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Testing serum cobalt and chromium in people with metal-on-metal hip replacements

Metal-on-metal hip replacements and resurfacings are associated with higher than acceptable failure rates, and particularly high-risk devices have been recalled. While the number of patients exposed to high-risk prostheses in New Zealand is low, the media coverage of the issue is likely to have caused anxiety in the large number of people who have received hip replacements. Identifying patients who have received a metal-on-metal hip prosthesis and regularly reviewing any symptoms and monitoring serum cobalt and chromium levels will help to detect those with potentially failing devices, and provide reassurance to others.

Hip replacements and metal toxicity

A metal-on-metal hip prosthesis refers to a device in which the head on top of the femoral stem and the bearing surface of the acetabular cup are made of a cobalt-chromium alloy rather than ceramic or polyethylene. In New Zealand the number of people with metal-on-metal hip prostheses is low relative to other countries. Of the approximately 7000 hip replacements performed in New Zealand each year,¹ metal-on-metal implant prostheses account for only 8% of the total.² A small percentage of these metal-on-metal devices are considered at higher risk for failure. However, world-wide media coverage of this issue is likely to cause anxiety among people with a hip replacement regardless of their actual risk. In 2012, Medsafe issued a statement advising orthopaedic surgeons to contact patients who have had a higher risk metal-on-metal prosthesis implanted, notifying them of the potential problem. These devices have now been recalled and are no longer used.

Modern prostheses rarely fail, regardless of construction material. Metal-on-metal hip prostheses have a failure rate that is higher than is generally acceptable for medical devices, however, the majority of people with a metal-on-metal hip replacement will have few or no problems with the prosthesis.

Failure of a metal-on-metal prosthesis is a complex end-point, which primarily occurs due to one of two reasons. Firstly, the level of natural lubrication that occurs in shallow artificial acetabular components, i.e. the piece that forms the cup of the joint, is less than ideal. In addition, when uneven loading on the outer edge of the implanted cup occurs due to poor placement of the components, friction increases. These two factors accelerate wear, generating more wear debris.³ These fragments, which are small and contain high levels of metal ions, accumulate in the joint and in the surrounding tissue, causing soft tissue and bone damage. Eventually these ions diffuse into the blood stream, potentially (but rarely) causing toxicity and hypersensitivity reactions. The metal ions are excreted through the kidneys.³

The second major cause of wear debris is from the head/stem junction of the prosthesis, where the stem is connected to the ball-like head of the joint. This is called the taper junction, as the insert is shaped like a tapered cone. Wear at this connection is caused by loosening of the taper junction, and rubbing between the insert and its socket. This is of particular concern, and much more likely, if the head diameter of the joint is large, due to increased torque. This wear leads to a similar end-

point of tissue and systemic damage from the resulting particulate and metal ion production.⁷

Patients may require surgery to remove and replace the worn device, and for resection of necrotic tissue associated with the high levels of ionic metal in the tissue around the artificial joint.

Which devices are more likely to require revision?

The **majority** of people with metal-on-metal or metal component hip replacements will not require revision (replacement of the faulty prosthesis), or be exposed to excessive metal ions.⁴

The prostheses associated with increased risk are larger sized metal-on-metal hip joint replacements and hip resurfacing implants. The **ASR** made by DePuy, Johnson & Johnson, has received the most extensive media coverage and is well known to be high-risk, but all similar devices are also of concern. People with a prosthesis that has a smaller femoral head (i.e. 28 and 32 mm), especially "**Metasul**" brand, appear to have lower rates of artificial joint failure requiring surgery over the long-term.

Metal-on-metal devices were primarily used in younger people with a longer expected lifespan and a higher level of physical activity. This was because metal devices were originally thought to have a **lower rate of wear**, would not fracture, were "self polishing" and were less likely to require replacement over the life-time of the patient.

Warning signs that a metal-on-metal prosthesis has failed include **osteolytic cysts** in the adjacent bone and bone loss around the margins of the implant. This may be initially identified in a primary care setting as **soft tissue swelling** and pain around the joint.

Metal-on-metal hip prostheses are divided into **four** groups based on their risk of revision, although all four groups have a greater than acceptable failure rate. The groups are, from lower risk to higher risk:

1. Metal-on-metal hip resurfacing implants
2. Metal-on-metal total hip replacements with head diameter < 36 mm
3. Metal-on-metal total hip replacements with head diameter ≥ 36 mm
4. DePuy ASRTM hip replacements comprising:
 1. ASR acetabular cups for hip resurfacing arthroplasty or total hip replacement
 2. ASR surface replacement heads for hip resurfacing arthroplasty
 3. ASR XL femoral heads for total hip replacement

How high is the failure rate?

