best tests

December 2012

Metal-on-metal hip replacements

When to use fasting glucose

bpac nz
better medicine

We would like to acknowledge the following people for their guidance and expertise in developing this edition:

Mr P. James Burn, Christchurch

Dr Cam Kyle, Auckland

Best Tests is published and owned by bpac^{nz} Ltd

Bpac^{nz} Ltd is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

Bpac^{nz} Ltd has five shareholders: Procare Health, South Link Health, General Practice NZ, Pegasus Health and the University of Otago.

Bpac^{nz} Ltd is currently funded through contracts with PHARMAC and DHB Shared Services.

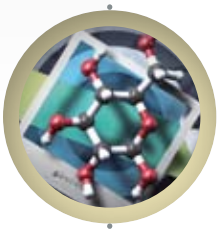
Contact us:

Mail: P.O. Box 6032, Dunedin
Email: editor@bpac.org.nz
Free-fax: 0800 27 22 69

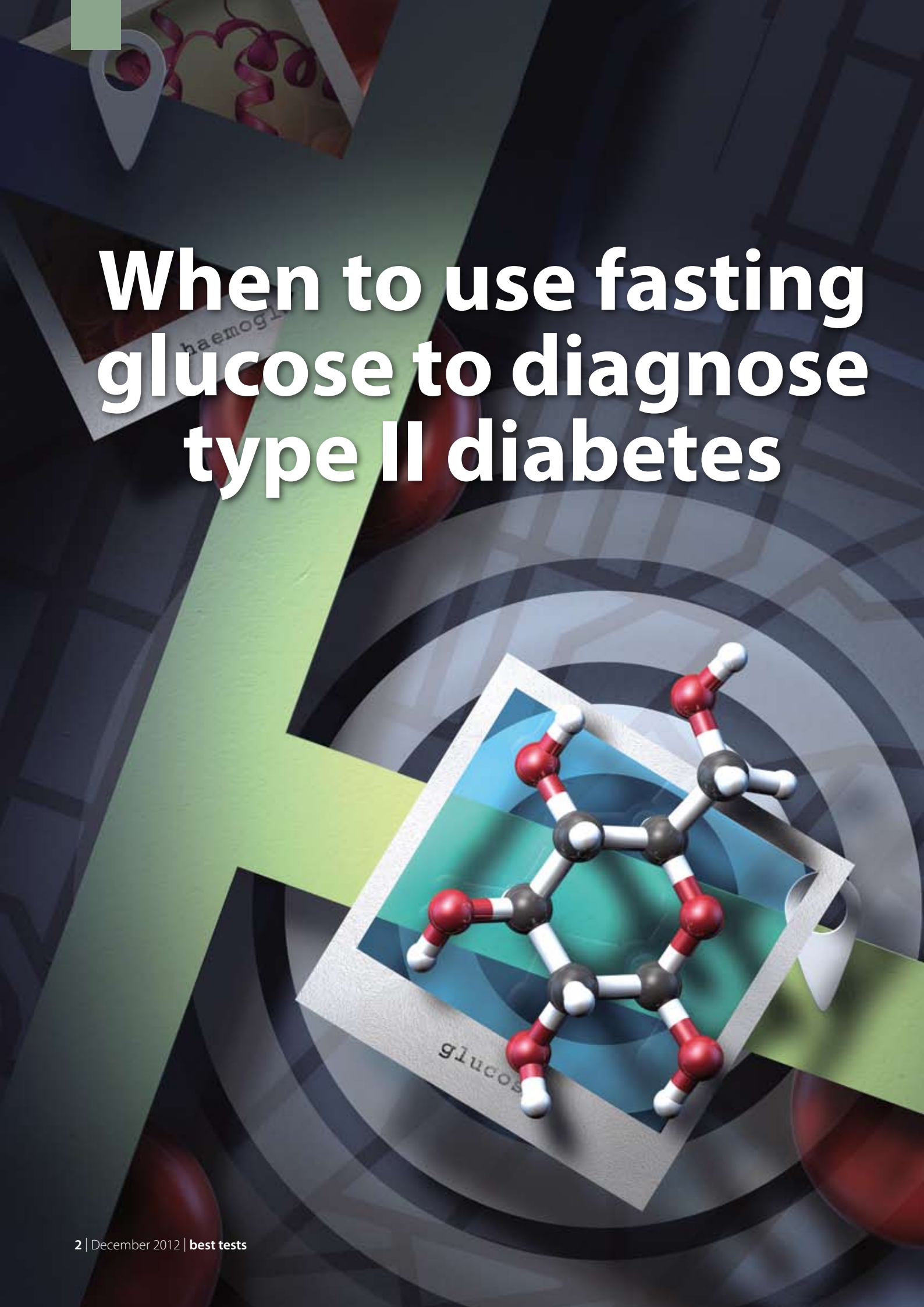
www.bpac.org.nz

facebook.com/bpacnz

CONTENTS



When to use fasting glucose to diagnose type II diabetes



Until recently, fasting plasma glucose, and in some situations, oral glucose tolerance testing, have been the investigations of choice for diagnosing people with type II diabetes. Recently, recommendations in New Zealand have changed and HbA_{1c} has become the primary assay for diagnosing type II diabetes, along with its continued role in monitoring glycaemic control. Other countries, such as the UK, USA and Australia, have also recently placed more importance on the use of HbA_{1c} in diagnosing type II diabetes. However, there are some clinical scenarios where HbA_{1c} is unreliable, and fasting plasma glucose should be used in preference.

HbA_{1c} is the recommended test for diagnosing type II diabetes in most situations

In September, 2011, the New Zealand Society for the Study of Diabetes (NZSSD) changed its recommendation regarding choice of test for diagnosing type II diabetes, stating that glycated haemoglobin (HbA_{1c}) was the preferred test over fasting glucose.[1] In addition, it is now recommended that HbA_{1c} is the test of choice for population screening programmes.[2] However, there are some scenarios where measuring HbA_{1c} for diagnostic purposes may give misleading or inaccurate results (see bullet list and Table 1 over page), and therefore a fasting plasma glucose is recommended.[1] Oral glucose tolerance testing (OGTT) is no longer recommended for most people as a test for type II diabetes.[2] N.B. OGTT is still used for diagnosis of women with gestational diabetes.

For further information on the change in guidance and the use of HbA_{1c}, see: "The new role of HbA_{1c} in diagnosing type 2 diabetes", BPJ 42 (Feb, 2012), and "Understanding the new HbA_{1c} units for the diagnosis of Type 2 diabetes" Braatvedt G et al, NZMJ 2012;125(1362).

HbA_{1c} results may be misleading in some people and situations

Fasting plasma glucose should only be used to test for type II diabetes in situations when the use of HbA_{1c} is inappropriate.[1] The two primary situations where HbA_{1c} may be inaccurate are when serum glucose levels have risen too quickly for glycation rates to provide an accurate picture, or where a condition is present that will affect the accuracy of HbA_{1c} over the long term. Where serum glucose

