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## Risk Factors for Aseptic Loosening Following Total Hip Arthroplasty

Scott J. MacInnes, Andrew Gordon and J. Mark Wilkinson  
*Academic Unit of Bone Metabolism and Department of Orthopaedics,  
 University of Sheffield, Sheffield,  
 United Kingdom*

### 1. Introduction

Total hip arthroplasty (THA) is one of the most successful orthopaedic procedures and has relieved pain and improved hip function in millions of patients worldwide. Despite the success of modern prosthetic designs and bearing surfaces, around 10% of THA prostheses still fail within 10 years<sup>1</sup>. Improvements in surgical technique and prosthesis design have decreased the incidence of deep sepsis, dislocation and fracture, however aseptic loosening, the clinical end point of osteolysis, remains the most frequent complication and in the UK accounts for 63% of all revision surgery (Table 1)<sup>2</sup>. Prosthesis loosening results in pain and disability, requiring revision surgery. Revision THA is associated with a 3 to 8-fold greater in-hospital mortality, poorer functional outcome, longer hospital stay, and higher cost than primary surgery<sup>1,3-5</sup>.

The problem of osteolysis has been recognized in Judet's acrylic hemiarthroplasty introduced in the 1940s. Prosthesis loosening complicating THA in the 1950's and 1960's was poorly understood and attributed to unconfirmed sepsis<sup>6</sup> and prosthesis motion<sup>7</sup>. In the 1980's loosening was thought to be the result of "cement disease"<sup>8</sup>, arising due to a foreign body reaction to methyl methacrylate. When the development of cementless prostheses

National Joint Registry hip Annual Report Data 2009		
	Number	%
Total procedures	72,432	
Primary procedures	65,229	90%
Revision procedures	7,203	10%
<b>Indication for revision</b>		
Aseptic Loosening	3,524	49%
Osteolysis	999	14%
Pain	2,035	29%
Infection	1,020	14%
Dislocation/ subluxation	1,141	16%
Periprosthetic fracture	618	9%

Table 1. Summary of hip surgery data from 7<sup>th</sup> Annual Report National Joint Registry for England and Wales<sup>2</sup>

failed to eliminate this problem, wear at the bearing couple was subsequently identified as the main source of particulate debris giving rise to osteolysis.

Advances in prosthesis materials, design and surgical technique have improved the wear performance of prostheses, which will decrease the future incidence of osteolysis. However, an ageing population combined with younger more active patients now undergoing joint arthroplasty suggests that osteolysis and resulting prosthesis loosening will continue to be the major complication of THA.

## 2. Pathophysiology of osteolysis

The term aseptic loosening describes mechanical failure of the prosthesis-host interface, and arises primarily as the end result of focal periprosthetic inflammatory bone loss occurring at this interface. This pro-inflammatory microenvironment is driven by particulate wear debris, which is generated primarily at the articular bearing surface and at other non-articular prosthesis or cement surfaces<sup>9</sup>. Willert first proposed the involvement of prosthetic debris in the development of osteolysis. He identified a resultant foreign body reaction and granuloma formation which included macrophages and multinucleated giant cells<sup>10</sup>. This foreign body reaction has subsequently been reproduced in animal models<sup>11</sup>. Once particulate wear debris has been dispersed into the joint fluid it may initiate a foreign body reaction at contact surfaces with the host tissues. Schmalzried coined the term "effective joint space" to describe all areas where open communication with the joint pseudo-capsule may allow circulation of the joint fluid and particulate debris<sup>12</sup>. The effective joint space is thus dynamic and may advance along a tissue plane as osteolysis progresses. Variations in hydrostatic pressure within the joint space during activity may contribute to this circulation<sup>12</sup>.

As well as its role in the migration of wear particles, hydrostatic fluid pressure changes within the joint have been implicated as an osteolytic stimulus. Aspenberg showed in an animal model that fluid pressure alone can lead to osteolysis<sup>13</sup>. Skoglund also showed that the osteolytic effect of fluid pressure on the bone was greater than that of particles<sup>14</sup>. However, it remains unclear what contribution this potential mechanism makes to the development of osteolysis clinically. Early migration of the femoral component may predict early and mid-term prosthesis failure. It has been suggested that this migration may lead to instability resulting in locally high fluid pressures which may, in turn, lead to osteolysis<sup>15</sup>. However, it is also likely that the predictive value of early migration measurements is due to the identification of failures of initial prosthesis fixation, resulting in loosening due to technical failure.

## 3. The biology of osteolysis

The process of aseptic loosening is characteristically accompanied with the development of a fibrous membrane at the bone-cement interface. Histological analysis of this membrane has shown a synovial-like fibrovascular tissue containing cells including macrophages, fibroblasts and foreign body giant cells<sup>9,16</sup>. The predominant cell types driving osteolysis, the macrophage and fibroblast, signal through various pro-inflammatory cytokines (including the interleukins, TNF alpha, and vascular endothelial growth factor VEGF) following either phagocytosis of the particles or through surface contact<sup>17</sup>.

The biological process through which wear particles induce this inflammatory response is still not fully understood. It has become clear that the innate immune system is involved in

the initiation of the biological response. The innate immune system is the body's first defense against foreign pathogens. Its ability to recognize and eliminate pathogens relies on pattern recognition receptors (PRR). PRRs are expressed by several cells in the monocyte cell lineage and include toll-like receptors (TLR) and the NOD-like receptors (NLR). These subfamilies evoke an inflammatory response either through the activation of transcription factors or through the formation of inflammasomes (Figure 1). Inflammasomes are large cytoplasmic complexes that activate inflammatory caspases required for the catalysis of pro-IL-1 $\beta$  and pro-IL-18 into their active forms<sup>18</sup>. Disorders of inflammasome signaling are associated with a number of auto-inflammatory conditions.

