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Review

Spinal implant wear particles: Generation, characterization, biological impacts, and future considerations

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SUMMARY

The generation of wear debris from orthopedic implants is a known cause of implant failure, particularly in joint replacements. While much research has focused on wear particles from knee and hip implants, spinal implants, such as total disc replacements (TDRs), have received less attention despite their increasing clinical use. Spinal implants face unique biomechanical challenges, including a wider range of motion and higher loads, leading to complex tissue interactions. Studies reveal that TDR wear particles, though similar in size to those from knee implants, cause a stronger immune response, with more macrophages and giant cells found in the surrounding tissue. This may explain the high revision rates seen in spinal surgeries, with some interventions failing in over 30% of cases within 10 years. The younger population undergoing spinal surgery, combined with the productivity losses associated with implant failure, underscores the need for greater understanding. This review discusses recent research on the generation, characterization, and biological impacts of spinal implant wear debris. It draws on retrieval analysis, wear simulation, *in vivo* models, and a survey conducted with the AO Spine Knowledge Forum Degenerative to assess current clinical practices and highlight gaps in knowledge. Additionally, this critical review explores future strategies to reduce the biological impact of wear particles and improve the safety and longevity of spinal implants through better therapeutics and design innovations. By combining literature and clinical insights, this paper aims to guide future research in addressing the complexities of spinal implant wear and its biological consequences.

INTRODUCTION

Low back pain (LBP), a leading cause of disability worldwide, affected more than 619 million people globally in 2020.[1] The number of patients with LBP is expected to rise significantly, to 843 million cases by 2050, due to population growth and aging.[2] LBP is one of the most expensive health conditions globally. The average healthcare annual expenditure in Europe for LBP is approximately 2% of its gross domestic product.[3] In the United States, the annual cost associated with LBP was US$134 billion in 2016.[4] In Australia, LBP affects 4 million Australians (16% of the population) and incurs more than $3 billion (23% of national expenditure on musculoskeletal conditions) in direct healthcare costs annually. In 2019 alone, the equivalent of 300,000 working years was lost in Australia due to LBP disability.[5] Studies to investigate the clinical and economic burdens of LBP in selected low- and middle-income countries have revealed an annual total cost of US$1227 per patient.[6] These statistics emphasize the substantial burden of LBP in terms of healthcare expenditure and the overall societal impact, highlighting the imperative for effective strategies to manage the associated consequences.

LBP is a well-established consequence of spinal disc degeneration caused by aging, structural defects, and repetitive trauma.[7,8] With regeneration of the spinal discs via tissue engineering approaches currently not feasible, spinal implants (e.g., total disc replacement; TDR, spinal fusion cages, rods,

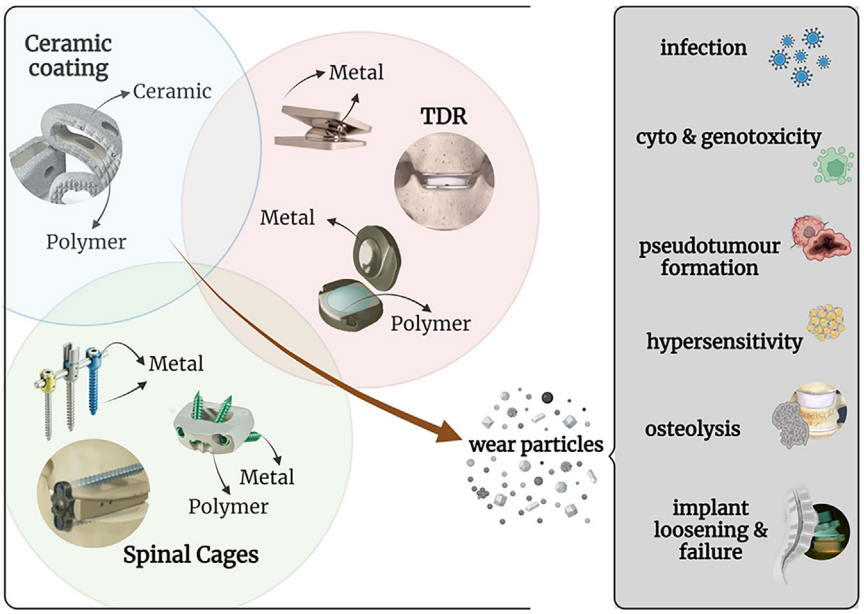

Figure 1. Spinal implants and wear particles

Spinal implants, such as total disc replacements (TDRs), spinal cages, and connecting rods and screws, combine metals and ceramics to form articulations like metal-on-metal, metal-on-polymer, and metal-on-ceramic. Continuously subjected to multidirectional stresses and diverse loading regimes, these implants generate wear particles that may damage periprosthetic tissues, induce hypersensitivity reactions, and provoke cytotoxicity, genotoxicity, neurological symptoms, inflammation, and osteolysis. Additionally, they may contribute to pseudotumor formation, ultimately leading to implant failure [Created by BioRender.com].

and screws) play a crucial role in the management of LBP.[9,10] Spinal implants are essential in providing stability to the spinal column and play a crucial role in the treatment and management of patients with different spinal disorders such as herniated discs, degenerative disc disease, spinal fractures, scoliosis, and stenosis. TDRs are often used to preserve motion and maintain normal kinematics of the spinal column while reducing degeneration-related pain. They support the spine movement by restoring disc height, offering spinal stability, and transmitting load leading to improved quality of life for patients. TDRs often consist of metal and polymeric components creating metal-on-metal or metal-on-polymer (predominantly ultra-high molecular weight polyethylene; UHMWPE) articulations (Figure 1). Spinal fusion devices including segmental and non-segmental cages, rigid and non-rigid connectors, rods, plates and screws intend to promote bone growth within the degenerated disc space to limit the range of spinal motion and alleviate pain associated with spinal instability (Figure 1). With the limitation of spinal implants to fully recapitulate the structure, biomechanical function, and kinematics of their native counterparts, their clinical benefit may be suboptimal. While challenges to developing advanced spinal implants to address the current issues still exist, concerns regarding the production of wear products (particles and metal ions) and their biological consequences have recently emerged.[11]

The production of wear debris leading to joint implant failure has been a global health concern for many years.[12,13] Extensive research on knee and hip implants has demonstrated that metallic wear debris and ions can trigger tissue inflammation, cytotoxicity, and hypersensitivity and can also form pseudotumours.[14] It has been found that small (<1-μm size) wear particles of polymer debris initiate a series of biological reactions that lead to bone loss (osteolysis) and loosening of the implants.[15,16] *In-vitro* studies have characterized the cytotoxicity of wear particles on macrophages and fibroblasts through their contribution to the production of osteolytic mediators including tumor necrosis factor-alpha (TNF-α), and interleukin 1β.[17–19] Biological complications such as necrosis, pseudotumors, and pain are also believed to result from metal wear particles and soluble debris from the implant surfaces.[12] While a large number of studies have shown the biological complications of wear particles from knee and hip implants, investigations into wear particles from spinal implants have been sparse limiting our understanding of the associated biological consequences. This current gap in knowledge could be attributed to previous assumptions that the spine does not have synovial joints and has relatively limited motion; hence, wear particles from spinal implants were not believed to be a clinically relevant topic. However, numerous studies have shown that wear particles from spinal implants can cause inflammation, induce osteolysis and metallosis, and form pseudotumors similar to failing hip arthroplasties.[20–23] Clinical investigations of periprosthetic tissues and *in vitro* studies have revealed that wear debris from spinal implants can also reduce astrocyte and microglial cell viability in the spinal cord.[24–27] A comparative post-clinical study showed that, with almost a similar size range, UHMWPE wear particles from TDRs were smaller than those generated by total knee implants. Subsequently, a higher number of macrophages and giant cells were present in TDR periprosthetic tissue, compared to those surrounding knee implants.[20] This observation can be attributed to the complex nature of spinal implants, which experience a wider range of motion, higher loads, and interact with multiple tissue interfaces. Additionally, some spinal interventions have revision rates exceeding 30% within 10 years post-operation.[28] This issue is particularly significant as patients with lower back problems are generally younger at the time of intervention, impacting their ability to work and productivity. The majority of spinal implant failures beyond 3–5 years are primarily attributed to wear.[29] Given the lack of a recent comprehensive review of spinal implant wear particles and the importance of the matter, the current review paper aims to present an update on the generation, isolation, and characterization of wear particles from spinal implants, explain current research approaches at multiple

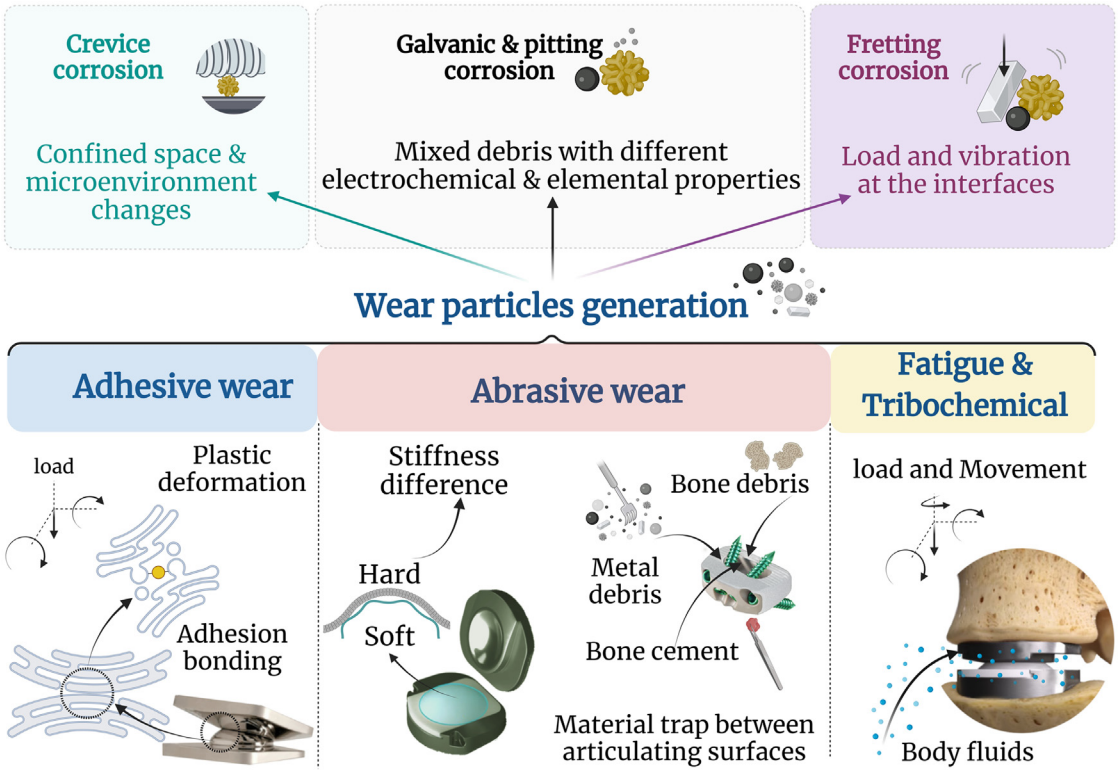

Figure 2. Wear particles and corrosion from spinal implants

Mechanisms of wear particle production and corrosion in metal-on-polymer and metal-on-metal articulating [Created by BioRender.com].

levels (retrieval analysis, wear simulation and biomechanical studies, *in vivo* animal models, and simulation), clarify the biological consequences and pathogenesis of related complications from spinal wear debris, identify the existing knowledge gap, and inform future strategies that contribute to the development of advanced therapeutics and safer spinal implants.

REVIEW METHODOLOGY

For this research, two distinct approaches were employed. First, an extensive literature search was conducted using reputable databases, including PubMed and Web of Science, covering the period from 2000 to 2023. Relevant keywords, such as "spinal implants", "wear particles", and "wear debris", were utilized, and the bibliographies of identified studies (excluding conference papers) were reviewed for additional pertinent research. Concurrently, a survey on "spinal implant wear particles" was distributed to the members of the "AO Spine Knowledge Forum Degenerative," a specialized group of international spinal surgeons with expertise in intervertebral disc (IVD) degeneration. The survey aimed to assess current clinical practices and ultimately recommend strategies to prevent, reduce, or minimize the biological impact of spinal wear particles. Key aspects covered in the survey included participant demographics and backgrounds, clinical practices and awareness, diagnosis and management, preventive measures, outcomes and research data availability, as well as the participants' willingness to share data and collaborate, along with any identified limitations (see Appendix S1).

WEAR PRODUCTS FROM SPINAL IMPLANTS

Metals (titanium, cobalt chromium, and stainless steel) and their alloys, polymers (UHMWPE and polyether ether ketone known as PEEK) and ceramics (such as zirconia and silicon nitride) are biomaterials that have been widely used in the design and fabrication of various spinal implants.[30] Spinal implants are often under continuous multidirectional stresses and experience different loading types and magnitudes which leads to the production of wear particles that are released into the surrounding tissues. The mechanism of wear production in spinal implants is not fully understood; however, they are often modular, and therefore, a similar pathway to other total joint arthroplasties is assumed responsible for the generation of wear products.[31] Metal, polymer, and ceramic particles (from frictional articulations) and metal ions (from corrosion) are the most commonly observed wear products in total joint implants. Similar to knee and hip implants, abrasive, adhesive, surface fatigue and tribochemical reactions wear are plausible mechanisms of wear production in spinal implants (Figure 2).[32–35] The creation of adhesion bondings and plastic deformation due to high pressure between implants' contacting surfaces is responsible for adhesive wear, while stiffness differences between implant articulating surfaces cause abrasive wear. The combination of adhesion

Table 1. Mechanisms of corrosion in spinal implants

Mechanism	Type	Route cause
Mechanical	fretting	Occurs at the biomaterial interface under load or vibration[51]
Electrochemical	crevice	Local corrosion in a confined space (such as between screws and rods) occurs due to changes in microenvironmental properties (low oxygen and pH levels or high concentration of electrolytes).[35,52]
	pitting	Occurs due to elemental impurities[53]
	galvanic	Occurs due to a combination of biomaterials (mixed-metal spinal implants) with different electrochemical properties (oxidation-reduction process)[51,54,55]

and abrasion is the dominant wear mechanism in metal-on-polymer and metal-on-metal articulating spinal implants (Figure 2).[36] When particles such as bone, bone cement or metal particles are trapped between implant articulating surfaces, abrasive wear is likely to occur.[37] The exposure of spinal implants to body fluids, repeated mechanical loading, and cyclic movements can result in the generation of wear particles through mechanisms of surface fatigue and tribochemical reactions.

