Neurological and Cerebrospinal Fluid Accumulation Effects of Noncobalt Metal Ions from Joint Implants: Cognition, Peripheral Neuropathy, and Movement Disorders

Ryan Marra, O.M.S. and Liam Wright, O.M.S.

Duquesne University Nasuti College of Osteopathic Medicine

Conflict of interest statement: The author declares no potential conflicts of interest.

Keywords

joint arthroplasty; metal ions; cerebrospinal fluid; neurotoxicity; implant-related complications

Introduction

Joint arthroplasty remains one of the most impactful interventions in orthopedic surgery, enabling pain relief and restoration of mobility for millions of patients annually. With improvements in implant materials and surgical technique, and with patient demographics expanding to include younger, more active individuals, long-term systemic consequences of implant wear and corrosion are coming under increasing scrutiny. Historically, the primary concern centered on cobalt and chromium ions released from metal-on-metal hip designs and their systemic toxicity. However, emerging evidence indicates that noncobalt metal ions, including titanium (Ti), niobium (Nb), zirconium (Zr), and vanadium (V), may also accumulate in systemic circulation and in the cerebrospinal fluid (CSF), raising the possibility of neurologic sequelae such as cognitive impairment, peripheral neuropathy, and movement disorders.

This review synthesizes current mechanistic and clinical evidence regarding noncobalt metal ion exposure from joint implants and its potential neurologic implications. We begin by delineating the background and rising interest in this field, then describe mechanisms of ion release and neurologic targeting, summarize current evidence, including functional outcomes, discuss clinical implications and application in practice, highlight limitations of existing data, and close with future directions and concluding remarks. The rationale for this comprehensive review lies at the intersection of orthopedic biomaterials science, neurotoxicology, and clinical neurology; as patients live longer with implants, neurologic health must become part of the outcome equation.

Methods

This narrative review was conducted with a targeted search of PubMed/MEDLINE, Scopus, and Google Scholar to identify mechanistic, translational, and clinical studies evaluating metal ion release from orthopedic implants and associated neurologic outcomes. Search terms included combinations of joint arthroplasty, metal ions, titanium, niobium, zirconium, cerebrospinal fluid, neurologic toxicity, cognition, peripheral neuropathy, and movement disorders. The search included English-language publications from January 2000 through October 2025. Reference lists of relevant articles were manually screened to identify additional studies. The final literature search was completed on October 15, 2025.

Implant-Derived Metal Ion Exposure

Metallic joint implants, including total hip, knee, and shoulder arthroplasties, are subject to mechanical wear, micromotion at modular junctions, and electrochemical corrosion in vivo, leading to the release of metal particles and ions.[1,3] Although Ti-based alloys — for example, Ti–6Al–4V and Ti–Nb — and Zr-coated components were long thought to be biologically inert, more recent work has shown that, under certain mechanical or electrochemical conditions, ionic release still occurs.[4,15] The vast majority of early literature focused on cobalt–chromium alloy corrosion and what has been termed "arthroprosthetic cobaltism," associated with systemic cardiovascular, thyroid, auditory, and neurologic consequences. However, the field has begun to shift as newer implant designs emphasize modularity, mixed alloys, and increased lifespans, all factors that may increase cumulative systemic exposure even in "noncobalt" systems.

A landmark cross-sectional study by Rakow et al. demonstrated that patients with large joint replacements exhibited significantly higher whole-blood levels of Ti, Nb, and Zr and measurable elevations of these ions in CSF, as compared with matched controls.[5] This finding directly indicates that implant-derived ions cross neural barriers and accumulate in compartments historically less considered. The rising interest in neurologic endpoints of implant exposure is driven by several converging trends: younger and more active recipients, more modular implant designs with the potential for fretting and corrosion, heightened analytic capability of low-level CSF ion detection, and the recognition that neurologic dysfunction — involving cognition, peripheral nerves, and movement — may manifest insidiously and be misattributed to aging or coexisting disease. Hence, the rationale for this review is to bring together mechanistic, exposure, and outcome evidence regarding noncobalt metal ions and neurologic health in arthroplasty patients, thereby informing orthopedic and neurology practitioners alike.