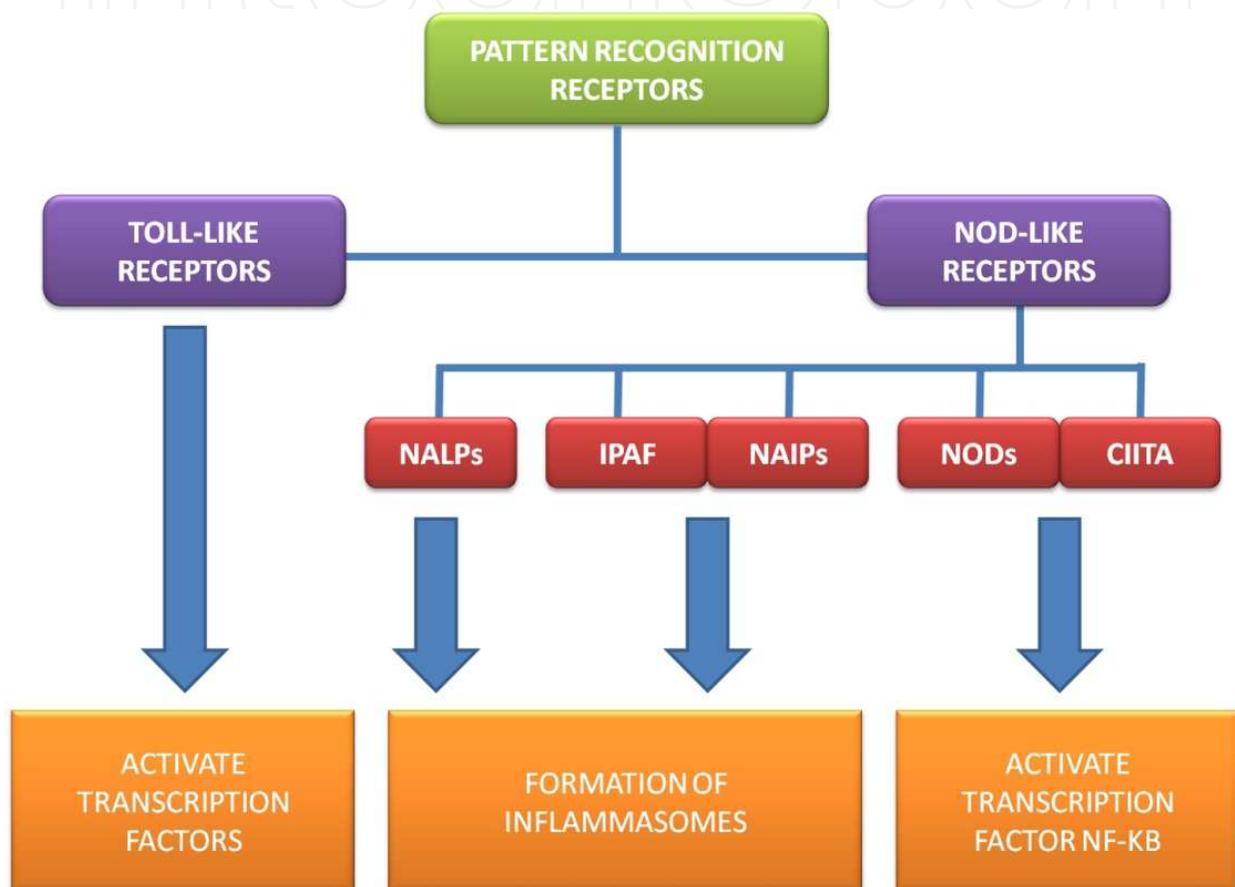


Fig. 1. Summary of pattern recognition receptors and their effector pathways. NALP = NACHT, LRR and PYD domain-containing proteins, IPAF = Ice protease activating factor, NAIP = neuronal apoptosis inhibitory protein, NOD = nucleotide-binding oligomerization domain proteins, CIITA = Major histocompatibility complex class-2 transactivator

Caicedo et al found that metal implant debris stimulated an inflammatory response in macrophages through inflammasome signaling (Figure 2)<sup>19</sup>. Maitra found that UHMWPE wear particles are phagocytosed causing intracellular activation of NACHT, LRR and PYD domains-containing protein 3 (NLRP3) leading to inflammasome formation. In addition alkane polymers generated by UHMWPE activate TLRs through cell surface contact. This leads to the activation of transcription factors including NF-KB resulting in cytokine release<sup>20</sup>. St Pierre *et al* showed in a mouse model that titanium particles also induce an inflammatory response through the activation of the NLRP3 inflammasome<sup>21</sup>.

