

# Pseudotumors following total hip and knee arthroplasty

## Table of contents

Executive summary	4
Introduction	6
Purpose of review	13
Clinical questions	14
Data sources and search strategy	14
Results	19
Summary	52
Questions raised from current review	52
Areas of uncertainty	53
Recommendations for future research	53
References	54

**JE**



**AUTHORS**

**Laura Quigley, BSc**  
**Sheila Sprague, MSc**  
**Mohit Bhandari, MD**

**SUBJECT MATTER EXPERTS**

**Joseph Daniel FRCS, MS (Orth)**  
**James Holland FRCS, FRCS (Orth)**

Published April 2010, Copyright © 2010 by KLEOS, Oberneuhofstrasse 10d, 6340 Baar, Switzerland  
 T +41 41 766 22 55, F +41 41 766 22 95, kleos@smith-nephew.com  
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**LIST OF TABLES**

Table 1:	Medline Search Strategy	10
Table 2:	Embase Search Strategy	10
Table 3:	Additional Medline Search Strategy	10
Table 4:	Levels of Evidence for Primary Research Question	11
Table 5:	Yearly cumulative percent revision of primary total resurfacing hip replacement	20

**LIST OF FIGURES**

Figures 1, 2, 3:	Radiograph and CT scan image of a pseudotumoral mass	4
Figure 4:	Total Hip Prosthesis	5
Figure 5:	Total Knee Arthroplasty	8
Figure 6:	Arthrogram of a “pseudoabscess” in relation to a metal-on-polyethylene hip...	16
Figure 7:	The explants from two hip...	17
Figure 8:	A scanning electron microscope image...	18
Figure 9:	The explants from two hip...	18
Figure 10:	The causes and local adverse effects of excess metal debris...	22
Figure 11:	Showing the wide spectrum of clinical problems ...	23
Figure 12:	Radiographs, clinical photograph, and MRI images of the left hip in Case 1	24
Figure 13:	Recent radiographs of left hip in Case 1	24
Figure 14:	Schematic representation of the presentation and probable pathogenesis in Case 1	25
Figure 15:	Radiographs, MRI image showing the effusion... Case 2	25
Figure 16:	Schematic representation of the presentation and probable pathogenesis in Case 2	26
Figure 17:	Radiographs and MRI image in Case 3 showing the pseudotumor	26
Figure 18:	Showing (A) the explanted femoral component... Case 3	27
Figure 19:	Schematic representation of the presentation and probable pathogenesis in Case 3	27

**LIST OF ABBREVIATIONS**

ALVAL	Aseptic Lymphocytic Vasculitis and Associated Lesions	IAEA	International Atomic Energy Agency
ARMD	Adverse Reactions to Metal Debris	LTT	Leukocyte Transformation Test
ASR	Articular Surface Replacement	M	Male
AVN	Avascular Necrosis	MM	Metal on Metal
BHR	Birmingham Hip Resurfacing	N	Sample Size
CRP	C-Reactive Protein	PMMA	Polymethylmethacrylate
CT	Computed Tomography	ROM	Range of Motion
DTH	Delayed-Type Hypersensitivity	THA	Total Hip Arthroplasty
DVT	Deep Vein Thrombosis	TKA	Total Knee Arthroplasty
ESR	Erythrocyte Sedimentation Rate	UHMWPE	Ultra-High Molecular Weight Polyethylene
F	Female	USG	Ultrasonography

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## Executive summary

Pseudotumor is a term originally used to describe a disease which produced signs and symptoms of an intracranial tumor (pseudotumor cerebri) in the absence of a mass or a space-occupying lesion. They have also been used to describe granulomatous lesions in relation to conventional total hip or knee arthroplasties and now in relation to metal-on-metal hip resurfacings and replacements. They are large focal solid or semiliquid masses around the prostheses mimicking the local effects of a neoplasia or infection in the absence of either of these.

Some of these pseudotumors have been described as locally destructive masses requiring early revision surgery. The incidence of symptomatic pseudotumors following metal-on-metal hip arthroplasty is variously reported to be between 0.1 to 3% at follow-up periods ranging up to 10 years. Among revisions for hip replacements with different types of bearings, the incidence is 4.6% of revisions for all reasons, and in metal-on-polyethylene resurfacings it is 5.8%. The purpose of this report is to provide a systematic review of the literature to determine the occurrence of pseudotumors following total hip and knee arthroplasty. This review will also determine the difference in occurrence between different types of prosthesis (ie, metal, polyethylene, ceramic). This literature review will combine all available evidence pertaining to pseudotumors following total hip and knee arthroplasty. In particular it will examine the presenting symptoms, causes, prevalence, and treatment of pseudotumors.

Our search strategy identified 138 potentially relevant articles in both of the databases combined, 37 potentially relevant articles from the secondary Medline search, 24 articles identified through expert opinion and the examination of bibliographies, and one article identified from the Internet search. Altogether, 24 clinical articles and 3 review articles were included in this review. The results from these articles are discussed in terms of presenting symptoms, causes, prevalence, and treatment of pseudotumors.

## Introduction

When it was first coined around the beginning of the 20th century, the term “pseudotumor” referred to a condition associated with the symptoms and signs of an intracranial tumor (headache, nausea, visual and ocular disturbances, papilledema, and raised intracranial pressure) in the absence of an actual mass or a space-occupying lesion. Since then the term pseudotumor has been used to describe a variety of nonneoplastic, noninfective masses. They have been described depending on their locations as orbital, intra- or retroperitoneal, vesical, thenar, etc, and depending on their presumed etiology as inflammatory, foreign body, hemophilic, etc.

Harris et al (1976) [1] were the first to describe aggressive granulomatous lesions in cemented metal-on-polyethylene total hip arthroplasty (THA), a condition of localized tumor-like bone resorption in the definite absence of infection. Others have described them in relation to cementless metal-on-polyethylene replacements too (Figures 1 to 3) and many found the lesions to grow rapidly in size accompanied with extensive bone loss. [2, 3, 4, 5] Among the early descriptions there is also a histiocytoma mimicking infection in relation to a cemented conventional THA stem. [6] These are often associated with either discomfort or pain or with bony erosion, [7] or with pressure effects on vital structures in the vicinity including venous, [8] neurological, [5, 9] and ureteric [10]. These swellings are almost always granulomatous masses filled with polyethylene debris-laden macrophages. Thus, with respect to conventional joint replacements periprosthetic granulomatous masses or pseudotumors have been reported for over 30 years.

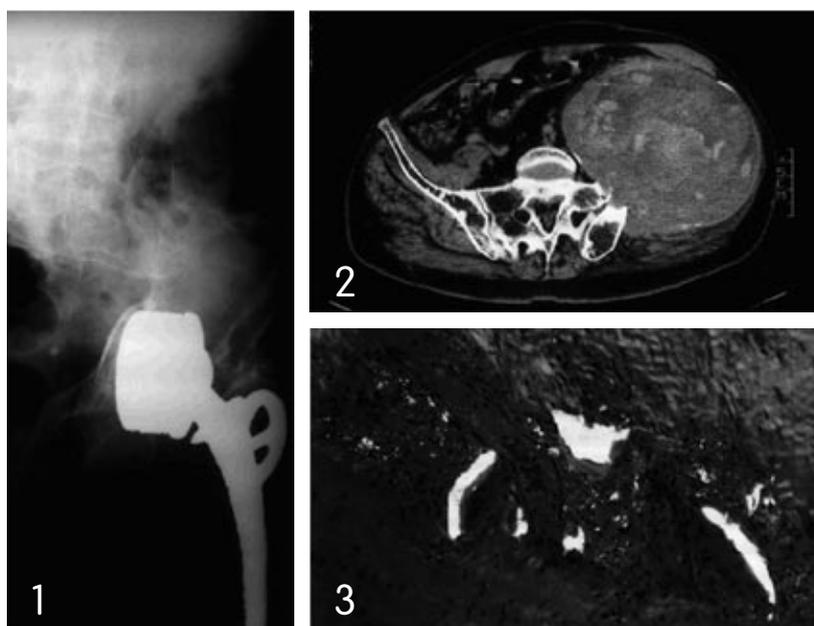


Figure 1 to 3: Radiograph and CT scan image of a pseudotumoral mass in relation to an uncemented total hip replacement, compressing the pelvic viscera. Photomicrograph of a representative section of tissue showing histiocytic response consistent with a foreign body reaction. Polarized light microscopy revealed birefringent polyethylene particles .

The problem of hypersensitivity to metal in patients with metal-on-metal bearings [12, 13] has also been suspected, investigated and debated [14, 15] for over 30 years. More recently it has been found that the lymphocyte-dominated histological pattern [16, 17, 18] in metal-on-metal bearing hip failures is very different [19] from the particle-storing multinuclear/macrophage dominated pattern [20, 21] seen in metal-on-polyethylene failures. In relation to metal-on-metal bearings, the occurrence of a destructive periprosthetic cyst [22] or locally destructive nonneoplastic mass [23, 24] affecting soft tissue and muscle has been recognized only recently, and since then the term “pseudotumors” [25] has come into usage.

Although the possibility of osteolysis induced by metal wear was known for some time, interest in the potential severity of this failure pattern in metal-on-metal bearings was highlighted after a report [26, 27] showing 60 out of 643 early revisions after one particular 28 mm metal-on-metal total hip arthroplasty. The device used in that cohort was the DePuy Ultima TPS femoral stem used in combination with the Ultima metal-on-metal articulation (Johnson and Johnson DePuy International Ltd, Leeds, UK). The bearing used was a low-carbon on high-carbon combination cobalt-chrome bearing which has now been withdrawn from usage. [28] Since then there have been other reports with different types of metal-metal hip resurfacings and replacements. [29, 30] Some of these were fluid-filled cystic swellings, while others were granulomatous solid or semiliquid masses.

## Total hip arthroplasty

A THA is performed to replace both the femoral and acetabular articulating surfaces of an arthritic hip joint with artificial bearing surfaces made of metal alloys, high-grade plastics, polymers, ceramics or composites. The cup is usually fixed to the acetabular socket through a metal fixation surface or with the use of acrylic bone cement. The femoral ball is generally fixed to the femur through a long stem fixed in the medullary canal of the femoral shaft (Figure 4). In terms of enhancing quality of life, total hip arthroplasty has been described as one of the most successful and cost-effective major operations ever devised. [31] However, the longevity of conventional hip replacements depends on device usage and the secondary effects of device wear. Younger and more active patients tend to place higher demands on its usage resulting in an earlier need for revision. The Swedish Hip Register found young patients to be the “supreme challenge” to conventional hip replacement. [32] It was for this specific group of young and active patients who perform poorly with a conventional THR that modern metal-on-metal hip resurfacing was developed.