Corrosion of metallic spinal implants, another source of concern, releases metal ions into the periprosthetic tissues. Spinal implant corrosion and associated biological consequences have been fully discussed in other studies.[38–42] Size reduction of wear particles due to corrosion provides a large surface area and high surface energy for metal ion release. These metal ions, from implant or wear particles, can potentially spread throughout the body evidenced by particles from spinal implants found in lymph nodes, liver, and other tissues and their shape and size may affect a host response.[13,43–47] Additionally, an increase in serum metal levels has been reported in patients with metal-on-metal lumbar disc arthroplasty.[48–50] Understanding the mechanism of corrosion in spinal implants plays an important role in exploring the biological consequences they may cause. Mechanical and electrochemical pathways (Table 1) are the main mechanisms thought to play a role in the corrosion of spinal implants.

Metal ion release was detected intra-operatively and within a month following instrumented spinal fusion for two cases of adolescent idiopathic scoliosis. Titanium, niobium and aluminum levels from wound irrigation fluid and cell-saver blood samples were markedly higher when compared to serum levels.[46] Other studies have revealed a high concentration of titanium ($\approx$1.8 μg/L) in the serum of patients after spinal fusion surgery.[56,57] Serum ion levels (mainly cobalt 4.57 ± 2.7 μg/L and chromium 1.1 ± 1.2 μg/L ions) in patients managed with Maverick metal-on-metal total disc arthroplasty have been found to be elevated, in a similar way to those who underwent metal-on-metal total hip arthroplasty.[58] Studies have shown that typical spinal implants made of stainless steel are susceptible to pitting and crevice corrosion mainly at the screw-rod interface, while titanium-based implants exhibit a lower overall corrosion rate.[51,52,59] Spinal implants (posterior spinal fixation systems) which were tested under a peak load of 300 N for 5 million cycles showed a higher amount of corrosion at the stainless steel - stainless steel interface when compared to titanium-titanium and titanium–stainless steel interfaces.[54] Crevice and fretting corrosions are believed to be the predominant corrosion mechanisms in metal-on-metal spinal implants. Corrosion was qualitatively less when titanium constructs were coupled with stainless steel systems, suggesting that the use of implants with dissimilar metal compositions may reduce the rate of corrosion.[45,54,55,60] Special caution in material selection should be executed for the design of new implants, as macroscopic rim and surface impairments characterized by radial cracking, plastic deformation and third-party damage leading to the generation of polymeric wear particles, have been reported in spinal implant retrieval studies.[61–63]

WEAR PARTICLES FROM SPINAL IMPLANTS: LESSONS LEARNED FROM RETRIEVAL ANALYSIS

Spinal implants consistently generate wear particles which trigger adaptive immune responses and periprosthetic tissue damage.[64] Wear particles from interconnecting mechanisms in spinal instrumentation have been a clinical concern since the late 1990s and attempts have been made to identify their clinical and pathological consequences.[65,66] Late-operative site pain associated with the use of large spinal implants, a common problem reported by patients, was initially thought to be caused by metal allergies or bacterial infection.[67,68] However, a few studies have discussed the possibility of the contribution of wear particles and metal ions in the development of late-operative spinal pain.[69,70]

A range of biological responses associated with spinal implant wear particles have been reported. These include hypersensitivity, cyto- and genotoxicities, neurological symptoms, and inflammation as well as forming pseudotumors and osteolysis.[19,25,26,71,72] The adverse effects of spinal implant wear particles on the spinal cord, due to its proximity to the spinal column, have also brought growing concerns.[24,27,73] It is believed that local cell reactivity and hypersensitivity, determined by immune cell interactions with wear particles from spinal implants, are linked to aseptic implant failure.[74–76] In a study of fourteen patients who underwent spinal implantation, the accumulation of a large number of stainless steel particles led to the formation of fibrous tissue that contained a large number of macrophages. This study suggested that an autologous tissue reaction to the metallic wear particles, which was not allergic, may be the cause of site pain.[71] A clinical case study evaluated the role of polyethylene wear particles on the failure of the Charité TDR by analyzing periprosthetic tissues in four patients. While the extent and severity of wear of the polyethylene core in the implant were different, the presence of inflammatory fibrous tissue and multinucleated giant cells were reported in all patients. Additionally, this study identified both abrasive wear and rim impingement

as the mechanisms that change the biomechanical properties of the implant causing osteolysis leading to implant failure.[29] Another study that explored the presence of wear and corrosion of spinal rods and pedicle screws in three retrievals, suggested bacterial infection-induced corrosion as the main mechanism for corrosion rather than electrochemical reactions.[77] Regardless, wear particles and corrosive by-products from spinal implants form fibroinflammatory zones in periprosthetic tissues where proinflammatory cytokines, macrophage, and reactive oxygen mediators create a discrete layer of cells with epithelial characteristics and induce inflammation as well as tissue damage.[78] The challenges in studying spinal implants, particularly in periprosthetic tissue response, arise from limited tissue availability during revision surgeries. Unlike the hip and knee joints, where capsule tissue plays a key role in periprosthetic responses, the spine's complex anatomy and limited surgical approaches restrict access to sufficient tissue for analysis. This makes it difficult to assess macrophage involvement, recruitment, and activation in particle-induced inflammation and tissue degradation. The periprosthetic tissue surrounding spinal implants primarily consists of fibrous tissue, which differs structurally and biologically from the capsule tissue observed in large joint implants like the hip and knee. It is believed that macrophages in the spine can be derived from these fibrous tissues, bone marrow, or circulating monocytes. However, the limited availability of periprosthetic tissue and the risks associated with invasive surgery means that implants are rarely retrieved, and hence macrophage behavior is rarely studied. More research is needed to fully understand the role of periprosthetic tissue and macrophages in spinal implants, focusing on refining techniques for tissue retrieval and detailed analysis of inflammatory responses.

Comparisons between fixed- and mobile-bearing spinal implants revealed the significant impact of implant design on wear particle quantity, size, and morphology.[79,80] It was reported that mobile-bearing implants (i.e., Charité) generated more but less elongated UHMWPE wear particles compared to fixed-bearing devices (i.e., ProDisc-L). It was also observed that periprosthetic tissues around mobile-bearing implants were moderately vascularized with isolated necrotic regions, while tissues surrounding fixed-bearing implants were more vascularized but less necrotic.[79] The histological evaluation of periprosthetic tissues from Charité III spinal disc replacement in 83 patients showed a strong association between the presence of wear particles and chronic inflammatory reactions.[81] The inflamed tissue contained a high concentration of the inflammatory cytokines TNF-α and IL-6. Moreover, this study found that more than 60% of the particles were smaller than 5 μm. A positive correlation was also reported between the number of wear particles and the length of implantation time.[81] The impact of the implant sterilization process on the generation of UHMWPE wear particles was the subject of several studies, revealing that sterilization in an inert environment (i.e., in air) generally produced a lower number of wear particles while gamma sterilization led to higher rim oxidation or UHMWPE degradation, generating more wear products.[82,83] A comparative study to compare periprosthetic tissue reactions between TDR (Charité) with total hip arthroplasty revealed that the majority of UHMWPE wear particles were smaller than 6 μm in both cases; however, a higher number of giant cells and macrophages were found in the spinal implant periprosthetic tissues.[20] A similar study also reported that UHMWPE wear particles from spinal implants (Charité) were lower in concentration and smaller in size with different shapes (often more round) compared to those from knee (Biomet Hexloc) implants (Figure 3).[84]

The observation of a positive correlation between increasing particle size in the spinal periprosthetic tissue and rim penetration suggested that pain rather than osteolysis was the major reason for spinal revision surgery.[84] A clinical study of retrieved spinal instruments revealed that localization of both stainless steel and titanium wear particles provoked a macrophage-mediated inflammatory response resulting in increased local production of proinflammatory cytokine TNF-α causing osteoclastogenesis and cell apoptosis.[85] A lymphocytic reaction, caused by CD4/CD8 T-cells, leading to significant symptomatic metal hypersensitivity was also deemed responsible for the early failure of metal-on-metal spinal disc prostheses in 4 patients.[86] The formation of pseudotumor with substantial neurologic, vascular, and visceral complications due to wear debris was further reported in a 49-year-old patient who underwent L4-5 TDR.[87] This observation was also consistent with other clinical studies that reported the formation of granulomatous masses surrounding a Maverick spinal implant and delayed hypersensitivity reaction associated with a metal-on-metal TDR.[88–92] A review of clinical reports on the complications of wear debris from metal-on-metal spinal arthroplasty devices identified similar clinical, radiographic, histologic, gross anatomic, and device-related features to those reported in total hip arthroplasty.[93]

In vitro studies have suggested that the use of PEEK-based spinal implants may reduce the biological side effects often observed in metallic counterparts[94–96]; however, retrieval analysis of PEEK rods from spinal posterior fusion revealed that PEEK debris [<60 μm] can also generate inflammation.[97] A two-year clinical follow-up on 39 patients who underwent nucleus disc arthroplasty with the NUBAC device showed no major intra- or post-operative neurological or vascular complications.[98] NUBAC is an articulating nucleus disc implant with inner ball/socket articulations made of PEEK. The biostability analysis of Dynesys - a dynamic non-rigid pedicular stabilization system composing of titanium screws, polycarbonate urethane spacers, and polyethylene terephthalate cords - in four patients showed minimal surface changes after 19 months of implantation, with no sign of biodegradation or particulate generation.[99] The results from this short-term study were contrary to the findings from a longer-term investigation (2.5 years implantation) that revealed degradation, permanent deformation, wear, fracture and cracks in the polymeric component of Dynesys. Wear particles associated with polycarbonate urethane spacer biodegradation [in 10 implants out of 75] were linked to longer-term retrievals.[100]

Based on spinal implant retrieval studies, a strong correlation between spinal implant-related biological complications and the presence of wear debris in periprosthetic tissues was found (Box 1). Hence, understanding the host reaction and the mechanisms of pathogenesis related to biological issues caused by spinal implant wear particles is central to the optimization of patient

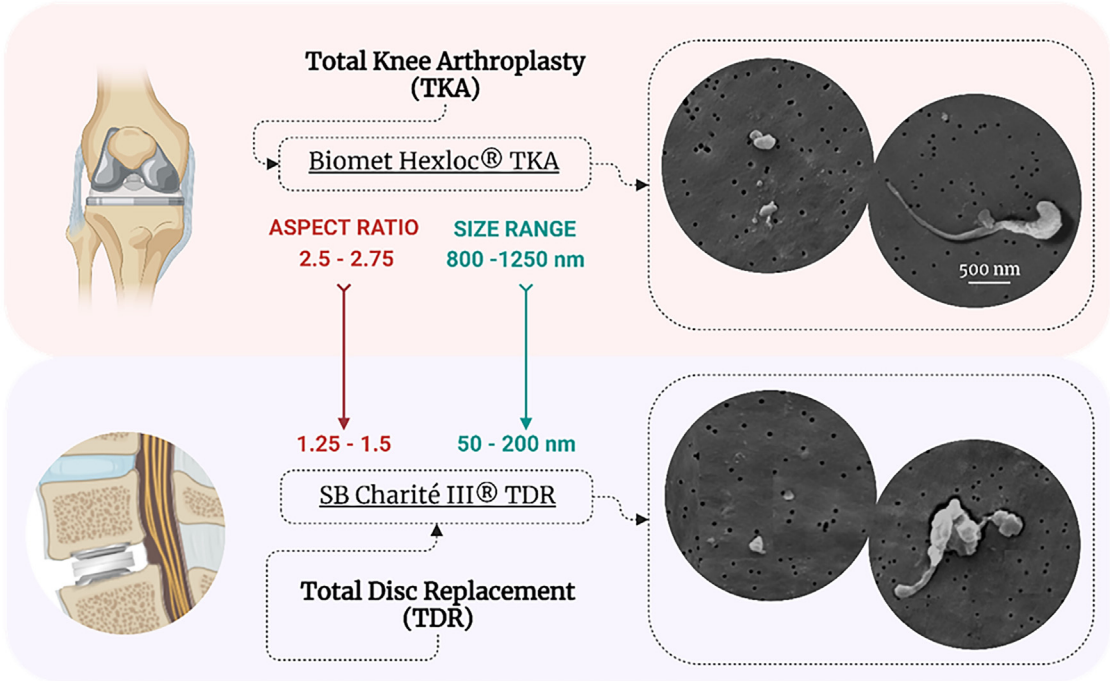

Figure 3. Comparison between Knee and dis implants in particle generation

Total disc replacements generate smaller UHMWPE wear particles compared to total knee arthroplasties[84] (adapted with permission from ref.[84]).

care and enhancement of the design, safety, and efficacy of spinal implant procedures.

SPINAL WEAR PARTICLES AND HOST RESPONSE

Wear particles represent a predominant challenge impacting spinal implant success mainly due to the host biological responses and tissue interactions causing long-term complications (Box 2). Periprosthetic osteolysis leading to implant aseptic loosening is another major issue.[101] Retrieval investigations have revealed that host biological responses to wear debris were highly associated with the material type, chemical composition, size, shape, volume and number of particulates.[102] However, despite advancements in research, our understanding of the immunobiology and biological responses (e.g., inflammation, osteolysis, genotoxicity, and pain) to spinal implant wear particles remains incomplete. Further studies are essential to fully discover the wear-related host responses in spinal implants and identify the complex interplay between wear particle characteristics and relevant biological responses. Due to limited relevant research, it is difficult to precisely describe the associated biological pathways and mechanisms; however, it is thought that biological responses to wear debris from spinal implants share similar mechanisms as observed in hip arthroplasty. This notion is rooted in the similarities observed in the size of particulates from metal-on-polymer spinal implants with those from the hip.[18,84,103–107] Therefore, the current review paper has also utilized findings reported for biological responses to hip implant wear particles. However, the nature and magnitude of these responses may differ due to anatomical, biomechanical, and physiological variations between the two categories.