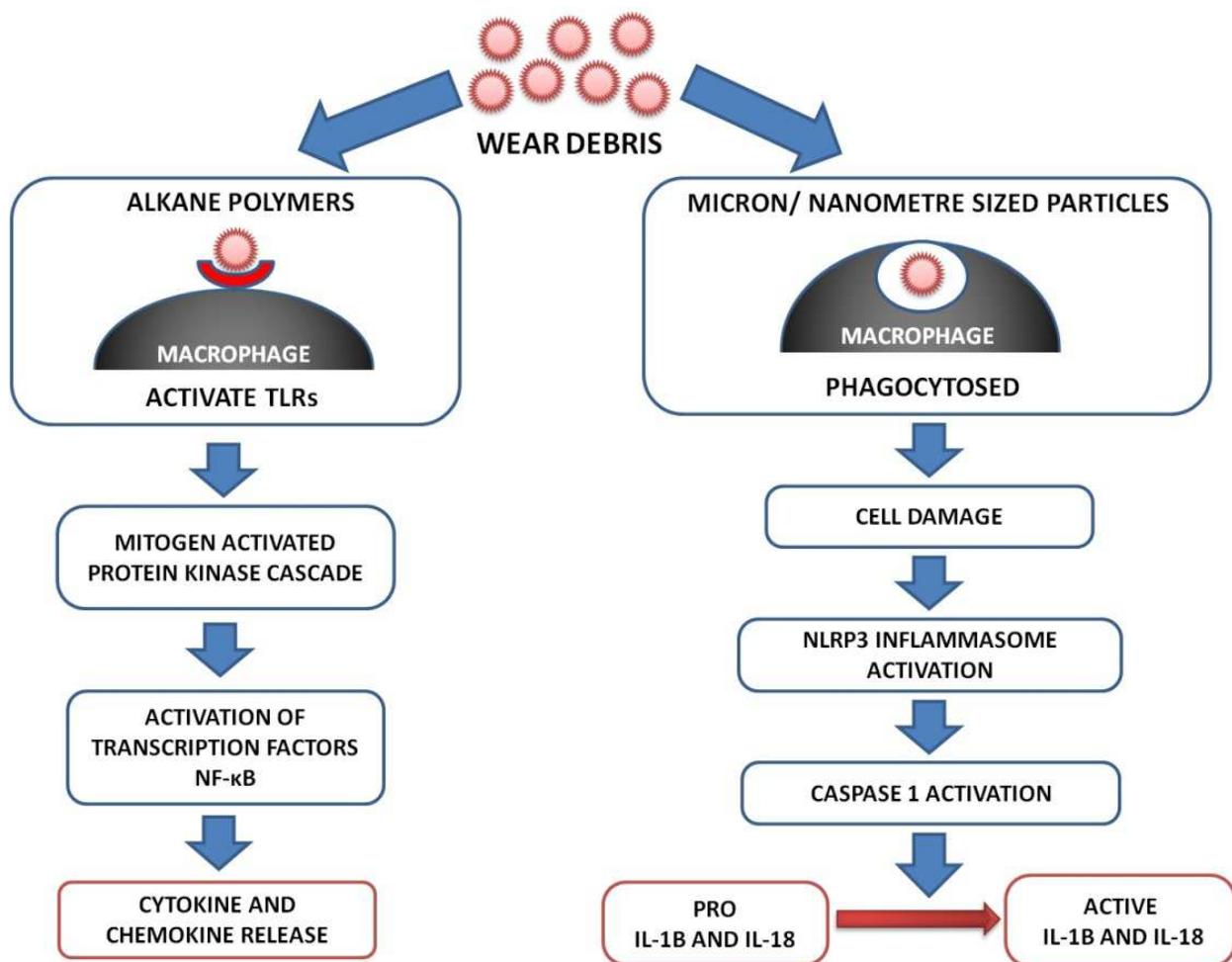


Fig. 2. Toll-like receptor and inflammasome signaling in response to wear debris

The released pro-inflammatory cytokines, in turn, modulate the activation of other cell types in the periprosthetic environment, including osteoblasts. Osteoblasts closely interact with osteoclasts in coupled bone remodeling, regulating bone resorption through the activation of osteoclasts<sup>22</sup>. Activated osteoblasts stimulate the monocyte / macrophage cell lineage through activation of receptor activator of nuclear factor  $\kappa$  B (RANK) by its ligand (RANKL) and macrophage colony stimulating factor (M-CSF). Together these induce expression of genes required for the development and maturation of polykaryon osteoclasts and activation of their function of bone resorption<sup>23</sup>. This upregulation of periprosthetic bone resorption results in failure of the integrity of the prosthesis-host construct and loosening of the prosthesis. Activated macrophages also produce matrix metalloproteinases (MMPs) that directly degrade demineralized collagen matrix.

Fibroblasts are the most frequent cell type found in the loosening membrane, and also play a role in the pathogenesis of osteolysis. They produce the fibrous collagenous matrix which surrounds the prosthesis and in addition, secrete RANKL and IL-6 which are both osteoclastogenic and stimulate the formation of multinucleated giant cells<sup>24,25</sup>. In addition to upregulation of the osteoclastic response, particulate debris suppresses differentiation of mesenchymal stem cells (MSC) into mature functioning osteoblasts and reduces synthetic activity of mature osteoblasts further shifting turnover balance in favor of net bone loss<sup>26</sup>.

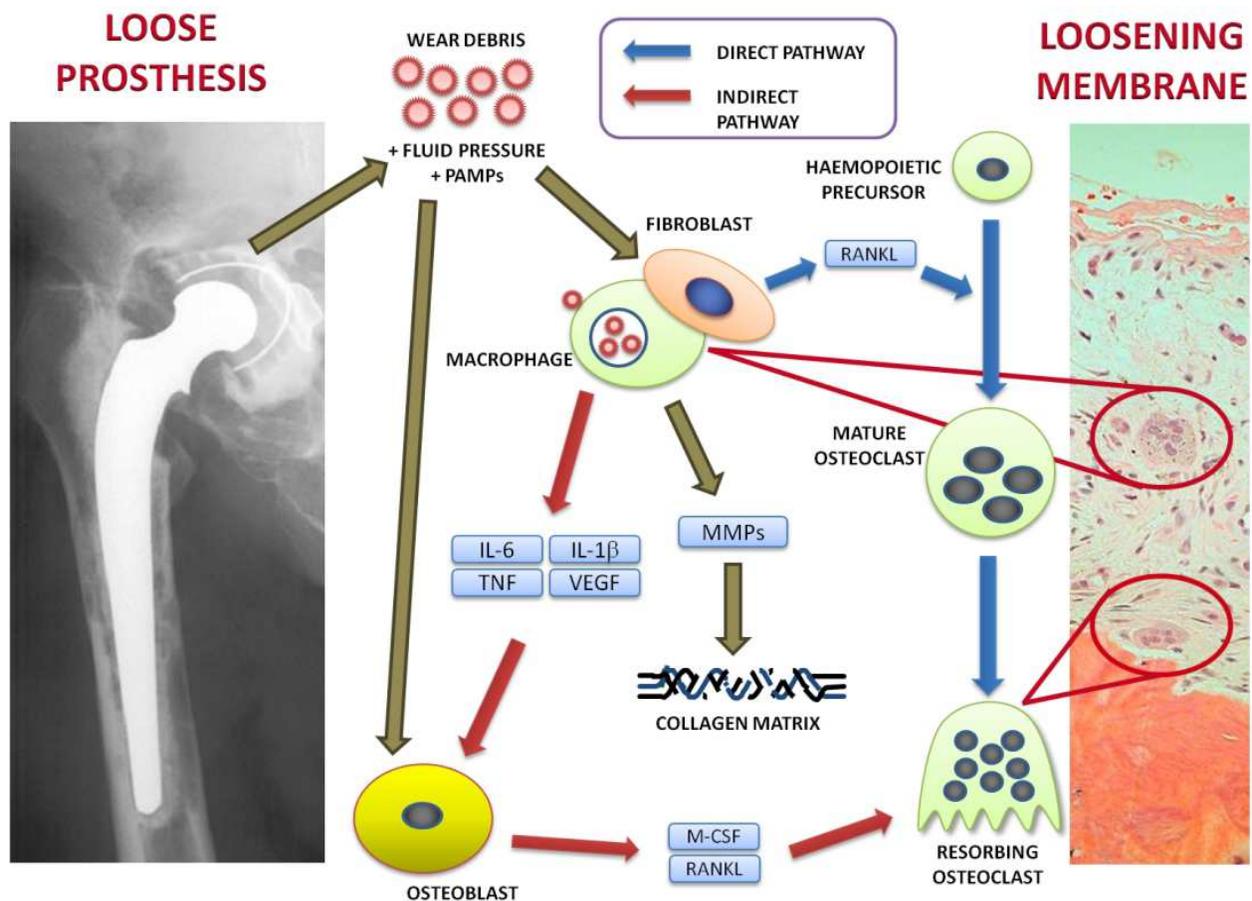


Fig. 3. Summary of biological response to wear debris. Recruitment and activation of osteoclasts may occur directly through the production of RANKL by fibroblasts, or indirectly through the production of pro-inflammatory cytokines that stimulate the production of RANKL by the osteoblast. TNF may stimulate osteoclast differentiation and activation through both routes.

other cell types may also be involved in the inflammatory response to wear particulate debris. These include lymphocytes and mast cells. The presence of lymphocytes suggests involvement of the adaptive immune system. It is suggested that particulate debris may undergo opsonisation which allows them to be targeted by B and T lymphocytes. Degranulated mast cells have been found in the periprosthetic tissue surrounding loose prostheses confirming their activation in the process of osteolysis<sup>27</sup>

Although aseptic loosening, by definition, occurs in the absence of bacterial infection, recent evidence suggests that bacterial endotoxin may contribute. Gram-positive and gram-negative bacteria produce (as constituent components of their cell walls or as toxins) a number of molecules including endotoxins and peptidoglycans, collectively termed pathogen associated molecular patterns (PAMPs) that act as ligands for PRRs. The presence of PAMPs has been confirmed in the periprosthetic tissue of patients undergoing revision surgery for aseptic loosening<sup>28</sup>. Using RNA gene sequencing, the presence of bacteria in the periprosthetic biofilm surrounding loose prostheses has also now been confirmed<sup>29</sup>. It has been shown both in vitro and in animal models that PAMPs adherent to particulate debris activate PRRs on macrophages, increasing the biological activity of wear particles<sup>30</sup>.