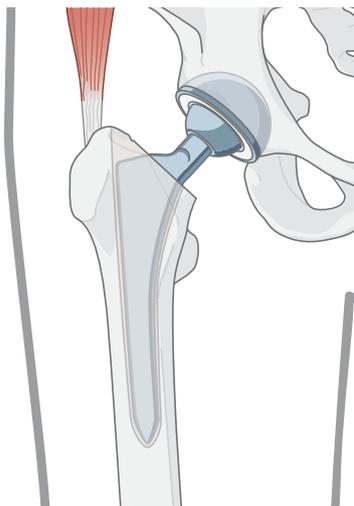


Figure 4: Total hip prosthesis

Hip arthritis, whether primary or secondary, manifests through the final common pathway of articular surface loss. Being essentially a surface problem it has always attracted surgeons to apply a surface solution [33]. In the early 1960s, Charnley used what has come to be termed the first-generation resurfacing made of polytetrafluoroethylene bearing surfaces and experienced early failures with the device. Other materials including polyethylene, ceramics and metals were used in several second-generation hip resurfacings with no improvement in survivorship. The high failure rates were due to accelerated volumetric wear and osteolysis from the large-diameter femoral component articulating against polyethylene cups [34]. This led to resurfacings being rejected as a bad concept altogether in the late 1980s leaving stemmed total hip replacements with conventional metal-on-polyethylene bearings as the only treatment option for severe hip arthritis. These perform extremely well in older, less demanding patients. High activity levels adversely affect their long-term success in young patients.

## Hip resurfacing and other conservative hip arthroplasty procedures

Derek McMinn's pioneering work signaled the beginning of the new era of modern hip resurfacings in 1991, [35] leading eventually to the development of the Birmingham Hip Resurfacing and inspiring several others to launch other metal-on-metal resurfacings. The best candidates for these resurfacings are young active patients with severe hip arthritis with good hip morphology and bone quality. [36] It is in this group that a hip resurfacing works best, and the McMinn Centre results demonstrate a 12-year survivorship of 98.9% in patients under the age of 55 years with osteoarthritis [36].

Although modern hip resurfacing has proved itself to be a viable option for young active patients, it requires the presence of good femoral head bone quality and a relatively normal proximal femoral anatomy. The results of resurfacing have not been found to be as good in patients with femoral head osteonecrosis, who fail with a high rate of femoral neck fractures and late femoral head collapse. [37] Other patients with severe slipped capital femoral epiphysis and Perthes disease can also be unsuitable for resurfacing in view of their abnormal proximal femoral morphology. [38] In these patients the short-stemmed conservative device Birmingham Mid-Head Resection is proving a useful alternative to resurfacing, but medium-term results are yet to be published. It does not depend as much on the quality of femoral head bone as a regular resurfacing and yet remains conservative since it does not invade the medullary canal of the femoral shaft. All resurfacings and the mid-head resection devices currently employ metal-on-metal bearings and therefore may be studied collectively for purposes of wear-debris-related local adverse reactions.

Total hip arthroplasty and resurfacing arthroplasty in well-selected patients restore mobility and quality of life to hundreds of thousands of patients annually worldwide. In 2008, a total of 64,722 primary hip arthroplasty procedures were carried out in England and Wales at an average age of 68 years (62.5–77.4 years) [39]. 12.4% of all primary hip arthroplasties were performed in patients under the age of 55 years. Eight percent of the 64,722 procedures were hip resurfacings and 7% were large-head metal-on-metal total hip replacements. The average age of patients who underwent a resurfacing was 54 years (range, 48.3 to 60.2 years). These figures are based on the data from the United Kingdom National Joint Register 2009 which has a capture rate of 92.5% of all operations carried out during this period [39]. The Australian Register 2009 [40] shows that between September 1999 and December 2008, 12,093 hip resurfacings (7.9%) were performed out of a total of 224,390 hip arthroplasty procedures and 74% of the resurfacings were performed in men. 52% (6,258) of all resurfacings were performed in patients in the age group less than 55 years and 39% (4,700) between 55 and 64 years.

It is estimated that in the USA during the years 2003–2004 among adults 18 years of age and over, there were approximately 428,000 knee replacements per year and 282,000 nonfracture hip replacements. [41] During the 13-year period between 1990 and 2002 the rate of primary total hip arthroplasties per 100,000 persons increased by approximately 50% and the corresponding rate of primary total knee arthroplasties almost tripled. [42] Current projections for the United States suggest that between 2005 and

2030, the number of THAs will increase by 174% to nearly 600,000 procedures per year. [43] In Canada, the number of hip replacements increased by 52% compared to 1994–1995, and by 6.1% compared to 2003–2004. The thin-walled rigid large-diameter components needed for a resurfacing are currently possible only through the use of metal-on-metal bearings. However, the low-wear, low dislocation rate advantages of metal-on-metal bearings have now found extended usage in stemmed total hip replacements too. This increasing number of younger patients exposed to orthopedic metal alloys causes concern about the long-term biological effects. In addition, the population is regularly exposed to a variety of metals through food, water, occupation and the environment, and the potential risk from exposure is assessed and forms the basis of regulatory guidelines imposed to protect the health of individuals.

## Total knee arthroplasty

Early knee replacements were true stemmed replacements but most modern knee replacements are in effect resurfacings because the components transmit weight essentially through the prepared bony surfaces as in a hip resurfacing rather than through a long stem (Figure 5). The knee joint is a more complex articulation compared to the simple single-compartment, highly congruent ball-and-socket geometry of the hip joint. Therefore, while the hip joint lends itself to being replaced with a metal-on-metal bearing with the potential for fluid film lubrication, this is not possible with a knee joint. Hence, all currently available knee joints, we are aware of, employ hard-on-soft bearings. The concept of mobile-bearing knees improves both congruency of surfaces and kinematics of the knee. In selected patients with a single compartment arthritis, unicompartmental replacements may offer better results and better revision prospects.

The clinical and economic effectiveness of total knee arthroplasty in alleviating the adverse consequences of knee arthritis has been widely recognized. The 15- to 20-year results in many studies show greater than 90% implant survivorship. [45, 46, 47, 48] This effectiveness is reflected in the increasing numbers of these procedures being performed. [49] The mechanism of wear from a knee replacement is also different and occurs through delamination, pitting and fatigue failure of the polyethylene surface rather than just an abrasive wear particle release. Thus, the wear debris in a knee replacement differs from that in a hip replacement. One study [50] showed significant elevation of serum metal ion levels in patients with well-functioning total knee replacements and another study [18] showed that the synovial fluid from a replaced metal-polyethylene bearing knee replacement joint had a DNA-damage potential equivalent to that in the synovial fluid of a metal-on-metal hip replacement. Therefore, knee replacements are also associated with potential systemic and local adverse metal ion effects.

## Pseudotumors

A pseudotumor is a granulomatous mass or a destructive cystic lesion which is neither infective nor neoplastic, when developing in relation to an arthroplasty device can potentially cause extensive collateral damage. The exact cause of pseudotumors is unclear. The common factor in these patients has been increased wear either due to a wear-prone bearing or due to suboptimal component positioning, although this is not universal. Often there is the formation of a synovial-like biomembrane with the capacity to produce collagenase, interleukin 1, and tumor necrosis factor which may mediate the absorption of bone. [51] It is often associated with osteolysis which may be asymptomatic or may present pain. [52] The patient has a periarticular mass and may present with compression symptoms that can include neuropathy and venous compression or thrombosis [46] or compression of other vital structures. There is often a latent period of 2 to 15 years following the initial total joint replacement before this foreign-body reaction becomes clinically or radiologically apparent. [2]

## Purpose of review

The purpose of this report is to provide a systematic review of the literature to determine the occurrence of pseudotumors following total hip and knee arthroplasty. The review also will determine the difference in occurrence between different types of prosthesis (ie, metal, polyethylene, ceramic). This literature review will combine all available evidence pertaining to pseudotumors following total hip and knee arthroplasty. In particular it will examine the presenting symptoms, causes, prevalence, and treatment of pseudotumors.

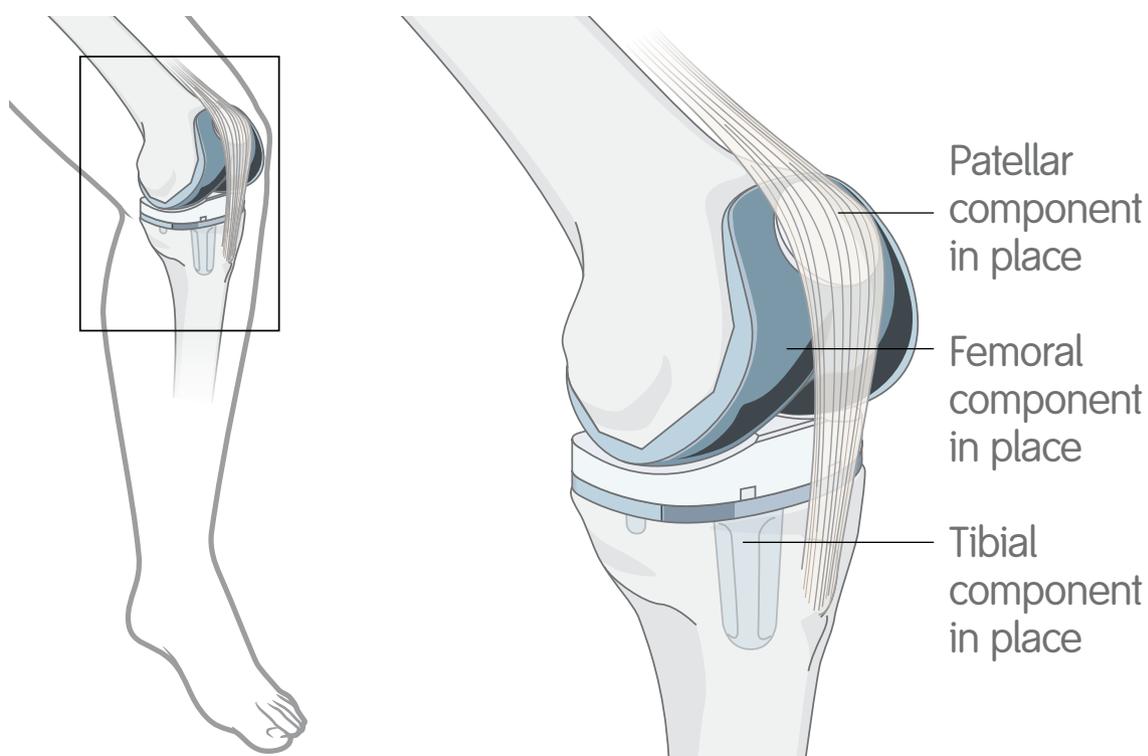


Figure 5: Total knee arthroplasty

## Clinical questions

This report will address the following clinical questions:

- 1) what are the reported symptoms of pseudotumors following total hip or knee arthroplasty?
- 2) what are the reported causes of pseudotumors following total hip or knee arthroplasty?
- 3) what is the prevalence or incidence of pseudotumors following total hip or knee arthroplasty? and
- 4) what are treatment options and outcomes for pseudotumors following total hip or knee arthroplasty?

## Data sources and search strategy

A thorough search was conducted of both major databases Embase (1980 to 2009 Week 14) and Medline (1950 to March 2009 Week 4) to identify studies which included the results of studies which examined the occurrence of pseudotumors following total hip or knee arthroplasty. Specifically, the inclusion criteria were: 1) skeletally mature patients, 2) human subjects (not cadavers), and 3) pseudotumors or granulomas. Articles that were not published in English were excluded. Review articles were included in the literature search.