Wear particles and pathogenesis of osteolysis

UHMWPE wear debris in hip periprosthetic tissues can potentially initiate macrophage-mediated immune responses leading to osteolysis.[108–110] The higher concentrations of UHMWPE wear particles were shown to intensify the risk of bone resorption with macrophage infiltration positively correlated with particle size and concentration.[110] While wear debris smaller than 1 μm is likely to exhibit the most biological activity, three different biological responses were linked to the size of particles.[111] Wear particles smaller than 0.15 μm were pinocytosed and particles with the size range of 0.15 μm–10 μm were phagocytosed; however, those with a bigger size than 20 μm formed multinucleated giant cells.[101,112] Pathogenesis of osteolysis was shown to be mainly driven by reduced osteoblast activity and rise in osteoclastogenesis and proinflammatory enzymatic bone resorption.

Understanding the physiology of bone remodeling, osteoclastogenesis in particular, is central to osteolysis associated with wear particles. Osteoclastogenesis, a process by which osteoclasts, cells responsible for bone resorption, are formed and activated is central to bone remodeling and maintenance of bone integrity.[113] Briefly, receptor activators of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor are two growth factors that mediate osteoclastogenesis (Figure 4). Cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) stimulate RANKL expression.[114] Via a synergistic feedback loop, RANKL boosts TNF-α production which activates nuclear factor-κB (NF-κB). When exposed to RANKL and macrophage

Box 1. Spinal implants, wear particles, and retrieval analysis

Wear particles from spinal implants and their clinical and biological impacts have been a concern since the 1990s. However, there remains a limited number of retrieval studies available due to challenges associated with tissue availability during revision surgeries. The complex anatomy of the spine and restricted surgical access limit the availability of sufficient tissue for detailed analysis.

Key findings from the current retrieval studies include:

(1) Contribution of wear particles and metal ions to the development of late-onset spinal pain.
(2) Association with biological consequences such as hypersensitivity, cytotoxicity, genotoxicity, neurological symptoms, inflammation, osteolysis, and pseudotumor formation due to spinal wear particles.
(3) Accumulation of wear particles in periprosthetic tissues, leading to fibrous tissue formation rich in macrophages.
(4) Impact of implant design on wear particle quantity, size, and morphology.
(5) Lower biological activity of PEEK particles compared to metal debris, though they can still induce inflammation and post-operative neurological or vascular complications.

Box 2. Spinal wear particles and host response

Wear particles from spinal implants pose significant challenges due to host biological responses such as inflammation, osteolysis, genotoxicity, which can result in long-term complications like implant loosening and pain. Although the exact mechanisms remain incompletely understood, shared characteristics with hip arthroplasty wear particles suggest common biological pathways. Continued research is critical to elucidate these mechanisms and improve spinal implant outcomes.

Key findings from the current literature include:

(1) Macrophage activation by spinal wear particles leads to the release of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α), which stimulate the RANK-RANKL pathway. This promotes osteoclast differentiation and activity, resulting in bone resorption, osteolysis, and eventual implant loosening.
(2) Hypersensitivity reactions after spinal surgery, are driven by wear particles and metal ions, involve delayed-type hypersensitivity mediated by T lymphocytes and antigen-presenting cells. These processes contribute to chronic inflammation, tissue damage, and pseudotumor-like reactions.
(3) Spinal wear particles induce inflammation through immune cell activation, oxidative stress, and the activation of redox-sensitive transcription factors, which upregulate pro-inflammatory mediators.
(4) Metal particles, particularly cobalt and chromium, contribute to genotoxicity through mechanisms such as DNA damage via reactive oxygen species, metal ion interactions, and structural disruptions. These effects can lead to carcinogenesis and significant tissue damage.
(5) Additionally, spinal wear particles stimulate the release of IL-1β, TNF-α, VEGF, and NGF, which promote inflammation, neurogenesis, and angiogenesis. These processes foster neural invasion, heightened nociceptive signaling, and severe discogenic pain, often surpassing that caused by disc degeneration.

colony-stimulating factor, monocytes and osteoclast progenitors undergo fusion and differentiation, leading to the formation of osteoclasts.[115] Osteoblasts express tartrate-resistant acid phosphatase and cathepsin K, two enzymes that are central to osteolysis. On the other hand, osteoprotegerin (OPG) which is an osteoclastogenesis inhibitory factor produced by osteoblasts, regulates the production of NF-κB and inhibits RANKL stimulation and osteoclastogenesis (Figure 4).[116]

Studies have shown that the expression of the RANKL/OPG system and the increase of the RANKL/OPG expression ratio in the spine can significantly change osteoblast-osteoclast genesis leading to bone resorption and implant failure.[117,118] The impact of wear particles on osteolysis leading to implant failure can be sought from three different viewpoints: innate immune system, cellular, and mediator responses. The innate immune response is the body's first line of defense against wear particles which is a rapid and non-specific response for immediate protection upon encountering a foreign invader. The activation of multiprotein complexes such as NALP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome, NF-κB, and proinflammatory cytokines TNF-α, and IL-1β upon exposure to UHMWPE was reported as an indication of innate immune response to wear particles.[101,119–121] At the cellular level, different cell types including monocytes, macrophages, dendritic cells, osteoblasts and fibroblasts were shown to play crucial roles in developing lumbar spine osteolysis due to UHMWPE wear debris.[122,123] Osteoblasts can phagocytose UHMWPE wear particles and alter cellular signaling, reduce the secretion of osteoprotegerin and expression of procollagen α1 mRNA and express RANKL and macrophage colony-stimulating factor (MCSF) (Figure 5).[101,114,124–127] Additionally, osteoblasts were shown capable of stimulating mediators such as TNF- α and interleukins (i.e., IL-1β, IL-6 and IL-8) intensifying the innate immune response.[124,125,127] Dendritic cells contributed to the phagocytosis and infiltrate UHMWPE wear debris to form multinucleated giant cells and increase the expression of proinflammatory cytokines such as IL-1, IL-6, IL-12, TNF-α, and INF-γ leading to the activation of NALP3 inflammasome and enzymatic osteolysis (Figure 5).[112,128] Upon phagocytosis of wear debris, macrophage and monocyte cells secreted proinflammatory cytokines (TNF-α, IL-1β, IL-6) leading to osteoclast differentiation. Fibroblasts, monocytes, and macrophages together formed multinucleated giant cells, activated TNF-α and IL-1β and expressed RANKL to ultimately induce osteoclast differentiation.[131–133] UHMWPE wear particles from spinal implants were found to trigger inflammation and activate macrophages via the activation of Toll-like receptors (TLRs) which advocate phagocytosis and initiate immune responses mediated by NF-κB activation (Figure 5).[102,129,130] Additionally, TRLs were stimulated by damage-associated molecular patterns in response to infection or tissue damage due to wear particle exposure and alteration of their chemical properties.

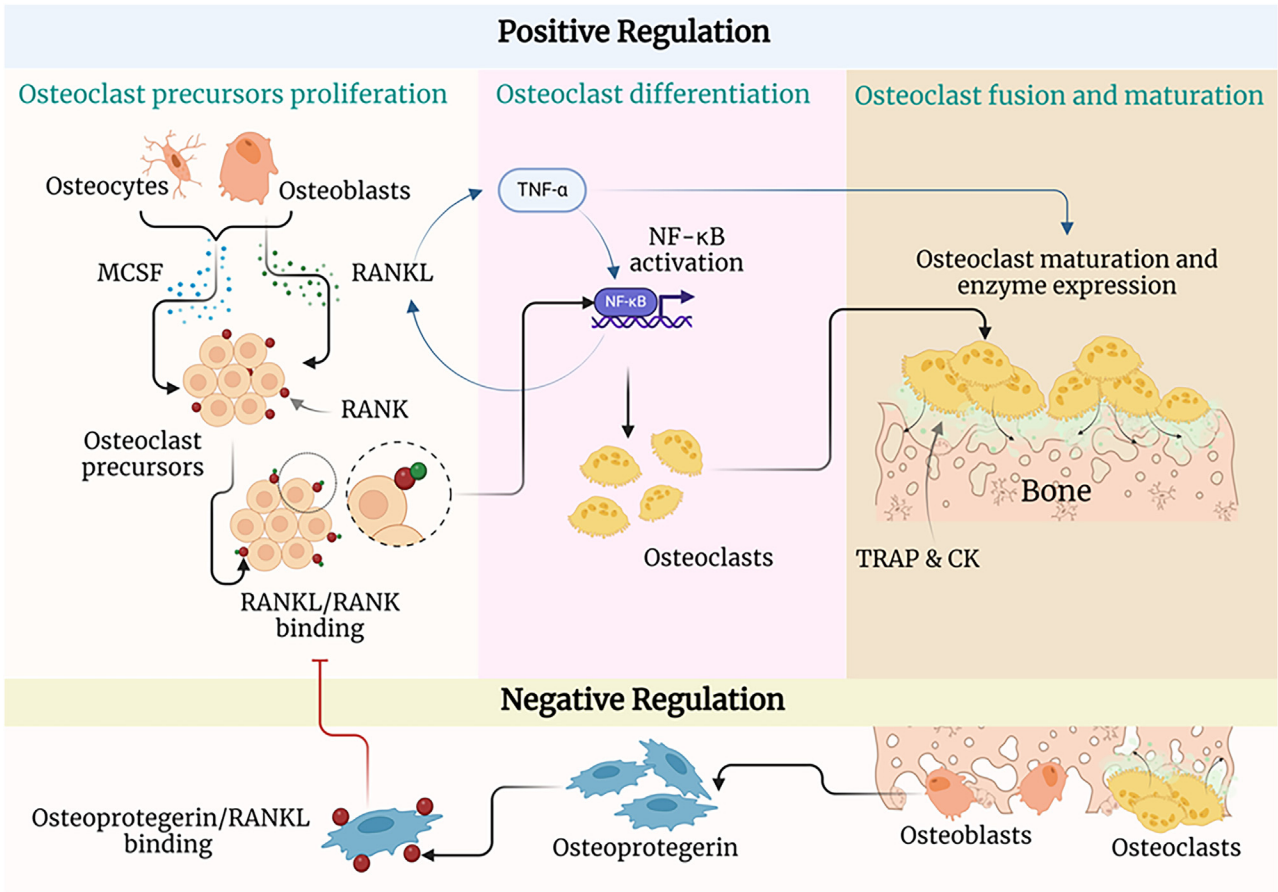

Figure 4. Physiology of bone remodeling and osteoclastogenesis

MCSF and RANKL, produced by bone cells (i.e., osteocytes and osteoblasts) play an important role in the survival and proliferation of osteoclast precursors. Binding of RANKL to RANK (on the surface of osteoclast precursors) lead to the activation of NF-κB which lead to the osteoclast differentiation. Matured osteoclasts express enzymes (including TRAP and CK) for bone resorption. TNF-α boosts the production and activation of RANKL and NF-κB. Osteoblasts produce osteoprotegerins which bind to RANKL inhibiting osteoclastogenesis [Created by BioRender.com]. MCSF: Macrophage colony-stimulating factor; RANKL: Receptor activators of nuclear factor-κB ligand; TNF-α: Tumor necrosis factor-α; NF-κB: Nuclear factor-κB; TRAP: tartrate-resistant acid phosphatase; and CK: cathepsin K.

It was found that UHMWPE wear debris with higher oxidation levels exhibited a higher tendency (≈140-fold) to activate TLRs.[134] The failure of immune cells to phagocytose UHMWPE wear particles (2–10 μm) from scoliosis spinal implants led to endosomal instability, cathepsin release and reactive oxygen species generation which activated NALP3.[112,134,135] A similar pathway was reported for UHMWPE particles with a size bigger than 20 μm, which led to the formation of multinucleated giant cells. Bigger particles can activate Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidases that generate reactive oxygen species promoting NALP3 inflammasome activation.[136] In conjunction with TLR-induced cytokine transcription, the activation of NALP3 inflammasome and subsequent caspase-1 activity enable interleukins (such as IL-1β and IL-18) to participate in the progression of osteolysis.

At the mediator level, NF-κB which is activated by RANKL was introduced as the key player in the stimulation of osteoclastogenesis.[109] Additionally, it was observed that TNF-α, IL-6 and IL-1 stimulated RANKL expression and activated Mitogen-Activated Protein Kinase to boost osteoclastogenesis and inhibit osteoclast apoptosis.[115,116,137–140] TNF-α was also shown to suppress the expression of procollagen 1 and increase the production of IL-1 and IL-1R mediators to promote osteoclast survival.[127,137,140] By boosting osteoclast differentiation and activation along with inhibiting their apoptosis, TNF-α, IL-1β, and RANKL significantly contributed to the development of osteolysis (Figure 5). Matrix metalloproteinases (mainly MMP 1, 2, 3, 9, 10,12, 13) were shown to be responsible for the degradation of the periprosthetic extracellular matrix.[141,142] A summary of the role of molecular effectors in the pathogenesis of osteolysis is presented in Table 2.