#### 4. Risk factors for osteolysis

Although the final pathway to the development of aseptic loosening is process of mechanical failure of the construct driven by inflammatory-mediated bone loss, multiple factors mediate an individual's susceptibility to this process. These may broadly be divided into patient, surgical, and prosthesis-related factors (Figure 4). Although not an exhaustive list, some of these proposed factors that have been identified and validated will be discussed.

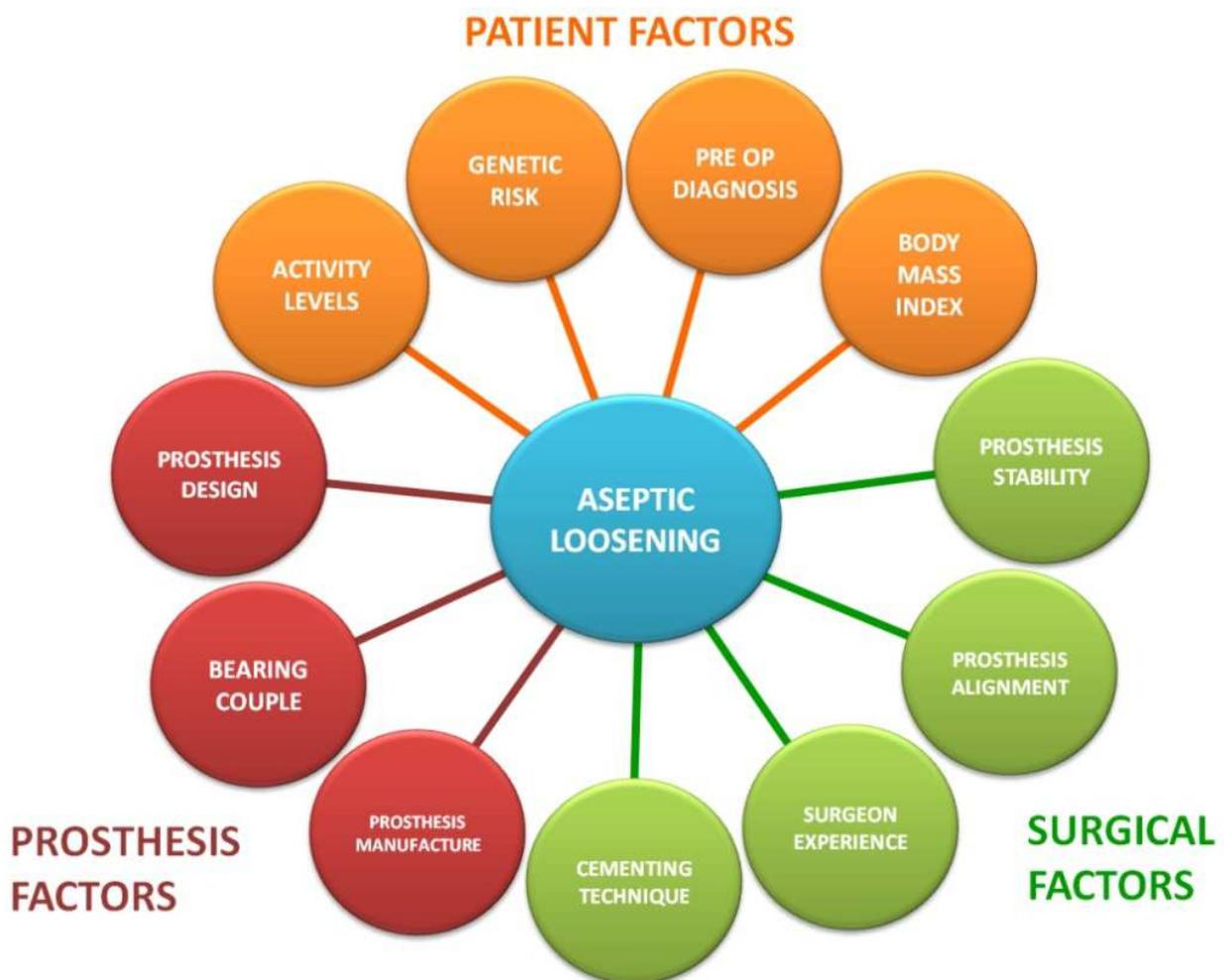


Fig. 4. Summary of risk factors that influence the development of aseptic loosening

#### 5. Patient risk factors

##### 5.1 Preoperative diagnosis

The most common indication for THA is idiopathic osteoarthritis. Within this diagnosis group, those with an atrophic pattern of bone response to osteoarthritis are at increased risk of acetabular prosthesis loosening<sup>31</sup>. Proximal femoral bone geometry may also affect prosthesis survival, with large non-tapering femoral canal shape (stove-pipe) being associated with an increased risk of aseptic loosening<sup>31</sup>.

Higher rates of prosthesis loosening also occur in patients who have undergone arthroplasty for post-traumatic arthritis and osteonecrosis when compared with primary osteoarthritis. However, it is thought that this finding may relate to higher activity levels and increased bearing surface wear, rather than being a function of the pre-operative diagnosis<sup>32,33</sup>.

A number of preoperative diagnoses carry a possible increased risk of prosthesis failure through associated medication. Patients taking systemic steroids have been found to have a higher risk of reoperation<sup>34</sup>. Non-steroidal anti-inflammatory drugs (NSAIDs) have been implicated in impaired bone healing, and patients taking NSAIDs have higher reoperation rates, although NSAID use may be acting as a marker of a painful prosthesis rather than contributing directly to prosthesis failure<sup>34</sup>.