Mechanisms of Neurologic Exposure and Injury

Ion Release and Accumulation

Release of metal ions and particles from joint implants results from mechanical wear at articulation surfaces, fretting and corrosion at modular junctions — such as head–neck tapers and dual-modular necks — and electrochemical degradation of alloy surfaces in vivo. Szczęsny et al. provided a detailed overview of electrochemical processes in orthopedic metals such as Ti, Cr, Co, Ni, V, and Al, highlighting how metal–protein interactions may form antigenic complexes and drive inflammatory responses rather than simply inert corrosion.[3] Kim et al. reviewed Ti toxicity and showed that Ti particles deposit systemically and can reach remote organs, including neural tissues.[1] Abd-Elaziem et al. further described how Ti–Nb alloys and composites, although engineered for improved biocompatibility, can still undergo ionic release under certain conditions.[4]

Once in the circulation, metal ions — for example, Ti^{2+}, Nb^{5+}, Zr^{4+}, and V^{3+}/V^{5+} — may cross the endothelial blood–brain barrier (BBB) or the blood–CSF barrier, possibly through metal transporters such as DMT1 or through barrier disruption by oxidative stress.[11] In the NeuroWear study, Rakow et al. demonstrated that patients with implants had significantly higher Ti, Nb, and Zr in CSF than controls; for example, median Ti was 0.75 µg per liter versus 0.57 µg per liter in controls, thereby confirming that neural barrier penetration occurs.[5] The study also observed a strong correlation for cobalt ($r=0.82$ between blood and CSF), suggesting a more direct transport mechanism, but weaker correlations for Nb and Zr, suggesting that accumulation may depend on serum elevation first.[5]

Neurologic Targets: Cognition, Peripheral Neuropathy, and Movement Disorders

Within neural tissues, metal ions may exert toxicity through multiple overlapping mechanisms. These include oxidative stress and reactive oxygen species (ROS) generation, leading to mitochondrial dysfunction, glial activation, and neuronal injury.[11] For instance, TiO_2 nanoparticles in vitro induced paracellular leakiness in human BBB models and proinflammatory cytokine up-regulation (interleukin-1 and interleukin-6) in endothelial cells, implicating barrier disruption and neuroinflammation.[11] Venkatraman et al. described a case of spasticity after bilateral hip arthroplasty with elevated cobalt levels; after revision, improvement occurred, thereby demonstrating reversibility of neurologic injury if caught early.[9] Moretti et al. reported severe peripheral neuropathy in the context of failed hip arthroplasty. Although these reports emphasize cobalt and chromium, the biologic mechanism is transferable to other metal ions capable of neural penetration.

Cognitive impairment is another recognized target: Green et al. found a mean Mini–Mental State Examination (MMSE) score of 24.2 and a Beck Depression Inventory (BDI) score of 27.6 among 10 patients with metal-on-metal hip failure and elevated Co and Cr, reflecting memory, attention, and mood impairments.[10] A more recent study by Beba et al. examined correlations between blood metal concentration, including Ti, and cognitive and neuroimaging outcomes among 113 patients with total joint arthroplasty, finding associations between elevated metal levels and neuroimaging markers, though not yet cognitive scores.[17] With respect to movement disorders, Clark et al. demonstrated subtle brain structural alterations involving the basal ganglia and optic pathways in patients 8 years after metal-on-metal hip replacement, raising concern for long-term neuromotor sequelae.[20]

Timing of Exposure and Clinical Effect

Although ion release begins soon after implantation, the latency to neurologic manifestations is heterogeneous and likely influenced by cumulative exposure, patient clearance through renal and hepatic function, age, vascular risk, and implant design. In the NeuroWear cohort, some CSF accumulation of Ti, Nb, and Zr was observed after implants had been in situ for less than 10 years.[5] In the cobalt literature, case reports often emerge 2 to 4 years after implantation when serum cobalt levels exceed 7 to 10 μg per liter.[9] The implication is that neurologic injury is likely a multiphase process: initial systemic exposure, accumulation, barrier penetration, neuronal injury, and clinical manifestation. Thus, long-term surveillance is essential, especially in younger, more active recipients.