The inter-test variability between HbA_{1c} and fasting glucose

When choosing the most appropriate diagnostic test for people with suspected type II diabetes, it is important that practitioners understand the limitations of each test.

Multiple studies have shown that HbA_{1c} and fasting plasma glucose tests are frequently discordant when used to diagnose type II diabetes.[3] In some populations, such as Indo-Asian people, HbA_{1c} diagnostic cut-off levels of 48 mmol/mol (a lower threshold than is used in New Zealand) identify fewer individuals as having type II diabetes than glucose-based tests.[3] However, in the majority of study populations this discordance is minor, and HbA_{1c} and fasting plasma glucose generally identify similar numbers of people with diabetes.[4] In addition, the convenience of HbA_{1c} testing is thought to significantly increase the absolute number of people diagnosed with type II diabetes, making it a more effective test for screening populations. HbA_{1c} may not accurately reflect levels of glycaemic control in some situations or individuals (over page), but in comparison with fasting plasma glucose, it has greater analytic stability and less daytime variability in any individual patient, as well as far less stringent patient requirements, particularly the lack of required fasting.

has risen quickly, HbA_{1c} should not be used. In clinical situations where HbA_{1c} may be misleading, measuring glycation rates may still be useful, although consideration should be given to using fasting plasma glucose.

Where serum glucose levels have risen rapidly, do not use HbA_{1c}

A recent UK consensus statement recommended that HbA_{1c} should not be used in the following patients or situations where blood glucose levels may have risen too fast to affect HbA_{1c}:[5]

- All children and young people or anyone with suspected type I diabetes, regardless of age
- People with a short duration of diabetes symptoms
- Women who are pregnant or have been pregnant in the previous two months
- People at high risk of diabetes who are acutely unwell ($HbA_{1c} \geq 50$ mmol/mol confirms pre-existing diabetes, but a value < 50 mmol/mol does not exclude it in an unwell patient and such patients should be retested once the acute episode has resolved)
- People taking medicines that may cause rapid glucose rise, e.g. corticosteroids or antipsychotics (for two months or less). HbA_{1c} can be used in people taking such medicines long-term (over two months) who are not clinically unwell.
- People with acute pancreatic damage or who have had pancreatic surgery

In these situations, where symptoms have only been present for a short period (less than three months) and glycation of haemoglobin is unlikely to have occurred, it is more appropriate to request fasting plasma glucose than HbA_{1c}.[5] In addition, in some clinical settings self-monitoring blood glucose (SMBG) measurement, may be indicated to establish glucose levels to guide an acute intervention, such as hospital admission, in patients with suspected hyperglycaemia.

