaltemia, and overt cobaltism, with or without sentinel hip symptoms. Systematic monitoring of MoMHR implantees has not been recommended by the FDA, the MHRA, or by American or European orthopedic profession organizations.[24] [27]

Asymptomatic resurfacing MoMHR implantees with mean [BCo] of 1.7 BET have been studied and found to have echocardiographic cardiomyopathy compared to matched non-cobaltemic MoPHR implantees.[28] Patients with failed ASR or BHR resurfacing MoMHR have mean [BCo] > 10 BET with exceptional patients having levels > 90 BET.[29] [30]

Our serendipitous discovery of the first cases of cobaltism from MoMHR lead us to review the literature for other APC cases and for reports of cobaltism from other etiologies.[31] We found that cobalt poisoning from ingestion has been a known entity since 1948 from use of cobalt as a hematemic or from industrial exposure with neurologic, cardiac, and thyroid manifestations similar to those noted APC case reports. The identification of further Alaskan APC cases in patients implanted with the still popular Birmingham Hip Resurfacing (BHR, Smith and Nephew) leads us to believe that cobaltemia of 10-100 BET and cobaltism may be common in patients implanted with failed stemmed and resurfacing MoMHR of various designs and brands.[32]

This is a three-part study of APC. First, we reviewed published case reports of APC to define the common manifestations and the natural history of cobaltism. Next, the patients that lent their MoMHR explants to the Alaskan Total Joint Explant and Implant Registry (AkTJEIR) were reviewed to determine if they were cobaltemic, experienced manifestations of cobaltism, and whether their cobaltemia and their possible resultant illness resolved after MoMHR explantation. Finally, we reviewed the patients that ST implanted with MoMHR for cobaltemia and manifest.

Materials and Methods

Review of 15 Reports of APC

We used "*Google Scholar*" to perform a keyword search of cobalt poisoning, hip replacement, and cobaltism, to identify published case reports of APC. The references of these reports were reviewed to identify additional cases. Seven reports note a MoCWM, including a fatality from cardiomyopathy. [1 33-38] Eight reports describe a MoMWM: four Australians, three Alaskans, and one European.[2 3 7 32 39-43]

The cases were then rank ordered by illness severity and the latency to a particular cobaltism manifestation was abstracted (Table 1). We categorized the symptoms and findings of cobaltism as being constitutional, psychological, neurological, cardiac, or thyropathic and they were classified as being prodromal, mild, moderate, severe, or potentially fatal (Table 2).

Table 1: The 15 case reports of Arthroprosthetic Cobaltism (APC)

Case Report	Rank order by Illness severity	Cobaltism Class	[BCo] (BETs)	Wear Mechanism	Sex	Age at time of MoMHR	(MPC)	[BCo] * (MPC)	Months to illness	Months to severe neuro or cardiac problem	Months of surplus illness	Manifestations of Cobaltism	Reversibility
Quickenborne	1	Mild	64	MoM	F	49	60	3840	36		24	Deafness.	Complete.
Tower #2	2	Mild	23	MoM	M	49	41	943	8		33	Moody, vertigo, cardiomyopathy.	Largely complete.
Mao #2	3	Mild	15	MoM	M	56	49	746	36		13	Fatigue, weakness, cramps, and memory problems.	Largely complete.
Mao #1	4	Mild	24	MoM	F	68	57	1379	49		8	Imbalance, cognitive decline, weight loss, depression, dysgeusia.	Largely complete.
Ng	5	Moderate	45	MoM	F	34	60	2700	60		1	Minor blindness.	ASR hip not yet revised.
Tower #3	5	Moderate	74	MoM	M	49	38	2818	19		19	Dysgeusia,irritability, disorder sleep, tinnitus, deafness, anxiety, major depression, cognitive decline.	All improved except deafness.
Tower #1	6	Moderate	122	MoM	M	49	42	5124	6		36	Rashes, tinnitus, deafness, mood disorder, minor blindness , cardiomyopathy.	Largely complete.
Machado	7	Severe	14	MoM	M	67	99	1343	72	99	27	Cardiomyopathy requiring hospitalization.	Largely complete.
Megaterio	8	Severe	500	CoM	M	47	16	8000		6	10	Profoundly neuropathic, thyropathy, pericardial effusion.	Not noted.
Steens	9	Severe	398	CoM	M	50	36	14328		24	12	Deaf, neuropathic, blind.	Hearing, sensation, and partial sight return.
Ikeda	10	Severe	400	CoM	F	54	24	9600		20	4	Malaise, deafness, profound neuropathy, thyropathy.	All symptoms and findings improve.
Rizzetti	11	Severe	549	CoM	F	57	18	9882		10	8	Profoundly deaf, blind, and neuropathic, thyropathy.	Improved but still quite blind at 8 months.
Pelcholva	12	Severe	506	CoM	M	50	20	10120		14	6	Profoundly neuropathic, thyropathy, pericardial effusion.	Neuropathy improved, persistent deafness.
Apel	13	Severe	446	CoM	M	60	75	33450	60	72	12	Neuropathy, cardiomyopathy, severe blindness, bulbar palsy.	All problems nearly resolved at 8 months.
Oldenburg	14	Potentially fatal	625	CoM	M	53	9	5625		6	3	Fatigue, cognitive decline, depression, myopathy, dysgeusia, weight loss, neuropathy, deafness, thyropathy, cardiomyopathy requiring ICU.	Heart and thyroid improve but neurologic problems do not. Blood cobalt climbing due to revision to CrCo rather than ceramic head.
Gilbert	15	Potentially fatal	1085	CoM	M	46	14	15190		6	8	Listlessness, 10 kg weight loss, thyropathy, profound cardiomyopathy.	Died of multiple organ failure secondary to cardiomyopathy
Females 5		Means	306			52	41	7818	38	29	14		
Males 10		Medians	260			50	40	5375	36	14	11		

[BCo] Highest noted blood cobalt, BETs multiples of the Biologic Exposure Threshold for Cobalt, (MPC) Months of Likely Cobaltemia, CrCo Chrome-Cobalt

Table 2: The constitutional, psychological, neurologic, cardiovascular, and thyropathic Manifestations of Cobaltism