Wear particles and hypersensitivity

Hypersensitivity has been reported in spine surgery mainly due to wear particles and metal ions from metal-on-metal implants.[23,40,75,86,88,93,145] Metal ions from spinal implants form antigens through binding with the host proteins to induce hypersensitivity which also triggers pseudotumor-like

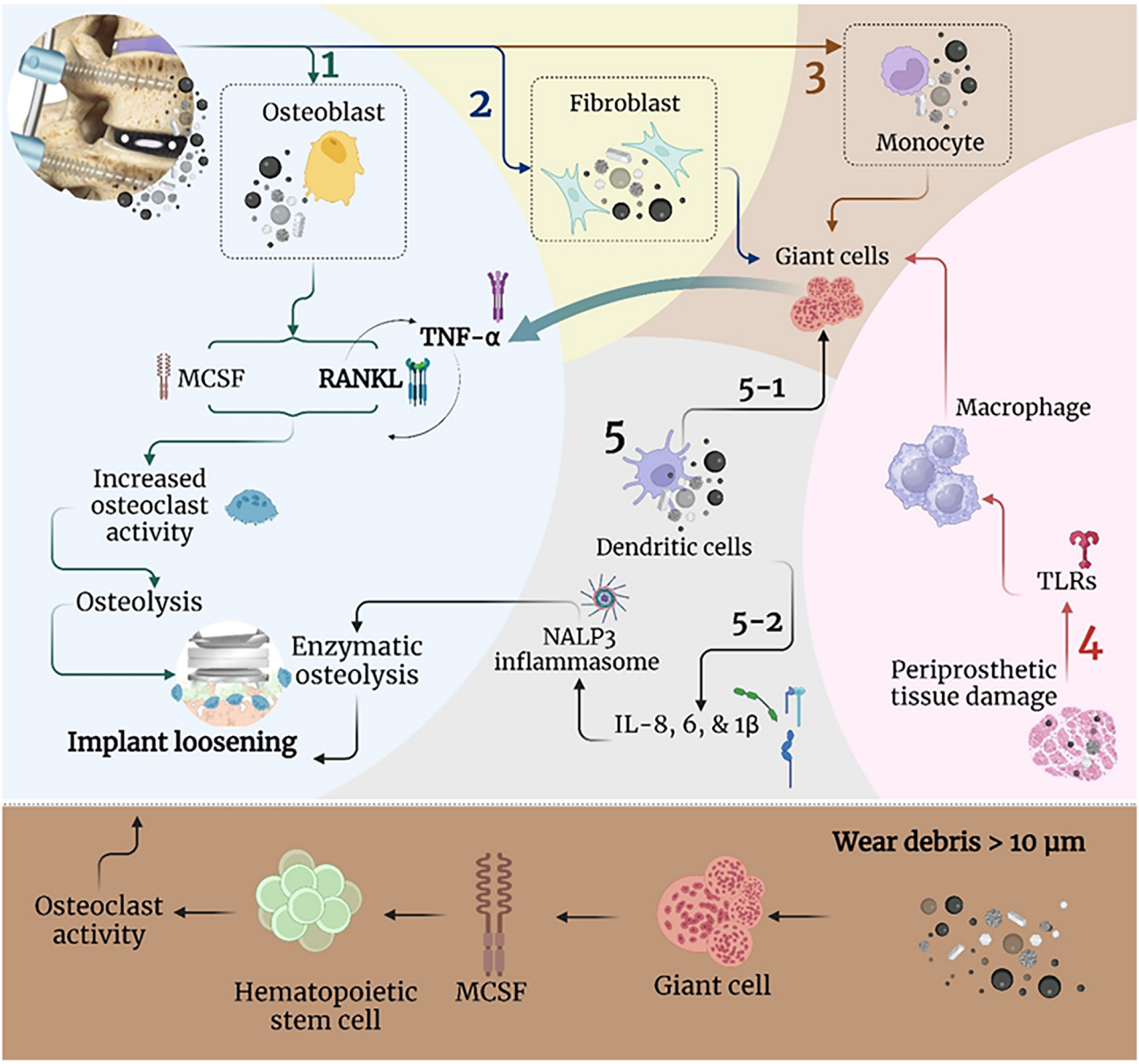

Figure 5. Mechanism of osteolysis

Different cell types including osteoblasts (1), dendritic cells (2), monocytes (3), fibroblasts (4), macrophages (5), and periprosthetic tissue damage (6) increase osteoclast activities leading to osteolysis and implant loosening with relevant pathways depends on wear debris size. Small UHMWPE debris pathway (top): Osteoblasts can phagocytose wear particles to reduce the secretion of osteoprotegerin, express RANKL and macrophage colony-stimulating factor (MCSF), and stimulate inflammatory mediators.[101,114,124–127] Dendritic cells, macrophage, monocytes, and fibroblasts contribute to the phagocytosis of wear debris to form multinucleated giant cells, increase the expression of proinflammatory cytokines and intensify the osteoblast effector's mechanism. Additionally, dendritic cells can activate NALP3 inflammasome leading to enzymatic osteolysis.[112,128] Additionally, TLRs are stimulated by damage-associated molecular patterns in response to infection or tissue damage due to wear particle exposure and activate macrophage.[102,129,130] Large UHMWPE debris pathway (bottom): Macrophages form multinucleated giant cells around large wear and stimulate MSCF and activate immune cells (such as hematopoietic stem cells) to increase inflammation and osteoclast activity. [Created by BioRender.com].

reactions. Delayed type hypersensitivity associated with wear particles, known as type IV hypersensitivity, involves a complex immune response that is primarily mediated by T lymphocytes (specifically $CD3^+$ and $CD4^+$), $CD11c^+$ macrophage and dendritic cells, as well as cells with ample expression of Major Histocompatibility Complex class II (MHC-II) molecules.[146,147] MHC-II molecules are cell surface proteins that are often observed on antigen-presenting cells such as macrophages. If antigenic stimuli remain present for a long time, chronic delayed hypersensitivity reactions can contribute to the chronic inflammatory milieu associated with pseudotumor-like reactions.[148]

Table 2. The contribution of key molecular effectors in the pathogenesis of osteolysis

Contribution	Molecular effectors
Inhibiting osteoclast apoptosis	RANKL,[137] IL-1,[116] and TNF-α[137]
Increasing RANKL expression	TNF-α,[116] IL-1,[116,140] and IL-6[138]
Osteoclastogenesis augmentation	TNF-α,[115] IL-1,[140] and TLR[134,143,144]
Inhibiting procollagen 1 expression	TNF-α[127]
Increasing IL-1 and IL-1R expression	TNF-α[140]
Activating MAPK and NF-κB	IL-1,[139] IL-6,[112] IL-18,[139] and TNF-α[139,140]
Stimulating TNF-α	IL-6[101]
Activating cathepsin and ROS	NALP3 inflammasome[112,134–136,139]
Activating pro-IL- 1β and pro-IL-18	Caspase-1[112,139]
Degradation of periprosthetic ECM	MMPs 1, 2, 3, 9, 10, 12[141,142]

Delayed type hypersensitivity is often characterized by delayed onset of inflammation and tissue damage. The response typically involves afferent and efferent phases.[149] The afferent phase includes the initial sensitization of the antigen toward the production of pro-inflammatory cytokine to activate other immune cells. The afferent phase involves several stages. Initially, wear particles in periprosthetic tissue are phagocytosed by immune cells, mainly macrophages and dendritic cells (stage 1: particle phagocytosis). The immune cells process the ingested debris and present peptide fragments on their MHC-II molecules forming antigen-presenting cells (stage 2: activation of antigen-presenting cells). Antigen-presenting cells then interact with $CD4^+$ T lymphocytes, known as helper T cells, bearing T cell receptors specific to the presented peptide fragments to ultimately activate $CD4^+$ T cells (stage 3: T cell activation). Pro-inflammatory cytokines such as interferon-gamma and TNF-α are then released by $CD4^+$ T cells to activate other immune cells (stage 4: cytokine release and inflammatory response).[150–153] The efferent phase represents the T lymphocytes' response upon being re-exposed to the antigen. Throughout this phase, T lymphocytes which were activated during the afferent phase migrate to the antigen site where they are re-exposed to the antigen and exhibit an inflammatory response. This response is characterized by the activation of macrophages and other immune cells to release cytokines. This inflammatory response results in delayed-type hypersensitivity. In general, the sensitization of T lymphocytes to antigen occurs in the afferent phase, while the efferent phase encompasses T lymphocyte response via re-exposure to the antigen. As seen, the activation of macrophages triggering T lymphocytes occurs via a perpetual biological loop causing significant tissue damage.

Wear particles and inflammation

Wear particles induce inflammation through a variety of mechanisms involving immune cell activation, cytokine release, complement activation, oxidative stress, and interactions with cellular components (Figure 6).[129]

The activation of redox-sensitive transcription factors such as NF-κB, and activator protein 1 (AP-1) by wear particles upregulate genes encoding pro-inflammatory cytokines, chemokines, adhesion molecules, and enzymes leading to inflammation.[22,154,155] Additionally, reactive oxygen species can directly produce inflammatory mediators such as IL- 1β, IL-6, TNF-α, and IL-18 to promote inflammation.[156,157] The expression of TNF-α represents a primary inflammatory response to wear debris from UHMWPE in TDRs.[158]

Wear particles and genotoxicity

Wide dissemination of nanoparticles across the body, due to their nanoscale nature, is a growing concern that potentially can lead to the formation of tumors in locations distant from the metallic implant and periprosthetic tissues.[159] As evidenced by numerous studies, cobalt and chromium particles and their ions which are often observed in periprosthetic tissues are carcinogenic.[160–162] Chromium (Cr) particles often produce three distinct forms of Cr ions: Cr III, Cr II and Cr VI.[163] DNA damage including the formation of covalent bonds between DNA strands (DNA cross-links), chemical modification of DNA through the development of permanent bonds at nucleotide bases (DNA adduct)], and breakage of one or two DNA strands (single- or double-strand breaks) are often caused by Cr III ions.[164] In addition, Cr III ions can damage DNA by being exposed to reactive oxygen species (oxidative DNA damage), which alters the DNA structure such as strand breaks or base modification (Figure 7). Cr VI ions when entering cells can cause harm to the cell and damage DNA and organelles via chemical reduction to Cr III ions and generating free radicals such as hydroxyl and thyl. Such DNA damage can disrupt replication by interfering with DNA polymerase, inhibiting transcription, and ultimately leading to genetic mutations. Consequently, these adverse factors may trigger apoptosis, resulting in necrotic tissue formation.[165] Studies have shown that the induction of genotoxicity mainly depends on the size of wear particles with smaller debris demonstrating higher genotoxicity. While wear particles may enter nuclei and cause direct DNA damage, they can induce indirect genotoxicity via increasing the lysosomal release of DNases and generating reactive oxygen species mediated by NADPH-oxidase or mitochondria dysfunction (formation of mitochondrial free radicals). Additionally, metal wear particles can produce metal ions which can directly induce DNA damage or lead to mitochondria dysfunction and result in the generation of more reactive oxygen species.[166–168] It was also revealed that larger wear particles or the agglomeration of smaller wear debris could deform or disrupt cell and nuclear membranes leading to DNA damage (Figure 7).

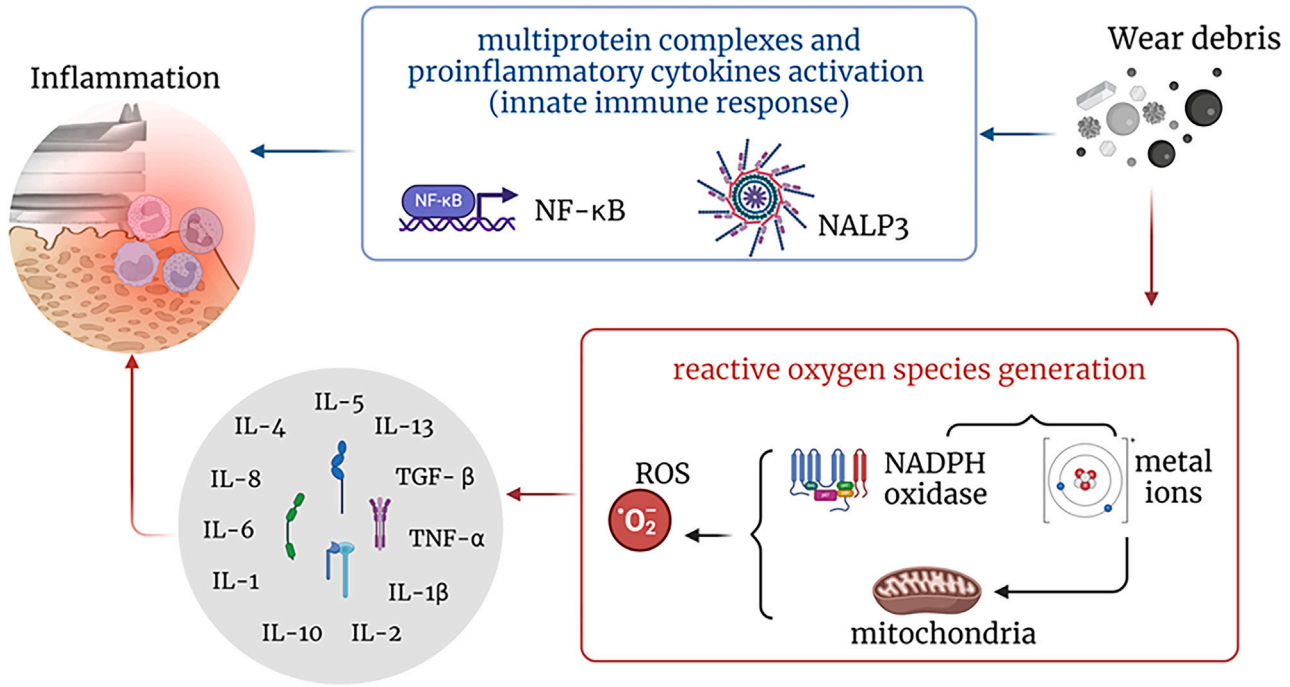

Figure 6. Spinal wear particles and inflammation

Wear particles from spinal implants can induce inflammation through different mechanisms including the activation of multiprotein complexes and proinflammatory cytokines, and the generation of reactive oxygen species. [Created by BioRender.com].