Poorer prosthesis survival might be expected in patients with inflammatory arthropathy due to its inflammatory pathogenesis and the historic frequent use of corticosteroids in its treatment (that are associated with loss of bone mass through osteoblast suppression). However, Furnes *et al*, in a large arthroplasty registry-based study, found no difference in THA survival between patients with rheumatoid arthritis versus those with osteoarthritis<sup>35</sup>. Rud-Sorensen *et al* found that the risk of stem revision due to aseptic loosening was lower in rheumatoid patients versus primary osteoarthritis, whilst acetabular prosthesis survival was similar<sup>36</sup>.

Furnes *et al* and Bordini *et al* have reported higher acetabular revision rates due to aseptic loosening in patients with a primary diagnosis of developmental dysplasia of the hip compared to primary osteoarthritis<sup>37,38</sup>. Rates of acetabular prosthesis failure are higher in younger patients and those with greater graft coverage of the cup<sup>39</sup>. The role of these factors is unclear, but may relate to activity levels, or mechanical factors influencing prosthesis support.

### 5.2 Body mass index and obesity

The Health Survey for England 2009 showed that over the last 16 years there has been marked increase in the proportion of the population that are obese. This proportion increased from 13% of men in 1993 to 22% in 2009 and from 16% of women in 1993 to 24% in 2009<sup>40</sup>. The mean BMI of a patient undergoing THA in England and Wales has increased over the last 5 years from 27.4 to 28.4. Likewise the percentage of patients classed as either obese or morbidly obese has risen from 29% in 2004 to 37%

Historically, obesity has been deemed a relative contraindication for THA<sup>41</sup>, as the joint reaction force experienced at the hip is directly proportional to body weight, and thus obesity was considered a risk factor for prosthesis failure. Obesity is associated with a higher incidence of perioperative complications including cardiovascular and respiratory events<sup>42</sup>, venous thrombosis<sup>43</sup>, wound infection<sup>44</sup>, and dislocation<sup>45</sup>. However, despite the increase in joint load in these patients, no consistent increase in bearing wear or osteolysis has been shown across study populations<sup>46,47</sup> and thus obesity is not a clear risk factor for osteolysis.

### 5.3 Bearing-surface wear and activity level

Patient activity level associates with osteolysis. It is thought this association operates primarily through the production of wear of the bearing surface. Flugsrud showed that patients who undertake intermediate to intense activity are four times more likely than the less-active to develop acetabular prosthesis loosening<sup>48</sup>. A recent study with five to ten year

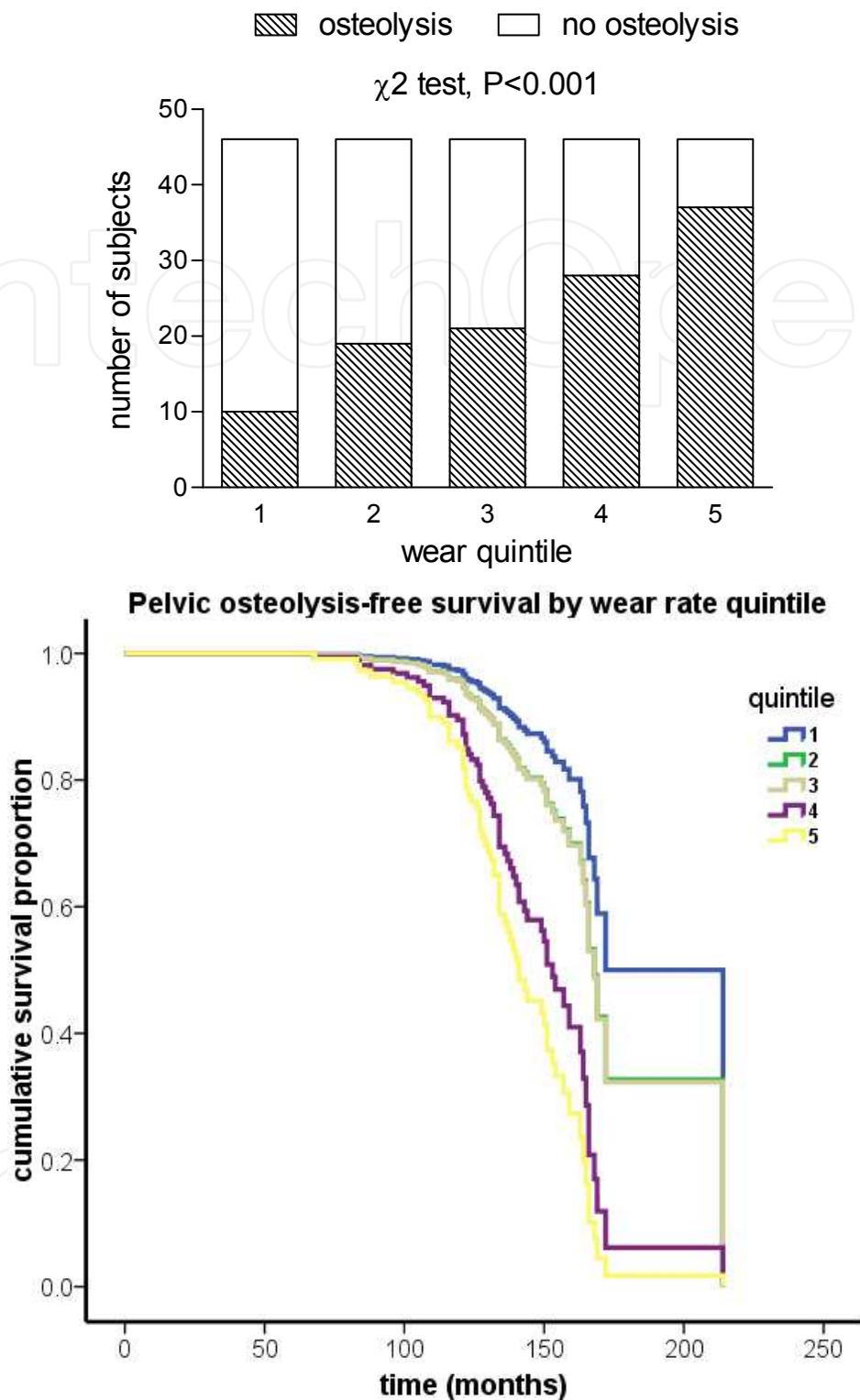


Fig. 5. Continuous dose-response relationship between prosthesis bearing wear and risk of osteolysis. Top panel shows data from a study of 115 cases and 115 controls after Charnley THA with consistent increase in proportion of subjects with osteolysis with increasing wear rate (by quintile)<sup>57</sup>. Bottom panel shows survivorship analysis in a cohort study of 319 hybrid THAs followed for a minimum of 10 years, and showing a similar dose-response relationship between osteolysis and polyethylene wear<sup>58</sup>.

follow up has shown that 24% of patients who have engaged in high levels of activity developed femoral osteolysis, and had higher revision rates<sup>49</sup>.