The primary search strategy is summarized in Table 1 and Table 2. Additionally, the use of expert opinion and recommendations, a scan of related clinical article bibliographies, and an Internet search was conducted to identify abstracts and articles that may be relevant. A second search of Medline was conducted because the term “foreign-body granuloma” was not included in the initial search, and we felt it may provide additional valuable articles (Table 3). Specifically, the inclusion criteria for this review were: 1) clinical study with levels of evidence of I, II, III, and IV, 2) patients who received total hip or knee arthroplasty, and 3) articles which report clinical outcomes or descriptive studies. The search was limited to English language articles and only those studies which include human subjects. All case studies were excluded. The titles of the articles retrieved from this search were scanned to determine which articles would be potentially relevant. Key terms in the titles for the articles selected as potentially relevant were 1) pseudotumor, 2) granuloma, and 3) mass.

Our search strategy identified 138 potentially relevant articles in both of the databases combined (Appendix A), 37 potentially relevant articles from the secondary Medline search (Appendix B), 24 articles identified through expert opinion and the examination of bibliographies, and one article identified from the Internet search. Altogether, 24 clinical articles and 3 review articles were included in this review (Appendix C).

Table 1: Medline search strategy

	SEARCHES	RESULTS
1	arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or hip prosthesis/ or knee prosthesis	300002
2	granuloma/ or granuloma, plasma cell/	18117
3	Bursitis/	2078
4	periarticular mass.mp.	2
5	(pseudotumor or pseudotumour or pseudo-tumor or pseudo-tumour).mp. [mp=title, original title abstract, name of substance word, subject heading word]	6189
6	synovial cyst/ or popliteal cyst/	2032
7	cystic mass.mp.	1762
8	(inguinal mass or pelvic mass).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	1581
9	8 or 6 or 4 or 3 or 7or 2 or 5	30619
10	1 and 9	114

Table 2: Embase search strategy

	SEARCHES	RESULTS
1	hip arthroplasty/ or knee arthroplasty/ or total hip prosthesis/ or total knee replacement/	26594
2	granuloma/ or plasma cell granuloma	8769
3	Bursitis/	1580
4	exp Synovitis/ or exp granulomatous synovitis/ or periarticular mass.mp	6788
5	Pseudotumor/	2658
6	popliteal cyst/ or synovial cyst/	1198
7	cystic mass.mp.	1652
8	(inguinal mass or pelvic mass).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	1498
9	8 or 6 or 4 or 3 or 7or 2 or 5	23494
10	1 and 9	279

Table 3: Additional medline search strategy

	SEARCHES	RESULTS
1	exp Granuloma, Foreign-Body	1311
2	exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty, Replacement, Hip/	14912
3	exp Hip Prosthesis/	14670
4	exp Knee Prosthesis/	6447
5	4 or 3 or 2	30179
6	1 and 5	54

## Levels of evidence

Clinical articles will be evaluated for the strength of evidence following the criteria set below (Table 4). Articles with the highest level of evidence will be given the most attention.

Table 4: Levels of evidence for primary research question

LEVELS OF EVIDENCE FOR THERAPEUTIC STUDIES – INVESTIGATING THE RESULTS OF TREATMENT <sup>1</sup>	
Level I	<ul style="list-style-type: none"> <li>– High-quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals</li> <li>– Systematic review<sup>2</sup> of Level-I randomized controlled trials (and study results were homogeneous<sup>3</sup>)</li> </ul>
Level II	<ul style="list-style-type: none"> <li>– Lesser-quality randomized controlled trial (eg, &lt;80% follow-up, no blinding, or improper randomization)</li> <li>– Prospective<sup>4</sup> comparative study<sup>5</sup></li> <li>– Systematic review<sup>2</sup> of Level-II studies or Level-I studies with inconsistent results</li> </ul>
Level III	<ul style="list-style-type: none"> <li>– Case-control study<sup>7</sup></li> <li>– Retrospective<sup>6</sup> comparative study<sup>5</sup></li> <li>– Systematic review<sup>2</sup> of Level-III studies</li> </ul>
Level IV	Case series <sup>8</sup>
Level V	Expert opinion

1. A complete assessment of the quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (eg, with cemented hip arthroplasty) compared with patients treated another way (eg, with cementless hip arthroplasty) at the same institution.
6. Study was started after the first patient enrolled.
7. Patients identified for the study on the basis of their outcome (eg, failed total hip arthroplasty), called “cases,” are compared with those who did not have the outcome (eg, had a successful total hip arthroplasty), called “controls.”
8. Patients treated one way with no comparison group of patients treated another way.

This chart was adapted from material published by the Centre for Evidence-Based Medicine, Oxford, UK. For more information, please see [www.cebm.net](http://www.cebm.net).

## Quality of the literature

Twenty-four relevant studies and three review articles were identified from our literature search. From our search strategy, we did not identify any randomized controlled trials (level I evidence). Since the literature of high methodological quality was quite limited, we included lower methodological quality studies including prospective comparative studies, retrospective comparative studies, and case series, levels of evidence II, III, and IV, respectively. We did not identify any relevant prospective comparative studies (level II evidence). Two retrospective comparative studies (level III evidence) were identified in addition to 24 case series (level IV evidence). The majority of the literature on pseudotumors consists of small case reports. There were approximately 84 case reports involving a pseudotumor or a granuloma. However, these case reports are not discussed within this report.

## Results

### Wear products

Metal-on-metal wear leads to the release of metal particles which are insoluble and metal ions which are soluble. Metal ions enter the systemic circulation and therefore are responsible for systemic exposure risk. However, since there is an effective renal clearance mechanism for these ions a progressive systemic buildup of metal ions does not occur. [53] With respect to prosthesis-derived wear particles, some of these are phagocytosed or pinocytosed by macrophages and giant cells where intracellular chemicals such as peroxides and chlorides and organelles such as lysosomes have the potential to enzymatically degrade them partially into soluble metal ions. Additionally, metal particles are transported through the lymphatic system and are deposited in the regional lymph nodes, liver, and spleen. [54]

Modern metal-on-metal bearing development was based on the finding that some historic metal-on-metal total hip replacements showed excellent survivorship and a low incidence of osteolysis after 20 and more years of usage. Furthermore, modern resurfacings benefitted from technological advances which led to much improved implant design, manufacturing tolerances, and fixation methods, and thereby raised the prospect of further reduced wear. It was therefore expected that the problem of osteolysis and local adverse reactions to metal debris would not be a major issue with metal-on-metal bearing resurfacings or replacements. Hence, in the past several years, interest had not centered as much on the local effects of wear debris release as on the potential systemic adverse effects of elevated circulating levels of metal ions.

### Systemic adverse effects of elevated metal ion levels

Cobalt, chromium, molybdenum, and nickel are essential trace elements. They are present in the natural water supply and food, and they are needed for the normal metabolic functions of the cells and tissues. Detectable levels of metal ions are present in the systemic circulation and urine of subjects with no artificial metal devices in the body. Deficiency states have been described for both cobalt and chromium. Cobalt is the only metallic element in cyanocobalamin (vitamin B12) and is critical for its metabolic function. Other cofactors such as methionyl aminopeptidase also contain cobalt ions. Molybdenum is also an essential cofactor for a number of enzymes involved in amino acid metabolism such as sulfite oxidase, which assists in the hydroxylation of drugs and toxins in the breakdown of nucleotides. Chromium is essential for all the energy functions of the cell. It is part of the cellular structure that facilitates insulin response. Being essential trace elements there is an efficient renal clearance mechanism in place to handle elevated levels of systemic metal ions.

Although elevated systemic metal ion levels have been reported following conventional hip and knee replacements too, the elevations following metal-on-metal replacements particularly cause concern for two reasons. First the levels here are significantly higher than with other bearing combinations. Second these bearings are often used in young patients and the concern that the long lifetime usage of these bearings would allow the potential metal ion adverse effects with their prolonged lag periods to become real.

A patient with a metal-on-metal resurfacing prosthesis will have a measurable increase in cobalt and chromium ion levels. However, there is wide variability in the measured elevations from patient to patient. To date, an absolute unsafe level has not been determined. The urine and blood metal ion levels from patients who underwent resurfacing arthroplasty have been analyzed at various intervals after implantation. The mean levels increase after implantation and reach a peak at 6 to 12 months postoperatively. [55, 56] A steady decrease occurs over the next year, showing that mean blood chromium levels at 2 to 6 years were significantly lower than they were at 1 year. Malorientation of the components is associated with higher ion levels. A high cup angle of inclination (above 55°) and a low angle (below 20°) are associated with high ion levels. Cup inclination is only one aspect of component malorientation, other factors being anteversion of the cup and femur, and also bearing materials and bearing design including diametral clearance and

sector angle of articulation of the cup. Different models of resurfacing have been shown to be forgiving to a different degree to minor errors of component malposition. [57]

Ionic chromium exists predominantly in two valencies, 3 and 6. The essential cellular functions of chromium are carried out in its trivalent form. The International Atomic Energy Agency (IAEA) classifies trivalent chromium as a human noncarcinogen, and hexavalent chromium as a potential carcinogen with a threshold effect. Excessive administration of cobalt produces goiter. Cobalt-induced cardiomyopathy, polycythemia, and cancer have been described. The above-mentioned adverse effects of elevated systemic metal ion levels were either observations in nonhuman experiments or in people subjected to occupational exposure where the levels and nature of exposure and the mechanism of exposure are different from that which occurs in an arthroplasty patient.

Metal ions and engulfed metal particles can induce cytotoxicity, chromosomal damage and oxidative stress. One cross-sectional study [58] in patients with predominantly metal-on-polyethylene hip replacements showed that there is an increase of nonspecific translocations and aneuploidy in these patients and that there were differences between cobalt-chrome- and titanium-containing implants. Patients with titanium prostheses had a nearly 5-fold increase in aneuploidy but no change in chromosomal translocations. Those with cobalt-chrome prostheses had a 2.5-fold increase in aneuploidy and a 3.5-fold increase in chromosomal translocations. Another longitudinal study [59] performed at the same center on patients with metal-on-metal hip replacements showed an increase in chromosome aberrations in these patients too, but the changes were not as great as those previously reported for the metal-on-polyethylene prostheses in the cross-sectional study mentioned above. Furthermore, no significant relationship was found between the chromosome changes and the blood levels of cobalt or chromium. A further study [60] from the same center also demonstrated that ceramic-ceramic bearing replacements also show similar chromosome changes in the peripheral blood. A recent review [61] on the biologic effects of implant debris declares that, “despite the potential toxicologic possibilities, the association of metal release from orthopedic implants with a metabolic, bacteriologic, immunologic or carcinogenic toxicity remains speculative”, and that, although these concerns are as yet incompletely addressed, they have been largely mitigated given that these devices have been used for more than half a century.

Metal ions are not only a measure of systemic exposure but also an indirect surrogate measure of wear. Increased bearing wear is likely to lead to an increase in both ionic and particulate debris. Therefore, elevated metal ion levels also denote elevated likelihood of periprosthetic adverse reactions.