Wear particles and discogenic pain

Studies have shown that wear particles share the same process to induce pain as nucleus pulposus cells do in degenerated discs. The mechanism is mainly based on the release of specific inflammatory cytokines to stimulate nerve and vascular endothelial growth factors (NFG and VEGF) which foster neurogenesis and angiogenesis, respectively.[169] Inflammatory cytokines are central to the development of discogenic pain as they facilitate changes in nociceptive channel activity and dorsal root ganglia cell apoptosis.[170] Angiogenesis and neurogenesis (recruiting vasculature and unmyelinated fibers to the lumbar spine) are widely accepted as primary mechanisms underlying the pathogenesis of degeneration- and wear-induced discogenic pain.[171] However, it is believed that pain induced by wear particulates is more significant compared to disc degeneration as a higher concentration of effectors such as IL-1β, VEGF, and substance P (a pain-related peptide) were found in periprosthetic tissues compared to disc degenerated tissues (Figure 8).[158,172,173]

Wear particles from spinal implants trigger inflammation by stimulating the release of specific cytokines. A strong positive correlation was reported between the levels of TNFα, IL-1β, VEGF, NGF, substance P, and macrophages with an increased number of blood vessels.[172,174] On the other hand, secreted cytokines can modulate neurotropic factors such as NGF, brain-derived neurotropic factor (BDNF), and neurotrophin-3 (NT3) and upregulate their receptors including tropomyosin receptor kinase (Trk) A, B and C.[14] NGF fosters the growth and survival of unmyelinated fibers and its receptor trk-A which is the first step toward neural growth and pain (Figure 8).[169,175,176]

IN VITRO BIOMECHANICAL STUDIES – WEAR SIMULATION

In vitro, biomechanical studies and wear simulation have been widely used to explore wear characteristics of new materials or novel designs for spinal disc arthroplasty.[177–180] Understanding the wear resistance of spinal implants is one of the key factors affecting the associated longevity (Box 3). The accurate replication of *in vivo* conditions (kinematics, mechanics, and lubrication) using wear simulators can provide feedback to enhance the design of spinal implants. Currently, two international standards are available to establish wear simulation test protocols for TDR implants: ISO 18192-1 and ASTM F2423-05.

ISO 18192 (2011) specifies guidelines to investigate the relative angular movement between articulating components in TDRs (minimum sample size = 6) emphasizing the pattern, force magnitude, speed (1 Hz) and duration of testing (Table 3). The execution of wear simulation was suggested to start with lateral bending followed by flexion and extension and finally axial rotation. The combination of test kinematics and the use of 20 ± 2 g/L calf serum protein provides a detailed specification for the test environment to simulate physiological circumstances.

ASTM F2423-05 (2011), the Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses, utilizes the same concentration of calf serum lubricant compared to ISO 18192 (2011) standard. However, the suggested load and

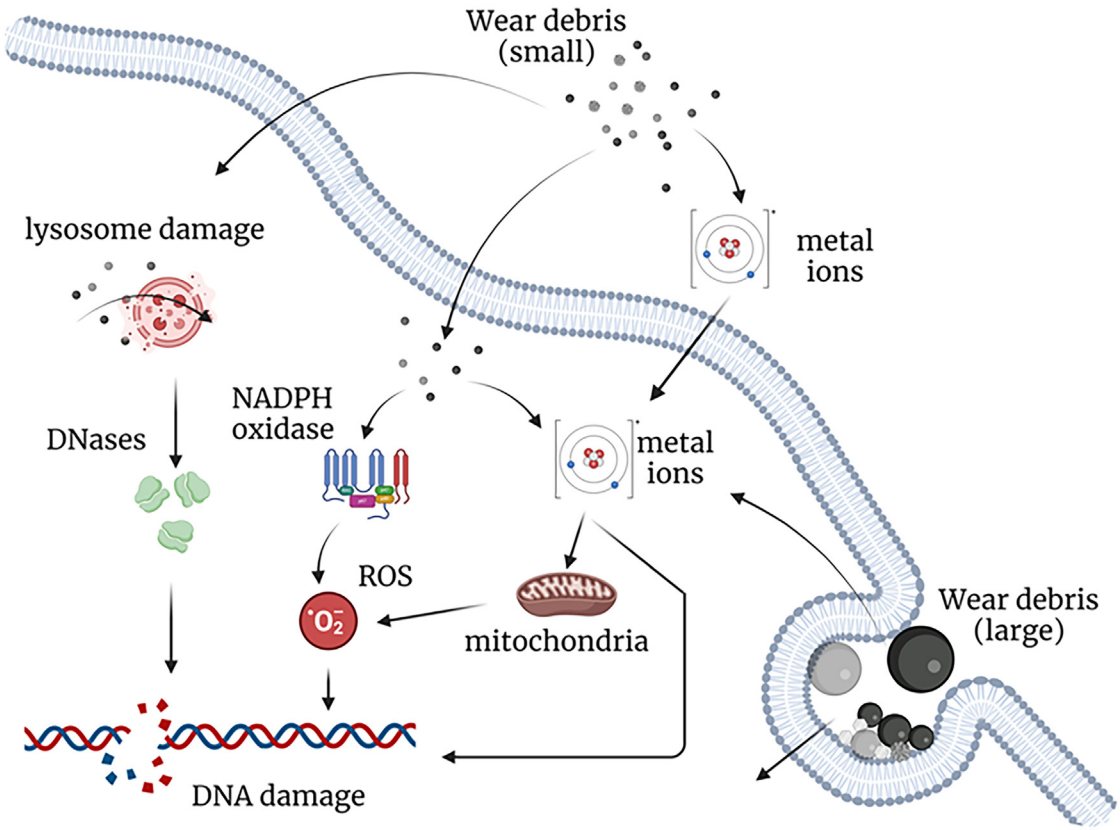

Figure 7. Spinal wear particles and genotoxicity

Wear debris can cause genotoxicity via damaging DNA. Wear particles from mainly metal-on-metal spinal implants can damage DNA by increasing lysosome permeability and generating reactive oxygen species. Bigger particles or the agglomeration of smaller wear debris deform or disrupt cell and nuclear membranes leading to DNA damage. [Created by BioRender.com].

kinematic profile, speed (lower than 2 Hz), and minimum sample size (# 5) are different. The two guidelines share a similar load and kinematic profile for the lumbar spine. For the cervical spine, both standards suggest a similar range of motion and load magnitudes, but the level of axial rotation is higher in the ASTM F2423-05 guidelines (Table 4).

In a comparison study, wear simulation was employed to explore the impact of loading and kinematic patterns on the wear of active L lumbar TDRs using two distinct protocols [ISO 18192-1 and ASTM F2423-05]. It was found that wear rates between these two protocols were significantly different with a higher wear rate (approximately 20-fold) observed when the ASTM protocol was used. It was believed that the pure unidirectional motion in ASTM protocol was clinically irrelevant and did not reflect the *in vivo* kinematic of TDR. The multidirectional movement pattern in the ISO protocol created a cross-shear stress on the UHMWPE component leading to more reliable results.[181] This finding was also consistent with a retrieval study on Bryan and Prestige metallic spinal prostheses that revealed the number of wear particles that were generated *in vivo* were significantly lower (5- to 10-fold) than those predicted by *in vitro* biomechanical simulation.[182] Additionally, loading regimes in ISO 18192 involve only 4 degrees of freedom; hence, another 2° of freedom (anterior and posterior shear and lateral shear) loading - which is often observed in the spine *in vivo* - were overlooked. Using ProDisc - L, a comparative study that employed anterior and posterior loads (+175 and −140 N, respectively) to apply 5° of freedom loading scenario revealed a slightly lower associated wear rate (11.6mg per million cycles) compared to 4 degrees of loading (12.7 mg per million cycles).[183] Later in 2015, test conditions (axial load and flexion/extension magnitude) of the ISO standard were modified to lower cross-shear input kinematics resulting in the reduction of wear rate.[184] While this study proposed new wear phenomena not previously reported in standard ISO cycle results, without the availability of a large pool of clinical data from periprosthetic tissues, the clinical relevance of the developed methodology was not clear.

Recent biomechanical studies have shown that the wear rate in metal-on-metal spinal implants (6–16 mm^3 per million cycles) was significantly higher (approximately 10 times) than metal-on-metal hip counterparts (both made of stainless steel) indicating a potentially significant public health issue.[185,186] It was also noted that wear debris from spinal implants was different in shape and size compared to hip implants. Wear particles from metal-on-metal spinal implants shared a more irregular shape compared to those generated from hip implants which

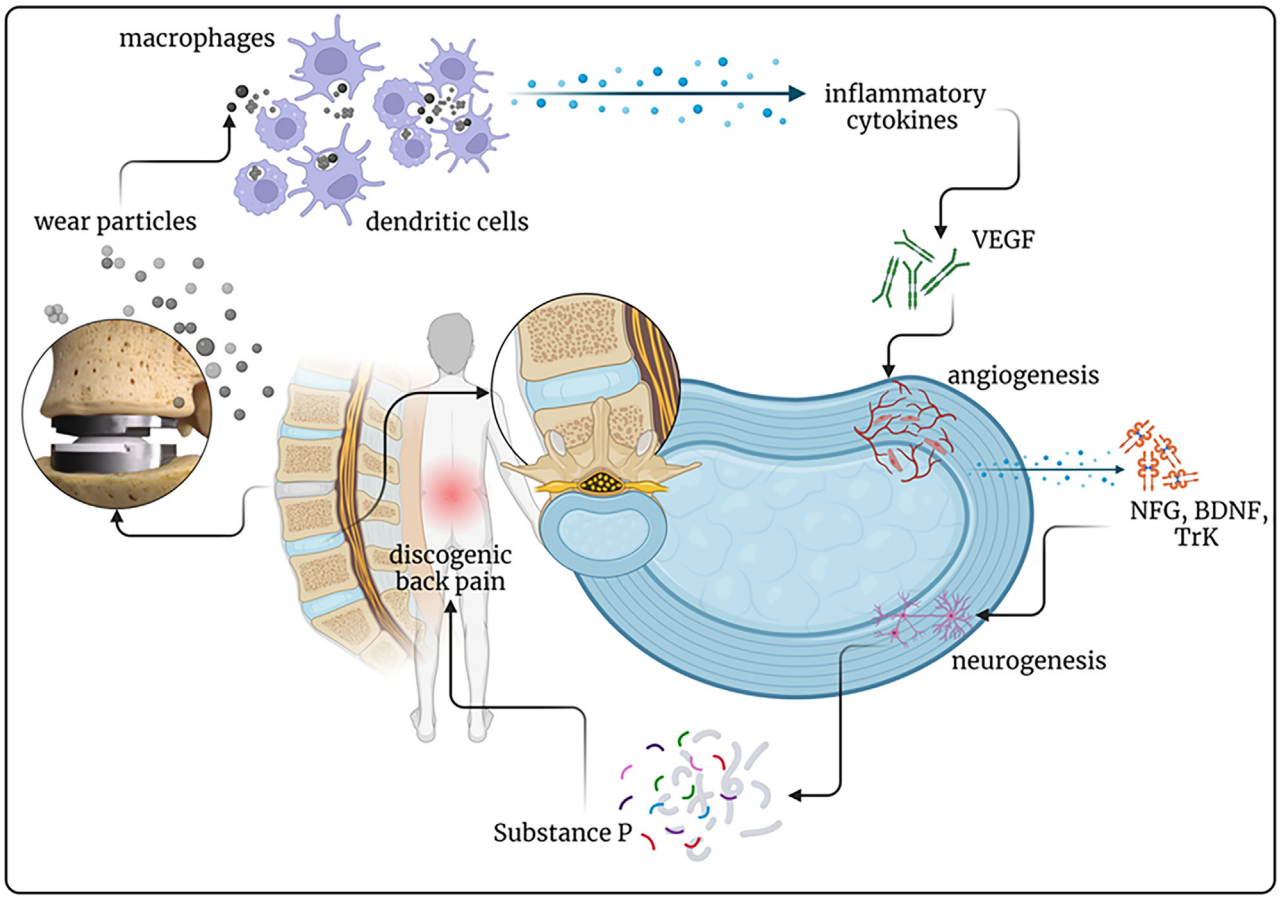

Figure 8. Spinal wear particles and back pain

Macrophages and fibroblasts, activated by wear debris, prompt the release of various cytokines that trigger an inflammatory cascade inducing pain. Additionally, activated fibroblasts can produce vascular endothelial growth factor (VEGF), fostering neovascularization within the disc. Consequently, new endothelial cells secrete neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), promoting disc neural invasion and transmitting nociceptive signals utilizing substance P and calcitonin gene-related peptide (CGRP). The transmission of these signals to the dorsal root ganglion can cause pain. [Created by BioRender.com].

were more round and oval.[186] The spatial variation of wear of Charité lumbar TDRs revealed that the surface roughness of UHMWPE was time-dependent and increased after 2 million cycles due to material build-up. Additionally, this study found uneven wear on the superior and inferior sides of the TDR.[187] In another study, the generation of UHMWPE wear particles from Charité spinal discs was assessed *in vitro* for 10 million cycles of flexion-extension and lateral bending (±7.5°). The average wear (size range: submicrometer to >10 μm) and total height loss of the implants were reported as 13 mg per million cycles and 0.2 mm, respectively.[188] The average size and aspect ratio of UHMWPE wear particles that were collected at 12 intervals over 5 million cycles (according to ISO 18192-1:2011) from Charité TDRs were 0.1–1 μm (mode = 0.88 μm) and 1.55, respectively. A decrease in particle size was also reported as the number of loading cycles increased.[189] Fibrillar morphology was reported as the dominant shape of wear particles for loading cycles of less than 3 million; whereas, both spherical and fibrillar wear particles were found for a higher number of (up to 5 million) cycles.[189] The shape of wear particles was shown to exhibit different biological behaviors with elongated particulates (aspect ratio >3) being pro-inflammatory.[23] Another study evaluated serum-saline ratios for fluid simulator testing and revealed that type of the fluid had a great impact on the average size and type of wear debris generated in metal-on-metal spinal implants. The over-protection of serum proteins was shown to emphasize the importance of using both saline and serum in wear simulation tests (10 million cycles, with flexion of 11.3 and the extension of 5.6° coupled with the axial rotation of ±4°). A higher amount of spinal wear debris was generated when saline was merely used, and interestingly, the addition of 20% serum protein significantly reduced the generation of wear debris.[190]

Different *in vitro* biomechanical studies have been used to identify the feasibility of using PEEK in spinal implants with a focus on wear properties.[191,192] One biomechanical study aimed to simulate the impaction process and determine whether the impaction of titanium-coated PEEK cages into the disc space generated wear or induced structural delamination of the

Box 3. In vitro biomechanical studies, wear simulation, and finite element modeling

In vitro biomechanical studies, wear simulations, and numerical modeling have been extensively employed to investigate wear characteristics of new materials and innovative designs for spinal disc arthroplasty.