In clinical conditions where HbA_{1c} may be misleading, use with caution

Certain clinical conditions may also affect the accuracy of an HbA_{1c} test – the HbA_{1c} may be falsely low and lead to false-negative results, or falsely elevated and lead to a false-positive result for type II diabetes. Some conditions have variable effects on HbA_{1c} results and may increase or decrease HbA_{1c} levels. Table 1 lists the most common conditions and factors that affect HbA_{1c}. HbA_{1c} may still be useful in these situations, but it should be used with caution, and consideration given to using fasting plasma glucose.

These conditions need to be viewed within the clinical context of the patient. For many, the degree of effect on HbA_{1c} results is modest. For example, iron deficiency tends to modestly raise HbA_{1c} for unknown reasons.[11] However, if the rate of blood loss is enough to cause anaemia then HbA_{1c} will typically fall due to increased red blood cell turnover, i.e. HbA_{1c} will be falsely low, rather than high. A similar situation exists with patients who undergo venesection for haemochromatosis where HbA_{1c} results can be very low. In general, HbA_{1c} will still be useful, however, results should be viewed with caution and when there is clinical suspicion about the validity of the HbA_{1c} result, discussion with a clinical biochemist (pathologist) may be appropriate.

Note that there is also a possible age-related effect when using HbA_{1c}, which rises approximately 0.3% each decade in people with normal glucose tolerance.[12] This does not limit the use of HbA_{1c} in older people, but clinicians should be aware of the possible effect.

Where HbA_{1c} results are borderline or further investigation of the result is necessary, such as in a patient with two discrepant HbA_{1c} results, a fasting plasma glucose test may be useful if the result would change the management of the patient. However, waiting six months before retesting HbA_{1c}, with lifestyle interventions in the interim, would generally be the recommended management strategy.

Fasting plasma glucose as a diagnostic test for type II diabetes

If a fasting plasma glucose test is indicated, rather than HbA_{1c}, this can be undertaken and interpreted in accordance with previous type II diabetes testing guidance.

Patients are required to fast (i.e. no caloric intake) for at least eight hours, but ideally 12 hours, prior to testing.[13] Advise patients that they may drink water during the fasting period.

Table 1: Factors influencing HbA_{1c} results, modified from Gallagher[6,7]

	HbA_{1c} result		
Factor	**Increased**	**Decreased**	**Variable**
Red Cell Survival (erythropoiesis)	Iron deficiency Vitamin B12 deficiency Renal impairment Alcoholism	Iron supplementation Vitamin B12 or folate supplementation EPO treatment Reticulocytosis Chronic liver disease	Iron deficiency anaemia[8–10]
Erythrocyte destruction or removal	Splenectomy	Blood loss Splenomegaly Rheumatoid arthritis Certain medicines, e.g. antiretrovirals, dapsone Some haemoglobinopathies	
Glycation rate	Vitamin C or E deficiency Some haemoglobinopathies Chronic kidney disease		Some genotypes, e.g. sickle cell disease
Altered haemoglobin		Recent blood transfusion (previous three months)[1]	Some haemoglobinopathies Methaemoglobin
Assays	Hyperbilirubinaemia Carbamylated haemoglobin Alcoholism Aspirin (large doses) Chronic opiate use Hydroxyurea		Some haemoglobinopathies

In symptomatic people a single fasting plasma glucose result of ≥7.0 mmol/L can be considered diagnostic of type II diabetes for the majority of people.[1] Repeat testing is recommended where the result is borderline or there is clinical doubt about symptoms.

In asymptomatic people a fasting plasma glucose result of ≥7.0 mmol/L strongly indicates type II diabetes; however, a second test is required for confirmation.[1] The test should be performed on a separate occasion,[13] ideally within two weeks.[5] Lifestyle interventions should be encouraged during the waiting period. If the second result is discordant, repeat testing again in three to six months is recommended, with lifestyle interventions continuing in the interim.

The disadvantages of fasting plasma glucose as a diagnostic test for type II diabetes

The fasting plasma glucose test has several disadvantages, many of which contributed to the NZSSD and WHO decisions to recommend that HbA_{1c} be used as the preferred test for the diagnosis of type II diabetes.[1, 6]

The primary disadvantage of fasting plasma glucose is that it **requires the patient to fast** prior to testing, which can be difficult in practice.