## Local adverse effects of wear debris release

It is a well-known fact that all artificial joints generate debris. If it is above a threshold level, all types of debris whether polyethylene or metal debris, can trigger off a lysosomal cascade in the periarticular tissues leading on to osteolysis. Therefore, a high-wear bearing is likely to cause osteolysis more frequently than a wear-resistant bearing. This is an expected and normal response to excessive release of an abnormal substance and should not be confused with hypersensitivity. Hypersensitivity is an abnormal exaggerated immune reaction to an otherwise innocuous antigen leading to adverse effects on normal tissues. Metal ions or particles by themselves may not initiate a hypersensitivity response. They can however react with an existing organic substance such as a protein, or form a metal-protein complex to create an antigen which has the potential to initiate an immune response.

Osteolysis and aseptic loosening of the components are the net local results of the wear-debris-induced pathological processes set in motion around a failing hip. These give rise to pain and loss of function of the hip and the need for a revision arthroplasty in order to prevent it from progressing on to extensive bone loss and catastrophic structural failure. Late avascular changes in the femoral head of a hip resurfacing may give rise to femoral loosening and similar symptoms in the presence of normal wear.

The wear resistance of cobalt-chrome alloy stems from the presence of very hard inclusions called “carbides” in their metallurgical structure. These carbides can be depleted by starting with a low-carbon form of the alloy or by employing postcasting heat treatment processes during manufacture. Clinical studies

clearly demonstrate that low carbon CoCr bearings have high failure rates from aseptic loosening. In 1988, the Mestasul bearing was introduced, which employed high-carbon wrought cobalt-chrome components and in 1994, the Sikomet SM21 was introduced, which was made of low-carbon alloy. Both were small diameter total hip replacements with a polyethylene sandwich construct. Good medium-term results have been reported with the high-carbon Metasul replacements from several centers [62, 63] while the low-carbon Sikomet SM21 showed high aseptic loosening rates. [64, 65] Other series involving low-carbon bearings [66] and heat-treated bearings [67] have also shown high osteolysis-related failures.

Laboratory investigations have shown that the local effects of wear debris are a function of the total wear volume and some specific characteristics of the released particles including particle size and number, particle shape or aspect ratio and bioreactivity. Although laboratory studies show that the gravimetric rates in metal-metal bearings [68] is one or two orders of magnitude lower than that with conventional bearings, metal particles are considerably smaller [69] with the result that the total number of particles released in metal-on-metal bearings is more than two orders of magnitude higher than that with conventional bearings. [70] This implies that the surface area of the released metal debris is much higher than polyethylene debris, leading to a greater potential for corrosion and biological activity. There have been reports that particles within the size range of 0.2 to 7  $\mu\text{m}$  are believed to be best suited for phagocytosis, which is the first step in the proinflammatory cascade of wear-induced osteolysis. Polyethylene particles have a statistical mode which happens to fall within that range while metal debris is smaller and nanogram-sized (mean <50  $\mu\text{m}$ ). [71] Furthermore metals being more soluble than polyethylene are cleared better from the local tissues than polymers.

There are therefore differences between the tissue clearance, immune mechanisms and pathways, [72] and the histopathology [73] of metal-on-metal bearing failures and conventional metal-on-polyethylene bearing failures. Conventional failures have a macrophage and foreign-body-granuloma-dominated histology with an abundance of birefringent polyethylene-debris-laden histiocytes. [20] With metal-on-metal bearing failures diffuse and perivascular infiltrates of T-lymphocytes and plasma cells, increased endothelial vascularity, fibrin exudation and necrosis along with macrophages with inclusion bodies or metal particles are often seen. [16] These histological appearances were first observed by Willert, [15] who found this pattern to be a variation of a Type-IV-Delayed Hypersensitivity and termed it Aseptic Lymphocytic Vasculitis and Associated Lesions (ALVAL).

Whether the local adverse effects described here occur as a result of an innate hypersensitivity to metals or whether this is an adaptive immune response to excess wear is another contested issue. Caicedo et al (2009) [74] have shown a dose-related response of the “Inflammasome Danger-Signaling Pathway” to cobalt alloy debris (both ions and particles). The inflammasome is an intracellular multiprotein complex which through a series of intermediate steps sets off the activation of cytokines like IL-1 $\beta$ , TNF $\alpha$ , and NF $\kappa$ B leading to an array of inflammatory responses including inhibition of osteoblasts and maturation of osteoclast precursors leading to osteolysis. This dose-related response and the work of others [75] suggests that painful metal-on-metal bearing failure is an expected response to an overload of debris from a failed arthroplasty rather than a hypersensitive tissue response to a well-functioning arthroplasty.

## Pseudotumors and granulomatous lesions

Pseudotumors have been found in relation to conventional metal-on-polyethylene bearing hip and knee replacements for several years [2, 46] and more recently in relation to metal-on-metal bearing hip replacements. [22, 24, 25, 60, 70] These are often granulomatous lesions developing in the vicinity of a total hip or knee arthroplasty and resembling a tumor (Figure 3). They can be small or large, solid or fluid-filled masses around the prosthesis with or without a communication to the joint and often requiring revision surgery. In the case of metal-on-polyethylene pseudotumors, the lesions cause local pressure effects, osteolysis, and prosthetic loosening. However, in the case of metal-on-metal pseudotumors, in addition to the soft-tissue mass and the bony changes of osteolysis and erosions, they are also associated with limited or extensive collateral damage to the periarticular soft-tissue envelope leading on to soft-tissue and muscle necrosis, bony denudation, pathological fractures, and dislocations. Initially, these were reported from replacements using cobalt-chrome bearings which included a low-carbon component. [24, [25, [60 Subsequently they have been reported with all types of metal-on-metal hip arthroplasties including high-carbon devices. [76, 22, 24]

## Results of studies examining pseudotumors specifically

The literature review identified 24 clinical articles which examined some aspect related to the nature and outcome of pseudotumors. None of the articles come to definitive conclusions. However, each one raises an interesting perspective pertaining to the prevalence, cause or treatment of granulomas or pseudotumors arising as a result of hip arthroplasty.

### Presenting symptoms of pseudotumors

Whether seen in relation to a metal-on-metal or a conventional bearing arthroplasty, pseudotumors often present with pain, discomfort, a palpable swelling, or distal pressure effect. [24] Tallroth et al (1989) [4] found that the first clinical sign of a granuloma was usually stress pain, which led to radiographic examination and detection of lesions around the prosthesis stem. Some studies have identified radiographic osteolytic areas as a precursor to pseudotumors. [77] In one study, 65% of patients had discrete ovoid lucencies in or around the calcar, or on the medial aspect of the shaft of the femoral component. In the presence of these radiological adverse features a high index of suspicion for potential pseudotumors is warranted.

With respect to metal-on-metal bearing arthroplasties cysts, [21] solid [22] or semiliquid masses [24] have been described. Some of these were highly destructive, [24, 26] and the presenting symptoms included pain, rash, pathological fractures, [25] spontaneous dislocations, femoral nerve palsy, [78] and the presence of a lump.

### Causes of pseudotumors

As we have seen earlier, the pathological reaction to polyethylene debris and metal debris appear fundamentally different and therefore the pathogenesis of pseudotumors in these different bearings are likely to be different.

There have been several studies exploring the pathogenesis of polyethylene-debris-related pseudotumors. Griffiths et al (1987) [2] examined patients who had pseudotumors following a conventional THA or a TKA and defined these as a foreign body reaction to methylmethacrylate, polyethylene, or metal adjacent to a total joint implant. The debris is taken up by macrophage giant cells which release prostaglandin E<sub>2</sub>, which resorbs bone loosening the prosthesis and leading on to a vicious cycle of wear, loosening, and more wear. Howie et al (1991) [79] explored bursal masses in patients with metal-on-polyethylene hip resurfacings (Figure 6) and identified excessive wear of the polyethylene component as the cause of the masses. Santavirta et al (1990), [80] Austin and Stoney (1982), [81] and Santavirta et al

(1991) [82] recognized excessive polyethylene debris as the primary factor in the causation of these granulomatous reactions. Willert et al (1990) [20] also found that polyethylene wear products alone can cause massive osteolysis by triggering foreign-body granuloma formation at the bone-cement interface.

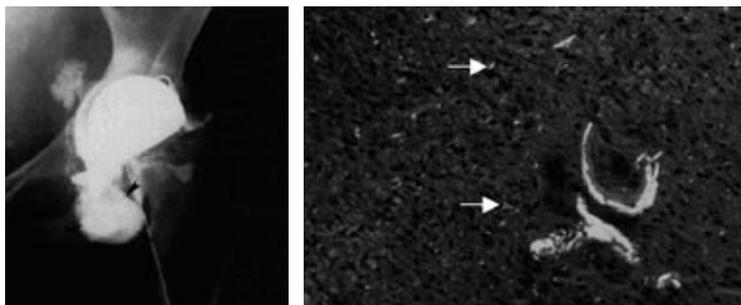


Figure 6: Arthrogram of a "pseudoabscess" in relation to a metal-on-polyethylene hip resurfacing and the histological picture showing small polyethylene particles (arrows) contained in macrophages and large polyethylene particles surrounded by multinucleate giant cells

Nygaard et al (2006) [83] compared three bearing materials (polyethylene on zirconia, CoCr on CoCr, and alumina on alumina) and found that granulomatous inflammation is a common finding in nonloose implants as early as 12 months after the operation. The study did not demonstrate a difference in macrophages and granuloma formation with the various bearing materials. However, backside polyethylene wear could have been a common factor in these patients irrespective of the bearing used. Santavirta et al (1990) [80] found that aggressive granulomatosis is seen even in cementless THA and suggest that this development does not depend on the chemical nature of the irritant, but rather represents a nonspecific foreign-body reaction. [76]

Merritt and Brown adapted Koch's postulates as proof of allergic response to a metal device. [84] Extending the postulates to the field of arthroplasty would require that a patient with a suspected immune reaction to a device should undergo 1) a laboratory test (such as a lymphocyte transformation test) to confirm an immune response, 2) device removal with disappearance of symptoms, 3) reinsertion of a similar device would lead to reappearance of symptoms, and 4) demonstration of a positive laboratory test response for immunity again. These have been used in dermatological and dental disciplines but steps 3 and 4 are inadvisable in orthopedics.

Metal-induced hypersensitivity is in some ways similar to the delayed (Type IV) variety hypersensitivity reaction. Unlike the other types, it is not antibody-mediated but rather a cell-mediated response. The antigen is processed by an antigen-presenting cell (APC) which presents it along with the major histocompatibility complex on its surface to T-cells [CD8 (cytotoxic) or CD4 (helper)]. The APCs also release interleukin 1 to stimulate the proliferation of further CD4 cells, which release more cytokines, which act as immune response mediators. Activated CD8 cells destroy target cells on contact, while activated macrophages produce hydrolytic enzymes and can transform into multinucleated giant cells.

Willert et al [16] studied periprosthetic tissues obtained from nineteen consecutive revisions of MM hip replacements. Radiolucent lines were found in five hips and osteolysis in seven hips. At revision, both components were found to be well fixed in nine patients. None of them had pseudotumors. Fourteen had the MM device revised to a non-MM articulation while five received a second MM THA. The former had permanent relief of pain after revision while the pain remained persistent in the latter which suggests the possibility of a metal hypersensitivity reaction according to the postulates mentioned above.

