Nanomed J. 12(3):344-353, Summer 2025

REVIEW PAPER

The role of nano-particles in nerve tissue engineering: opportunities and challenges

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ABSTRACT

Neurodegeneration, scar tissue formation, and communication disruption between neurons and cells are the primary concerns associated with nerve damage. Despite advancements, regenerating nerve tissue at the injury site remains a significant hurdle in medical treatment. Nerve tissue engineering presents a promising avenue in regenerative medicine for addressing these challenges in repairing damaged or diseased nervous systems. However, achieving an optimal neural guidance system is still a considerable endeavor. One approach that shows potential in aiding nerve regeneration involves the utilization of nanoparticles. These minute entities, situated at the forefront of nanotechnology, possess unique size-dependent characteristics that offer promise in surmounting numerous obstacles encountered in tissue engineering. They facilitate cell adhesion, proliferation, and differentiation, while also supporting neurite growth—a vital aspect of nerve regeneration. Additionally, nanoparticles serve diverse roles, including nerve guidance, pollution mitigation, transportation of growth factors, and reinforcement of scaffold structures, among others. Various studies have explored the application of nanoparticles. This review focuses on commonly utilized types of nanoparticles and analyzes their advantages and challenges in nerve regeneration.

Keywords: *Nanoparticles, Nerve regeneration, Tissue engineering, Nanotechnology*

How to cite this article
Ebrahimi-kia Y, Ofoghi H, Davoudi P. The Role of Nanoparticles in Nerve Tissue Engineering: Opportunities and Challenges. Nanomed J. 2025; 12(3):344-353. DOI: 10.22038/nmj.2025.78808.1932

INTRODUCTION

Peripheral nerve damage can occur due to various reasons, such as traumatic injury or complications during orthopedic surgeries. In case of severe injuries where the nerve is completely severed, nerve function is lost. However, the regenerative processes in the proximal segments of the nerve may eventually lead to restoring function over time. The peripheral nervous system (PNS) has natural regenerative capabilities, where growth cones from regenerating axons can bridge the gaps formed by injury. But in cases where extensive injuries cannot heal naturally, intervention through neural tissue engineering methods may be necessary.

There are several conventional techniques for repairing nerve injuries. One approach is coaptation, which involves suturing the lesions in the severed nerves to promote healing. Another approach is transplantation or grafting, where tissue can be sourced from either allografts (donor tissue from the same species) or xenografts (donor tissue from a different species). Allografts can also include autologous tissue harvested from another part of the patient's body. However, these conventional methods have their limitations [1]. Autografts, which use the patient's nerve tissue, are considered the gold standard in nerve repair. However, they do have certain limitations, such as the formation of neuromas and constraints related to the availability of donor tissue. To overcome these challenges, neural tissue engineering focuses on cell therapy, particularly using Schwann cells, and explores the regenerative potential of stem cells for nerve restoration. Additionally, researchers are actively working on developing suitable scaffolds to create nerve guidance conduits (NGCs) using both synthetic and biological materials. These NGCs aim to provide structural

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Note. This manuscript was submitted on March 16, 2024; approved on February 03, 2025.

support for effective nerve repair processes [2].

