

## Correspondence

# Particle disease really does exist

## An evidence based rebuttal to Dr. Mjöberg's opinion letter

Sir,—In a recent correspondence, Dr. Mjöberg questions the role of wear particles in the pathogenesis of periprosthetic osteolysis (Mjöberg et al. 2017). In Dr. Mjöberg's view, implant wear and wear particles are innocent bystanders in a process that is driven by micromotion of poorly fixed implants, and subsequently, increased fluid pressure at the bone / implant interface. Indeed, as summarized by Dr. Mjöberg, increased fluid pressure has been reported from the tissues surrounding loose implants, and increased pressure can induce osteolysis in certain animal models. Nevertheless, we feel that Dr. Mjöberg's strong conclusion that particle disease does not exist is not supported by the vast body of existing scientific literature.

The particle disease paradigm states that periprosthetic osteolysis is driven by wear particles continuously released from the implant, or from the interface between the implant and the surrounding bone (Willert and Semlitsch 1977, Purdue et al. 2007, Gallo et al. 2013, Landgraeber et al. 2014). These biomaterial particles cause acute/chronic inflammation that culminates in local bone resorption with foreign body granuloma and periprosthetic connective tissue weakening, and ultimately, to the loss of implant fixation. Macrophages play a central role in the pathogenesis of the condition by secreting multiple pro-inflammatory mediators upon contact with implant debris (Ingham and Fisher 2005, Nich et al. 2013). Macrophage derived pro-inflammatory mediators stimulate the recruitment and formation of osteoclasts and bone resorption. At the same time, particles directly suppress the differentiation and function of osteoblasts and their progenitors (O'Neill et al. 2013, Pajarinen et al. 2017a). Thus, wear particles both increase bone resorption and suppress formation, resulting in net loss of bone in the periprosthetic tissues.

In the following paragraphs we summarize the evidence supporting this sequence of events.

1) Osteolytic lesions with clearly inflammatory characteristics often appear many years after the initial surgery, and develop around mechanically stable implants. There is strong evidence that clinically sound implants often require reoperation for aseptic loosening 15 to 20 years after the primary procedure (Garellick et al. 2014, Bedard et al. 2015, Junnila et al. 2016). Therefore, the pathological process had to start much later than the immediate postoperative period, and be

driven by factors other than poor initial fixation of the implant. Otherwise, the loosening process would have appeared much earlier, as is described by Dr. Mjöberg, but usually this is not the case. Furthermore, numerous researchers have documented the wear particle-induced activation of inflammatory pathways in retrieved tissue samples from aseptically loose implants (Gallo et al. 2014).

2) There exists a strong correlation between implant wear and periprosthetic osteolysis, even in mechanically stable implants. Clinical studies have exhaustively documented this positive correlation between implant wear and the risk for periprosthetic osteolysis and aseptic loosening (Dumbleton et al. 2002, Gallo et al. 2010). Dr. Mjöberg argues that the accelerated wear is a consequence of progressive implant loosening rather than its cause. However, recent observations from implants with hard-on-hard bearings and those that use highly cross-linked polyethylene show minimal wear and a corresponding reduction in wear related complications including loosening and osteolysis (Paxton et al. 2015, Hanna et al. 2016, Tsukamoto et al. 2017). Together these observations strongly implicate wear as a causative agent in so called "particle disease".

3) Wear particles activate inflammatory pathways in cell culture, and cause bone loss in different animal models. Macrophages exposed to wear debris in cell culture respond by secreting the same pro-inflammatory and chemotactic mediators that have been detected in the tissues surrounding loose implants (Ingham and Fisher 2005, Nich et al. 2013, Pajarinen et al. 2013, Lin et al. 2014). Similarly, mesenchymal stem cells lose their ability to differentiate to osteoblasts, and osteoblasts lose their ability to produce bone, if exposed to particle debris (Goodman et al. 2006, O'Neill et al. 2013, Lin et al. 2015, Pajarinen et al. 2017a). Most importantly, animal models have repeatedly demonstrated the inflammatory and osteolytic nature of wear particles following either an acute or chronic particle exposure (Shanbhag et al. 1997, Merkel et al. 1999, Wooley et al. 2002, Ma et al. 2008, Greenfield et al. 2010, Ren et al. 2011, Gibon et al. 2012, Bechtel et al. 2016, Nabeshima et al. 2017, Samelko et al. 2017). For example, wear particles implanted on mouse calvaria cause rapid inflammation and osteolysis (Merkel et al. 1999, Bechtel et