	Prodromal	Mild	Moderate	Severe	Potentially Fatal
Constitutional	New malaise. Deterioration in sleep quality.	New fatigue. New headaches not resulting in diagnostic tests or treatment. New disordered sleep resulting in hypnotic prescriptions. New notable unusual rashes.	New generalized weakness and pain. Ten to twenty pound unintentional weight loss. New or altered headaches resulting in diagnostic workup or prescription medications.	New listlessness. Greater than twenty pound unintentional weight loss.	Cachexia.
Psychological	New anxiety, irritability, increased or depressed mood that does not result in medical consultation.	New mood symptoms for which medications are prescribed. New minor difficulties with memory or learning.	Diagnosis and treatment of new major mood or thought disorder. Notable new problems with memory or learning.	Dementia or hospital admission for new psychiatric diagnosis.	New involuntary psychiatric inpatient admission. New suicide attempt.
Neurological	New transient numbness hands or feet. New tinnitus.	New high frequency hearing loss. New problems with balance. New sensory neuropathy by electro-diagnostics. Minor non-refractive visual changes. Changes in taste or smell.	New motor-sensory polyneuropathy by electro-diagnostics. New major deafness. New minor blindness from optic neuropathy or retinopathy. New tremor.	New major blindness. New rampant Parkinsonism. New requirement of ambulatory aides because of motor-sensory neuropathy. Hospitalized for new neurologic diagnosis other than CVA.	New seizures.
Cardiovascular	Elevation of resting heart rate. Relative exercise intolerance. New altitude intolerance. New diagnosis of hypertension.	New breathlessness that results in cardiopulmonary work-up.	New non-CAD cardiomyopathy, pericardial effusion, or pericarditis.	New non-CAD cardiomyopathy, pericardial effusion, or pericarditis requiring treatment.	New non-CAD cardiomyopathy, pericardial effusion, or pericarditis requiring intensive care.
Thyroid	New elevations in thyroid antibodies.	New rising TSH, thyroid supplementation not yet indicated.	New symptomatic hypothyroidism, thyroid supplementation indicated.	New profound hypothyroidism or goiter.	Goiter with airway compromise.
	CAD Coronary Artery Disease, CVA Cerebral Vascular Accident				

The Alaskan Series of revised MoMHR

Revision hip surgeons in Anchorage Alaska have encouraged patients to participate in the Dartmouth Biomedical Engineering Center's (DBEC) explant analysis program for 20 years. The Alaskan Total Joint Explant Implant Registry (AkTJEIR) includes all explants from Alaska submitted to DBEC. Patients whose explants are sent to DBEC consent to the analysis of their explants and to the use of their redacted clinical information for research and publication. This collaboration between Alaskan surgeons and DBEC described the mechanism of early catastrophic failures of a popular brand of contemporary thin polyethylene hip socket liners.[44] This work preceded any published recognition of this problem by the arthroprosthetic industry. Industry is charged by the FDA to perform post market surveillance of their implants. The collaborative work of AkTJEIR and DBEC contributed to the redesign of the polyethylene socket liner of many contemporary MoPHR.

Patient Characteristics: Included in the study are all patients with MoMHR explants in the AkTJEIR that had been in situ > 1 year. The MoMHR were revised between 2008 and 2013. There were 26 patients with 28 explanted hips (2 patients with bilateral revision), 13 males and 13 females. The mean age of the group at the time of MoMHR implantation was 48.9 $\pm$ 1.6 years; there was no significant difference in age between genders ($p<0.546$). The average time from primary implantation to revision was 36.8 $\pm$ 4.1 months, with no difference by gender ($p<0.996$). Indications for revision of the MoMHR included progressive mild (4 patients), moderate (12 patients) or severe (7 patients) pain, together with noise from the hip (11 patients) and varying degrees of constitutional, neurologic or cardiovascular symptoms and findings (10 patients). Five of the arthroplasties were hip resurfacings. This series includes three previously published cases of APC. [3 32]

Patients were considered to be cobaltemic if their blood cobalt level was found to be greater than the BET (1 mcg/L) on multiple occasions. Our 26 patients are listed in order of highest noted blood cobalt level in Table 3 with their demographics, explant characteristics, hip symptomatology (pain or noise), and latency to hip symptoms, hip revision surgery, blood cobalt level determination, and whether the patients developed manifestation of cobaltism. Cobaltemic patients were thought to have cobaltism if they developed any of the symptoms or findings of cobaltism noted in Table 1. The diagnosis was considered confirmed if the manifestations of cobaltism improved after MoMHR revision.