Traditionally the rate of polyethylene wear has been reported as a function of time. The results from ex-vivo hip simulator experiments have shown that the number of hip cycles is proportional to the rate of wear of prosthesis surface<sup>50</sup>. In vivo, there is a great range of wear rates between individual as a consequence of differing activity levels<sup>51</sup>. Several validated assessment tools have been developed to measure activity levels in arthroplasty populations<sup>52</sup>, and Schmalzried *et al* showed that wear in patients is a function of activity<sup>53</sup>. There are no clear guidelines outlining what levels of activity can be undertaken following THA although the proportion of patients participating in athletic activity following THA ranges between 52 - 83%<sup>54-56</sup>. Whilst low-impact activities such as walking, swimming and cycling have always been recommended following THA, some patients participate in more high-impact and competitive sports. The increasing participation in athletic activity and higher post-operative expectations can partly be explained by the increasing numbers of younger patients undergoing THA. 42% of men and 31% of women who underwent THA in England and Wales in 2009 were under the age of 65 years<sup>2</sup>. A large number of patients over the age of 65 are also participating in high levels of activity<sup>49</sup>.

Several investigators have shown a relationship between high levels of polyethylene wear and osteolysis/aseptic loosening, and the concept of a wear-rate 'threshold' (commonly defined as 0.1mm/year) below which osteolysis occurs very rarely, has been suggested. Wilkinson *et al* quantitated the association between wear and osteolysis and found no evidence to support this concept. In a case-control study of 230 hips after cemented Charnley THA with a metal on polyethylene bearing they showed that the risk of osteolysis increased with each quintile increase in wear, from very low levels of wear, below the suggested threshold, through to high levels<sup>57</sup>. They subsequently showed that the risk of osteolysis showed a similar pattern of consistently increasing risk ratio with each wear rate quintile in a separate cohort study of patients with 319 hybrid THAs using a metal on conventional polyethylene bearing (Figure 5).

#### 5.4 Genetic factors

Within a given ethnic population the sequence of DNA between individuals is 99.5% identical. However, variability within the code does occur and gives rise to the phenotypic variability within the population. These variants occur at approximately every 1000 nucleotide base pairs of the code. This variation, where it occurs in >1% of the population is termed a polymorphism. The most common type of variant is a single letter change in the DNA sequence, termed a single nucleotide polymorphism (SNP). There are thought to be around 10 million common SNPs in the human genome. The individual specific risk of common diseases is thought to be influenced by the sum of many genetic variations, each potentially causing small changes in biological function and consequently subtle changes in phenotype<sup>59</sup>.

Patients vary in their osteolytic response to particulate wear debris. Some show little bone resorption in the presence of marked prosthesis wear whereas others undergo marked osteolysis following a small amount of prosthesis wear (Figure 6)<sup>57</sup>. Macrophage responsiveness to in-vitro particulate debris stimulation also varies between individual<sup>60</sup>,

and monocytes (PBMCs) taken from patients with a susceptibility to osteolysis exhibit quantitatively greater inducible cytokine responses to particulate debris in-vitro versus patients without this susceptibility<sup>61</sup>. It is suggested that this inter-patient variability may have a genetic basis.

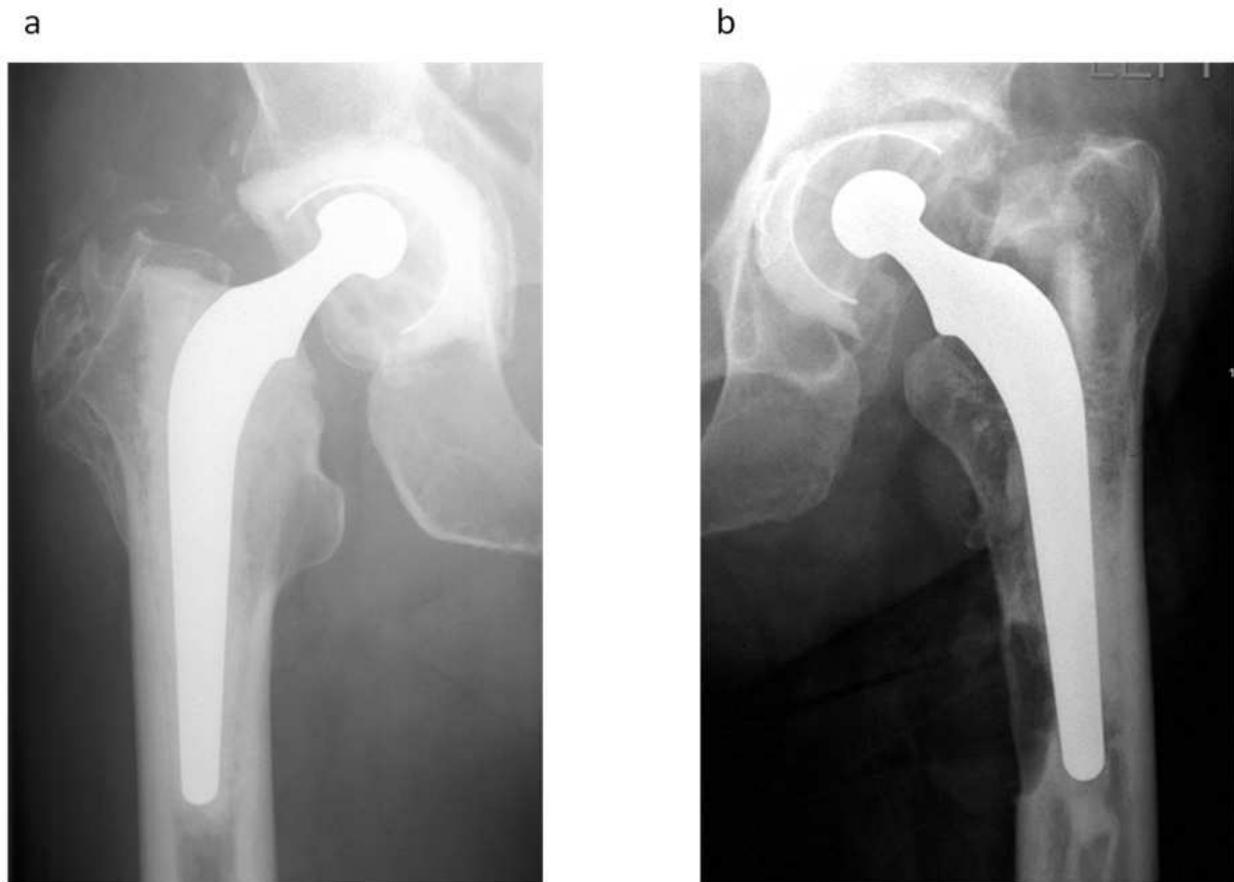


Fig. 6. Patients exhibit variable osteolytic responses to wear debris. a) radiograph showing marked polyethylene wear, but no osteolytic response, b) radiograph showing mild wear but pronounced femoral and acetabular osteolysis with prosthesis loosening.