Histology of their tissue specimens revealed an active cellular reaction with diffuse and perivascular infiltrates of lymphocytes and plasma cells, increased endothelial venules, fibrin exudation, accumulation of macrophages with drop-like inclusions, and infiltrates of eosinophilic granulocytes and necrosis. Only a few metal particles were detected. This histology was an atypical Type IV (DTH) reaction and they described

it as ALVAL. The report does not include a retrieval analysis to establish the possibility of excessive wear.

Dorr with his extensive experience in metal-on-metal bearings studied failures from unexplained pain in patients with MM bearings and suggests that over-the-threshold wear debris generation is the primary cause of the histopathological changes, rather than an inherent genetically determined hypersensitivity to metal. [69]

Pandit et al (2008a) [25] believe that multiple factors give rise to pseudotumors. The authors found that necrotic granulomatous response and inflammatory infiltrate is typically seen in the context of a delayed hypersensitivity reaction and would suggest that a type IV immune response plays a role in pseudotumor pathogenesis.[85] Even though metal wear particles were found in every case examined histologically, they suggest that there is only weak evidence of component malposition since there were several well-positioned implants also in their series as judged by an acceptable cup inclination. However, the absence of data on anteversion may render the assessment of component position incomplete in this study. They suggest that in some cases the pseudotumor may be the result of a toxic effect of abundant particulate wear debris resulting from edge loading, whereas in other cases it is an idiosyncratic response to a moderate release of cobalt-chrome particles. Further retrieval analysis was performed on the components explanted from these pseudotumor patients from Oxford. The components were grouped together with components revised for other causes such as fracture and infection and the tribologist performing the tests was blinded to the cause of revision. It was found [86] that all the components revised for pseudotumors showed signs of edge loading leading to excess runaway wear. Furthermore, no explant without evidence of edge loading had failed through a pseudotumor.

Nolan et al [26] who found periprosthetic fluid-filled cavities along with extensive soft-tissue necrosis, major tendon avulsions, proximal femoral diaphyseal necrosis, pathological fractures and dislocations, attribute some or all of these changes to the finding that the femoral stems in all of these cases showed pitting corrosion though firmly fixed to the cement mantle.

Langton et al [87] showed that all resurfacings are not the same and that their overall results suggest that the reduced arc of cover of the fourth-generation ASR cup leads to an increased failure rate due to increased debris, reporting that explant analysis showed excess wear occurred in small-diameter bearings especially in the presence of high cup inclination and anteversion. This failure rate is 3.4% in the ASR resurfacings as a group, and 7% in ASR devices with femoral components less than or equal to 47 mm. They did not experience debris-related adverse reactions with the Birmingham hip resurfacings.

McMinn et al [88] showed that periprosthetic effusions are secondary to excess wear from either edge loading or impingement. This is almost always due to component malposition, either too high or too low cup inclination (outside the range of 30° to 55°), or a suboptimal combined anteversion of the cup and femoral neck (greater than 45°, or both. All of these situations, vertical cup or excess combined anteversion, lead to edge loading and runaway wear (Figures 7 and 8).

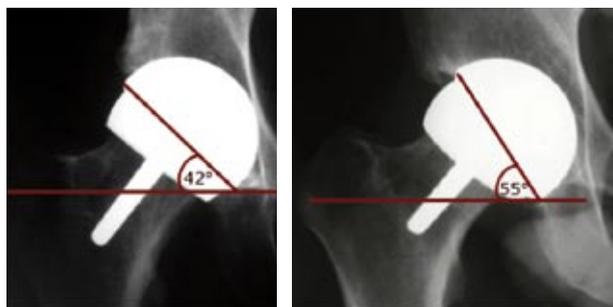


Figure 7: The explants from two hip resurfacings revised for different reasons other than pseudotumors are presented. The femoral components are well positioned but cup inclinations vary, with Figure A being ideal and Figure B too high. In Figure 7-A the measured combined wear rate of head and cup was 2.3 mm/year and in 7-B the combined wear rate was 31.2  $\mu\text{m}/\text{year}$ , nearly fifteen times greater than that in the former.

Abnormal cup inclination and excess combined anteversion of the cup and femoral neck can also lead to posterior impingement of the femoral neck on the edge of the acetabular component and excess wear (Figure 9). McMinn et al (2009) [88] stress that one of the reasons why these reactions are more common in women is because of the high incidence of undetected dysplasia with the associated unrecognized torsional deformity in young women with premature arthritis. If femoral neck anteversion is between 20° and 45° it can be compensated by reducing cup anteversion. Femoral neck anteversion in excess of 45° is unsuitable for resurfacing unless it is combined with a preplanned derotation subtrochanteric femoral osteotomy. They stress that component malposition cannot be ruled out unless femoral neck anteversion also is taken into account. Malviya and Holland (2009) [89] also believe that edge wear/impingement are responsible for pseudotumors.

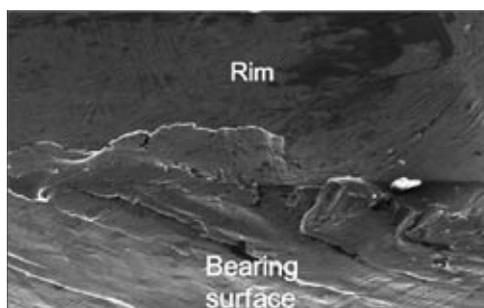


Figure 8: A scanning electron microscope image through the edge of a resurfacing cup showing the runaway wear resulting from edge loading. Edge loading can be avoided by proper component positioning in both planes. Edge loading can occur from high cup inclination and/or excess anteversion of the cup and femoral neck. All alternative bearing devices are less forgiving towards edge loading.

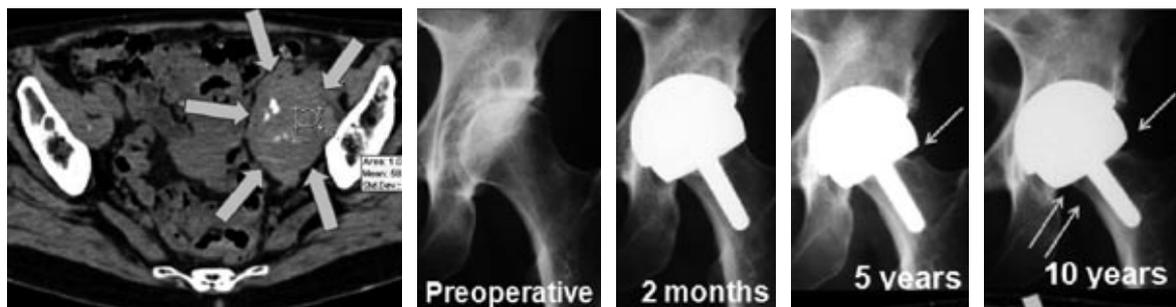


Figure 9: A 55-year-old female with mild hip dysplasia who underwent a resurfacing, later developed periprosthetic effusion at 10 years. Thin arrows show signs of impingement at the superior margin of the femoral neck and neck thinning secondary to the effusion inferiorly. Thick arrows show the multislice CT scanning image of the same patient demonstrating the pseudotumor. The cup inclination (35°) and anteversion (27°) measured from multislice CT were reasonable but her combined cup and femoral neck anteversion was excessive (57°).

As the experience with explant analysis from retrievals of failed resurfacings increases it is becoming apparent that, in many cases, periprosthetic adverse reactions are primarily related to excess wear from component malposition rather than an innate hypersensitivity. Diagnosis of component malposition may need more than a single-plane measurement of cup inclination. Undiagnosed excess femoral neck anteversion has to be borne in mind especially when treating women.

### Prevalence and incidence of pseudotumors

With metal-on-polyethylene bearings, Tallroth et al (1989) [4] obtained a lesion incidence rate of 4.6% in revision THA with a preponderance in males. The granulomatous lesions were multifocal at first diagnosis in 13 of the 19 patients, and twelve patients had lesions around the upper stem. Ten of the lesions started in the lesser trochanter region. There were granulomas around the lower part of the stem in eleven of the patients, and around the tip in two patients. In the study by Wirta et al (1990) [77] lesions were multifocal in twelve hips. In nine hips there were granulomas around the upper part of the stem, and in seven cases they were in the lesser trochanter region. In eleven hips there were granulomas around the lower part of the stem and four around the tip. Three of the hips in this study had solitary granulomas around the distal part of the stem. The study by Austin and Stoney (1982) [81] only included eleven patients; however, six of these patients had a granulomatous reaction at a time greater than 24 months post initial surgery. Howie et al (1991) [79] found that 5.8% of their revisions for a Wagner arthroplasty had a bursal mass.

In the general population, the prevalence of skin reactions to nickel-containing costume jewellery is high (of the order of 10%), as is the prevalence of positive patch test to nickel. If all the metals contained in the cobalt-chrome alloy are considered, the prevalence is even higher. However, metal-on-metal bearing failure secondary to hypersensitivity is a relatively rare phenomenon.

With modern metal-on-metal hip resurfacings, an Australian national review [90] of failures in 3,497 metal-on-metal resurfacings implanted during a 5-year period, reported only one case of presumed hypersensitivity that led to a revision. In a more recent review [29] of approximately 1,500 hip resurfacings implanted by three surgeons, they reported four cases (0.27%) which needed revision for persistent groin pain.

A recent survey of nine of the eleven academic centers which perform metal-on-metal hip resurfacings showed a pseudotumor incidence of 0.09% in a total of 3,400 cases at a mean follow-up of 3.5 years. [91]

Malviya and Holland [89] found two cases of pseudotumors out of 670 consecutive metal-on-metal Birmingham hip resurfacings over a 10-year period (0.3%), one of which was secondary to femoral component loosening (noninvasive effusion, normal wear) and another due to impingement (locally destructive debris mass, excess wear). McMinn et al (2009) [88] reported eight revisions (also 0.3%) for periprosthetic effusions in 3,014 resurfacings, over an 11-year period. Furthermore, in contrast to the findings in some centers, they did not find muscle group necrosis, major tendon avulsions, proximal femoral diaphyseal necrosis, pathological fractures or dislocations in the revisions performed at their center. Excess wear either from edge loading or impingement was a common cause in these. Updating these results Daniel et al (2010) [92] reported ten revisions (0.3%) in 3,095 resurfacings at 12 years. Using Kaplan-Meier survival analysis, they report a 10-year survivorship of 99.6% with revision for pseudotumors as the end point. Excess wear either from edge loading or impingement was a common cause in these. None of them required rerevisions. With well-positioned Birmingham hip resurfacings these pseudotumors are rare events. Furthermore, the lesions they encountered were mostly fluid-filled effusions and not granulomatous masses nor masses of thick semiliquid pus-like fluid.

Pandit et al (2008a) [85] assessed the incidence of pseudotumors in a group where three types of metal-on-metal resurfacings were used. They reported a 1% incidence of cystic or solid masses and in some cases semiliquid contents associated with soft-tissue necrosis, pathological fractures, and dislocations within 5 years of implantation. All the patients were female, raising the possibility that preoperative sensitization to metal may be a factor.