Table 3-1: The 26 Alaskan Patients revised for failed MoMHR

Revised Case #	Sex	Age*	Months MoMHR Implanted (MoMoM)	Explant Company Class Type	Latency to hip symptom (Mo)	Progression of hip symptoms	Periprosthetic Indication for Revision	Root causes of arthroplasty failure	Cobalt-ism	Latency to [BCo] (Mo)	Highest [BCo]	[BCo] * (MoMOMHR)
AK01	F	54	16	Wright LHS Conserve	14	Pain with activity, then limp, then rest pain.	Acute severe pain, Acute late periprosthetic sepsis	Indolent ARMD, Late sepsis	No	16	12.0	192
AK02	F	50	13	Biomet LHS Magnum	11	Never pain free then markedly increased pain after some falls. Before revision not able to bear weight.	Increasing severe pain, Migration of shell	Indolent ARMD, Loose Shell	No			
AK03	M	49	21	Zimmer LHS Durom	1	Never pain free and progression to rest pain and limp and the need for a crutch before revision surgery.	Increasing severe pain	Acute ARMD	No	21	0.5	10.5
AK04	M	51	13	Zimmer LHS Durom	1	Never pain free and progression of pain and limp with marked increase in symptoms week of revision surgery raising the question of acute infection.	Increasing severe pain, Late infection	Acute ARMD Late sepsis	No	11	0.5	5.5
AK05	F	47	12	Biomet LHS Magnum	6	Initially did well then progressive pain after jumping to the point or limp and crutches.	Increasing severe pain	Indolent ARMD, Loose Shell	No			
AK06	M	59	28	Biomet LHS Magnum	12	Did well for a year then progressive noise to the point of apparent flatulence with each step.	Progressive mild pain, Progressive noise, Shell migrated	Shell loose, Edge loading	No	16	30.0	840
AK07	M	49	42	DePuy LHS ASR	10	Noted progressive pain with cycling at one year. Over the next three years rest pain and noise progress.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	Yes	10	122.0	5,124
AK08	M	48	41	DePuy LHS ASR	18	Stiffness of hip, rest and activity related pain.	Increasing moderate pain	Indolent ARMD	Yes	15	23.0	943
AK09	F	52	13	S&N MAS R-3	2	Return of groin pain with pushing a bed, pain progressive until revision surgery.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	No	7	46.0	598
AK10	F	45	33	S&N HRA BHR	33	She had no symptoms at the hip.	Osteolysis	Asymptomatic ARMD, Edge Loading	Yes	31	43.0	1,419
AK11	M	68	16	S&N MAS S-3	12	Only hip symptom was noise.	Increasing noise	Asymptomatic ARMD Edge Loading	No	15	60.0	960
AK12	M	46	22	S&N HRA BHR	10	First pain then crepitation, both progressive.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	Yes	21	312.0	6,864
AK13*	F	49	22	S&N HRA BHR	22	Had no symptoms at right hip. Mild pain and grating at the left hip.	Mild stiffness, Milld pain	Indolent ARMD, Edge loading	No	14	140.0	3,080
AK14	F	33	22	Biomet LHS Magnum	16	Increasing pain since time of implantation but marked increase at 16 months.	Chronic moderate pain	Chronic pain not improved by revision surgery	No	19	1.9	42
AK15	F	29	91	Biomet MAS M2A	67	First occasional noise with mild post activity pain. Both progressed until surgery but were never limiting.	Mild increasing pain, Progressive noise	Indolent ARMD, Edge loading	No	80	148.0	13,468

Table 3-2: The 26 Alaskan Patients revised for failed MoMHR continued

Revised Case #	Sex	Age*	Months MoMHR Implanted (MoMoM)	Explant Company Class Type	Latency to hip symptom (Mo)	Progression of hip symptoms	Periprosthetic Indication for Revision	Root causes of arthroplasty failure	Cobalt-ism	Latency to [BCo] (Mo)	Highest [BCo]	[BCo] * (MoMOMHR)
AK16	M	49	38	S&N HRA BHR	3	Squeaking with snow shoeing, then popping and grinding, no pain until 30 months.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	Yes	30	74.0	2,812
AK17	F	55	72	DePuy MAS Ultramet	69	Hip never completely pain free but return to high level of function. During ski vacation markedly increased pain use of a stick.	Sudden increase in pain, Osteolysis, Stem fracture	Asymptomatic ARMD Catastrophic stem failure	No	72	4.4	317
AK18	M	41	60	Zimmer LHS Durom	23	Hip was never symptom free with episodic activity related pain that progressed.	Increasing moderate pain	Indolent ARMD, Edge loading	Maybe	6	4.8	288
AK19	M	44	41	S&N LHS BHRM	5	Started with a squeak, then increasing grinding, then activity pain, then rest pain.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	Yes	38	44.0	1,804
AK20	F	44	38	Biomet LHS Magnum	18	Hip was improved by never symptoms free. Hip became progressively painful and noisier as activities increased.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	No	38	8.7	331
AK21	F	46	33	S&N MAS S-3	8	Progressive grinding and pain that started at about the same time.	Increasing severe pain, Progressive noise	Indolent ARMD, Edge loading	Yes	23	65.0	2,145
AK22	M	43	64	Biomet MAS M2A	47	Increasing pain and grinding at the hip and swelling of the hip area with numbness of the anterior thigh and of the foot.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	Yes	63	62.0	3,968
AK23*	M	45	43	Biomet LHS Magnum	27	Progressive noise and pain, left hip more so than right.	Increasing moderate pain, Progressive noise	Indolent ARMD, Edge loading	Yes	39	116.0	4,988
AK24	F	60	74	Zimmer LHS Durom	72	Progressive grinding and pain that started at about the same time.	Increasing moderate pain, Progressive noise, Migrated shell	Loose shell	No	40	8.9	659
AK25	M	59	62	Zimmer LHS Durom	62	No hip symptoms	No periprosthetic symptoms	Asymptomatic ARMD, Fretting of CrCo Ti taper	Maybe	51	13.0	806
AK26	F	58	54	S&N LHS BHRM	23	Never pain free but improved considerably up until about a year then pain got progressively worse.	Increasing moderate pain	Indolent ARMD	No	40	5.3	286
Means		49	38		23					30	56	2,165
	Females 13	MAS (Modular Acetabulum Stemmed), HRA (Hip Resurfacing Arthroplasty), LHS (Large Head Stemmed)									Median	Median
	Males 13	S&N (Smith and Nephew), ARMD (Adverse Reaction to Metallic Debris), CrCo (Chrome-cobalt), Ti (Titanium)									37	892

The serum cobalt levels, expressed as mcg/L (equivalent to ppb), were measured by inductively coupled plasma mass spectrometry at NMS. Blood was drawn by standard venipuncture, with several red top tubes drawn before the trace element tube (Monoject Trace Element Blood Collection Tube-royal blue top) was filled to flush the needle.

For analyses, patients were divided into two groups, toxic and non-toxic. There were 9 potentially toxic males, 2 toxic females, and 4 nontoxic males and 11 nontoxic females. Nine of the 11 potentially toxic patients had their acquired manifestation of cobaltism improve after explant of their MoMHR. This group was compared the 13 patients that did not develop any problems consistent with cobaltism.

The 11 potentially toxic patients were rank ordered by manifest illness severity and the latency to prodromal, mild, moderate, severe, or potentially fatal constitutional, neurologic or cardiovascular problems tabulated (Table 4).