Variation within the genes encoding inflammatory cytokines have been associated with osteolysis. Wilkinson *et al* showed an association between variability within the DNA encoding the tumor necrosis factor (TNF) promoter region (dbSNP rs361525) and risk of osteolysis following THA<sup>62</sup>. Subjects with osteolysis were approximately twice as likely to carry the variant DNA code as those subjects with no osteolysis. This association has been replicated in an independent population by Ambruzova *et al*<sup>63</sup>. Gordon *et al* have reported genetic variation within the genes encoding Interleukin-1 receptor antagonist (IL-1RN) and IL-6 is also associated with osteolysis<sup>64</sup>. Similar associations have also been identified in other populations<sup>65-67</sup>.

Variation within genes that regulate bone turnover also associate with osteolysis. Gordon *et al* showed that carriage of the dbSNP rs288326 variant in the FRZB gene encoding secreted frizzled-related protein-3 (Frp3), a regulatory glycoprotein within the osteogenic Wnt signaling pathway that modulates mesenchymal stem cell differentiation of osteoblasts<sup>68</sup>, associated with susceptibility to osteolysis following THA<sup>69</sup>. Its carriage also associated with

the development of heterotopic ossification following THA. Malik *et al* have also shown associations between aseptic loosening and other candidate loci within the genes encoding matrix metalloproteinase 1 and the vitamin D receptor<sup>67</sup>, mannose-binding lectin<sup>70</sup>, and the RANK/OPG pathway<sup>71</sup>.

Recent studies using beadchip assays have shown that many genes are differentially expressed in wear debris-induced cells and tissues<sup>72-74</sup>, and have highlighted our limited understanding of the spectrum of biological mediators involved in the pathogenesis of osteolysis. The identification of further risk loci is required to further understanding of the pathogenesis of aseptic loosening. This would potentially allow for the development of screening tools, and provide investigational targets for prophylaxis or treatment with the aim of reducing the need for revision surgery, and its associated morbidity and mortality.

## 6. Prosthesis risk factors

### 6.1 Prosthesis design

Prosthesis design factors, aside from those that modulate wear, contribute to risk of osteolysis. Modularity allows intra-operative adjustment of bearing surfaces, prosthesis length and offset. However, it also creates additional interfaces within the construct at which generation of debris through wear may occur. Such interfaces include the trunion between the femoral head and stem at which corrosive wear may occur, and backside wear between an acetabular liner and its shell at which abrasive wear may occur, and potentially several other prosthetic component junctions in highly modular systems. Hydroxyapatite coating of the prosthesis may prevent osteolysis following injection of intra-articular particles by sealing the implant-bone interface from their ingress though the promotion of osseointegration at this interface<sup>75,76</sup>, but may also be a source of third-body wear. Selection of bearing diameter is also a factor. The use of larger head sizes reduces the risk of dislocation, but increase volumetric wear<sup>77</sup>. The need for a thinner liner to accommodate the larger head may also cause increased contact stresses and an increase in wear.

### 6.2 Polyethylene wear

The metal on polyethylene bearing couple remains the gold standard for THA. However, the manufacturing and sterilization process of polyethylene has changed over time with the aim of improving its wear rate characteristics. The earliest prostheses were made with non-cross-linked ultra-high molecular weight polyethylene (UHMWPE) that was irradiated to render it sterile for patient use. The process of sterilization with ionizing radiation leads to cross-linking within the polymer. Cross-linking improves wear resistance of the material, but also causes the formation of free radicals. Free radical species cause the oxidation of UHMWPE over time. Polyethylene oxidation degrades UHMWPE, and decreases its wear resistance.

Several production techniques have been developed to reduce the generation of free radicals, including annealing and melting. Melting reduces free radical concentration more than annealing but adversely affects the yield stress and fatigue resistance of the polymer. Annealing below melting point has a less adverse effect on the mechanical properties, but is less effective than melting at free radical removal. Sterilization in an oxygen-free environment also produces more cross-linking and reduces free radical production<sup>78</sup>. Irradiation in an inert gas and vacuum packing is also now routinely carried out to reduce pre-implantation oxidation, however this does not prevent oxidation occurring *in vivo*. Faris

*et al* compared the wear rates of UHMWPE produced using three combinations of polyethylene production and sterilization techniques<sup>79</sup> and found the best wear rates were achieved in sterilization by radiation in an inert gas with molded polyethylene. Irradiation sterilization of ram extruded components in an inert gas and in air had 11% and 16% more wear respectively.

Highly cross-linked polyethylene has exhibited reduced wear rates clinically in short-term studies<sup>80,81</sup>, and thus their potential role in reducing the incidence of osteolysis is promising. Further developments in polyethylene modification techniques are currently being explored to further reduce oxidization *in-vivo* and optimize the wear performance of UHMWPE without compromising its other mechanical properties, and include doping with antioxidants such as vitamin E and cycling of annealing and irradiating. However, the macrophage response in osteolysis is influenced by the size, composition and number of wear particles<sup>82,83</sup>. Particle size and number vary with the extent of cross-linking within the material. Although cross-linking reduces the total amount of wear debris generated versus conventional UHMWPE, the particle size produced is smaller, and the number of particles is increased, which may enhance their osteolytic potential *in-vivo*. Also, whilst increased cross-linking results in enhanced wear resistance there is a reduction in fatigue strength potentially leading to mechanical failure<sup>84</sup>.

### 6.3 Alternate bearing couples

Although metal on polyethylene bearings have most commonly been used in THA, there is a long history of use of other bearing couples, including metal on metal, ceramic on ceramic, and ceramic on polyethylene.

Metal on metal bearings have reduced wear rates compared with metal on polyethylene. Jacobsson reported a 77% 20-year survivorship of the metal on metal McKee Farrar THA compared to 73% for the Charnley THA<sup>85</sup>. Metal on metal prostheses also have the advantages of allowing a larger bearing diameter, improving stability characteristics, and are self-polishing. Although the volumetric wear rate of metal on metal bearings is low, the particles generated are in the nanometer range and the number of particles is far greater<sup>86</sup>. These particles circulate widely within the body and their systemic effects remain unclear. At a local level metal release can cause an adverse surrounding tissue reaction, termed aseptic lymphocytic vasculitis associated lesions (ALVAL), and inflammatory masses<sup>87,88</sup>. Metal hypersensitivity may also occur<sup>87</sup>.