The Oxford group also investigated subjects who had undergone resurfacings in the past and were asymptomatic currently to assess the prevalence of asymptomatic pseudotumors in them. They performed ultrasonography or MR imaging and found that 5% of these patients also had pseudotumors. These patients with asymptomatic pseudotumors however had inferior Oxford scores compared to the others indicating that these patients were not strictly asymptomatic. Furthermore, their blood metal ion levels were significantly higher than the others suggesting the possibility that these were also a result of excess wear from possible component malposition. McMinn et al (2009) [88] investigated their first 124 consecutive Birmingham hip replacements, all performed in 1997, at their post 10-year follow-up with metal ion levels and multislice CT scans with metal artefact reduction and found that none of those patients had asymptomatic pseudotumors. These findings combined with the retrieval analysis of components from Oxford suggest that the high incidence of symptomatic and asymptomatic pseudotumors reported from

Oxford are related to excess wear from edge loading in malpositioned components. Metal-on-metal hip resurfacings like other alternative bearings (including ceramics and cross-linked polyethylene) are less forgiving towards component malposition. Surgeons and patients should be aware of this phenomenon and malpositioning of components should be avoided.

### Implant factors in pseudotumors

There are a few reports of high incidence of pseudotumors which are implant specific and are related to specific component factors including their metallurgy or design characteristics. With metal-on-metal total hip replacements using a low-carbon component as one or both of the bearing surfaces the incidence of metallosis and revisions for periprosthetic effusions with collateral damage is also high. Nolan et al [26] reported 60 (9.3%) revisions out of 643 metal-on-metal hip replacements over a 9-year period, 13 for peri-prosthetic fracture and 47 for extensive symptomatic peri-articular soft-tissue changes with one specific metal-on-metal total hip replacement with demonstrated excess stem corrosion of the Ultima TPS stem (DePuy Johnson and Johnson, Leeds, UK). Legenstein et al (2007) [66] reported 20.8% revisions for metallosis, a quarter of whom were associated with dislocations with the PPF (proximal press fit) metal-on-metal total hip replacements. In a recent report [89] of unexpected early-failure rate in 370 primary total hip replacements utilizing a 38 mm diameter CoCr on CoCr (M2A 38 bearing, Biomet), there were eleven clinical failures (3%) including four pseudotumors (1.1%). Pathologic analysis showed mixed lymphocytic/fibroblastic infiltrate with soft-tissue necrosis in a majority of revised hips.

Langton et al (2009) [87] reported 17 (3.4%) failures from adverse local reactions to metal debris and high wear rates, at a mean follow-up of 35 months, out of 495 hip resurfacings or replacements using the ASR (DePuy Johnson and Johnson, Leeds, UK) metal-on-metal bearings. They found no such reactions with the Birmingham Hip Resurfacing device confirming the fact that component factors play a significant role in pseudotumor development. The high incidence of pseudotumors in the Articular Surface Replacement (ASR) device is reported to be due to its reduced articulation angle which makes it less tolerant to major or minor component malposition especially in the smaller diameter bearings. Furthermore, it is possible that the thinner cup and the reduced diametral clearance in the ASR bearings render them susceptible to component deformation and increased wear and friction. The Australian National Registry also confirms the increased revision rate of the ASR and other resurfacings, although it does not specify the reasons for revision.

Table 5: Yearly cumulative percent revision of primary total resurfacing hip replacement

HEAD COMPONENT	ACETABULAR COMPONENT	1 YR	3 YR	5 YR	7 YR	8 YR
ASR	ASR	3.6 (2.6, 4.9)	6.0 (4.6, 7.8)	8.7 (6.6, 11.5)		
Adept	Adept	0.7 (0.2, 2.7)	1.9 (0.7, 5.1)			
BHR	BHR	1.5 (1.3, 1.8)	2.5 (2.2, 2.9)	3.6 (3.2, 4.1)	4.8 (4.2, 5.6)	5.0 (4.3, 5.8)
Bionik	Bionik	4.3 (1.6, 11.1)	6.7 (2.6, 16.4)			
Conserve	Conserve Plus	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)			
Conserve Plus	Conserve Plus	3.2 (0.8, 12.3)	5.1 (1.7, 15.1)	9.7 (4.1, 22.1)	9.7 (4.1, 22.1)	
Cormet	Cormet	1.6 (0.5, 4.8)	3.8 (1.8, 7.9)	5.3 (2.8, 10.1)	16.0 (7.1, 33.6)	
Cormet 2000 HAP	Cormet	6.3 (2.9, 13.5)	8.4 (4.3, 16.1)	9.5 (5.0, 17.4)		
Cormet HAP BiCoat	Cormet	2.8 (1.3, 5.8)	5.0 (2.6, 9.5)			
Durom	Durom	3.0 (2.0, 4.5)	4.7 (3.4, 6.7)	6.7 (4.7, 9.7)		
Icon	Icon	1.1 (0.2, 7.9)	2.5 (0.6, 9.6)			
Mitch THR	Mitch THR	1.4 (0.6, 3.1)				
Recop	Recop	5.0 (2.3, 10.8)	7.6 (3.8, 15.0)			

### Patient factors in pseudotumors

In most series a common finding has been the high incidence of pseudotumors in female patients. Preexisting sensitization to metals in women has been forwarded as one cause for this phenomenon. Other causes include the smaller component sizes required in women, which are known to be associated with increased wear and are known to be less tolerant to minor component malposition. Furthermore, developmental dysplasia of the hip is a frequent etiological factor in the development of premature arthritis in females. Developmental hip dysplasia is a complex problem associated with acetabular malorientation and deficiency, and also with abnormal femoral neck anteversion all of which can compromise component positioning, leading on to excessive wear.

From the above discussion it is apparent that the incidence of pseudotumors, periprosthetic effusions, and granulomatous lesions is a function of wear, whether it arises due to the relative wear-prone metallurgy of the components or due to design deficiencies [81] or the malpositioned components of an otherwise wear-resistant device. While the prevalence of true hypersensitivity in patients with MM replacements is unknown, metal sensitivity should be borne in mind while investigating a patient with local or systemic signs of hypersensitivity related to device implantation.

### Surgeon factors in pseudotumors

Several studies [81, 82, 86] have shown that complications associated with hip resurfacing including accelerated wear and local adverse reactions are related to surgical technique and component position. Suboptimal cup inclination and anteversion, failure to identify and adjust cup position for excess femoral neck anteversion are key factors that can lead to edge loading and excess wear in these bearings. Women with premature arthritis often present with a degree of acetabular dysplasia and abnormal socket inclination and version, and excess femoral neck valgus and anteversion. Often these patients need preoperative multislice CT scanning in order to assess these deficiencies accurately. Reliable component positioning therefore involves identifying the optimal position for a given patient and implanting the component in the desired position with the least error possible. Certain design features such as a reduced angle of articulation (as in the ASR) reduce the margin of error allowed before the components start to wear excessively and the need for a smaller-diameter bearing reduces this margin of error even further. Excessive coverage from an increased articulation angle of the device is also a disadvantage since it can lead to impingement/subluxation and excess wear with minor errors in component positioning. Training and familiarity with a difficult exposure in young fit patients is paramount.

### Investigations for pseudotumors

Groin pain can result from a number of causes. Campbell et al (2008) [30] outlined a practical list of the steps necessary to diagnose the cause of pain. This includes radiographic imaging to exclude aseptic loosening, femoral-neck stress fracture or collapse of the femoral head or femoro-acetabular impingement. Components can be accurately assessed for orientation using EBRA software, to rule out excessive inclination or version. [93] Multislice CT scan is necessary to allow assessment of femoral-neck anteversion. Magnetic resonance imaging (with-metal-artefact reducing sequences) is useful in the assessment of soft-tissue masses or fluid collections.

Local soft-tissue problems such as psoas tendonitis or bursitis and referred pain from intra-abdominal or intrapelvic pathology, inguinal hernias and spinal conditions should be excluded. Hematologic testing and microbiological assessment of joint aspirations are needed to assess infection. Positive isotope bone scan studies indicate infection or loosening.

Skin patch testing has been used in the assessment of contact dermatitis. This test may not have a direct relationship to the incidence of deep hypersensitivity. Furthermore, there is the risk of sensitization following skin testing. Therefore, the value of skin testing in the assessment of metal hypersensitivity is limited. Two other in vitro tests which have been used in the assessment of metal hypersensitivity include the lymphocyte transformation test and the leukocyte migration inhibition factor test. The lymphocyte transformation test involves measuring the proliferative response of lymphocytes following activation. A radioactive marker such as [<sup>3</sup>H]-labelled thymidine is added to lymphocytes along with the desired

activating agent. The radioactive [H3]-thymidine gets incorporated into the DNA during cell division and allows quantification of the proliferation response. The difficulties involved in the transport of blood samples with vital cells to a specialist laboratory within hours of drawing the sample, the technical difficulties involved in the test itself, and the cost of Leukocyte Transformation Testing (LTT) limit its use in clinical testing for metal hypersensitivity.

Assuming some patients are more sensitive or sensitizable to metals, the ultimate prognostic benefit from in vitro testing would be the development of a sensitive and reliable screening test that would preoperatively diagnose whether a person has a genetic predisposition to hypersensitivity to a specific metal or group of metals. That would enable a patient and his/her clinician to make an informed decision regarding the choice of bearing material in that individual case.

Several terms have been used to describe the spectrum of conditions resulting from abnormal periprosthetic soft-tissue reactions in arthroplasty (Figures 10 and 11). The term “pseudotumors” [2] was originally used to describe solid granulomatous masses [1] related to prosthetic wear debris leading to pressure effects or extensive tissue necrosis [1] and the usage of this term should ideally be restricted to such phenomena. All types of unexplained groin pain leading on to resurfacing revisions do not fall into this category. In some patients there is no granulomatous mass but an effusion with little or no periprosthetic necrosis. In others there is no mass and only minimal fluid collection but unexplained groin pain requiring a revision. Langton et al [87] use the term “Adverse Reactions to Metal Debris” (ARMD) to describe these lesions ranging from effusions to pseudotumors, in order to explain the wide spectrum of this disease. There is no evidence to suggest that all effusions eventually develop into granulomatous masses or lead on to extensive necrosis with the passage of time.