The diagnostic range of fasting plasma glucose is narrow compared with the **biological variation** between individuals when tested with fasting glucose, which is

The diagnostic criteria for type II diabetes[1]

HbA_{1c} *	Fasting glucose*	Diagnosis	Comments
≥50 mmol/ mol, with symptoms	≥7.0 mmol/L, with symptoms	Diabetes	
≥50 mmol/ mol, no symptoms	≥7.0 mmol/L, no symptoms	Diabetes	A second test above the threshold, with either fasting glucose or $HbA_{1c,}$ is required to confirm diagnosis
41 – 49 mmol/mol	6.1 – 6.9 mmol/L	Intermediate hyperglycaemia	Offer lifestyle advice. Perform CVD risk assessment and follow guidelines for treatment. Repeat testing every 6 –12 months
≤40 mmol/mol	≤6.0 mmol/L	Diabetes unlikely (normoglycaemia)	Normal range Repeat testing at next CVD assessment or when clinically indicated

* Requesting both HbA_{1c} and fasting plasma glucose together in at-risk, asymptomatic people is unnecessary and discouraged.[5] However, if HbA_{1c} and fasting plasma glucose are measured together, and results are discrepant with regards to a diagnosis of diabetes, the test above the diagnostic cut point should be repeated after three to six months.[1]

approximately 4.5%.[14] This means that if a group of patients have a fasting plasma glucose level of 7.0 mmol/L, most will have an actual value between 6.7 – 7.3 mmol/L (4.5% biological variation), but some will have a value outside of this range. Given the narrow diagnostic range for diabetes, with fasting plasma glucose, this can be significant.

The **sample processing** of fasting glucose is more complex than for HbA_{1c}, leading to a greater potential for errors. Variation can be up to 1 mmol/L or more after one to two hours, with an average of approximately 0.4 – 0.5 mmol/L (even if a fluoride tube is used).[15] When added to the biological variation, this difference can have a significant effect on the diagnostic accuracy of the test.

The **reproducibility of fasting plasma glucose** is lower than HbA_{1c}. An abnormal or borderline HbA_{1c} result is far more likely to be abnormal on repeat than a borderline fasting glucose result.[16]

Fasting plasma glucose has an inferior **ability to predict long-term** outcomes, particularly beyond 15 years.[17]

Monitoring patients where the use of HbA_{1c} is misleading

All people with type II diabetes should have regular follow-up in general practice to monitor glycaemic control, risk level and disease progression. HbA_{1c} is the recommended test for measuring glycaemic control during follow-up. In the presence of the co-morbidities discussed in Table 1, HbA_{1c} may not accurately reflect the level of glycaemic control. Alternative methods for assessing control may be more appropriate, such as fasting plasma glucose and a series of self-monitoring blood glucose measurements for people using insulin. If therapeutic changes are being considered and there is clinical concern of the validity of the HbA_{1c} test, discussion with a diabetologist is recommended. Measurement of fructosamine may be an alternative option for some people, however, the availability of this test varies, so it should be discussed with a clinical pathologist or diabetologist first. Fructosamine is a glycated protein that indicates glycation levels over the preceding 14 – 21 days.[18]

How regularly should follow-up occur

Follow-up of people with type II diabetes should occur at least annually. In people with multiple co-morbidities

Who should be screened for type II diabetes?

Current recommendations are for asymptomatic men aged over 45 years and women aged over 55 years to be screened for type II diabetes as part of a joint diabetes/cardiovascular risk assessment. Screening of asymptomatic Māori, Pacific and Indo-Asian people should begin at age 35 years for men and age 45 years for women.

Screening should be undertaken every three to five years depending on risk.

New Zealand Guidelines recommend screening ten years earlier in people with multiple risk factors:[1]

- A family history of early onset type II diabetes (more than one first-degree relative)*
- A history of gestational diabetes*
- Known ischaemic heart disease, cerebrovascular disease, or peripheral vascular disease*
- Central obesity or increased BMI (BMI > 30 or >27 kg/m^2 for Indo-Asian people)*
- Long-term steroid or antipsychotic treatment*
- Intermediate hyperglycaemia on previous assessment, e.g. HbA_{1c} 41 – 49 mmol/mol or fasting plasma glucose 6.1 – 6.9 mmol/L
- An adverse lipid profile, e.g. TC/HDL ratio ≥7.0
- High blood pressure, e.g. ≥160/95 mm Hg
- Polycystic ovary syndrome
- Current smoker (or have quit within the last twelve months)

NZSSD also recommends that children and young adults with BMI >30 (or >27 kg/m^2 in Indo-Asian children) should be screened if:

- There is a family history of early onset type II diabetes or;
- They are of Māori, Pacific or Indo-Asian ethnicity

* Screening should be undertaken from age 25 years in people with multiple high risk factors, as indicated

PHO Performance Indicators for diabetes

There are currently two PHO Performance Programme (PPP) indicators involving diabetes; diabetes detection and diabetes follow-up after detection. Both of these indicators are still active under the new funding scheme for diabetes: the Diabetes Care Improvement Package.