al 2016). Likewise, continuous infusion of wear particles to mouse distal femurs causes systemic recruitment of macrophages, inflammation, and local bone loss similar to what is seen in the clinical setting (Ma et al. 2008, Ren et al. 2011, Gibon et al. 2012, Nabeshima et al. 2017). Indeed, we recently showed a positive correlation between the amount of particles infused in the mouse distal femur and local bone loss (Pajarinen et al 2017b).

4) The molecular pathways activated by the wear particles are similar to what has been demonstrated for other particulate materials. Our field is not the only one investigating the potential adverse effects of phagocytosed particulate materials. Indeed, urate and cholesterol crystals, as well as air pollutant microparticles cause inflammation via similar cellular pathways that have been implicated in the adverse response to implant wear, including endosomal damage and activation of intracellular danger signaling pathways (Dostert et al. 2008, Caicedo et al. 2009, Rajamäki et al. 2010, So and Martinon 2017). Furthermore, the distinct adverse reactions caused by polymeric (such as polyethylene and polymethylmethacrylate) and metallic (CoCr particles and ions) wear particles strongly suggest that the characteristics of the particles released from the implant are a crucial determinant of the biological response elicited by the implant (Davies et al. 2005, Willert et al. 2005, Gallo et al. 2014). Particles have been shown to bind both endogenous and exogenous danger signal molecules which further exacerbate their adverse biological effects (Greenfield et al. 2010, Bechtel et al. 2016, Takagi et al. 2017).

5) Excessive joint fluid is most likely related to the process of acute/chronic particle induced inflammation. One unanswered question in the purely mechanical hypothesis of loosening is the pathogenesis of the abundant amount of joint fluid. In contrast, similar to the synovitis in cases of gout (urate crystals) and pseudogout (calcium pyrophosphate dihydrate crystals), particle induced synovitis readily explains the fluid accumulation. Thus particle-induced inflammation can be directly linked with excessive joint fluid secretion, and pre-dates the bone destruction seen in periprosthetic pathologic fractures and loosening seen with extensive osteolytic lesions.

Taken together, there is a wealth of pre-clinical and clinical data supporting the role of wear particles in the pathogenesis of periprosthetic osteolysis and aseptic loosening. However, we do not aim to diminish the importance of mechanical events in the pathophysiology of aseptic loosening and believe that these two factors work in concert. Local fluid dynamics play a role in distributing wear debris around the implant (“the effective joint space”) and it is furthermore possible that the combined effect of wear and increased pressure contribute to the osteolytic process. There most likely exists a wide variability in the contribution of biological and mechanical factors in aseptic loosening in specific patients. In some patients, early aseptic loosening is probably due to poor initial mechanical fixation, either due to suboptimal placement or poor cement

technique, or compromised bone ingrowth in cementless implants. However, particle disease is the cause of aseptic failure in the majority of patients, especially in those patients with late aseptic loosening. In this respect, the opinion espoused in the letter by Dr. Mjöberg cannot be scientifically supported.

**Jukka Pajarinen<sup>1</sup>, Jiri Gallo<sup>2</sup>, Michiaki Takagi<sup>3</sup>, and Stuart B Goodman<sup>1</sup>**

<sup>1</sup> Department of Orthopaedic Surgery, Stanford University, Stanford, CA, USA

<sup>2</sup> Department of Orthopaedics, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

<sup>3</sup> Department of Orthopaedic Surgery, Yamagata University Faculty of Medicine, Yamagata City, Yamagata, Japan  
Email: jukka.s.pajarinen@helsinki.fi

Bechtel C P, Gebhart J J, Tatro J M, Kiss-Toth E, Wilkinson J M, Greenfield E M. Particle-induced osteolysis is mediated by TIRAP/Mal in vitro and in vivo: Dependence on adherent pathogen-associated molecular patterns. *J Bone Joint Surg Am* 2016; 98 (4): 285-94.