Current Evidence

Randomized Trial Findings

To date, no randomized, controlled trials have been conducted with neurologic endpoints specifically in arthroplasty patients stratified according to noncobalt metal ion exposure. The lack of randomized, controlled trials with cognition, neuropathy, or movement disorder as primary outcomes remains a critical gap in the literature.

Cohort and Registry Data

The NeuroWear study by Rakow et al. stands as the first large-scale, cross-sectional human study measuring a broad panel of arthroplasty-relevant metals in blood and CSF, showing elevated Ti, Nb, and Zr in implant patients as compared with controls.[5] Among registry and cohort analyses, Tamagawa et al. studied 59 patients with CoCr rods and 29 with Ti alloy rods in scoliosis surgery and

found mild elevation of Ti levels versus controls, though no clinical neurologic correlation was established.[16] Crutsen et al., in a systematic review of 62 cases of prosthetic hip–associated cobalt toxicity (PHACT), reported cognitive or memory dysfunction in 25.8% and paresthesia in 21%.[6] Although these data are cobalt-centric, they highlight the broader paradigm of implant-derived neurologic risks. Other mechanistic reviews include Kim et al. cataloguing Ti toxicity, Shelly et al. showing Ti nanoparticle neurotoxicity, and Szczęsny et al. detailing metal–protein interactions triggering inflammation.[1,3,11]

Evidence and Functional and Patient-Reported Outcomes

Functional neurologic outcomes such as cognitive testing, nerve conduction studies, and movement disorder scales remain poorly represented in the arthroplasty literature. Among the few studies, Green et al. documented neuropsychiatric deficits in patients with metal-on-metal implants.[10] Beba et al. found associations between blood Ti, Co, and Cr levels and neuroimaging markers but not yet cognitive performance.[17] Clark et al. found subtle structural brain changes in patients with metal-on-metal implants.[20] The critical deficiency remains the absence of large longitudinal cohorts linking noncobalt ion levels, including Ti, Nb, and Zr, to validated neurologic endpoints with patient-reported outcomes and functional testing.

Clinical Applications

Patient-Selection Considerations

From a combined orthopedic–neurology viewpoint, certain patient profiles warrant particular attention. Patients with preexisting neurologic conditions, such as mild cognitive impairment, peripheral neuropathy, or a movement disorder; renal or hepatic impairment, which may reduce clearance of metal ions; younger age at implantation, with long-term exposure potential; and high activity levels may represent higher-risk groups. In these patients, implant-design decisions — such as favoring ceramic heads, monoblock stems, fewer modular junctions, or nonmixed alloy tapers — may mitigate long-term exposure risk. Preoperative baseline neurologic screening, including cognitive assessment, peripheral nerve examination, and movement screening, may provide a reference for later surveillance.

Integration into Practice, Technical Pearls, and Safety Profile

Preoperative patient counseling should routinely include discussion of systemic risks of metal-ion release, including potential neurologic sequelae, albeit rare. Intraoperative technique remains critical: ensuring optimal component alignment, minimizing modular interfaces, avoiding mixed-alloy combinations, and selecting lower-wear bearing pairings can reduce ion release. Postoperatively, high-risk patients may benefit from periodic whole-blood metal ion measurement, including Ti, Nb, and Zr if available, and baseline and serial neurologic screening — for example, MoCA, neuropathy symptom inventory, and tremor or ataxia assessment. However, specific thresholds and monitoring intervals for noncobalt ions, such as titanium, niobium, and zirconium, are not currently standardized, and such surveillance should be considered precautionary pending longitudinal outcome data linking exposure levels to neurologic endpoints. In symptomatic patients with new-onset neuropathy, tremor, or cognitive decline and elevated ion levels, referral to neurology and consideration of CSF sampling may be appropriate. Although the overall safety profile of modern implants remains favorable, recognition that neurologic injury may present years after implantation must inform long-term monitoring strategies.