Table 4: The 11 Alaskans rank order by the severity of acquired cobaltism manifestations

Rank order by illness severity	Identifier	Gender	MoMoHR	[BCo]	First systemic problem	Months to first systemic problem	[BCo] * MoMoHR	Class of Cobaltism	Progression of constitutional and neurologic illness	Resolution of cobaltism manifestations after revision surgery
1*	AK18	M	60	4.8	New hypertension	18	288	Prodromal		Not resolved.
2	AK10	F	33	43.0	Irritability, Anxiety, Tinnitus.	29	1419	Prodromal	Gradual onset, symptoms relatively minor.	Mood and cognition returned to baseline post revision, tinnitus less notable.
3	AK19	M	41	44.0	Irritability	33	1804	Prodromal	Followed by forgetfulness and minor depression.	At one year follow up after revision operation all psychological symptoms resolved
4	AK22	M	64	62.0	Tinnitus	47	1968	Mild	Followed by destabilization of pre-existing mood disorder with increased anxiety and depression. Sleep quality and cognition decline.	Largely resolved and residual anxiety may related to increased psychosocial stresses.
5	AK08	M	41	23.0	Irritability, Vertigo	8	943	Mild	Followed by relative depression. Progressive minor deafness, minor cognitive decline.	Mood and cognition improved notably.
6*	AK25	M	66	13.0	Imbalance	30	803	Moderate	The urinary urgency. Minor increase in ventricles, got a VP shunting procedure without improvement. Over the next year develops memory issues and problems getting lost and with spatial issues	Not resolved.
7	AK21	F	33	65.0	Irritability	8	2145	Moderate	Following by destabilization of pre-existing depression, manic features become major issue required marked escalation in care. Headaches become more severe and change to a frontal pattern. Tinnitus, deafness, and memory issues come later.	Markedly improved mood, function, and headaches. Psychotropic medications reduced as well as frequency of ER visits.
8	AK16	M	38	74.0	Tinnitus, Irritability, Poor Sleep	19	2812	Moderate	Followed by diminished taste, then 16 months post irritability and poor sleep, mind racing, increased anxiety, at 18 months major depression, then poor memory, spatial skills, and difficulty with numbers. Metallic taste from 30 months to revision	Mood and cognition improved notably and relatively quickly.Deafness and tinnitus remain, he is considering hearing aides.
9	AK07	M	42	122.0	Poor Sleep, Increased Anxiety, Irritability	6	5124	Moderate	Followed by hypomania, panic attacks, obsessive compulsive behaviors tinnitus, deafness, imbalance, tremor, depression, retinopathy, and minor cognitive decline. See figure 1.	Remarkable improvement in mood and cognition during first several months post MoM explant. Then continued gradual improvement.
10	AK12	M	22	312.0	Irritability, Increased Anxiety and Panic Attacks.	16	6864	Moderate	Followed by tinnitus and deafness, moderate cognitive decline (memory). Progressive deafness, patient cannot afford recommended hearing aides.	Memory definitely improved. Other problems largely unchanged.
11	AK23	M	43	116.0	Progressive Parkinson's	7	4988	Severe	Followed by depression, anxiety, panic attacks, poor memory, auditory hallucinations, and difficulty finding words. Unable to work in accustomed profession.	He feels much better was able to turn off brain stimulator and reduce Parkinson's medications. Mood and anxiety much better.
		1* and 6* not yet confirmed by reversibility, [BCo] Highest noted blood cobalt, MoMoMHR Months MoMHR implanted								

ST first implanted a MoMHR in 2006 and last implanted one in 2007, all the MoMHR that he performed during that interval were identified and those cases reviewed (Table 5).

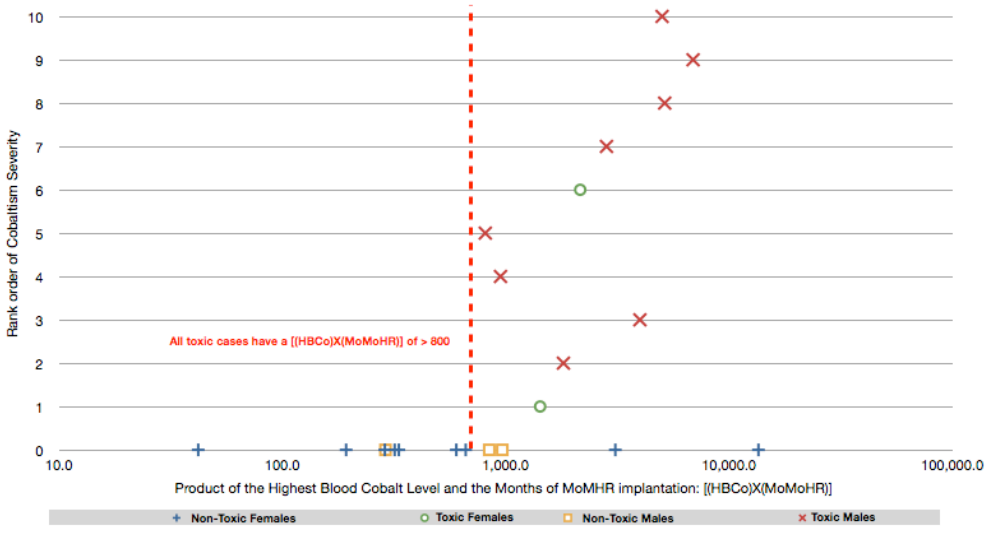
Table 5: The six Alaskans that ST implanted with MoMHR

