Orthopaedic implants and metal hypersensitivity

Identifying hypersensitivity reactions with MELISA® testing

Background

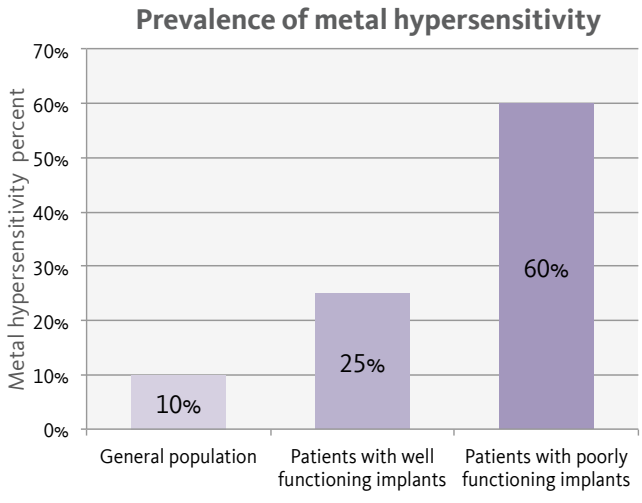
Orthopaedic prostheses play a key role in restoring patients' quality of life. However, with increasing reports of adverse responses to metals comes the need to identify biocompatible materials for susceptible patients.

As the number of arthroplasties increase, so do the number of hypersensitivity reactions to protheses [1,2,3]. Although delayed hypersensitivity reactions are infrequent, when they do occur there is a "recognized association with devastating morbidity and substantial decrease in the quality of life of those affected." [4] There is growing evidence that metal hypersensitive patients experience poorer outcomes after surgery. Despite this, it is not known whether implant failure is caused by metal allergy or whether metal allergy results from sensitisation due to metal ion release from failing devices. [5]

Metal hypersensitivity and orthopaedics

The need for biocompatible components and allergy testing in susceptible patients is well recognized by both implant manufacturers [6,7] and by surgeons/researchers alike [8,9].

The prevalence of metal hypersensitivity in patients with implants is significantly higher than in the general population, with an even higher prevalence rate among patients with failed implanted devices [10]. With an implant in place, metal exposure may cause the incidence of sensitisation to rise as high as 25%. [11, 10] If the implant mechanically fails, the incidence can be as high as 60%. [10]



Data from Hallab et al 2001

Getting it Right First Time

"Listen to patient's concerns about metal allergy if the concern arises."
Teo 2017 [14]

"In addition, use of an LTT test in high risk or self-proclaimed metal sensitive patients may be of value to consider in the future so as to document and have on hand appropriate metal wear reduced implants for use in such high-risk patients"
Lionberger 2018 [15]

"Patient perception is important, however, and among patients who report multiple allergies of any kind, a higher percentage are likely to be dissatisfied with their knee replacement"
Barrack 2018 [16]

"It is a generally thought that hypersensitivity testing should be performed using validated methods in patients with a documented or suspected medical history of metal allergy"
Granchi 2012 [2]

US FDA investigates immune responses to metals in implants

Reports of **adverse reactions to medical devices include both local symptoms**: joint pain, impaired wound healing, rashes [12] as well as more **systemic effects**. "*Reported systemic symptoms include fatigue, rash, joint and muscle pain, and weakness. Although uncommon and varied, these symptoms can sometimes mimic more well-established inflammatory conditions, such as systemic lupus erythematosus.*" [13]

MELISA® DIAGNOSTICS

MELISA® testing

Metal hypersensitivity is an adaptive immune response, manifested as delayed type IV hypersensitivity. It is an abnormal response to a small amount of metal ions, that occurs in people with an allergic predisposition [17]. Since metals ions bind to enzymes and proteins in the body, these modified structures may be considered foreign and can activate the immune system, leading to inflammation.

As blood tests, lymphocyte transformation tests (LTT) are more suitable for diagnosing possible implant-related metal sensitivity than patch testing on the skin [5,10]. MELISA is an optimised, standardised and clinically validated version of LTT [18]. In addition, MELISA provides a cost effective alternative to patch testing (within the NHS).

The MELISA test may be used in two ways for orthopedic patients:
Prior to surgery. Patients reporting metal allergy may be pre-tested to ensure that they receive the most suitable implant.
Post-surgery. MELISA can identify if metal hypersensitivity is responsible for any new symptoms that develop after surgery.

Allergy versus toxicity

Serum metal ion levels may be elevated in normally functioning implants, and ion levels do not accurately predict outcomes of patient satisfaction or implant function. [19]

Metal-on-metal implants, particularly cobalt-chromium implants, have been linked to raised levels of metal debris in the blood of affected patients. All implants release metal ions, but some metal-on-metal prostheses release many more ions than previously thought [5]. The ions may leak into the surrounding tissue and cause reactions that destroy both bone and muscle which leaves those affected with permanent disabilities. [5]

MELISA does not assess the levels of metals in tissue, instead it identifies whether the patient's immune system reacts to specific metals.

Accessing MELISA® testing

1. Order kit: info@melisa.org or call 020 8133 5166
2. Draw blood: Keep at room temperature and do not centrifuge
3. Ship: by FedEx to arrive at MELISA lab in Germany within 48 hours

The amount of blood needed depends on how many antigens are to be tested. For a screening of "Orthopaedic pre-test", which includes 15 metals, 54 ml blood, or 6 x 9ml tubes of blood, is needed. Alternatively, a bespoke panel can be created from over 30 antigens. Steroids or other immunosuppressant drugs may affect the test result.

MELISA® testing method

Lymphocytes are isolated from whole blood and re-suspended in autologous serum, before being cultured for 5 days with a panel of metals, based on current or planned exposure. Two or three non-mitogenic concentrations of each metal solution are used. Three negative controls and one positive control (Pokeweed) are also established.
The lymphocyte reaction is measured by two separate methods: uptake of radioisotope by dividing lymphocytes and evaluation by microscope. The test report shows the strength of the reaction to the metal antigens as a Stimulation Index (SI). The SI is derived by dividing the counts per minute (cpm) in each metal test well by the mean of the negative controls. A positive reaction is defined as SI >3. SI>10 indicates a strongly positive reaction and SI 2-3 a weakly positive reaction. Possible positive cultures are analysed morphologically to ensure that macrophages have not been counted and that lymphoblasts and diving lymphocytes are present.

MELISA® testing panels

Cobalt Chrome	Chromium, Cobalt, Manganese, Molybdenum, Nickel (0.5%), Tungsten
Stainless steel	Chromium, Nickel, Molybdenum
Titanium alloy (Ti6Al4V)	Titanium dioxide, Titanium sulphate, Vanadium, Nickel (0.1%)
Oxinium	Chromium, Niobium, Tin, Zirconia*
Orthopaedic pre-test	Aluminum, Beryllium, Chromium, Cobalt, Manganese, Molybdenum, Nickel, Niobium, Tantalum, Tin, Titanium dioxide, Titanium sulphate, Tungsten, Vanadium, Zirconia*

** Clinical relevance of positive tests not established*

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