Limitations of Current Data

Despite growing interest, the evidence base has significant limitations. First, the number of neurologic-endpoint studies is very small; most data derive from case reports or small series.[9] Second, heterogeneity in implant types — hip, knee, and shoulder — materials, including Ti, Nb, Zr, Co, and Cr, measurement protocols, including which ion, which matrix, and timing, and neurologic outcome definitions, including cognition, neuropathy, and movement, make comparison and meta-analysis difficult. Third, follow-up durations are generally short, often under 10 years, whereas neurologic injury may manifest only decades later.[20] Fourth, coexisting conditions, including aging, vascular disease, diabetes, and neurodegenerative disorders, complicate attribution of neurologic findings to implant-derived metal exposure. Fifth, a predominance of cobalt–chromium-centric literature limits direct extrapolation to newer Ti, Nb, and Zr exposures; true threshold "safe" levels are unknown. Lastly, there are no randomized, controlled trials or large prospective neurologic outcome cohorts, and no consensus on monitoring or revision thresholds. In addition, no consensus exists regarding safe exposure thresholds or optimal surveillance intervals for noncobalt metal ions, limiting translation into standardized clinical guidelines.

Future Directions

To advance the field, several key initiatives are warranted. Prospective longitudinal cohort studies of arthroplasty patients stratified according to implant material and measured metal-ion exposures (Ti, Nb, Zr, and V), with repeat neurologic assessments, including cognitive tests, nerve conduction studies, and movement disorder scales, are essential to define dose–response relationships and thresholds. The development of standardized neurologic outcome batteries in arthroplasty populations — for example, MoCA, nerve conduction, and tremor or ataxia scales — would facilitate comparability across studies. Translational studies linking human exposure, including ion levels in blood and CSF, to biomarkers of neurologic injury, such as neurofilament light chain, glial fibrillary acidic protein, and MRI white-matter changes, are needed to move from exposure to injury to clinical effect. Materials-science research should continue progressing toward implants with ultralow ion release — for example, TiSiN or ZrN coatings — and long-term neurologic outcome data in such cohorts are needed. Clinical guidelines and surveillance protocols developed jointly by orthopedic, neurology, and toxicology societies should outline patient-risk stratification, monitoring intervals, revision considerations, and neurologic referral criteria. Finally, given the very large number of joint arthroplasties performed globally, modeling studies estimating the public health burden of subtle neurologic decline linked to long-term metal ion exposure will inform cost–benefit analyses of surveillance and prevention strategies.

Conclusion

Joint arthroplasty continues to be transformative in the management of end-stage joint disease. However, the field must evolve to consider not only mechanical and implant-survival outcomes but systemic neurologic health. There is strong mechanistic plausibility and emerging exposure data indicating that metal ions from implants, including noncobalt species such as titanium, niobium, and zirconium, can cross neural barriers and accumulate in CSF.[5] Case reports and cohort data document cognitive impairment, peripheral neuropathy, and movement disorders in the context of metal-ion exposure.[9,10,17] In current practice, orthopedic surgeons and neurologists should be cognizant of these possibilities, particularly for younger patients, those with long-life implants, modular designs, or preexisting neurologic

vulnerability. Key unanswered questions remain: What is the safe threshold for noncobalt ion exposure? What is the latency and cumulative dose–effect curve? Can early monitoring and revision prevent neurologic injury? How will next-generation implant materials alter neurologic risk?

By bridging biomaterials science, orthopedic surgery, and neurology, the next frontier of arthroplasty may lie as much in neurodefense as in joint restoration. With the adoption of implants with minimal ion release, systematic neurologic surveillance of high-risk patients, and rigorous epidemiologic and mechanistic research, joint replacement can continue to restore mobility while also safeguarding neurologic health over the patient's lifetime.