Case	Sex	Age*	Explant Company Class Type	Problem consistent with Cobaltism	Months to symptom consistent with cobaltism (MoToSxCobaltism)	BLood cobalt [BCo] mcg/L	[BCo] * (MoSxCobaltism)	Months to explant of MoMHR (MoMoMHR)	[BCo] * (MoMOMHR) at Explant	Months to hip symptom	Progression of hip symptoms
ST1 (AK06)	M	59	Biomet LHS Magnum	-	-	30.0	-	29	870	12	Did well for a year then progressive noise to the point of apparent flatulence with each step.
ST2 (AK08)	M	48	DePuy LHS ASR	New vertigo, hypertension, and cardiomyopathy	21	23.0	478	42	972	18	Stiffness of hip, rest and activity related pain.
ST3	M	41	Zimmer LHS Durom	Decompensated cardiomyopathy	53	16*	842*	-	-	-	Minimal stable symptoms at hip. MoMHR remains in situ.
ST4	M	60	Zimmer LHS Durom	New peri-aortic lymphoma	61	6.1	372	-	-	-	No symptoms at hip. MoMHR remains in situ.
ST5 (AK18)	M	41	Zimmer LHS Durom	New Hypertension	24	4.8	117	63	301	23	Hip was never symptom free but pain became progressive as 18 months.
ST6	M	47	Biomet LHS Magnum	Cor Pulmonale Death	17	16*	277*	-	-	-	No problems at the hip were noted during patients final hospitalization.
Means		49			35	16*	322	45		18	
Notes	* Cases ST3 [BCo], when last evaluated was not elevated but blood chromium was. He has been bed to chair for months because of a CVA, blood cobalt clears rapidly if the MoMHR is not being cycled, chromium lingers, we used the mean [BCo] of 16 from cases ST1, ST2, ST4 as an approximation of what ST3's level was before he was incapacitated. Case ST6 never had a [BCo], the mean value of 16 was also used as an approximation in that case.										

The MoMHR of three patients are explanted (AK06, AK08, AK18). AK08 had confirmed cobaltism. AK18's cobaltism is unconfirmed because his hypertension is unchanged 6 months after resolution of his cobaltemia. Three patients have not been revised, two developed decompensated cardiomyopathy, one with fatal outcome. Both men were alcoholic, cobalt and alcohol are known to be synergistically toxic to the heart. [45-49] The remaining patient developed an atypical abdominal lymphoma 61 months after implantation of his MoMHR. The tumor was in the lymphatic drainage of the hip. An increased incidence of lymphoma has been reported in MoMHR implantees. [50]

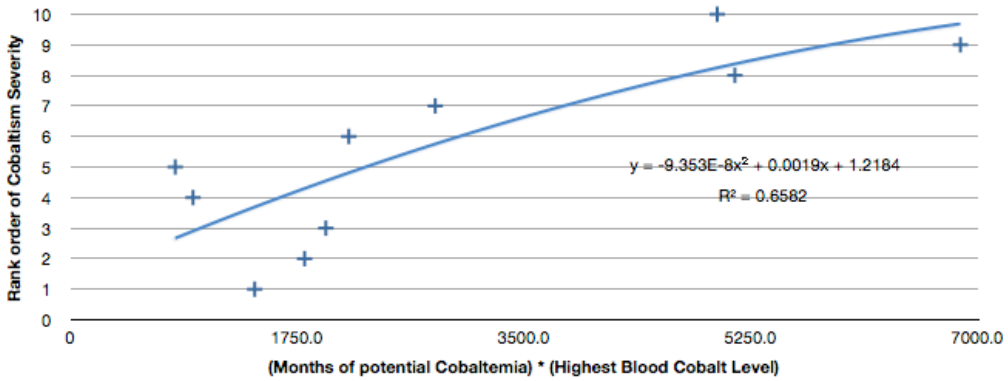
Results

Figure 2: Relationship of gender, blood cobalt, and MoMHR implantation time to manifest Cobaltism in 26 Alaskans.



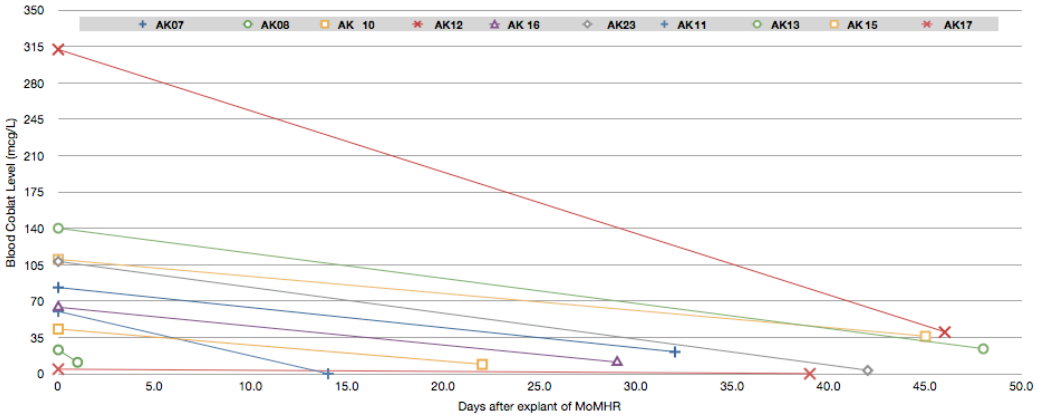
The manifestations and severity of cobaltism appear to be a function of the Months of MoMHR implantation (MoMoMHR), the degree of cobaltemia [BCo], and individual susceptibility. Males appear to be more likely to manifest cobaltism, and there are two outlying females with high blood [BCo] and high (MoMoMHR) that did not become toxic. Half of our subjects are women, only 2 became toxic. There was no significant difference between genders of age, [BCo], or (MoMoMHR). Our men were significantly more likely to manifest cobaltism than the women (Chi^2, p< ???). None of our patients with a ([BCo]) (MoMoMHR) < 800 developed toxicity.

Figure 3: Relationship of Cobaltemia and MoMHR implantation time to confirmed Cobaltism in 9 Alaskans.



In those patients that do become toxic, the severity of the manifest illness correlates significantly (R^2 = 0.655, p< 0.??) with the duration and magnitude of the cobaltemia.

Figure 4: Drop in blood [BCo] in 10 Alaskans 3-50 days post explant of MoMHR.



Nine of 11 potentially toxic Alaskans experienced constitutional, psychological, or audio-vestibular symptoms during their periods of cobaltemia that improved after revision surgery and decline of their [BCo]. The exceptional cases are only 6 months post revision surgery, one has not yet noted improvement of his neuropathy, the other's acquired hypertension remains unresolved. Disordered mood and diminished cognition recovered within months of explant of the MoMHR in the 9 patients with confirmed cobaltism. Acquired deafness, blindness, rashes and cardiomyopathies required years to resolve in our patients with longest follow-up, AK07 and AK08. AK23 experienced remarkable recovery of "soft" and "hard" neurologic deficits within the first year following his MoMHR explantation: his depression, cognitive decline, and severe Parkinsonism largely resolved. He has turned off his deep brain stimulator and reduced or discontinued psychotropic and Parkinson's medications. Our patients experienced on average 22 months of systemic illness before their MoMHR were explanted.