Key findings:

(1) ISO 18192-1 and ASTM F2423-05 are established standards for evaluating wear and related biological responses in spinal devices, each with distinct methodologies and purposes. ISO 18192-1 is particularly suited for simulating spinal wear particles under clinically relevant conditions, offering a realistic representation of the wear process and its functional implications for spinal implants.

(2) Recent biomechanical studies highlight that metal-on-metal spinal implants (e.g., stainless steel) exhibit wear rates significantly higher—approximately tenfold—than their hip implant counterparts. Furthermore, elongated wear particles (aspect ratio >3) generated by these implants are associated with pro-inflammatory biological responses due to their irregular morphology.

(3) PEEK-based materials have emerged as promising candidates for spinal implants, demonstrating favorable mechanical durability and reduced cytotoxicity of wear particles. However, wear rates and particle generation vary significantly based on implant design, reinforcement, and testing conditions. While reinforced PEEK formulations (e.g., glass fiber- or carbon fiber-reinforced PEEK) improve wear resistance and reduce debris production, challenges such as surface degradation, high wear rates under extended cycles, and size-dependent inflammatory responses of wear particles remain critical concerns.

(4) Finite element studies provide powerful predictive capabilities for wear behavior in spinal implants, simulating various factors such as loading scenarios, material properties, implant designs, and patient-specific conditions. By integrating these models with experimental and clinical data, researchers gain valuable insights into wear particle generation, implant performance, and strategies for improvement, ultimately enabling the development of safer and more effective spinal implants at reduced costs.

device.[193] It was observed that impaction during implantation resulted in the generation of wear particles smaller than 10 μm. While the size of the majority of particles in this study was in the phagocytosable size range, the associated risk of inflammation was not studied.[193] An *in vitro* biomechanical study evaluated the mechanical durability and wear properties of PEEK-UHMWPE cervical spinal implants. Generating 2.3 mg (per million cycles) of wear debris via abrasion, adhesion and fatigue wear, PEEK was considered a potential material to be used in the design and fabrication of artificial cervical disc implants.[194] Other research that evaluated the wear properties of a cervical TDR using a PEEK-on-PEEK bearing revealed that the wear rate was significantly higher compared to UHMWPE-on-CoCrMo counterparts indicating a severe long-term degradation of the bearing surfaces in all PEEK-based cervical TDRs.[195] The tribological performances of glass fiber–reinforced PEEK against UHMWPE in cervical disc implants showed a 25% reduction in friction coefficient leading to less wear debris production compared to non-reinforced PEEK.[196] Another study utilised Active C cervical artificial disc platform and examined the wear properties of PEEK and a carbon fibre-reinforced PEEK containing 30% polyacrylonitrile compared to UHMWPE-on-CoCr29Mo6.[53] This study found a significantly lower gravimetric wear rate for the carbon fibre-reinforced PEEK (0.02 ± 0.02 mg per million cycles) compared to PEEK (1.4 ± 0.4 mg per million cycles) and polyethylene-on-cobalt–chromium (1.0 ± 0.1 mg per million cycles) implants.[53] NuNec cervical disc implants were subjected to a constant axial compressive load followed by the motions given in ISO 18192-1 and found that wear rates for the first 2 and 2–5 million cycles were 4.8 ± 1.5 and 1.0 ± 0.9 mg/million cycles, respectively.[197] Wear particles from PEEK-OPTIMA, the most frequently used medical grade PEEK for interbody fusion spinal surgeries showed an elevated level of human macrophage viability or proliferation *in vitro*. However, compared to wear particles from PEEK and UHMWPE, PEEK-OPTIMA particulates exhibited less cytotoxicity and demonstrated a size-dependent cytokine release with an increasing trend toward smaller particles (10–2 μm).[198] A study on PEEK-on-ceramic cervical artificial discs (subjected to 10 million cycles using a spine simulator) revealed that PEEK endplates were the primary source of wear ranging from 0.9 ± 0.2 to 2.8 ± 0.6 mg/million cycles for low and high number of cycles, respectively. It was shown that PEEK particles (<2 μm in size) had a smooth and spheroidal morphology which was similar to other polymer-on-ceramic orthopedic articulations.[199] The relation between the protein concentration of the testing fluid and the generation of PEEK particles was investigated for NuNec, a hydroxyapatite-coated PEEK cervical TDR. It was observed that a higher protein concentration in the test fluid led a severe delamination in articulating surfaces and increasing the number of test cycles significantly increased the rate of wear (0.26 ± 0.01 mm^3 to 0.32 ± 0.02 mm^3/million cycle from 10 to 20 million cycles, respectively). However, wear particle production was independent of the suggested load and motion profiles when the implant was tested under ASTM F2423-05 compared to ISO 18192-1 standard.[200] Hydroxyapatite coatings have been widely used to reduce spinal implant failure via promoting osseointegration; however, a clinical study based on 23 patients who underwent lumbar fusion surgery revealed that hydroxyapatite faced rapid wear, compromising implant stability and generating biological consequences.[201] A pin-on-plate study to understand the relationship between the friction coefficient of different spinal implant materials and PEEK showed that the addition of polyvinyl alcohol lowered the friction coefficient of PEEK tested in both Ringer's solution and bovine calf serum.[202] Spinal implants might benefit from a polyvinyl alcohol capsule to reduce wear production or prevent them from migrating to surrounding tissues. Results from UHMWPE-on-titanium artificial cervical disc for 1.5 million cycles revealed that more wear particles were produced under flexion/extension compared to axial rotation motion. Additionally, the type of motion was shown to affect the wear generation. Linear wear scratches were found on the

Table 3. ISO 18192-1 (2011) mechanical kinematic conditions for TDR wear simulation

TDR	Range of motion [°] Lateral bending	Flexion - extension	Axial rotaion	Load [N]
Lumbar	±2	+6 to −3	±2	600–2000
Cervical	±6	±7.5	±4	50–150

Table 4. ASTM F2423-05 load profile and range of motion

TDR	Range of motion [°] Lateral bending	Flexion - extension	Axial rotation	Load [N]
Lumbar	±3	±7.5	±6	1200
Cervical	±6	±7.5	±6	100

implant surface in flexion/extension motion while wear surfaces with axial rotation showed arc-shaped wear tracks. The mechanism of wear generation was similar for both motion types.[203]

Several retrieval studies on lumbar and cervical TDRs have documented evidence of wear and damage caused by impingement. These studies encompass both fixed and mobile bearing designs, along with diverse material combinations such as polymer-on-metal and metal-on-metal.[173,204–206] The impingement of the endplate has been reported in the Charité, ProDisc-L, Activ L, and MobiDisc-L total spinal disc arthroplasties often occurring posteriorly.[29,204,207–209] A study identified a proper range of motion and developed a clinically relevant impingement test method that showed similar impingement regions and damage patterns compared to those found in retrieved Charité TDRs.[210] The application of −20° to +6° flexion-extension, ±2° for both lateral bending and axial rotation, and 600 to 2000 N axial load for 1 million cycles were found suitable to create experimental boundary conditions to replicate clinically relevant impingement damage including rim penetration and deformation.[210] A similar study was conducted to evaluate the impingement behavior of lumbar spinal disc arthroplasty in flexion, extension, lateral bending and combined flexion bending using Active L implant.[211] The impingement contact stress was developed under an angular displacement of ±2° with a constant bending moment of 8 Nm, which proved suitable to predict *in vivo* impingement behavior (damage pattern) often observed on retrieved devices.[211] These studies developed implant-dependent methodologies that were capable of reproducing clinically relevant impingement damage patterns; however, methodologies to generate wear particulates with similar characteristics (size and morphology) to those found in periprosthetic tissues yet to be explored.

Spinal implant design also has a great impact on the generation of wear particles. The size of the ball in ball-and-socket metal-on-metal spinal implants influenced the total volume of wear particles generated. A smaller ball radius (10–12 mm) exhibited lower friction compared to larger (16 mm) ones when exposed to flexion-extension, lateral bending, and axial rotation at different frequencies (0.25–2 Hz) and loads (50–2000 N).[212] Aligned with this observation, it was reported that the design of articular surfaces with different surface curvatures affected the volume of wear particles generated. Semi-spherical articular surfaces with multiple centers of rotation for flexion, extension, and lateral bending were found to be a better representation of human lumbar spine kinematics, and subsequently, generated fewer (<5-fold lower) particles compared to currently available commercial TDRs.[213]

Wear simulation approaches, while offering valuable insights into the performance and durability of spinal implants, are a simplified model of the complex biomechanics and biology often observed *in vivo*. Moreover, their clinical relevance may be limited due to differences between *in vitro* and *in vivo* conditions due to limitations in material properties, lubrication regimes, or environmental factors. Therefore, the results from wear simulation techniques must be carefully analyzed to interpret findings accurately and translate them into meaningful clinical applications.

SPINAL WEAR SIMULATION AND FINITE ELEMENT STUDIES

Finite element studies are valuable tools for investigating the biomechanical behavior of spinal implants and their interaction with periprosthetic tissues, including the generation and distribution of wear particles. Using this tool, it is possible to predict the generation of wear debris from spinal implants under different loading scenarios, material properties, and design configurations. Additionally, finite element studies can facilitate the evaluation of the durability, stability, and biomechanical properties of spinal implants before and after particle generation particularly targeting a patient-specific strategy.

By accurately selecting boundary conditions such as range of motion (from kinematic simulations of the spine containing a disc implant), disc and spine geometry (from computed tomography), loading conditions (from standards and kinetic simulations), the results from cervical TDRs wear simulations were similar to those observed *in vivo*.[214] The feasibility of using finite element studies to predict UHMWPE damage via impingement revealed the sensitivity of the simulation to physical characteristics (such as height and spine orientation), implant features (e.g., lordotic angle and anterior-posterior position) and loading conditions.[215,216] Through incorporating wear testing protocol ISO 18192, a finite element study showed the relationship between radial clearance in bearing surfaces and wear production in ceramic-on-ceramic TDRs.[217] The lower the radial clearance, the lower the volumetric wear production (after 10 million cycles), with minimum wear produced at 0.05 mm radial clearance.[217] Numerical simulations revealed that, under a similar testing protocol offered by the ISO 18192 standard, Alumina–Alumina bearing pairs in total disc arthroplasty generated lower volumetric wear compared to other ceramic types.[218] The addition of ligament segment structure and facet forces to the ISO 18192 test protocol, was shown to present a better spinal disc model to predict the generation of wear debris from cervical TDRs.[219] An adaptive finite element study employed a motion profile consisting of flexion-extension [6/−3°], lateral bending

[±2°], axial twist [±1.5°], and axial load (200–1750 N or 600–2000 N) to understand the impact of polyethylene elastic modulus, radial clearance, and thickness on wear production using the ProDisc-L implant platform.[220] The wear coefficient from an experimental spinal implant wear test (using the same motion profile for 10 million cycles and a similar disc implant design) was also used to calibrate the model. This study found that the chosen parametric design variations had a nonsignificant effect on the resultant wear rate (9.8–11.7 mg per million cycles).[220] A numerical wear prediction framework was proposed to characterize wear in UHMWPE-based cervical TDRs (Discover TDA implant design) considering head and C4-5 spinal segment motion ranges. This study revealed that with the absence of head movement, wear rates were one order of magnitude larger (3.32 mg per million cycles) causing broader damage to the implant compared to that with restricted *in vivo* head and spine movement.[221] Using the Charité TDR platform, a finite element study revealed that the local wear distribution, articulation kinematics, and wear rates were insensitive to the location of the implant relative to the angular actuators.[222] A preferential molecular orientation was observed at the surface of the UHMWPE component under physical articulation, and this was the basis for the development of a computational framework with a re-mesh finite element model.[106] Incorporating the cross-shear and polyethylene molecular orientation, it was shown that the generation of wear particles in a ProDisc-L TDR, was lower when motion was in the direction of the preferential molecular orientation compared to the motions that were transverse to the molecular orientation.[106] Simulation of friction-induced wear particles in a cervical TDR model revealed that the range of implant motion, bone-implant interface and facet joint forces were responsible for wear particle production. These parameters were shown to be highly affected by the implant position indicating the plausible correlation between wear particulate generation and human inaccuracies that may occur during implantation.[223] While finite element tool has been used in a limited number of studies on spinal wear particles, its crucial role in predicting wear behavior at low cost is apparent. In particular, if integrated with experimental studies and clinical observations, its contribution to the development of safer and more effective spinal implants is significant.