The purpose of the **diabetes detection** PPP indicator is to determine what proportion of the PHO population estimated to have diabetes has been diagnosed.[20]

The Indicator comprises 7.5% of a PHO's performance payment, with 2.5% for achieving the target in the total eligible PHO population and 5% in the high needs population.

The purpose of the **diabetes follow-up after detection** PPP indicator is to determine what proportion of the PHO population expected to have diagnosed diabetes has had a diabetes annual review.[20]

The Indicator comprises 9% of a PHO's performance payment, with 3% for achieving the target in the total eligible PHO population and 6% in the high needs population.

ACKNOWLEDGEMENT: Thank you to **Dr Cam Kyle**, Clinical Director of Biochemistry and Immunology, Diagnostic Medlab, Auckland for expert guidance in developing this article.

or where regular medicine adjustments are being made to achieve appropriate control, more frequent consultations and testing e.g. three to six monthly, should be considered.

A full list of risk factors and the regularity of required follow-up can be found in the "New Zealand Primary Care Handbook 2012", available from: **www.health.govt.nz/publication/new-zealand-primary-care-handbook-2012**

Follow-up should include measurement of HbA_{1c} (or an alternative method when HbA_{1c} is not appropriate), blood pressure and lipid levels, an assessment of diabetes related complications including cardiovascular disease (CVD) risk assessment, kidney disease assessment and checks for foot and retinal complications.[19] In addition, educational material and advice on diet, exercise and smoking cessation should be discussed and provided at each follow-up visit, as applicable. N.B. Some factors, e.g. retinopathy will only need to be assessed annually, even in the highest risk groups.

References

1. New Zealand Society for the Study of Diabetes. NZSSD position statement on the diagnosis of, and screening for, Type 2 diabetes. NZSSD; 2011. Available from: www.nzssd.org.nz (Accessed Dec, 2012).

2. Braatvedt G, Cundy T, Crooke M, Et al. Understanding the new HbA1c units for the diagnosis of Type 2 diabetes. NZ Med J 2012;125(1362):In press.

3. Malkani S, Mordes J. Implications of using hemoglobin A1c for diagnosing diabetes mellitus. Am J Med 2011;124(5):395–401.

4. Carson A, Reynolds K, Fonseca V, Muntner P. Comparison of A1c and fasting glucose criteria to diagnose diabetes among U.S. adults. Diabetes Care 2010;33(1):195–7.

5. John W. Expert position statement: Use of HbA1c in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011. Diabet Med 2012;29:1350–7.

6. World Health Organisation (WHO). Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. WHO, Geneva; 2011. Available from: www.who.int/diabetes/publications/report-hba1c_2011.pdf (Accessed Dec, 2012).

7. Gallagher E, Le Roith D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes. J Diabetes 2009;1:9–17.

8. Arnold J, McGowan J. Delay in diagnosis of diabetes mellitus due to inaccurate use of hemoglobin A1c levels. J Am Board Fam Med 2007;20(1):93–6.

9. Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. SIGN; 2010. Available from: www.sign.ac.uk (Accessed Dec, 2012).

10. Clinical Enquiry and Response Service (CLEAR). Does iron deficiency or anaemia affect the HbA1c test in diabetic patients, particularly those with chronic kidney disease? NHS, Scotland; 2010. Available from: www.knowledge.scot.nhs.uk (Accessed Dec, 2012).

11. Kim C, Bullard K, Beckles G. Association between iron deficiency and A1c levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care 2010;33(4):780–5.

12. Pani L, Korenda L, Et al. Effect of aging on A1c levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. Diabetes Care 2008;31(10):1991–6.

13. American Diabetes Association. Executive summary: Standards of medical care in diabetes 2012. Diabetes Care. 2012;35(Supplement 1):S4 –10.

14. Westgard QC. Desirable biological variation database specifications. Westgard; 2012. Available from: www.westgard.com/biodatabase1.htm (Accessed Dec, 2012).

15. Bruns D, Knowler W. Stabilization of glucose in blood samples: why it matters. Clin Chem 2009;55(5):850–2.

16. Selvin E, Crainiceanu C, Brancati F, Coresh J. Short-term variability in measures of glycemiz and implications for the classification of diabetes. Arch Intern Med 2007;167(14):1545–51.

17. Selvin E, Steffes M, Zhu H, Et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Eng J Med 2010;362:800–11.

18. American Diabetes Association. Fructosamine test. ADA, USA; 2012. Available from: http://professional.diabetes.org/Disease_Backgrounder.aspx?TYP=6&MID=262 (Accessed Dec, 2012).

19. New Zealand Gudelines Group. New Zealand primary care handbook 2012. 3rd ed. Wellington: New Zealand Guidelines Group; 2012.

20. DHBNZ. PHO Performance Programme. Indicator definitions. Version 5.5. 2012. Available from: www.dhbnz.org.nz/Site/SIG/pho/Operational-Documents.aspx (Accessed Dec, 2012).