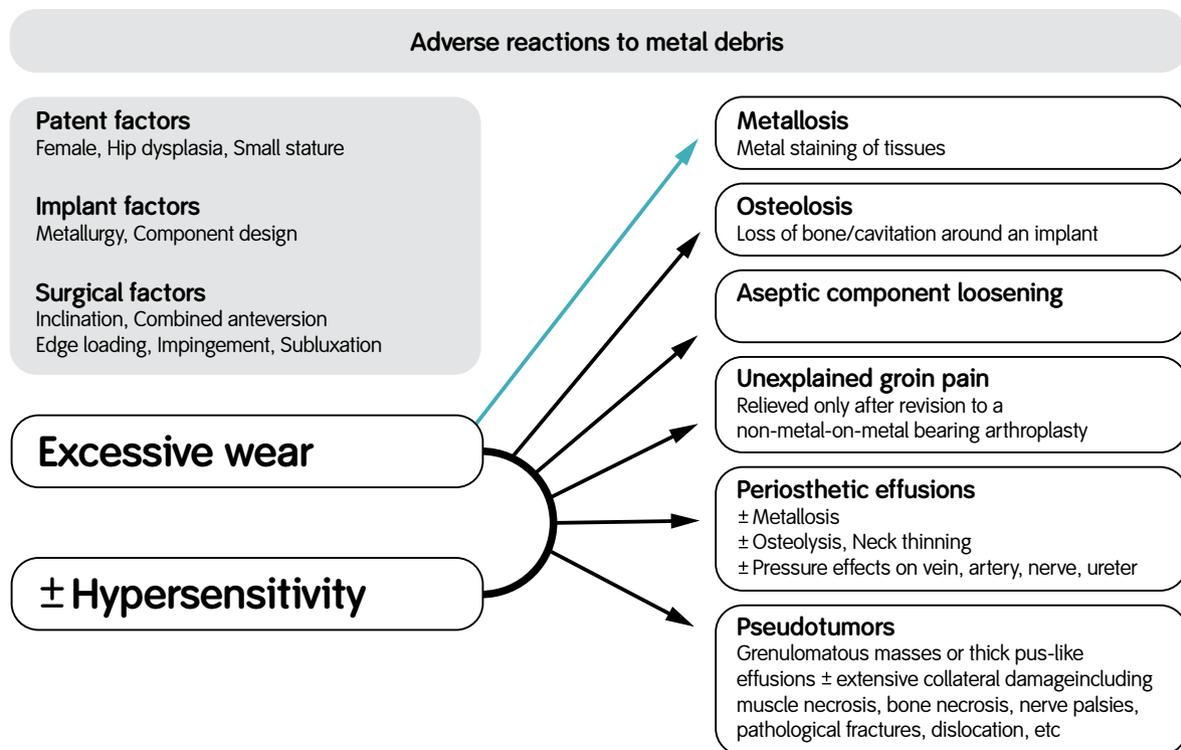


Figure 10: The causes and local adverse effects of excess metal debris. All of the above have been described in all types of arthroplasties and are by no means exclusive to metal-on-metal

Aseptic Lymphocytic Vasculitis and Associated Lesions (ALVAL) is a term coined by Willert et al [17] to describe characteristic histological features seen in tissue obtained from metal-on-metal arthroplasties revised for groin pain and should not be used as a clinical diagnosis or syndrome. In order to interpret the histological findings of ALVAL, Campbell [96] suggests grading retrieved tissue based on the degree of disruption of the synovial surface, the presence of inflammatory cells including T- and B-lymphocytes, and tissue organization, with a score of 1 to 10. Tissue with predominantly high wear has a typical median ALVAL score of 5 with a predominance of B-cells, small and few perivascular lymphocytic aggregates and many macrophages. Tissue from patients who present predominantly with pain and little evidence of wear typically have a median ALVAL score of 8 with a mixture of B- and T-lymphocytes and many large perivascular aggregates.

**Adverse reactions to metal debris**

Implant wear/corrosion/lead to release of metal ions particulare metal debris witch can initiate a dose-related allergic response

Infect must be ruled out as the first possibility.Other conditions such as femoral head AVN and soft-tissue (psoas) irritation can mimic an allergic response

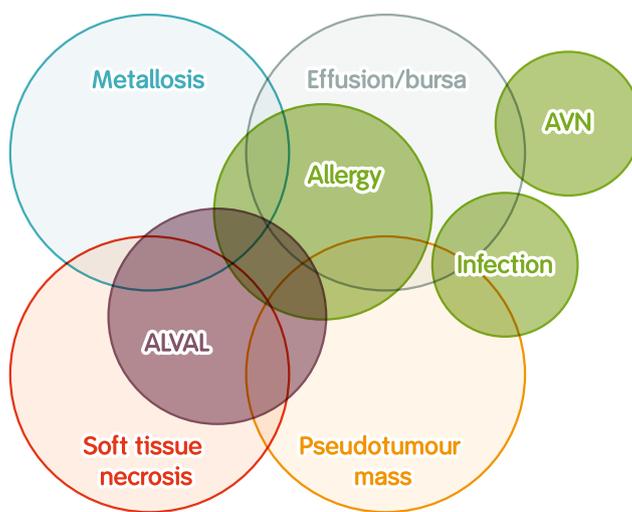


Figure 11: Showing the wide spectrum of clinical problems associated with excess metal debris

**Case studies**

**Case 1**

A female patient aged 39 received a BHR in September 1998, size 42 femoral head and 50 Dysplasia BHR cup (Figure 12 A, B). She had an excellent outcome until 2006 when she developed a painless lateral thigh swelling (Figure 12 C). Hip function was normal and inflammatory markers ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) were all normal. Magnetic resonance imaging scans showed a fluid-filled cyst communicating with the hip joint (Figure 12 D, E). Aspiration of the hip yielded sterile fluid.

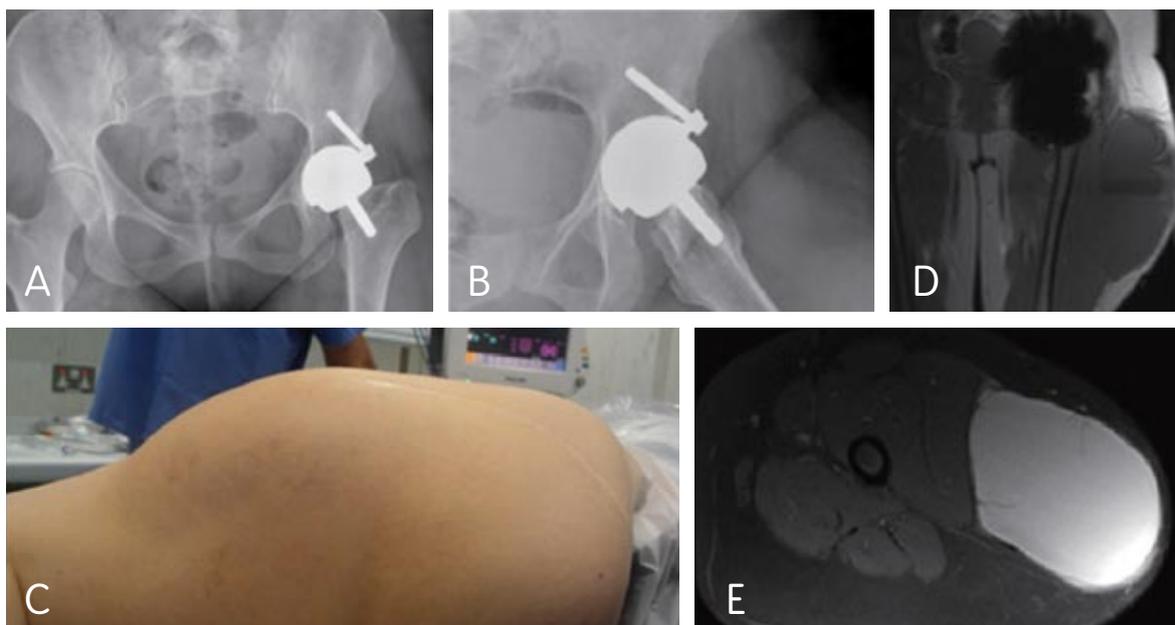


Figure 12: Radiographs, clinical photograph, and MRI images of the left hip in Case 1

Recent X-rays showed progressive anterior neck remodeling and recent neck narrowing and a lucent line around the stem (Figure 13).

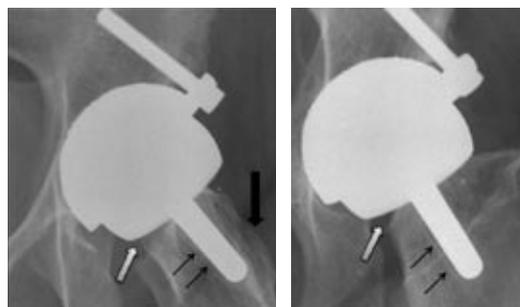


Figure 13: Recent radiographs of left hip in Case 1 showing stem radiolucent line (thin arrows) and progressive anterior neck remodeling (thick black arrow), and recent neck narrowing (thick grey arrows)

Wear analysis of the explanted femoral component showed head wear of 8.85 microns which was what would be expected at 8 years. Histology showed chronic nonspecific synovitis, metallic debris in macrophages but no significant changes of ALVAL. There was no solid mass, nor collateral damage in the form of necrosis of soft tissues or bony destruction and it would be inappropriate to term this as a pseudotumor. In the absence of excess wear and histological features of ALVAL, this case is one of late femoral head collapse from avascular necrosis associated with massive effusion (Figure 14).

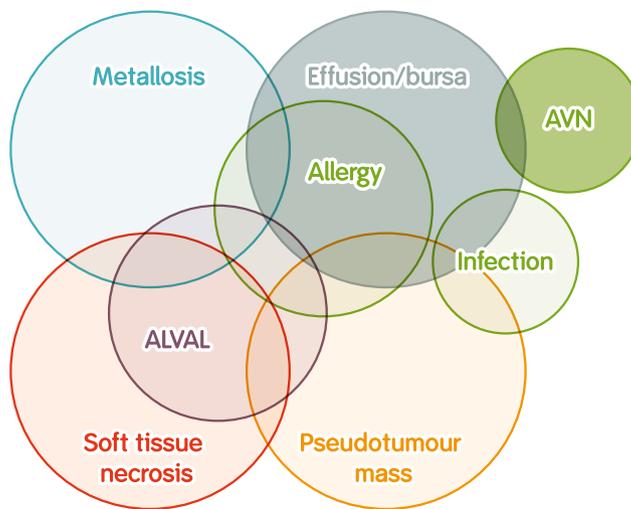


Figure 14: Schematic representation of the presentation and probable pathogenesis in Case 1

**Case 2**

A female patient aged 54 underwent a right-sided BHR, in the year 2000 42 mm femoral head and 48 mm cup. Four years later she underwent a left-sided BHR and was fine till 2009. She then presented to the vascular surgeons with a right-leg swelling and suspected deep vein thrombosis (DVT). There was no pain and she had normal hip function bilaterally with a Harris hip score of 100%. On ultrasonography (USG) and MRI scanning there was a 10 cm iliopsoas swelling and no DVT (arrow in Figure 15). X-Rays showed cup abduction of 41° and anteversion 16°. Blood metal ions were 2.3 and 2.5 mcg/l of cobalt and chromium respectively.



Figure 15: Radiographs, MRI image showing the effusion (arrow) and the explanted components showing good bony fixation

At revision, the components showed sound bony fixation, no evidence of femoral head avascular necrosis (AVN). Wear analysis showed cup wear of 7.5 microns and head wear of 10.7 microns which was normal expected wear at 9years. Histology showed chronic inflammatory response with foreign-body giant cells and macrophages and no significant changes of ALVAL. In the schematic this would fit into effusion with no other features. In the absence of excess wear this is a suspected case of metal hypersensitivity leading to effusion (Figure 15).