Bedard N A, Callaghan J J, Stefl M D, Liu S S. Systematic review of literature of cemented femoral components: what is the durability at minimum 20 years followup? *Clin Orthop Relat Res* 2015; 473 (2): 563-71.

Caicedo M S, Desai R, McAllister K, Reddy A, Jacobs J J, Hallab N J. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: a novel mechanism for implant debris reactivity. *J Orthop Res* 2009; 27 (7): 847-54.

Davies A P, Willert H G, Campbell P A, Learmonth I D, Case C P. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am* 2005; 87 (1): 18-27.

Dostert C, Pétrilli V, Van Bruggen R, Steele C, Mossman B T, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 2008; 320 (5876): 674-7.

Dumbleton J H, Manley M T, Edidin A A. A literature review of the association between wear rate and osteolysis in total hip arthroplasty. *J Arthroplasty* 2002; 17 (5): 649-61.

Gallo J, Havranek V, Zapletalova J. Risk factors for accelerated polyethylene wear and osteolysis in ABG I total hip arthroplasty. *Int Orthop* 2010; 34 (1): 19-26.

Gallo J, Goodman S B, Kontinen Y T, Raska M. Particle disease: biologic mechanisms of periprosthetic osteolysis in total hip arthroplasty. *Innate Immun* 2013; 19 (2): 213-24.

Gallo J, Vaculova J, Goodman S B, Kontinen Y T, Thyssen J P. Contributions of human tissue analysis to understanding the mechanisms of loosening and osteolysis in total hip replacement. *Acta Biomater* 2014; 10 (6): 2354-66.

Garellick G, Kärrholm J, Lindahl H, Malchau H, Rogmark C, Rolfson O. The Swedish Hip Arthroplasty Register Annual Report 2014. Available from: <https://registercentrum.blob.core.windows.net/shpr/t/Annual-report-2014-BJv-q8pil.pdf> (accessed on 16th of October, 2017)

Gibon E, Ma T, Ren P G, Fritton K, Biswal S, Yao Z, Smith L, Goodman S B. Selective inhibition of the MCP-1-CCR2 ligand-receptor axis decreases systemic trafficking of macrophages in the presence of UHMWPE particles. *J Orthop Res* 2012; 30 (4): 547-53.

Goodman S B, Ma T, Chiu R, Ramachandran R, Smith R L. Effects of orthopaedic wear particles on osteoprogenitor cells. *Biomaterials* 2006; 27 (36): 6096-101.