An acceptable failure rate for hip prostheses, regardless of construction material, is considered to be **less than 1% per year for all causes**. The rate for most hip prostheses is well under this.⁵ However, average failure rates for metal-on-metal prostheses at seven years are 11.8% for resurfacing and 13.6% for total hip replacement: higher than the acceptable minimum.⁶ **The DePuy ASR XL size device, now recalled, has a failure rate of 49% at six years.**⁷ The expected lifetime of a hip prosthesis is at least 15 years, although this varies with build material.³

Any metal component increases the risk of metal ion toxicity

Any artificial joint that contains at least one component that is made from cobalt-chromium metal will increase serum metal ion levels and has the potential to result in metal toxicity if the device is faulty, such as a loose metal head on a stem.

Consider other possible causes of cobalt or chromium toxicity

In a person **with raised metal ion levels**, practitioners should consider other possible causes that may explain abnormal findings, such as chronic occupational exposure (e.g. potters, ceramicists, metallurgists) other metal implants, excessive use of dietary supplements or renal insufficiency.

What can primary care do to reduce the risk of harm to these patients?

It is important that general practices are aware of those patients who have metal hip prostheses, know how to recognise local symptoms and identify increasing levels of metal toxicity, and know what to do if it appears a device is failing.

Identify patients who have had a hip replacement

Medsafe has recommended that orthopaedic surgeons contact all patients with ASR DePuy prostheses, and some other high-risk brands, to notify them of the increased likelihood of failure. Patients with the highest risk devices should therefore be aware of this.

General Practice may need to identify other patients with a lower risk metal-on-metal device. The patient's hospital discharge summary can be reviewed and the type of prosthesis used recorded in their notes. People with metal hip prostheses will require regular follow-up for the life of their prosthesis, and should have a prompt or note added to their patient record. It is important to emphasise to patients that the overall risk of failure or metal toxicity is low (unless they have one of the identified highest risk devices).

Recognising patients with a faulty or worn prosthesis

Patients with a worn or faulty prosthesis may present with localised symptoms or systemic illness due to metal ion toxicity or sensitivity reactions.

Local symptoms are caused by the build-up of nanoparticles of metal in the soft tissue around the joint, causing inflammation, metallosis (build-up of metals in soft tissue), osteolysis (bone loss) and tissue necrosis. Local symptoms associated with prosthesis wear or **failure** include:⁸

- Pain
- Swelling, due to fluid collection and inflammatory reactions
- Limping or trouble walking or moving the joint
- Noise coming from the joint such as clunking or squeaking

Patients with localised symptoms, or symptoms associated with prosthesis wear, should be referred to their orthopaedic surgeon.

Systemic symptoms are less likely, but are caused when the accumulation of metal in local tissues begins to be absorbed and metal ions enter general circulation.

The relationship between symptomatic illness and cobalt or chromium levels, or the effects of duration or level of exposure, has not been established.⁵ The direct clinical consequences of cobalt and chromium are also poorly understood.⁹ In addition, the symptoms related to elevated serum metal ion levels can be due to either true toxicity (often termed cobaltism) or due to a hypersensitivity reaction to serum metals.¹⁰ True cobaltism is rare and is generally only seen when serum ion levels rise above 20 - 200 times the normal reference ranges (see opposite). Hypersensitivity reactions, although also poorly understood, are more common and may occur at much lower metal ion levels in some people.

The symptoms of cobalt and chromium toxicity may include:^{5,8,11,12}

- Neurological dysfunction - co-ordination problems, cognitive decline, depression, vertigo, peripheral neuropathy, tremors, hearing loss and visual changes
- Cardiac disorders - arrhythmias and cardiomyopathy
- Hypersensitivity reactions
- Immune dysfunction

Patients with systemic symptoms thought to be related to their hip prosthesis should be referred to their orthopaedic surgeon.

Urine or whole blood cobalt and chromium testing is not recommended

Serum cobalt and chromium is the recommended test for detecting these metal ions in people with metal-on-metal hip replacements.

Whole blood cobalt and chromium testing can be used to monitor levels in people with metal hip replacements, but has limited availability in New Zealand. Reference values differ from levels observed in serum testing.

Urine testing is available for assessing occupational exposure to heavy metal ions. This type of testing is not appropriate for people with metal-on-metal implants as heavy metals are excreted too quickly in urine to be found at detectable levels from an implant. Heavy metals may be present in the patient's hair, which can provide a time-line, although this is unlikely to be of clinical relevance in primary care as the date of exposure is known.

Certain patients are at increased risk

Certain people may have an increased risk of soft tissue, and possibly systemic, reactions as a result of the debris produced by a failing joint.

Risk factors include:⁹

- Being very active
- Being significantly overweight
- Having renal impairment or insufficiency
- Having bilateral implants rather than unilateral

People who have several of these risk factors should be monitored more closely (see above), and have a lower threshold for referral to hospital care.