Ceramic on polyethylene and ceramic on ceramic bearing couples have lower wear and osteolysis rates versus metal on polyethylene bearings in some long-term studies<sup>89,90</sup>. Most ceramic wear particles are also in the nanometer range and wear volume is lower than that of metal on metal bearing couples. A prospective randomized multicenter study of 930 hips comparing alumina-on-alumina with cobalt chromium-on-polyethylene bearing couples reported an alumina-alumina survival rate of 96.8% at 10 years<sup>91</sup>. However, cases of osteolysis have also been reported in poorly functioning ceramic on ceramic prostheses. Yoon reported osteolysis rates of 22% in a series of patients with ceramic on ceramic prostheses<sup>92</sup>. Nam reported a case of alumina debris induced pelvic and femoral osteolysis in a well-functioning prosthesis<sup>93</sup>. Ceramics are also expensive, have a small fracture risk due to their brittleness, and are sensitive to component mal-positioning that may result in impingement damage and stripe wear. There are also some reports of squeaking associated with ceramic on ceramic bearing couples<sup>94</sup>.

## 7. Surgical risk factors

Regardless of prosthesis design and bearing surface, surgical technique is an important factor that affects prosthesis survival. Data from large national joint registries has recently facilitated examination of these factors in relation to prosthesis survival.

### 7.1 Hospital type and surgeon operating volume

Type of hospital and the surgeon undertaking the procedure can influence THA survival. Fowles *et al* showed that low operating volume is associated with increased risk of THA revision<sup>95</sup>. Similarly, Espehaug *et al*, using data from the Norwegian arthroplasty register, found the lowest revision rates amongst surgeons with the highest THA volume<sup>96</sup>. In the same study, university hospitals had higher revision rates than local and central hospitals. This may be attributed to the lower number of operations per surgeon at these hospitals or possible centralization of high-risk patients and more complex cases. Bordini *et al* found that prosthesis survival was negatively associated with lower surgeon skill<sup>38</sup>.

### 7.2 Prosthesis alignment and soft tissue balancing

Malalignment of prostheses may alter the articulation of prosthesis components with the potential to increase contact stresses and increase wear, this increases the incidence of edge loading and results in stripe wear in hard on hard bearing couples. Despite the advantage of larger femoral head size, soft tissue balancing remains important in the reduction of dislocation of the femoral head. Subluxation of the femoral head during the swing phase of gait, especially in metal on polyethylene couples, causes socket edge contact resulting in wear<sup>97</sup>. Complete dislocation of the femoral head may damage the head during dislocation-relocation, and can increase wear rates.

### 7.3 Prosthesis dislocation and interface micromotion

Prosthesis stability influences the development of aseptic loosening. Motion between the prosthesis and bone contributes to the formation of a fibrous membrane rather than bone<sup>98</sup>. Bechtold *et al* found that particulate wear debris prevents bone formation in the presence of prosthesis instability<sup>99</sup>. In addition, prosthesis motion alters local joint fluid pressures and can transport particles along the periprosthetic space.

### 7.4 Cementing techniques

Improvements in prosthesis survival have accompanied advances in cementation technique<sup>100</sup>. First generation cementing techniques involved finger packing of the cement without bone preparation, pressurization or use of a medullary plug. In the mid-seventies second generation techniques were adopted which involved improved canal preparation by pulsatile lavage that increased cement penetration and interdigitation, retrograde insertion of cement using a gun to reduce blood lamination, and the use of an intramedullary plug to limit the size of the cement column. Studies with 10 year follow up have shown that 2<sup>nd</sup> generation techniques were associated with a reduced the incidence in femoral loosening with rates of 3 to 7%<sup>101,102</sup> compared with rates of approximately 30% at 10 years in first generation reports<sup>103,104</sup>. Third generation techniques included vacuum mixing of cement to reduce cement porosity and increase fatigue strength<sup>105</sup>, and cement pressurization to

further improve cement interdigitation. Subsequently 4<sup>th</sup> generation cementation techniques have added distal and proximal prosthesis centralizers to improve the stem position allowing for an optimal and even cement mantle. Herbert, in a review of the Swedish THA Register examining 160,000 cases, reported that the evolution from 1<sup>st</sup> to 3<sup>rd</sup> generation cementing techniques over a 20 year period was associated with a reduced incidence of revision for aseptic loosening<sup>100</sup>.

## 8. Summary and future directions

Aseptic loosening is the end result of a complex interaction of variables leading to development of osteolysis. Although the last 30 years has seen many advances in the understanding of these factors, osteolysis will remain a problem for the foreseeable future. Newer bearing surfaces have shown potential in wear rate reduction. However, wear particles from all materials have the potential to trigger an inflammatory response. The local and systemic consequences of metal release also need to be more clearly defined and quantitated. Further studies looking at prosthesis bone anchorage in conjunction with particle and pressure effects need to be explored, and the factors that influence loosening membrane formation.

Currently the only effective treatment for aseptic loosening is revision surgery. Future advances in our understanding of the biological response to wear particles may lead to the development of biological markers for better prediction and early detection of osteolysis, and the development of non-surgical solutions for prophylaxis and therapy. Advances in genomic and bioinformatics technology have provided us with the opportunity to identify investigational targets for prophylaxis or treatment. Pharmacological and biological agents used in the treatment of osteolysis in metastatic disease and metabolic bone disease may have potential in osteolysis following THA.

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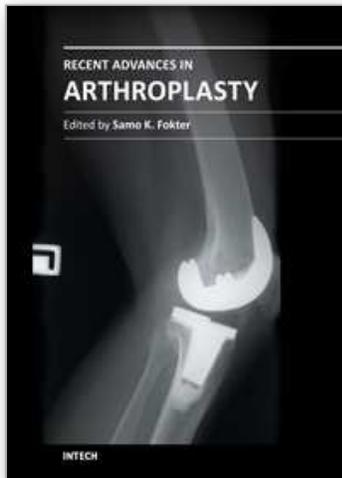
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## **Recent Advances in Arthroplasty**

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The purpose of this book was to offer an overview of recent insights into the current state of arthroplasty. The tremendous long term success of Sir Charnley's total hip arthroplasty has encouraged many researchers to treat pain, improve function and create solutions for higher quality of life. Indeed and as described in a special chapter of this book, arthroplasty is an emerging field in the joints of upper extremity and spine. However, there are inborn complications in any foreign design brought to the human body. First, in the chapter on infections we endeavor to provide a comprehensive, up-to-date analysis and description of the management of this difficult problem. Second, the immune system is faced with a strange material coming in huge amounts of micro-particles from the tribology code. Therefore, great attention to the problem of aseptic loosening has been addressed in special chapters on loosening and on materials currently available for arthroplasty.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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