The guidelines embraced by the FDA and American and European orthopedic organizations for monitoring patients with MoMHR rely on the patient presenting to their surgeon with increasing hip symptoms to trigger a screening [BCo]. Several of our toxic patients did not have hip symptoms. Many others developed tolerable hip symptoms after the manifestations of systemic illness.

Two patients (AK25 and Ak23) underwent neurosurgical procedures for neurologic problems likely secondary to their cobaltemia. Ak23 acquired motor-sensory peripheral neuropathy: a complication frequently noted in MoCWM case reports. His [BCo] was relatively low but he had a long duration of potential cobaltemia and a lengthy latency before neuropathic symptoms. Disordered mood was the presenting symptom in 9 of 11 of our potentially toxic patients and was the major morbid factor in our 9 confirmed cases.

Five of our ten toxic patients had echocardiograms before revision surgery and were found to have cardiomyopathy. Four of five of these male patients were mildly symptomatic: they developed relative exercise intolerance. Their baseline fitness returned within three years after MoMHR explantation. Only AK07 had a repeat echocardiogram at 2 years post revision surgery, his myocardial function returned to its pre-ASR hip baseline.

Discussion

The AkTJEIR has likely not captured all MoMHR explanted in Alaska. The number of Alaskans implanted with MoMHR is unknown, as is the incidence and magnitude of their cobaltemia. Despite these unknowns the Alaskan series provides some information about the epidemiology of cobaltemia and cobaltism in patients indicated for revision surgery of a MoMHR. Patients indicated for MoMHR revision are likely to be notably cobaltemic, many will have prodromal or mild cobaltism, some of the more severely exposed patients will have moderate or severe cobaltism, and some patients will not manifest toxicity despite notable cobaltemia of significant durations.

The relationship of cobaltemia to ARMD and eventual revision of MoMHR is known.[28] It is also know that MoMHR are being revised at accelerating rates.[51] Our finding that cobaltism is common in patients with a [BCo] > 20 BET suggests that cobaltism was either unappreciated or unreported in the tens of thousands of patients already explanted of their MoMHR and is likely to be experienced by hundreds of thousands of cobaltemic MoMHR implantees. Patients fitted with MoMHR are at risk to experience months or years of surplus systemic morbidity unless systematic blood cobalt screening programs for this at risk population are instituted.

The center that reported the European APC case has identified three additional cases of cobaltism (reversible deafness) in their patients with notable cobaltemia from resurfacing MoMHR. They have also surveyed their hip resurfacing patients with an instrument designed to screen workers for cobaltism and found that the constitutional, psychological, neurological, and cardiomyopathic symptoms of cobaltism are common in patients with [BCo] > 20 BET.[42 52] The clustering of known APC cases at centers and regions that published the sentinel reports of APC suggest that prodromal through moderate cobaltism are common in patients cobaltemic from their MoMHR. The paucity of reporting suggests that most cases of APC are either unrecognized, unreported, or that the rather common prodromal through mild manifestations of cobaltism are attributed to normal aging or to other etiologies.

Significant reversibility of the constitutional, neurologic, cardiac, and thyroid toxicity within months or years of removal of rapidly wearing chrome-cobalt hip implants with the normalization of [BCo] has been noted in most nonfatal cases of ACP, but the duration of reported follow-up in these patients is short. It is not know whether patients that experienced prolonged symptomatic or asymptomatic cobaltism are at increased risk for late presentation of thyropathy, or constitutional, psychological, neurological, cardiovascular, and oncologic problems long after the resolution of their cobaltemia. An increased incidence of lymphoma and leukemia has been noted in patients fitted with MoMHR, this risk has not been stratified by the degree of blood cobalt or chromium elevations. A generalized increase risk of malignancy has not yet been noted in patients fitted with MoMHR compared to patients with fitted with MoPHR or patients without hip implants.[50] ST4's atypical lymphoma downstream of his asymptomatic Zimmer Durom MoMHR is concerning, his [BCo] is 7 BET, and he had a likely period of cobaltemia of 5 years before his ureter became obstructed by the tumor. He has no hip symptoms and there is no evident ARMD on MRI.

Our five male patients with cardiac APC consume moderate alcohol. Epidemics of cardiomyopathy in largely male over-imbibers of certain brands of inexpensive beer with a head stabilizing cobalt additive were first reported 45 years ago.[53] Thyroid histopathology was a clue to the etiology of these case clusters although hypothyroidism and goiter were not commonly noted clinical manifestations in these patients that presented in Montreal in extermis.[54] Alcohol and cobaltemia are synergistically toxic to the heart.[45-49] However, alcohol consumption is not required for a patient to manifest cardiac cobaltism, the patient reported by Machado with isolated severe, reversible cardiomyopathy from MoMWM cobaltemia of 14 BET was noted to be teetotaler.[40] Cobalt concentrations in myocardial tissue and pericardial effusions are notably higher than that found in the blood in patients with cardiac cobaltism, this ability of myocardium to "concentrate" cobalt is concerning as patient's because patients with "well functioning" MoMHR may be cobaltemic for decades.[1 37 46 55-57] Chronic, low grade, cobalt exposure is a know risk factor for cardiomyopathy.[58]

Another concern pertinent to the aging population of a million MoMHR implantees is the eventual decline in their renal cobalt clearance. MoMHR with a 28 mm head were known to be tribolically superior to resurfacing MoMHR with the median [BCo] of patients fitted with the 28 mm MoMHR being < 1 BET. Several patients with renal failure unrelated to their 28 mm MoMHR were been reported to have [BCo] > 100 BET before starting dialysis.[59]