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

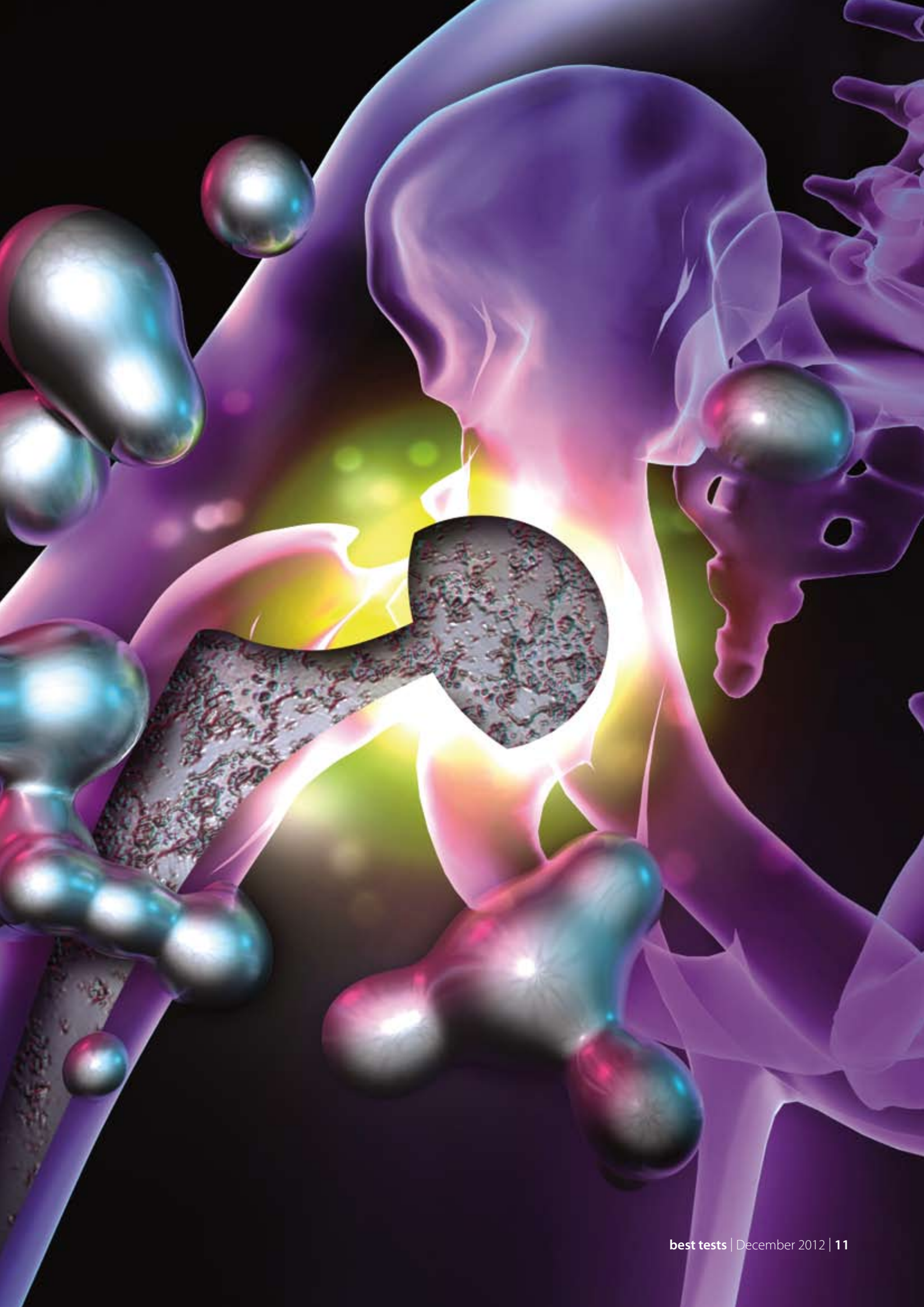
Metal-on-metal hip replacements and resurfacings are associated with higher than acceptable failure rates, and particularly high-risk devices have been recalled. While the number of patients who have high-risk prostheses in New Zealand is low, the media coverage of the issue is likely to have caused 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.[3]

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 resurfacings 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:
    - ASR acetabular cups for hip resurfacing arthroplasty or total hip replacement
    - ASR surface replacement heads for hip resurfacing arthroplasty
    - 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.