IN VIVO ANIMAL RESEARCH AND SPINAL WEAR PARTICLES

One of the earliest investigations into the biological impact of spinal-derived wear particles was conducted in 2002 where laboratory-generated polyolefin rubber particles from the AcroFlex prosthesis were either administrated to the dorsal subcutaneous air pouches of rats or placed onto the lumbosacral dura and nerve roots of sheep.[224] This study found that rubber particles can cause localized tissue reactions that resemble a typical foreign body response to large particles with no local or systemic toxic effects or migration from the site of implantation.[224] In another study, the impact of titanium wear particles on the development and maintenance of spinal fusion was investigated using a rabbit model. It was found that titanium wear particles (titanium powder with 1–5 μm diameter) limited the mechanical stability of the fusion. An increased level of local cytokines (TNF- α), osteoclast cells, and cellular apoptosis alongside regions of osteolytic resorption were observed in the titanium-treated sites.[225] Posterolateral arthrodesis at L5/6, fusion of adjacent vertebrae, in New Zealand white rabbits using iliac autograft and titanium particulates revealed no significant differences in systemic cytokine levels between the titanium or autograft treatments.[85] However, an increased level of local cytokines, including TNF-α, with higher osteoclast counts and wider osteolytic resorption regions were observed for autograft-titanium particle treatments.[85] Investigation of the biomechanical and histopathological characteristics of Porous Coated Motion cervical implant - made of cobalt-chromium-molybdenum alloy - using a mature goat model, reported no evidence of the presence of wear particles in the surrounding tissues; hence, no cellular apoptosis was found.[226] Titanium wear particles from spinal implants have been shown to provoke inflammatory cytokines release via increasing the expression of intracellular TNF-α, osteoclastic activity, and cellular apoptosis in a rabbit model.[227] Similarly, tissue reaction to CoCrMo-alloy particles was observed in a rabbit model characterized by mild macrophage and lymphocyte formation as well as multinuclear cell infiltration.[228] The injection of metal particles in animal studies has been widely used to evaluate the efficacy and safety of orthopedic devices, however, the current issue is that these models are using clinically irrelevant wear particles. Regardless of joint type, the isolation of wear particles from periprosthetic tissue is critical to understanding their characteristics *in vivo* and establishing protocols to generate more clinically relevant wear debris *in vitro*.[16] The presence of wear debris in soft tissues around the Dynesys implant was deemed responsible for the formation of local fibrous tissues and upregulation of cytokines IL-1α, IL-1β, and TNF- α in mature male baboons.[229] This finding was consistent with the observations from long-term implantation of Dynesys in humans.[100,230] A spinal implant (ball-on-socket; titanium-on-UHMWPE) that mimicked the characteristics of the Discover prosthesis was developed and implanted in a goat model for 6 months. Wear analyses revealed uneven and severe damage to the UHMWPE component leading to the generation of polyethylene wear particles (0.1–100 μm with an average size of 9.6 ± 16.3 μm) in the surrounding tissues making surface fatigue and deformation the most dominant modes of implant failure.[231] Interestingly, this study found a 25% increase in the young's modulus of the UHMWPE after explantation.[231] It is important to note that the use of commercially available wear particles in different 2D and 3D cell culture models, while providing an invaluable general view of the biological response to wear particles, imposes limitations. Commercially available wear particles are clinically irrelevant in terms of their size, shape, and surface characteristics and are often dissimilar to those that are often observed in spinal implant periprosthetic tissues. Additionally, they are not specific to the spinal fusion devices and TDRs, and therefore, these studies were excluded from the current research.

Box 4. Spinal wear particles: Isolation and characterization

Accurate characterization of wear particle shape, size, and chemical properties are crucial for understanding wear mechanisms and biological responses. Developing clinically relevant *in vitro* models requires wear particles that closely mimic those produced *in vivo* to ensure effective validation of wear simulation procedures.

(1) Challenges in Particle Isolation: The isolation of wear particles from periprosthetic tissues often involves tissue digestion and centrifugation, processes that risk altering particle size, morphology, and composition, as well as causing particle loss. Chemical digestion methods, while effective, may lead to oxidation or degradation, particularly with prolonged exposure or higher reagent concentrations.

(2) Advances in Enzymatic Digestion: Enzymatic digestion techniques, such as those employing proteinase K or papain, show promise due to minimal chemical alterations. However, these methods are often expensive and prone to contamination. Multi-step enzymatic approaches have demonstrated higher recovery rates for low-volume and nanoparticle debris, but issues like particle aggregation and handling losses remain significant obstacles.

(3) Particle Aggregation and Filtration: Nanoparticle aggregation complicates characterization and requires advanced techniques such as metal-selective high-density layers and sonication to achieve better dispersion. Filtration of nanoparticles, particularly in low wear volumes, poses further challenges, limiting accurate size and distribution analysis.

(4) Emerging Isolation Techniques: Innovative methods like density gradient ultracentrifugation, utilizing non-toxic media like sodium polytungstate, effectively separate wear particles by density with minimal loss or alteration to particle properties. These techniques, when combined with advanced filtration and sonication, hold promise for isolating small-scale wear particles more reliably.

Refining these methods is essential to overcome existing challenges and establish robust procedures for isolating and characterizing wear particles from spinal implants.

SPINAL WEAR PARTICLES: ISOLATION AND CHARACTERIZATION

Isolation of spinal implant wear particles from periprosthetic tissue and characterization of their shape, size, and chemical properties are critical to understanding the mechanism behind wear production and subsequent biological responses. This is also crucial to develop *in vitro* methodologies that generate clinically relevant wear particles with the same characteristics as those produced *in vivo*, which is essential for the validation of wear simulation procedures in both simulators and pin-on-plate devices (Box 4). The *ex vivo* isolation of wear particles from tissues surrounding failed implants is challenging and requires a variety of optimizations. The isolation process often involves tissue digestion and frequent centrifugations. Alkaline digestion of periprosthetic tissues may alter the size (mainly reduction), morphology and composition (surface oxidation) of wear metal particles specifically for longer incubation times or higher concentrations.[232] Alternatively, using other chemical reagents that contain proteins or lipids serums is a better option with minimal impact on wear particle chemical composition due to the creation of a protective layer and minimizing associated oxidation-reduction reactions.[233] The use of enzymatic digestion techniques yielded more promising outcomes compared to other techniques; however, they are often expensive and involve numerous processes to ensure contaminant removal.[103] An enzymatic digestion technique often involves frequent digestion and centrifugation, dilution, and washing via transferring between tubes and containers.[234] This may lead to particle loss, which is potentially problematic for low wear volumes or those that contain nanoparticles. Wear particulates, in particular from spinal implants, are small in size (nm to μm ranges) and volume, and therefore, particle loss during the isolation process is likely to occur.

The aggregation of nanoparticles is another problem making the particle characterization process difficult. It was shown that passing particles through several denaturant layers and a metal-selective high-density layer can reduce particle aggregation leading to the production of a well-dispersed particle system for size analysis.[186] Upon separation of wear particles from tissues, sometimes sample filtration is essential to understand the size distribution of isolated particles. If not impossible, collecting nanoparticles from filters specifically for low wear volumes is difficult which imposes severe limitations on the characterization of wear nanoparticles via image processing.

A variety of techniques for the characterization of wear particles from orthopedic implants, including different methodologies for tissue digestion and wear particle isolation, have been developed.[235–238] However, to date, characterization of metallic wear particles from around failed metal-on-metal TDRs has not been conducted and our understanding of characteristics of *ex vivo* polymeric particles from metal-on-polymer TDRs and spinal fusion devices is limited. So far, the characterization of wear particles from spinal implants has been mainly based on tissue histology (staining) and microscopic observations (light, transmission and scanning electron microscopies) followed by manual size and shape measurements.[239–241] We found few studies that have employed periprosthetic tissue digestion to isolate wear particles (mainly UHMWPE particulates) from spinal implants. Recently, a novel technique for the isolation of wear particles, based on a 4-step enzymatic digestion process using proteinase K, glycine, and papain, has been developed which is highly efficient for the recovery of low-volume wear particles from orthopedic implants.[242,243] Using 6.5% HNO_3 followed by multiple vacuum filtration steps, UHMWPE debris with submicrometer size were isolated from revised SB Charité III TDRs. Agglomeration of particles was prevented through dilution with methanol containing 2% (w/v) Nonidet P-40 and sonication. The impact of the proposed methodology on the shape and size of particles was not clear and whether particles were lost during filtration was not discussed.[84]

Apart from periprosthetic tissue digestion, the isolation of wear particles from lubricants from wear simulators has been the focus of different studies that rely on the use of high- and

low-density materials during ultracentrifugation.[105,244,245] These studies often use a highly soluble in water and nontoxic density gradient media (such as sodium polytungstate) to isolate wear particles from hydrolyzed protein and other contaminants.[105,244,245] Utilizing density gradient ultracentrifugation at 40K rpm for 4 h was shown to be capable of separating a wide range of wear debris from different material types based on density difference (1.1–3.0 g/cm^3 range) with no sign of particle loss.[244] Isolation of CoCrMo wear particles from lubricants from wear simulators was reported based on multiple long (>72 h) digestion and centrifugation (>24 h) approaches using different chemicals such as 0.01 M Tris, 0.5% sodium dodecyl sulfate, 0.05 M sodium sulfite, 9 mg/mL papain, 0.005 M EDTA, 10 mL of proteinase K, and 0.1 M sodium hydroxide.[246] While a large number of chemicals were used in the process, it was effective to just separate wear particulates in a range of 0.05–15 μm, and whether particles were lost during the process or their size, shape, and chemical components were affected by the harsh isolation process were not investigated.[246]

SPINAL SURGEONS' PERSPECTIVE

The issue of wear particles generated by spinal implants is an emerging topic of concern within the field of spinal surgery. These particles can potentially lead to adverse reactions such as inflammation, osteolysis, and pseudotumor formation, impacting patient outcomes. A survey conducted among members of the "AO Spine Knowledge Forum Degenerative" explored surgeons' experiences, awareness, and management strategies related to wear particles. The responses shed light on clinical practices, research involvement, and the barriers to further investigation into this issue.

Surgeon demographics and experience

The survey gathered responses from 25 surgeons, with 40% being neurosurgeons and 60% orthopedic surgeons. Most respondents were highly experienced, with 44% having over 10 years of experience and 28% having more than 20 years. Nearly all surgeons (92%) worked in university hospitals or academic centers, where exposure to complex cases is more likely. This professional background provides insight into the experience level and clinical exposure of surgeons dealing with spinal implant-related complications.

Awareness and detection of spinal wear particles

Awareness of spinal wear particles and their complications was notably divided among respondents. While 44% of surgeons were fully aware of the issue, an equal percentage had only a moderate understanding, and 12% were unaware of the complications entirely. Detection methods varied, with intraoperative visualization being the most common approach (84%), followed by imaging techniques like MRI, CT scans, and X-rays (60%), and histological analysis (36%). This variation in awareness and detection highlights the need for more uniform guidelines and training on recognizing and managing wear particles.

Clinical impact and management approach

In terms of clinical impact, 28% of surgeons encountered wear particles frequently or occasionally, while 68% reported rarely encountering the issue. Despite this, symptoms related to wear particles were diverse, with the most common being aseptic inflammation (76%), osteolysis (68%), and pseudotumor formation (52%). Management strategies focused primarily on preventing the spread of wear particles through surgical techniques such as thorough irrigation (84%) and careful implant placement (76%). These findings suggest that although many surgeons may not see wear particles as a common issue, the potential complications are well recognized and prompt management efforts are in place.

Research involvement and barriers

A significant gap in research participation was observed, with 88% of respondents indicating they were unaware of or had never been involved in spinal wear particle research. Only 12% had some familiarity with relevant studies. Despite this, 64% expressed interest in future research, though barriers such as lack of access to periprosthetic tissue banks (with only one respondent reporting access) and concerns about patient confidentiality (72%) were frequently cited. Surgeons also highlighted funding limitations and inadequate data collection tools as key obstacles. This suggests that while there is a strong interest in advancing research, structural and logistical challenges need to be addressed.

Research priorities and future directions

The majority of respondents recognized the importance of further research, with 96% identifying the impact of wear particles on clinical outcomes as a critical area of study. Other key research priorities included the prevalence of wear particles (76%), management guidelines (80%), and preventive measures (76%). Surgeons also emphasized the need for collaborative efforts, with 88% supporting the formation of specialized research groups and 80% advocating for shared registries to track patient outcomes. These findings point toward a clear pathway for future research initiatives, but also underline the need for better resources, funding, and collaboration to overcome current limitations.

Critical implications for clinical practices based on survey outcomes

The survey findings highlight several important implications for clinical practices regarding spinal implant wear particles. The majority of respondents were highly experienced surgeons (44% with over 10 years of practice, 28% with over 20 years), predominantly working in academic or university hospitals (92%). This indicates that the survey captures insights from practitioners who are likely to encounter complex cases, making their input valuable. The high level of expertise suggests that any knowledge gaps or inconsistencies in managing wear particles may also exist among less experienced surgeons, underscoring the need for widespread training. Academic centers, where advanced surgeries are performed, are well-positioned to lead research efforts and implement clinical guidelines for managing wear particles. The variation in awareness (44% fully aware, 44% moderately aware, and 12% unaware) reflects a lack of uniform understanding of spinal implant wear particle issues. Detection methods are also inconsistent, with intraoperative

visualization being most common (84%), followed by imaging (60%) and histological analysis (36%). Limited awareness, particularly among nearly half of the surgeons, may result in underdiagnosis or delayed identification of complications like osteolysis or pseudotumors. The reliance on intraoperative visualization suggests a reactive rather than proactive approach to wear particle detection. Incorporating imaging and histological techniques into routine practice could enhance early detection. Uniform guidelines and standardized training programs are needed to bridge knowledge gaps and promote consistent diagnostic practices. Although 68% of surgeons reported rarely encountering wear particles, complications such as aseptic inflammation (76%), osteolysis (68%), and pseudotumor formation (52%) were well recognized. Management strategies like thorough irrigation (84%) and careful implant placement (76%) were emphasized. The relatively low frequency of reported cases may indicate underreporting or limited detection capabilities rather than an actual rarity of wear particle complications. Preventive strategies in surgical technique reflect good practice, but there is a lack of post-operative management protocols specifically addressing wear particles. A focus on post-operative monitoring and early intervention could improve patient outcomes and reduce the progression of complications. The overwhelming majority of surgeons (88%) were unaware of or uninvolved in research on wear particles, despite 64% expressing interest. Barriers such as limited access to periprosthetic tissue banks, patient confidentiality concerns (72%), funding limitations, and inadequate data collection tools were highlighted. The lack of research involvement highlights a significant gap between clinical practice and academic investigation, limiting evidence-based advancements. Addressing logistical barriers like access to tissue banks and funding allocation is essential to foster active participation in research. Institutions could establish centralized tissue banks, shared registries, and secure data protocols to overcome confidentiality and resource limitations. Respondents identified the impact of wear particles on clinical outcomes (96%), management guidelines (80%), and preventive measures (76%) as critical research priorities. Collaborative initiatives, such as specialized research groups (88%) and shared patient outcome registries (80%), were strongly supported. There is a clear consensus on the need for further research, particularly regarding the clinical consequences of wear particles. This aligns with the broader goal of improving patient outcomes and refining spinal implant design. Collaborative efforts, including multicenter studies and registries, can enhance data collection and provide robust evidence for practice-changing guidelines. Future research should focus on improving wear particle detection, understanding their biological effects, and developing preventive strategies such as wear-resistant materials or coatings. The survey reveals a growing awareness of spinal implant wear particles as a clinical concern, but significant gaps in detection, management, and research persist. Addressing these issues requires standardized training to improve awareness and diagnostic consistency, the development of evidence-based protocols for the detection, prevention, and management of wear particle-related complications, and the establishment of tissue banks, shared registries, and collaborative networks to overcome logistical and funding barriers. By prioritizing these areas, the field of spinal surgery can better address the challenges posed by wear particles, ultimately enhancing patient care and implant longevity.