Ingestion of surplus cobalt has been known since 1948 to potentially result in fatigue, cranial neuropathy (usually audio-vestibular then optic), peripheral neuropathy, cardiomyopathy, hypothyroidism, thyroiditis, and goiters. An infant treated with cobalt chloride for anemia was the apparent index case report of iatrogenic cobaltism. His manifest toxicities included goiter, hypothyroidism, and heart failure.[53] The toxic manifestations in anemic adult patients treated with cobalt chloride included fatigue, tinnitus, deafness, blindness, and peripheral neuropathy.[60 61] Cases of industrial cobaltism have been reported over the past forty years, predominantly in male workers, hence the logic establishing a BET for [BCo], and monitoring [BCo] in workers exposed to cobalt powders and dyes. One male worker died of cardiomyopathy, and another male worker required a heart transplant after large and acute exposures to refined cobalt powder.[56] Deafness, blindness, vestibular dysfunction, and peripheral neuropathy were reported from other vocational exposures.[62] Cobaltism in a male Indian teenager who swallowed cattle magnets was recently published. He had the classic triad of neuropathy (optic), cardiomyopathy, and hypothyroidism with goiter.[63] A male predominance in the reports of iatrogenic, industrial, alcoholic, arthroprosthetic, and miscellaneous cobaltism suggests that males are generally more susceptible to cobaltism than females.

The pathophysiology of neurocobaltism and cardiocobaltism involves cobalt blocking oxidative metabolism at the mitochondrial level resulting in cellular dysfunction or death.[53 64 65] A recent publication confirms that this “hypoxic” mechanism of cobalt toxicity is likely responsible for cobalt’s periprosthetic toxicity.[66] The neurons in the cochlea and retina most susceptible to oxidative stress are those that die in experimentally induced neurocobaltism in rabbits.[67] The effects of cobalt or chromium on mood might be dictated by different mechanisms. Acute cobalt exposure increases neural activity and can result in seizures. Chronic cobalt exposure deletes dopaminergic pathways and is an experimental model for endogenous depression.[53 65] Chromium is known to potentiate antidepressant medication and may explain the antecedent irritability and anxiety noted in some of the Alaskan patients that later became depressed.[68] There is individual variability in serum protein binding of cobalt and the avidity of cell membrane metal transport proteins for cobalt that might explain why some individuals are relatively immune to cobalt’s toxic effects.[69]

Cobaltism by ingestion was noted in 1948, ARMD and arthroplasty related cobaltemia were described in 1975, and a case report of arthroprosthetic cobaltism was published 2001.[53 57 1] Yet, the seminal literature that promoted the reintroduction of MoMHR for resurfacing and stemmed application dismissed the possibility of periprosthetic or systemic toxicity of chrome-cobalt metallosis as theoretical abstractions.[70 71 72-74 6 75] It is notable that the principle authors of these publications are either design surgeons of MoMHR or arthroprosthetic industrial consultants and that these same “experts” are those that are crafting the monitoring guidelines embraced by American and European orthopedic organizations to monitor MoMHR implantees. They also write the review papers in the orthopedic literature that drive trends in arthroprosthetic practice.[8 22 23 76 24 77 78] The fundamental flaw in the arthroprosthetic implant premarket, market, and post-market processes that allowed for the a million patients to be implanted with a technology that over months or decades might poison them appears is that a cabal of surgeons, entangled with the arthroprosthetic industry, dominate arthroprosthetic research and the content that is presented to the orthopedists in publications and presentations. These surgeons are those that the FDA and the MRHA turn to for information to guide regulatory action.[79]

The cobaltemia resulting from the MoMWM is generally not as severe as that associated with the MoCWM and the reported illnesses less severe. Only one MoCWM cases report notes a prodrome of depression and “mental inefficiency” that predated deafness, blindness, hypothyroidism and heart failure.[34] It is possible that disordered mood or sleep, cognitive decline, and fatigue were a common prelude to the deafness, blindness, peripheral neuropathy, heart failure, and hypothyroidism or goiter common to the MoCWM cases but this prodrome became overshadowed by the later profound neuropathy, deafness, blindness and outright heart failure. Our APC cases and the others suggest that manifest cobaltism and its severity are a function of the magnitude and duration of the cobaltemia. Patients with greater degrees of cobaltemia likely have shorter latencies to manifest toxicity, multiple involved organ systems, and severe illnesses.

Some advocates of continuing resurfacing MoMHR are now concerned about the extreme cobaltemia common to patients with failed MoMHR but they are unconcerned about the low grade cobaltemia seen in most patients with a well functioning MoMHR:[23] *"Cobalt values less than 2 mcg /L are probably devoid of clinical concern, the threshold value for clinical concern is expected to be within the range of 2—7 mcg/L."* It is notable that an ad hoc committee composed partly of hip resurfacing advocates and scientists employed by chose to increase the BET 2 to 7 fold by fiat. Surgeons that worked with arthroprosthetic companies to study, develop, or market MoMHR technology have been slow to recognize the magnitude and frequency of the periprosthetic and systemic complications of periprosthetic chrome-cobalt metallosis, yet they are the "experts" that are commissioned by orthopedic organizations to draft guidelines for monitoring patients implanted with MoMHR.[8 22 80] Conflict of Interest among the orthopedic surgeons that influence arthroprosthetic practice may be counter to patient well being and the greater good.[79]

A recent study of 35 patients with well functioning MoMHR and a mean serum cobalt of 1.7 BET found a notable decrement in echocardiographic function compared to matched non-cobaltemic controls with MoPHR or Ceramic-on-Ceramic Hip Replacement.[28] This finding is consistent with a study that found subclinical echocardiographic cardiomyopathy in cobalt exposed Finnish workers compared to unexposed controls even though the work environment met strict criteria for cobalt dust exposure.[58]

Cobaltemia is common in one million at risk patients implanted with MoMHR and this at risk population is increasing because resurfacing MoMHR remains popular.[25] Scheduled review of the patients with replaced hips is variable by surgeon and patient. Patients may be released from orthopedic care at their first annual visit. Many patients and surgeons may dismiss mild sentinel hip symptoms of periprosthetic chrome-cobalt metallosis because the patient is still greatly improved at the joint compared to their pre-arthroplasty baseline. Many of the toxic patients in our series had significant cobaltism before they developed notable hip symptoms. Even if the surgeon recommends an annual review patient attendance is likely to be poor unless the patient perceives problems with the hip. Even if a patient with APC attends an annual review the surgeon might not inquire about the subtle constitutional, neurologic, and cardiovascular symptoms of cobaltism. The surgeon that implanted a given patient's MoMHR might be reluctant to obtain a [BCo] fearing the implications of an elevated result.