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

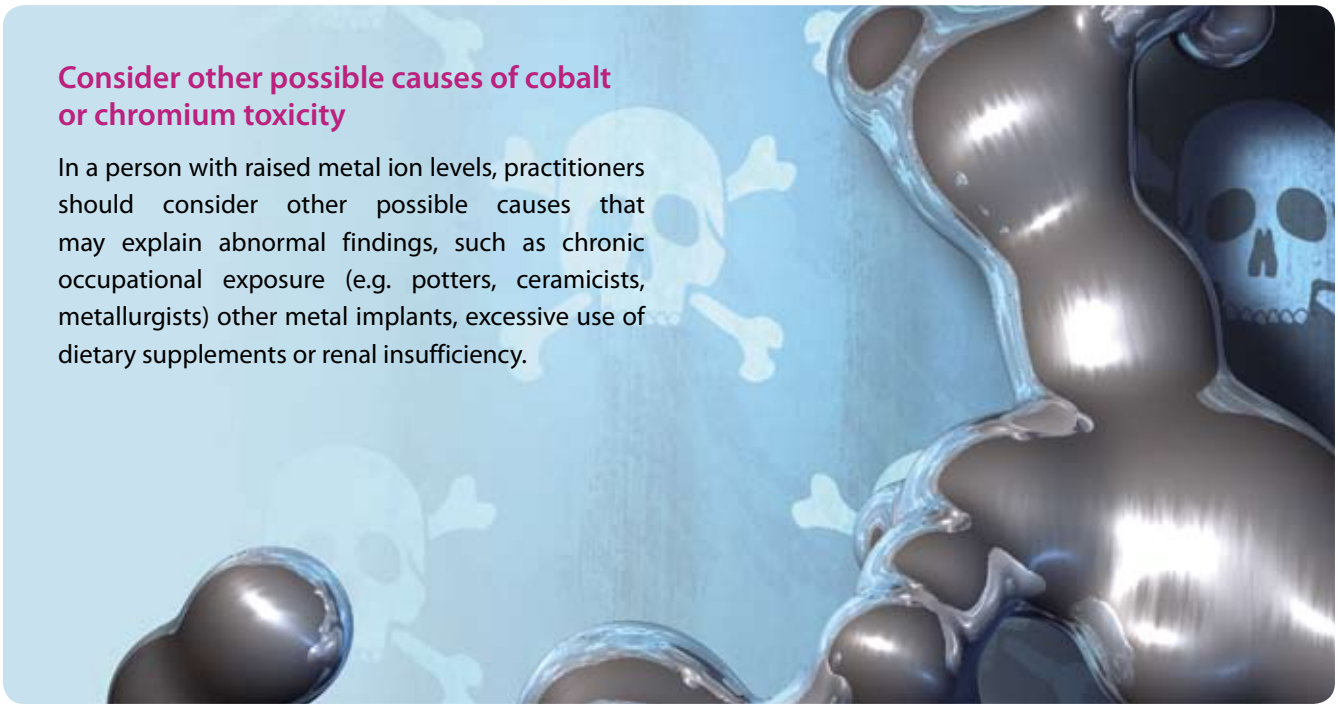
Patients with localised symptoms, or symptoms associated with prosthesis wear, should be referred to their orthopaedic surgeon.

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

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.

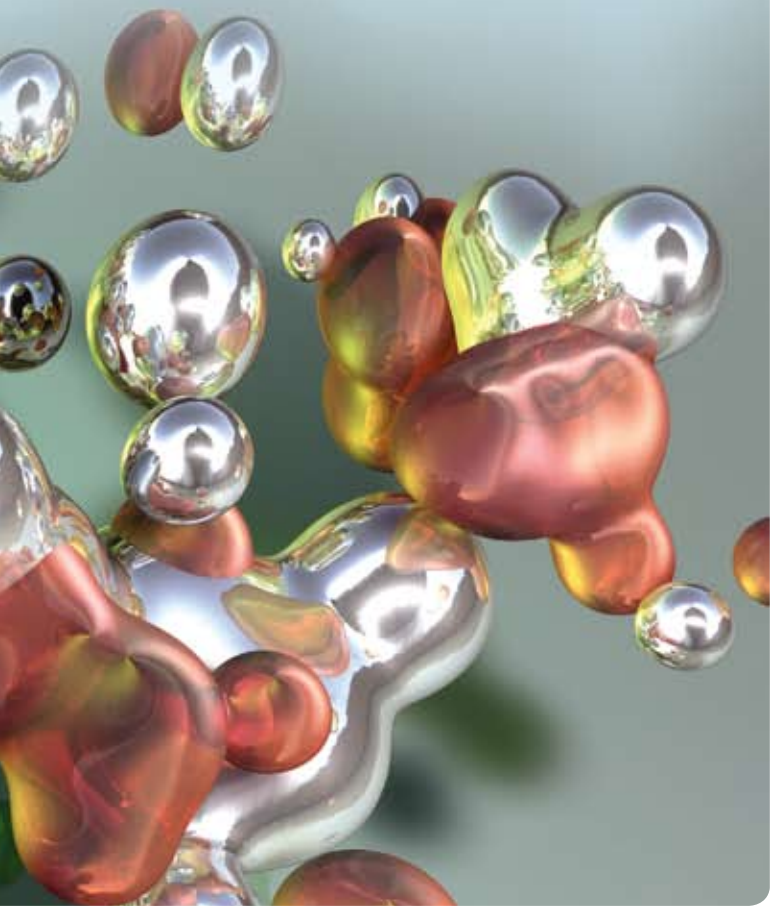


Urine or whole blood cobalt and chromium testing is not recommended

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.