- Greenfield E M, Beidelschies M A, Tatro J M, Goldberg V M, Hise A G. Bacterial pathogen-associated molecular patterns stimulate biological activity of orthopaedic wear particles by activating cognate Toll-like receptors. *J Biol Chem* 2010; 285 (42): 32378-84.
- Hanna S A, Somerville L, McCalden R W, Naudie D D, MacDonald S J. Highly cross-linked polyethylene decreases the rate of revision of total hip arthroplasty compared with conventional polyethylene at 13 years' follow-up. *Bone Joint J* 2016; 98-B (1): 28-32.
- Ingham E, Fisher J. The role of macrophages in osteolysis of total joint replacement. *Biomaterials* 2005; 26 (11): 1271-86.
- Junnila M, Laaksonen I, Eskelinen A, Pulkkinen P, Ivar Havelin L, Furnes O, Marie Fenstad A, Pedersen A B, Overgaard S, Kärrholm J, Garellick G, Malchau H, Mäkelä K T. Implant survival of the most common cemented total hip devices from the Nordic Arthroplasty Register Association database. *Acta Orthop* 2016; 87 (6): 546-553.
- Landgraaber S, Jäger M, Jacobs J J, Hallab, N J. The pathology of orthopedic implant failure is mediated by innate immune system cytokines. *Mediators Inflamm* 2014; 2014: 185150.
- Lin T H, Yao Z, Sato T, Keeney M, Li C, Pajarinen J, Yang F, Egashira K, Goodman S B. Suppression of wear-particle-induced pro-inflammatory cytokine and chemokine production in macrophages via NF- $\kappa$ B decoy oligodeoxynucleotide: a preliminary report. *Acta Biomater* 2014; 10 (8): 3747-55.
- Lin T H, Sato T, Barcay K R, Waters H, Loi F, Zhang R, Pajarinen J, Egashira K, Yao Z, Goodman S B. NF- $\kappa$ B decoy oligodeoxynucleotide enhanced osteogenesis in mesenchymal stem cells exposed to polyethylene particle. *Tissue Eng Part A* 2015; 21 (5-6):875-83.
- Ma T, Huang Z, Ren P G, McCally R, Lindsey D, Smith R L, Goodman S B. An in vivo murine model of continuous intramedullary infusion of polyethylene particles. *Biomaterials* 2008; 29: 3738-42.
- Merkel K D, Erdmann J M, McHugh K P, Abu-Amer Y, Ross F P, Teitelbaum S L. Tumor necrosis factor-alpha mediates orthopedic implant osteolysis. *Am J Pathol* 1999; 154 (1): 203-10.
- Mjoberg B. Does particle disease really exist? *Acta Orthop* 2017; Sep 15: 1-3. [Epub ahead of print] doi: 10.1080/17453674.2017.1373492.
- Nabeshima A, Pajarinen J, Lin TH, Jiang X, Gibon E, Córdova L A, Loi F, Lu L, Jämsen E, Egashira K, Yang F, Yao Z, Goodman S B. Mutant CCL2 protein coating mitigates wear particle-induced bone loss in a murine continuous polyethylene infusion model. *Biomaterials* 2017; 117: 1-9.
- Nich C, Takakubo Y, Pajarinen J, Ainola M, Salem A, Sillat T, Rao A J, Raska M, Tamaki Y, Takagi M, Konttinen Y T, Goodman S B, Gallo J. Macrophages-Key cells in the response to wear debris from joint replacements. *J Biomed Mater Res A* 2013; 101 (10): 3033-45.
- O'Neill S C, Queally J M, Devitt B M, Doran P P, O'Byrne J M. The role of osteoblasts in peri-prosthetic osteolysis. *Bone Joint J* 2013; 95-B (8): 1022-6.
- Pajarinen J, Kouri V P, Jämsen E, Li T F, Mandelin J, Konttinen Y T. The response of macrophages to titanium particles is determined by macrophage polarization. *Acta Biomater* 2013; 9 (11): 9229-40.
- Pajarinen J, Lin T H, Nabeshima A, Jämsen E, Lu L, Nathan K, Yao Z, Goodman S B. Mesenchymal stem cells in the aseptic loosening of total joint replacements. *J Biomed Mater Res A*. 2017a;105 (4):1195-1207.
- Pajarinen J, Nabeshima A, Lin T H, Sato T, Gibon E, Jämsen E, Lu L, Nathan K, Yao Z, Goodman S B. Murine model of progressive orthopaedic wear particle induced chronic inflammation and osteolysis. *Tissue Eng Part C Methods* 2017b In press. doi: 10.1089/ten.TEC.2017.0166.
- Paxton E W, Inacio M C, Namba R S, Love R, Kurtz S M. Metal-on-conventional polyethylene total hip arthroplasty bearing surfaces have a higher risk of revision than metal-on-highly crosslinked polyethylene: results from a US registry. *Clin Orthop Relat Res* 2015; 473 (3): 1011-21.
- Purdue P E, Koulouvaris P, Potter H G, Nestor B J, Sculco T P. The cellular and molecular biology of periprosthetic osteolysis. *Clin Orthop Relat Res* 2007; 454: 251-61.
- Rajamäki K, Lappalainen J, Oörni K, Välimäki E, Matikainen S, Kovanen P T, Eklund K K. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One* 2010; 5: e11765.
- Ren P G, Irani A, Huang Z, Ma T, Biswal S, Goodman S B. Continuous infusion of UHMWPE particles induces increased bone macrophages and osteolysis. *Clin Orthop Relat Res* 2011; 469 (1): 113-22.
- Samelko L, Landgraaber S, McAllister K, Jacobs J, Hallab N J. TLR4 (not TLR2) dominate cognate TLR activity associated with CoCrMo implant particles. *J Orthop Res* 2017; 35 (5): 1007-17.
- Shanbhag A S, Hasselman C T, Rubash H E. The John Charnley Award. Inhibition of wear debris mediated osteolysis in a canine total hip arthroplasty model. *Clin Orthop Relat Res* 1997; (344): 33-43.
- So A K, Martinon F. Inflammation in gout: mechanisms and therapeutic targets. *Nat Rev Rheumatol* 2017 In press. doi: 10.1038/nrrheum.2017.155.
- Takagi M, Takakubo Y, Pajarinen J, Naganuma Y, Oki H, Maruyama M, Goodman S B. Danger of frustrated sensors: Role of TLR and NOD-like receptors in aseptic and septic inflammations around failed total hip replacements. *J Orthop Translat*. 2017; 10: 1-18.
- Tsukamoto M, Mori T, Ohnishi H, Uchida S, Sakai A. Highly cross-linked polyethylene reduces osteolysis incidence and wear-related reoperation rate in cementless total hip arthroplasty compared with conventional polyethylene at a mean 12-year follow-up. *J Arthroplasty* 2017 In press. doi: 10.1016/j.arth.2017.06.047.
- Willert H G, Buchhorn G H, Fayyazi A, Flury R, Windler M, Köster G, Lohmann C H. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am* 2005; 87 (1): 28-36.
- Wooley P H, Morren R, Andary J, Sud S, Yang S Y, Mayton L, Markel D, Sieving A, Nasser S. Inflammatory responses to orthopaedic biomaterials in the murine air pouch. *Biomaterials* 2002; 23 (2): 517-26.