Patients with symptomatic APC are likely to present to primary care, mental health providers, dermatologists, cardiologists, neurologists, ENT specialists, ophthalmologists, nephrologists, and endocrinologists. It is critical that these practitioners are aware the million MoMHR implantees are at risk for cobaltism. The prodromal and mild manifestations of cobaltism are fatigue, rashes, disordered sleep or mood, cognitive decline, imbalance, tinnitus and high frequency hearing loss, and diminished exercise tolerance. The illness can progress to profound deafness, blindness, peripheral neuropathy, neuromuscular disorders, relative dementia, overt heart failure, and thyropathy.

[BCo] determinations are easily obtained. Samples may be drawn by standard venipuncture as long as several red top tubes are drawn before the trace element (royal blue stoppered) tube to flush the needle. Inductively Coupled Mass Spectrometer (ICMS) is the most sensitive cobalt measurement methodology and the test is usually performed at a reference lab. If cobaltemia is reported confirmation with a second sample is recommended.[23 31 81] A [BCo] above 1 mcg/L (the BET) elicits concern in industry.[4] Patients with well functioning MoMHR and an average [BCo] of 1.7 BET have poorer myocardial function that matched non-cobaltemic controls with MoPHR.[28] A blood cobalt above 5 BET is associated with increased risk of periprosthetic masses and tissue necrosis that may or may not be symptomatic.[28] Reported patients with overt arthroprosthetic neurocobaltism or cardiocobaltism had [BCo] of greater than 10 BET, and all but 3 had levels of greater than 20 BET.[1 3 15 33-40 42 82]

Even with the increased awareness of the APC among medical providers many at risk patients will not be optimally screened for cobaltemia unless systematic regional monitoring programs are established. We are in the process of establishing a registry of Alaskan patients implanted with MoMHR to allow for annual monitoring for cobaltemia and manifest cobaltism as recommended by the NPS.[20] Such an effort goes beyond the FDA and AAOS embraced guidelines that focus on recognizing symptomatic periprosthetic complications of chrome-cobalt metallosis at the risk of missing asymptomatic periprosthetic tissue necrosis and not identifying many cobaltemic patients that might be experiencing systemic toxicity without having notable hip symptoms. [18 22 25]

Hip resurfacing MoMHR remains popular. Most patients fitted with hip resurfacings are cobaltemic and are at risk for ARMD and cobaltism. Level I evidence showing offsetting merits of hip resurfacing over stemmed hip arthroplasty is lacking. Further hip resurfacing appear to be a questionable practice. [10 13 16 83 84 85]

Summary

1. Most patients fitted with MoMHR resurfacings are cobaltemic with a median [BCo] of 2 BET. Such levels have been associated with sub-clinical cardiomyopathy, poor memory, and learning deficits.
2. The expression of overt constitutional, neurologic, or cardiac symptoms of cobaltism is a function of the degree of cobaltemia, its duration, gender and individual susceptibility. Males are more likely to manifest cobaltism, and some females appear to be notably "immune" to it.
3. Overt neurologic and cardiac cobaltism has resulted from [BCo] > 10 BET when the period of MoMHR implantation exceeded 3 years. Patients with [BCo] > 20 BET may become symptomatic sooner. Patients with [BCo] > 300BET may become ill after only months of cobaltemia and they present to care with profound cranial and peripheral neuropathies, heart failure, and thyropathy.
4. About one million patients have been implanted with MoMHR over the past decade. Only a fraction of these patients have likely had a [BCo]. No systematic regional programs have been instituted to insure that MoMHR implantees are screened for cobaltemia and cobaltism. Annual [BCo] have been recommended by the FDA, the MHRA, and "consensus" groups of American, and European "stake holders" for patient subgroups with "high risk" MoMHR or those with "low risk" implants that have hip symptoms. These guidelines neglect the cobaltemic patient without hip symptoms and rely on the surgeon to order the [BCo]. There are no specific recommendations for the assessment of cobaltemic patients for constitutional symptoms, mood or cognitive disorders, peripheral or cranial neuropathies, motor disorders, or thryopathy outside of those furthered by the NPS.

Recommendations

1. All patients with MoMHR are at risk for cobaltemia as defined as a [BCo] above the BET of 1 mcg/L (1 ppb). Annual monitoring of [BCo] is indicated in all patients implanted with MoMHR. Such screening needs to be systematic and not dependent on the implanting surgeon because many cobaltemic patients will not have sentinel symptoms at the hip, the implanting surgeon might be loathe to order the test, and attendance at annual review with the surgeon might either not be recommended by the surgeon or not attended by the patient.
2. Patients found to be cobaltemic ought to have a confirmatory test and a through review for new constitutional symptoms (fatigue, rashes, disordered sleep or mood, headaches or impaired cognition, weight loss), cranial neuropathy (most commonly the audio-vestibular then optic), peripheral neuropathy (usually sensory then motor), neuromuscular dysfunction (tremor, weakness, cramping, or seizures), subtle clinical (exercise intolerance) or subclinical cardiomyopathy (contractile dysfunction, pericardial effusion, or pericarditis), and thyropathy (immune and non-immune thyroiditis, goiter, or hypothyroidism) should be conducted. This review and examination might be best accomplished by the patient's primary medical provider and it important that medical providers list implantation of a MoMHR on the patient's problem list.
3. Patients with [BCo] of greater than 10 BET are at high risk for failure of their MoMHR from ARMD and for overt cobaltism. Revision of the chrome-cobalt implants to titanium, polyethylene, or ceramic components ought to be considered.
4. The MoMHR debacle demonstrates that an arthroprosthetic implant development, regulatory, and post market surveillance systems that are dominated by industry can jeopardize public health. Significant reform of these processes are required to recognize and control the influence of the surgeons and researchers compensated by the arthroprosthetic industry on orthopedic professional organizations, regulatory agencies, the orthopedic literature, and the CME content at orthopedic meetings.

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