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.

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 opposite), 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]

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]

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]

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/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.

References

1. New Zealand Orthopaedic Association (NZOA). Statement regarding the withdrawal of DePuy hip resurfacing with extra large metal-on-metal hip bearings. NZOA, New Zealand; 2011. Available from: www.nzoa.org.nz (Accessed Nov, 2012).
2. New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Medical device recall actions - Metal-on-metal hip implants: questions and answers. Medsafe; 2012. Available from: www.medsafe.govt.nz (Accessed Nov, 2012).
3. Heneghan C, Langton D, Thompson M. Ongoing problems with metal-on-metal hip implants. BMJ 2012;344:e1349.
4. Pelt CE, Bergeson AG, Anderson LA, et al. Serum metal ion concentrations after unilateral vs bilateral large-head metal-on-metal primary total hip arthroplasty. J Arthroplast 2011;26(8):1494–500.
5. Mao X, Wong A, Crawford R. Cobalt toxicity - an emerging clinical problem in patients with metal-on-metal hip prostheses? Med J Aust 2011;194(12):649–51.
6. Cohen D. Revision rates for metal on metal hip joints are double that of other materials. BMJ 2011;343:d5977.
7. Hodgkinson J, Skinner J, Kay P. Updated guidance on large diameter metal on metal bearing total hip replacements. London: British Hip Society, British Orthopaedic Association,

National Joint Registry and Medicines and Healthcare products Regulatory Agency; 2011. Available from: www.britishhipsociety.com/pdfs/BHS_MOM_THR.pdf (Accessed Nov, 2012).

8. Polyzois I, Nikolopoulos D, Michos I, et al. Local and systemic toxicity of nanoscale debris in total hip arthroplasty. J App Toxicol 2012;32(4):255–69.
9. National Prescribing Service (NPS) Medicinewise. Monitoring for potential toxicity in patients with metal-on-metal hip prostheses: advice for health professionals. NPS Ltd, Australia; 2012. Available from: www.nps.org.au (Accessed Nov, 2012).
10. Keegan G, Learmouth I, Case P. A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Rev Toxicol 2008;38:645–74.
11. Tyson-Capper AJ, Lawrence H, Holland JP, et al. Metal-on-metal hips: cobalt can induce an endotoxin-like response. Ann Rheum Dis 2012;DOI 10.1136.202468.
12. Agency for toxic substances and disease registry (ATSDR). Chromium toxicity - What are the physiologic effects of chromium exposure? ATSDR, USA; 2011. Available from: www.atsdr.cd.gov/csem/csem.asp?csem=10&po=10 (Accessed Nov, 2012).
13. Editor: Kyle C. A handbook for the interpretation of laboratory tests. 4th ed. Diagnostic Medlab; 2008.
14. Medicines and Healthcare products Regulatory Agency (MHRA). Medical Device Alert - All metal-on-metal hip replacements. MHRA; 2012. Available from: www.mhra.gov.uk (Accessed Nov, 2012).
15. New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Medical Devices - Management of patients with metal on metal hip implants. Medsafe; 2012. Available from: www.medsafe.govt.nz (Accessed Nov, 2012).
16. Fary C, Thomas G, Taylor A, et al. Diagnosing and investigating adverse reactions in metal on metal hip implants. BMJ 2011;343:e7441.
17. New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Metal-on-metal hips - Updated recommendations. Medsafe prescriber update; 2012. Available from: www.medsafe.govt.nz (Accessed Nov, 2012).
18. Department of Health and Ageing. Metal-on-metal hip replacement implants. Therapeutic Goods Administration, Australia; 2012. Available from: www.tga.gov.au (Accessed Nov, 2012).
19. Accident Compensation Corporation (ACC). Treatment injury case study - Failure of hip replacement. ACC, NZ; 2012. Available from: www.acc.co.nz (Accessed Nov, 2012).

QUIZ FEEDBACK

Best Tests
October 2012

This quiz feedback provides an opportunity to revisit Best Tests, October 2012, which focused on following up on prostate cancer and testing for glandular fever.

This is now available from our website:

www.bpac.org.nz

visit us at **www.bpac.org.nz**

Call us on **03 477 5418** Email us at **editor@bpac.org.nz** Freefax us on **0800 27 22 69**