## Particle disease, late loosening and Occam's razor

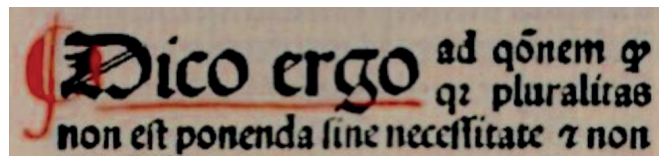
*Sir*—Thank you for the opportunity to respond to the letter of Drs Pajarinen, Gallo, Takagi, and Goodman, who raise some issues that I want to clarify.

The early migration detected by RSA (with a detection limit of 0.1–0.2 mm) after hip arthroplasty can typically not be discovered from standard radiographs. When first observed on radiographs, maybe years later, loosening is often assumed to be late loosening—but should actually be considered to be late detection of loosening. Similarly, apparently well-fixed prostheses that after many years develop osteolysis (often associated with pain) may also be loose to a degree that cannot be detected on standard radiographs.

That improved wear resistance reduces the incidence of loosening and osteolysis can be explained (as implicitly mentioned in my letter) by less eccentricity due to wear and hence less torque on such an acetabular component—and consequently (if loosening has been initiated) slower progression of loosening and thus less risk of accompanying periprosthetic osteolysis.

The rapid early migration of some prosthetic components strongly indicates that wear particles do not initiate prosthetic loosening (wear particles cannot be expected to have a major influence during the early period of rapid migration). On the other hand, wear particles may (as mentioned in my letter) possibly modulate the later stages of the loosening process.

Micromovements of a loose prosthetic component may cause bursts of high fluid pressure in the interstice between the prosthetic component and the bone, which induce oste-



From John Duns Scotus' book *Ordinatio* (around 1300): "Pluralitas non est ponenda sine necessitate", later known as Occam's razor.

olysis and spread necrotic cells and cell fragments from the interstice to the joint that cause inflammatory responses and excessive joint fluid.

The theory of early loosening, with its two different phases (early initiation and, if initiated, subsequent progression), is able to a great extent to explain the epidemiology of clinical failure of hip prostheses—without any need for the assumption of wear-particle-induced osteolysis.

I want to emphasize that, in my conclusion, the existence of particle disease as well as the possibility of a genuine late onset of loosening have not been disproved (and can actually never be disproved, because it is impossible to prove a negative; cf. Russell's teapot). However, by applying the principle of parsimony (Figure), which tells us to choose the simplest scientific explanation that fits the evidence, *ad hoc* assumptions such as particle disease, stress-shielding and metal sensitivity are avoided—not because they are proven false, but because they appear unnecessary.

**Bengt Mjöberg**  
*bengt.mj@telia.com*