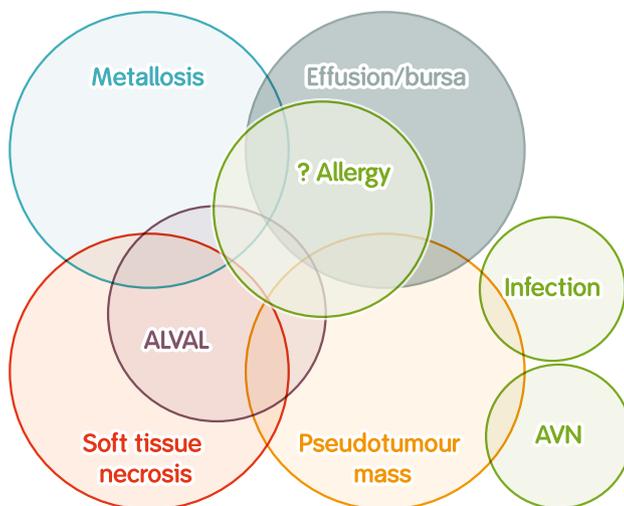


Figure 16: Schematic representation of the presentation and probable pathogenesis in Case 2

**Case 3**

Female patient aged 45 years underwent a BHR, in 2006 46 mm femoral head and 52 mm cup. She had an excellent outcome initially but 7 months later developed clicking, swelling, and discomfort. USG showed thickening of the psoas muscle. At 12 months she developed femoral nerve symptoms, and an MRI showed a psoas mass (Figure 17). Biopsy revealed eosinophilic debris. Aspiration and inflammatory markers excluded infection.

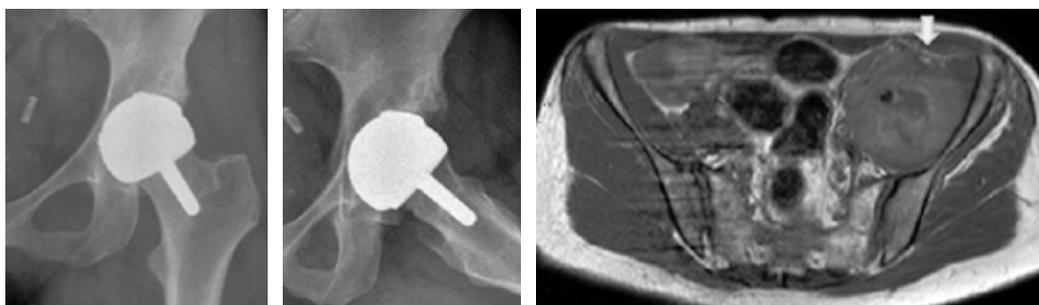


Figure 17: Radiographs and MRI image in Case 3 showing the pseudotumor (arrow)

The patient was revised in 2008. Her cup abduction was 52° and anteversion 20°. Metal ions were highly elevated and she was patch test positive for nickel allergy. There was gross metal staining with grey fluid and soft-tissue necrosis. Histology showed extensive eosinophilic inflammatory infiltrate with necrotic skeletal muscle but sparse lymphocytes, ie not ALVAL.



Figure 18: Showing (A) the explanted femoral component with an indentation in the posterior femoral neck from the impingement, seen radiographically (arrow in B), and shown schematically (C) along with the anterior subluxation and edge loading leading to excessive wear in Case 3

Retrieval analysis showed an impingement notch on posterior surface of the femoral neck (Figure 18 A and B). This correlated well with the radiographic finding of possible posterior impingement. There was 35 µm wear in the cup and 17.5 µm on the head, which was clearly excessive and may be attributable to the posteroinferior femoral neck-implant impingement and consequent subluxation/edge wear anteriorly (Figure 18 C).

Applying the schematic to this case it would be one of metallosis with a pseudotumor and soft-tissue necrosis (Figure 19).

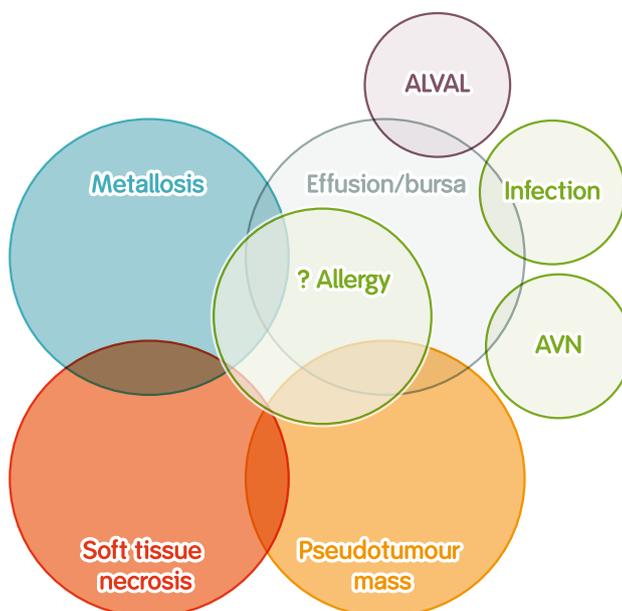


Figure 19: Schematic representation of the presentation and probable pathogenesis in Case 3

### Treatment of pseudotumors

With respect to granulomas developing in relation to conventional metal-on-polyethylene hip replacements, Eskola et al (1990) [5] conducted a study to evaluate the use of uncemented revision THA with the Lord prosthesis. Their results suggest that aggressive granulomatosis in cemented THA can be satisfactorily treated with a cementless revision prosthesis combined with cancellous-bone grafting when the granulomas are large. Howie et al (1991) [79] suggest that surgeons proceed to revision arthroplasty using techniques appropriate for aseptic loosening when confronted with pseudotumors. Tallroth et al (1989) [4] treat patients with aggressive granulomatous lesions by revision arthroplasty, using uncemented titanium prostheses and bone grafting. Wirta et al (1990) [77] examined the results of revision surgery for granulomatous lesions in hip arthroplasty. The series shows that aggressive granulomatosis can be well treated with revision and a new cemented THA; however, the risk of recurrence remains. Hoping to reduce this risk, the authors are now considering the use of uncemented prosthesis and bone grafting for revision.

With respect to metal hypersensitivity our understanding of these reactions in patients with metallic implants is still incomplete. Case reports and histological studies suggest that metal-on-metal bearings initiate a distinctive immune response. A high index of suspicion is essential while investigating a patient for persistent unexplained joint pain or swelling after an arthroplasty procedure. If investigations rule out any explicable cause such as infection, hypersensitivity should be considered in the differential diagnosis. In these cases of effusions, pseudotumors and other debris-induced adverse local reactions, especially in the presence of a positive test result which suggests hypersensitivity, exchange to a non-metal-on-metal bearing should be considered and performed early. Harvie et al [78] revised two cases of metal-on-metal resurfacings with pseudotumors and nerve palsies and advocate prompt revision in the presence of a neurological deficit.

### Results of pseudotumor revisions

Willert et al (2005) [16] reported the results of 19 revisions of painful metal-on-metal hip replacements. Fourteen of these were revised to a non-metal-on-metal articulation and five received another second-generation metal-on-metal total hip arthroplasty. The former had remission of symptoms but the latter who were revised to another metal-on-metal articulation had no decrease in symptoms. Now, several surgeons would agree with the principle that if a metal-on-metal bearing hip arthroplasty fails from a pseudotumor or a debris-induced local adverse reaction, it should be revised to a non-metal-on-metal bearing hip arthroplasty.

The Oxford group [97] reported poor outcomes following pseudotumor revisions to a total hip arthroplasty. There was a high incidence of serious complications including recurrent dislocations, nerve palsies and femoral artery stenosis. They compared these pseudotumor-related revisions of hip resurfacings to those resurfacings revised for other reasons such as femoral neck fractures, etc, and found that the postrevision hip function scores in patients revised for pseudotumors was significantly worse than in those revised for other reasons. Furthermore, the hip function in pseudotumor revisions was worse than the hip function before the primary resurfacing operation. Moreover, they reported a high incidence of rerevisions in patients revised for pseudotumors. Compared to these, McMinn et al (2009) [35] reported good results in patients who underwent hip resurfacings in their Center originally and were subsequently revised to a non-metal-on-metal hip replacement for periprosthetic effusions in the absence of soft-tissue destruction. They found no major complications such as those mentioned above. There were no rerevisions. The postoperative hip function in these patients was no worse than the postoperative hip function in the best comparative series reported by Oxford, ie primary total hip replacements. This suggests that outcome is dependent on the degree of this destruction at the time of revision, thus indicating early detection and treatment. These results are in agreement with the observation made by Willert et al [73] and Campbell et al [30] that when the patients who develop a debris-related effusion or failure from metal-on-metal bearing hip arthroplasties these may be revised to a non-metal-metal bearing hip replacement with the expectation of a good result if the soft tissue has remained intact.

## Summary

Pseudotumors are a rare but significant complication occurring with all types of arthroplasties. Metal-on-metal hip resurfacings like all other alternative bearings (including ceramic and/or cross-linked polyethylene components) are less forgiving towards component malposition. Surgeons and patients should be aware that malpositioned metal components will lead to runaway wear from either edge loading or impingement and result in early or mid-term failure along with debris-related collateral damage to the surrounding structures. A high index of suspicion for debris-related effusions or pseudotumors is necessary in the presence of unexplained hip pain in a patient who has had a hip arthroplasty in whom other causes of pain have been discounted.

## Questions raised from current review

Several questions have not been answered by this literature review, some of which are important in understanding the full impact of the development of pseudotumors and patient outcomes. The questions include: 1) What is the incidence of pseudotumors in well-positioned components among different designs of prostheses?; 2) Are pseudotumors purely a consequence of metal, ceramic or polyethylene debris, or is there potentiation from associated particulate debris such as polymethylmethacrylate (PMMA)?; 3) Is pseudotumor development related to an innate (genetic?) predisposition leading certain individuals to be sensitive to metals, and is there a preoperative screening test that can identify such subjects?; 4) Is it an adaptive immune response to excess metal, and is there a threshold level of debris that would lead to the development of pseudotumors?; 5) In addition to careful patient selection and meticulous surgical technique and component positioning, what potential strategies would reduce the development of pseudotumors?, and 6) Should national joint registries be used more effectively for surveillance of these problems and link device/unit revision rate?

## Areas of uncertainty

The results in this review are based on low-quality literature (case series) where different types of total hip or knee arthroplasties prostheses are not compared in terms of occurrence of pseudotumors. Results are only generalizable to similar patient groups and implant types as those included in each of the studies. The results of this review should be considered with caution and definitive conclusions have not been reached.

## Recommendations for future research

Improvements in implant design and alternative materials are being bench-tested in laboratories around the world for potential use in conservative hip arthroplasty. The introduction of these devices should be accompanied with high-quality cohort studies using validated, patient centered outcome measures and periodic monitoring with clinical, radiological and ion level assessments in order to determine the risks and benefits of these newer devices. The incidence of systemic and local adverse effects should be specifically assessed. Further studies to elucidate the causes and effects of pseudotumors and prevention strategies are needed.

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Smith & Nephew Orthopaedics AG  
KLEOS  
Oberneuhofstrasse 10d  
6340 Baar  
Switzerland  
T +41 41 766 22 55

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