CONCLUSION AND FUTURE DIRECTIONS

In contrast to other orthopedic joint implants, systematic investigations into wear particles from spinal implants have been limited restricting our understanding of the associated biological impact. Unfortunately, the growing number of young patients with LBP in recent years indicates that patients may host spinal motion preservation instrumentations for a longer time leading to increased incidences of adverse biological consequences. This overlooked clinical problem may cause a substantial health issue in the coming years and requires quick action. Future directions in studying wear particles from spinal implants will likely focus on several key areas to address current gaps in knowledge as identified in the current comprehensive review paper.

Host response to wear particles, novel biomarkers and innovative technologies

Host response to wear particles can be used as a basis for therapeutic and technology advancements. Wear particles from spinal implants trigger a variety of undesirable local and systemic biological side effects such as tissue inflammation, cytotoxicity and hypersensitivity leading to implant loosening and failure.[29,41,76,152] With the increasing incidence of LBP among younger patients in recent years, understanding the interaction between wear debris and the host immune system to propose novel therapies has gained more attention. While significant progress has been made in understanding the mechanisms behind wear particulate interaction with the host immune system, early detection of the immune system response has remained impossible. Therefore, the need for revision surgeries still exists and no effective clinical therapies to minimize the risk of implant failure or prevent detrimental biological side effects are available. Among of biological consequences associated with UHMWPE wear particles, osteolysis is the main cause of implant failure and its early detection can minimize the risk of implant revision. Current imaging techniques (e.g., CT scan, MRI, etc.) are not able to detect tissue inflammation and osteolytic lesions associated with early osteolysis.[247] Imaging technologies that utilize biomarkers (such as positron emission tomography imaging; and PET scan) to target inflammatory cells and are sensitive to macrophage-driven responses should be the focus of future studies.[248] The accuracy of imaging techniques to predict early aseptic loosening is highly related to the sensitivity of the biomarkers that can label biological effectors. However, the efficacy of the biomarkers highly relies on the microcarrier system.[249–252] Being water soluble, small (low molecular weight and size), specific, high binding affinity to protein or peptide receptors, and compatible with different imaging platforms is central to the development of new biomarkers to detect inflammation and subsequent implant aseptic loosening. Additionally, biomarkers should exhibit swift and substantial uptake, selectivity, and the capacity to remain in target tissues allowing proper imaging for a long time. Furthermore, biomarkers should possess minimal radiation, toxicity, and adverse side effects,

and be readily accessible with low capital outlay and long shelf life.

Computer vision for optimum wear debris characterization

Analyzing wear debris from spinal implants is challenging due to their morphological complexity, wide size range [from less than 50 nm to over 100 μm], and non-uniformity in size, shape, and intensity. Of particular importance, the identification of small wear debris is problematic due to contamination from biological components (i.e., protein), limitations in imaging resolution, and manual quantitative analysis rendering the process time-consuming. Utilizing computer vision and machine learning for the structural and morphological analysis of wear debris is the future direction for the characterization of wear particles. This approach offers increased efficiency in terms of resources and time, allows analysis of larger datasets, and minimize human errors.[253]

Therapeutic advancement, wear particles and host response

In addition to the development of technologies for the early detection of osteolysis, molecular markers can be used for future therapeutic advancement. For example, expression of TNF-α is central to regulating wear-induced osteolysis, and therefore, its inhibitors such as small interfering RNA and etanercept, can offer a viable treatment option to minimize the risk of implant failure.[254–256] The efficacy of these potential clinical treatments has been examined in animal models for both UHMWPE and titanium wear particulates but likely unsuccessful in preclinical settings.[257] Interleukin monotherapy (targeting interleukins such as IL-1 which are regulated by TNF-α to activate RANKL) is highly unlikely to provide viable clinical treatment, as TNF-α can independently cause inflammation and aseptic loosening.[258] Instead, IL-4, as a clinically useful cytokine to prevent osteolysis through inhibiting NF-κB and MAPK activation, is a better option; however, its impact on mesenchymal stem cell differentiation to osteoblasts leading to bone resorption should be considered.[259–262] NF-κB binds DNA and alters transcription to promote osteoclastogenesis and osteolysis leading to implant loosening.[154,263] Modulating NF-κB using competitor inhibitors, preventing NF-κB to binding to promoter sites of inflammatory genes (such as decoy oligodeoxynucleotides) can decrease the density of osteoclasts, prevent mesenchymal stem cells differentiation to osteoblasts through degradation of β-catenin and reduce the migration of macrophages to prevent osteolysis.[264–267] Additionally, NF-κB is a major contributor to the expression of NGF that promotes disc vascularization leading to discogenic pain, and therefore, inhibiting NF-κB is a potential therapeutic to alleviate discogenic pain associated with wear debris.[268] Microvasularization induced by wear debris leading to osteolysis was solely observed in the spine, which may offer a pathway for future actions toward developing new therapeutics.[71,123] With recent strategies to target inflammatory pathways (such as cytokines inhibition) that have not been fully effective, it seems that preventing wear-induced osteolysis in the spine can be addressed through therapies targeting neovascularization. This approach, if successful, may contribute to the reduction of pain in degenerative discs limiting the need for spinal implant surgeries.[123]

Clinical studies to improve *in vitro* experiments

While simple techniques including pin-on-plate, pin-on-disc, and sphere-on-disc have been widely used to generate wear particles *in vitro*, they are unable to resemble conditions that are often observed in clinical practice and therefore the generated wear particles are clinically irrelevant.[104] The development of multi-directional wear simulators has been central to the development of advanced methodologies and international standards of wear simulation which can be modified to closely mimic anatomical loading regimes and kinematics. While this procedure can establish uniform approaches to generating reproducible and comparable wear particles across the globe, they impose major drawbacks. One limitation, despite the similarities in wear mechanisms between the *in vitro* and *in vivo* devices, is that the degree of wear is not similar between *in vivo* implants and simulation regardless of implantation time. Therefore, attempts to develop new loading protocols and kinematics in wear simulation are essential.[181,210] Unfortunately, a comprehensive database to identify the size and shape characteristics of wear particles from spinal implants with different material types is currently lacking. Collaboration between research communities and spine retrieval centers to generate relevant resources based on comprehensive analysis of periprosthetic tissues from spinal implants can address this limitation leading to the development of more clinically relevant wear particles *in vitro*. Current *in vivo* animal studies often use commercial particles, and therefore, research to understand the biological side effects of wear debris is often clinically irrelevant.[16,24,85]

Subject-specific clinical studies examining the impact of spinal stability and patient lifestyle on the generation of wear particles remain limited. Spinal implants can profoundly alter the native biomechanics of the spine, influencing long-term stability and functionality. In a healthy spine, stability arises from the intricate interplay between vertebral structures, IVDs, and paraspinal muscles, enabling controlled motion during dynamic activities. However, spinal implants may disrupt this balance, resulting in altered load distribution and abnormal micromovements at implant interfaces. These changes often accelerate wear particle generation, particularly at material contact points like screw-bone or metal-polymer interfaces. Notably, studies on spinal stability using postural data suggest gender-based differences, with spinal stability varying between males and females,[269] potentially influencing the generation of wear particles. Additionally, mechanical stresses during daily activities such as walking, lifting, or bending are magnified in patients with spinal implants, especially when lifestyles involve high-impact movements or repetitive loading, such as those seen in prayer postures.[270] Over time, the accumulation of wear particles can provoke inflammatory responses, bone resorption, and aseptic loosening, all of which contribute to implant failure.

Patient-specific factors, including bone quality, weight, and activity level, also play a critical role in wear particle generation. Addressing these challenges requires more comprehensive clinical studies to explore the effects of lifestyle, daily activities, and spinal stability in patients with spinal implants. These

investigations could close existing knowledge gaps, optimize implant performance, and improve patient outcomes. Importantly, clinical findings could inform the development of new loading protocols for simulators, enabling *in vitro* studies to replicate wear particle generation under specific conditions more effectively.

Innovative *in vitro* models

With biological experiments using animal models being expensive, the use of innovative technologies such as microfluidic disc-on-a-chip models to host cells, molecular effectors, and wear products allows performing a variety of physiologically relevant experiments at low capital outlay.[271] The culture of wear particles with cells in combination with wear particles and molecular effectors using current methods is physiologically irrelevant. 2D or 3D cell culture models are oversimplified and fail to capture the disc's structural organisation, material, and mechanical properties. The use of *in vivo* animal models, while expensive, does not recapitulate the size, mechanics and biology of the human disc. The use of novel physiologically relevant organ models will address the limitations of current *in vitro* and *in vivo* animal studies by providing an accurately controlled 3D microenvironment to host wear particles, different cell types and mediators to generate clinically relevant hypotheses and proof-of-concept in laboratory studies.

Wear particles and spinal cord

The proximity of the spinal cord to the spinal column has raised significant concerns regarding the adverse effects of wear particles from spinal implants. The impact of ions and metal debris on neural structures is still largely unknown. Whether wear particles can disturb the protective barrier of the central nervous system (the meninges) and making the spinal cord and neighboring neural tissues vulnerable to exposure to tribo-corrosive byproducts is yet to be explored. Recent studies have demonstrated that exposure of porcine dural cells and dural organ cultures to cobalt chromium molybdenum (CoCrMo) nanoparticles leads to a notable increase in the levels of the pro-inflammatory chemokine IL-8.[19,25,27] This elevation in IL-8 levels adversely affects the integrity of the endothelial cell layer, compromising its barrier function. Furthermore, the presence of CoCrMo particles induces significant changes in the structural integrity of the dura mater, accompanied by heightened expression of matrix metalloproteinases (MMP-1, 3, 9, 13) and tissue inhibitor of metalloproteinase-1.[24] These observations suggest that tissue remodeling and loosening of collagen fibers are prevalent in the presence of CoCrMo particles. Consequently, these effects may facilitate the penetration of nanoparticles into the dura mater, potentially granting access to the cord tissue.[27] Evidence indicates that particles introduced epidurally can traverse both the dural barrier *in vivo* and the blood-spinal cord barrier, the latter of which has been utilized for drug delivery purposes. Moreover, rapid cerebrospinal fluid (CSF) flow from the subarachnoid space into the spinal cord canal through the perivascular spaces may allow nanoparticle infiltration into these tissues.[272] Further biomechanical studies are needed to elucidate how different types of wear particles interact with spinal tissues under varying mechanical loads. Understanding the biomechanics of wear particle generation and dispersion could inform strategies for mitigating their impact on the spinal cord. Investigating the inflammatory response elicited by wear particles within the spinal column is crucial for understanding their role in spinal cord pathology. Future research may explore the molecular mechanisms underlying inflammation induced by wear particles and identify potential therapeutic targets to modulate this response. Additionally, longitudinal studies are needed to assess the long-term neurological consequences of spinal wear particles, including their potential contribution to neurodegenerative diseases or chronic pain syndromes.

Optimization, spinal implant design, and wear particles

Cervical and lumbar spinal implants differ significantly due to their distinct anatomical, biomechanical, and functional characteristics, which in turn influence wear particle generation. Cervical implants are smaller and more delicate, designed to accommodate the smaller vertebral bodies and discs in the neck. In contrast, lumbar implants are larger and more robust to withstand the greater axial loads of the lower back. Lumbar interbody implants are designed with greater lordotic angles (up to 25°) compared to cervical implants (up to 8°) to account for the anatomical and biomechanical differences between these two regions. The types of implants also vary; cervical implants commonly include anterior cervical discectomy and fusion plates, cages, and motion-preserving artificial discs, emphasizing flexibility and motion preservation. However, lumbar implants, such as pedicle screws, rods, and interbody cages, prioritize stability and load-sharing, with artificial discs being larger and designed for high-load functionality. These structural and functional differences directly impact wear particle generation, as lumbar implants experience higher loads and stresses, leading to increased friction, wear, and debris formation compared to cervical implants. Furthermore, although materials like titanium or PEEK are commonly used in both cervical and lumbar implants, their specific formulations, coatings, and structural designs are tailored to meet the distinct biomechanical demands of each spinal region. Therefore, the type, size, and quantity of wear particles generated, along with their biological activity and associated risks, may vary. These differences underscore the need for implants tailored not only to the unique demands of each spinal region but also to minimize wear particle generation and its associated biological impacts. Further research is required to explore various designs of cervical and lumbar TDRs, aiming to offer a comprehensive evaluation of how design disparities and different bearing materials impact *in vivo* wear and related biological responses.[213] Special attention should be paid to interpreting data and describing the history of TDR failure and associated biological consequences from wear and wear-related incidents. A variety of preclinical and wear simulation studies should be performed comparing the wear characteristics of various bearing surfaces, coatings, and implant geometries to identify optimal configurations that minimize wear and particle release. It is also essential to perform longitudinal studies to evaluate the clinical outcomes associated with wear products in the long term for both spinal regions. Exploring factors such as spinal implant survivorship and wear-related complications can provide valuable insights into the behavior of wear particles

in vivo leading to the development of safer implants and durable designs for spinal surgeries.

Surgeon insights, challenges, and future research directions

In conclusion, the survey results highlight the growing recognition of spinal implant wear particles as a potentially significant source of complications, including inflammation, osteolysis, and pseudotumor formation. While not uniformly encountered by all surgeons, awareness of these issues is increasing, with many acknowledging the need for improved detection, management, and research. The responses also underline a substantial interest in further investigating wear particles, though significant barriers such as limited access to periprosthetic tissue banks, patient confidentiality concerns, and resource constraints remain. To advance this field, a concerted effort is needed to establish standardized guidelines, improve surgeon education on wear particle detection, and enhance collaborative research infrastructure through shared registries and specialized research groups. Addressing these challenges will be crucial to advancing the understanding and management of wear particles, ultimately improving patient outcomes in spinal surgery.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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