Investigations in people with metal-on-metal hip prostheses

Investigation of a patient with a suspected failure of a metal-on-metal hip prosthesis includes serum cobalt and chromium ion concentrations and referral for imaging with ultrasound scan. If more precise imaging is required CT scanning may be organised by the orthopaedic surgeon. MRI scanning image quality is degraded by metal particles in the tissues and by the implants themselves and is therefore less useful.

Who should be followed-up?

Organise laboratory investigations and imaging for patients with metal-on-metal hip replacements who have:

- Local symptoms
- Symptoms of metal toxicity
- A higher risk prosthesis (DePuy or devices with a head diameter ≥ 36 mm)

Annual testing will then be required for the life of the prosthesis.

Interpreting serum cobalt and chromium levels

Both chromium and cobalt can be tested from a single serum sample, and can be requested on a laboratory form as with other biochemistry investigations.

The laboratory reference range for cobalt is < 12 nmol/L and for chromium is $1 - 8$ nmol/L.¹³ However, cobalt and chromium levels are raised in most people in the first 12 - 18 months after a metal-on-metal implant is inserted, and will usually remain elevated for the life of the prosthesis.

There is currently no consensus on the threshold level of metal ions in the blood at which adverse systemic effects begin appearing or which should serve as a trigger for intervention. The United Kingdom's Medicines and Healthcare products Regulatory Agency suggests that serum levels above

119 nmol/L for cobalt or 134.5 nmol/L for chromium (7 parts per billion for both), are clinically significant.¹⁴ Below these levels, soft tissue reactions and damage appear to be less likely, although levels above these do not necessarily mean that damage is occurring.¹⁴

In general, serum cobalt and chromium will affect people with a metal-on-metal prosthesis in one of three ways:

1. The majority of people will have elevated levels of serum ions, often several fold, but will be asymptomatic and not require revision
2. In a small number of people, systemic reactions will occur due to elevated serum ion levels, however, the relationship of symptoms to ion levels is not well understood and is not linear. There may be an underlying immunological reaction to the serum metals, and these people will require further assessment.
3. A very small number of patients will have extremely high serum ion levels and exhibit true cobaltism (often several hundred times the reference ranges), and may require revision

If cobalt and chromium levels are abnormally elevated, repeat the tests after three months. If levels from the second test remain abnormally elevated, discussion with the orthopaedic surgeon is recommended.¹⁵

Funding for hip prosthesis revision and investigations

In some cases, the manufacturers of faulty devices are meeting the costs of revision surgery, should it be required. This would be arranged through the orthopaedic surgeon.

ACC provides a range of assistance for people with medical misadventures, depending on the specific nature of the injury and the person's circumstances. Revision of a hip prosthesis due to a faulty device may be covered. Assistance may include:

- Contributions towards treatment costs
- Compensation for lost income
- Compensation or help, e.g. with childcare, household activities

A claim should be lodged when prosthesis failure is identified.¹⁹

Ultrasound scanning of the joint

Patients with high-risk prostheses should be referred for ultrasound imaging.

If imaging shows soft tissue reactions, fluid collections or masses, referral to the orthopaedic surgeon is required.¹⁶ N.B. Smaller masses and collections are likely to be missed with ultrasound.

X-ray of the joint is not likely to be useful as changes are only visible in advanced lesions with complicated osteolysis and severe soft-tissue reactions.¹⁶ However, occasionally a "standing AP hips" view and a "shoot-through lateral" may be requested by the orthopaedic surgeon to identify patients with poor alignment of components, potentially refining the index of suspicion.

Regular follow-up is recommended thereafter

Annual follow-up, including serum ion testing and ultrasound of the joint, for the life of their prosthesis is required for people with:^{15,17}

- Metal-on-metal DePuy ASR replacement
- Hip prostheses with a femoral head larger than 36 mm
- Local symptoms
- Symptoms of metal ion toxicity

There is no consensus on routine testing in asymptomatic people with smaller femoral head replacements or a hip resurfacing. However, there is unlikely to be benefit in routine, annual testing of asymptomatic people in this group.^{14,18}

 Medsafe has produced a Question and Answer page that covers many of the issues for people with metal-on-metal hip replacements, such as "Is there an associated risk of cancer?" or "What should I do if I have a metal hip implant?"

Patients can be referred to this resource at: [www.medsafe.govt.nz](http://www.medsafe.govt.nz/hot/recallactionnoticesnew/metalonmetalhipimplants/MetalonMetalHipImplantsFAQ.asp)
(<http://www.medsafe.govt.nz/hot/recallactionnoticesnew/metalonmetalhipimplants/MetalonMetalHipImplantsFAQ.asp>)

ACKNOWLEDGEMENT

Thank you to **Mr P. James Burn**, Consultant Orthopaedic Surgeon, Canterbury DHB, Southern Cross and St George's Hospitals, Christchurch and **Dr Cam Kyle**, Clinical Director of Biochemistry and Immunology, Diagnostic Medlab, Auckland for expert guidance in developing this article.

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