References

1. Kim KT, et al. General review of titanium toxicity. Implant Dent 2019;28:505-536.
2. Sansone V, et al. The effects on bone cells of metal ions released from orthopaedic implants in vivo and in vitro. Int J Nanomedicine 2013;8:2733-2744.
3. Szczęsny G, et al. Toxicity, irritation, and allergy of metal implants: historical overview and future perspectives. Coatings (Basel) 2025;15:361.
4. Abd-Elaziem W, et al. Titanium-based alloys and composites for orthopedic implants. Mater Sci Eng C 2024;154:114294.
5. Rakow A, et al. Metal concentrations in blood and cerebrospinal fluid of patients with arthroplasty implants. JAMA Netw Open 2025;8.
6. Crutsen JRW, et al. Prosthetic hip-associated cobalt toxicity: a systematic review of the literature. EFORT Open Rev 2022;7:190-200.
7. Yan BW, et al. Neurologic dysfunction associated with mechanically assisted crevice corrosion after total hip arthroplasty. Arthroplasty Today 2021;11:217-221.
8. Rattay TW, et al. Chromium and cobalt intoxication mimicking mitochondriopathy. Neurol Res Pract 2021;3:25.
9. Venkatraman V, et al. Cobalt-induced toxicity and spasticity secondary to hip arthroplasty. Neurol Res Pract 2020;2:21.
10. Green B, Griffiths E, Almond S. Neuropsychiatric symptoms following metal-on-metal implant failure with cobalt and chromium toxicity. BMC Psychiatry 2017;17:33.
11. Shelly S, et al. Potential neurotoxicity of titanium implants: prospective in vivo and in vitro study. Biomaterials 2021;276:121039.
12. Zhong Q, et al. Prosthetic metals: release, metabolism and toxicity. Int J Nanomedicine 2024;19:345-362.
13. Catalani S, et al. Vanadium release in whole blood, serum and urine of patients implanted with a titanium alloy hip prosthesis. Clin Toxicol (Phila) 2013;51:105-110.
14. Posada OM, Tate RJ, Meek RMD, Grant MH. In-vitro analyses of the toxicity, immunological and gene expression effects of cobalt-chromium alloy wear debris and Co ions derived from metal-on-metal hip implants. Lubricants 2015;3:539-568.
15. Jure S, et al. Mid-term results of a cemented titanium–niobium nitride multilayered knee arthroplasty. Knee 2025;32:65-75.
16. Tamagawa S, Nojiri H, Sato T, et al. Comparison of blood metal ion levels in scoliosis patients following instrumented spinal fusion with cobalt-chromium and titanium alloy rods. Sci Rep 2025;15:16549.
17. Beba A, Peterson SM, Brennan PC, Vassilaki M. Correlation of blood metal concentrations with cognitive scores and neuroimaging findings in patients with total joint arthroplasty. J Alzheimers Dis 2023;90:1235-1246.
18. Underwood D. Neurological abnormalities following a metal-on-metal hip implant: literature review. Assumption College Honors Theses 2023;Paper 1130.

19. Tap MD, Bicleşanu FC, Honțaru O-S, Radu A-C. Patient-centricity — an empirical research on titanium dental implants and their adverse effects on health condition. Healthcare 2024;12:2207.
20. Clark MJ, et al. Brain structure and function in patients after metal-on-metal hip resurfacing. Eur Radiol 2014;24:618-626.
21. Wawrzynski J, et al. Hypersensitivity to orthopedic implants: a review of the literature. Allergy Rhinol 2017;8:8-17.
22. Kurtz MA, et al. Metal release in total knee arthroplasty: a review of wear, corrosion and ion dynamics. J Arthroplasty 2025;40:290-298.
23. Swiatkowska-Blank I. Toxicity of metal debris from hip implants: PhD thesis, University College London. 2019.