Since the challenges of developing innovative approaches for peripheral nerve regeneration (PNR) are formidable, there is increasing interest in exploring nanotechnology-based therapies. Nanoparticles, or nanomaterials, are approximately one-millionth of a millimeter in size, making them roughly 100,000 times smaller than the diameter of a human hair. Nanoparticles are usually not visible to the naked eye or even under conventional laboratory microscopes. These nanoparticles can come from natural or synthetic sources and can be synthesized in various sizes, ranging from 1.0 to 500 nanometers, and in different shapes such as cones, cubes, rods, tubes, and shells [3]. Incorporating nanoparticles into scaffolds and using them the sustained and controlled delivery of bioactive molecules at the injury site shows promise for reconstructing peripheral nerves. Nanoparticles offer advantages such as enhanced specificity and accelerated regeneration rates, attributed to their surface roughness resembling that of the extracellular matrix (ECM). In the field of bioengineering and biotechnology of peripheral nerves, many researchers have recently investigated the regenerative potential of nanoparticles or nanostructured biomaterials. Emerging evidence suggests that nanomaterials-based technologies have significant potential in remodeling the biomimetic environment, thereby facilitating the repair of peripheral nerves [4, 5]. Nanoparticles can act as antioxidants and anti-inflammatory agents, reducing oxidative stress and inflammation that hinder nerve repair. They can also guide axonal growth and support myelination, enhancing the regenerative process. With the potential for personalized medicine, nanoparticles can be tailored to individual patients' needs, improving the efficacy and safety of treatments [6]. Finding the most suitable type of nanoparticle for nerve tissue engineering is crucial for several reasons. Firstly, selecting the appropriate nanoparticle significantly impacts the scaffold's ability to support neurocyte outgrowth effectively. For instance, graphene has been identified as a promising material due to its biocompatibility, which is essential for promoting cell adhesion and growth [7]. Secondly, nanoparticles play a vital role in enhancing nerve regeneration processes by improving conductivity. Gold nanoparticles, for example, have shown promise in promoting neural differentiation and regeneration, highlighting their potential in improving nerve conductivity [8]. Additionally, creating anisotropic structures resembling the native extracellular matrix is crucial for guiding axon growth and reconnection. Incorporating nanoparticles like zero-valent iron within nanofiber scaffolds has demonstrated success in nerve tissue engineering by providing structures that mimic the native extracellular matrix [7].

By integrating various nanoparticles into scaffolds, researchers aim to address these challenges and advance the field of nerve tissue engineering towards more effective regeneration strategies.

Effects of Nanoparticles on Neural Cells

Nanoparticles have shown great potential in promoting neuronal cell proliferation, axonal growth, adhesion, and neuroprotection. They can easily penetrate cell membranes, modifying specific cellular signaling pathways that are crucial for differentiation. Different types of nanomaterials can affect surface ligands and various cell types, either inhibiting or activating cellular pathways [9]. Studies have demonstrated that nanoparticles can induce the differentiation of stem cells into neuronal cells. Additionally, nanoparticles can mechanically activate signaling pathways in stem cells, promoting the differentiation process. Moreover, the morphology of nanoparticles can influence their ability to enter cells, thereby impacting the differentiation of stem cells [10]. Nanospheres have a higher likelihood of entering cells compared to nanorods of the same size [11]. Similarly, the size of nanoparticles is important in eliciting a biological response. Studies have shown that the optimal size for inducing stem cell differentiation is between 20 nm and 70 nm due to size-dependent cellular uptake rates [10, 12]. 50-nm nanoparticles have been found to have increased cellular internalization, while smaller nanoparticles have shown greater cytotoxicity and larger nanoparticles have been less efficient [11, 13]. In a range of 80-90 nm, nanoparticles induced the differentiation of canine mesenchymal stem cells into neurons [14]. Calcium phosphate-lipid nanoparticles with a size of 30 nm also promoted neuronal differentiation [15]. Another study reported that prodrug nanoparticles with a size of 50 nm enhance neuronal survival [16]. This suggests that the type of nanoparticles plays a significant role in their effectiveness. Additionally, nanoparticle treatment not only induces neuronal differentiation but also improves functional or behavioral recovery in animal models [3]. However, despite their therapeutic potential, nanoparticles

raise safety concerns, as some have been reported to have inhibitory effects on neuronal cells, leading to adverse effects on neuronal differentiation [3, 17].

Effects of Nanoparticles on Tissue Engineering

In contemporary times, nanoparticles are increasingly utilized for repairing peripheral nerve injuries owing to their small size, surface customization, distinctive physical attributes, and chemical resilience. Various nanoparticles exhibit differences in electric charge, optical properties, and magnetic characteristics, contributing to their diverse functionalities in neural repair applications [18]. Nanoparticles play a crucial role in enhancing the mechanical properties and degradation rate of nerve scaffolds. Additionally, they mimic the nanostructure and microstructure of the ECM, facilitating cellular attachment and nutrient transport. The incorporation of nanoparticles into scaffolds influences their biological behavior, resembling autograft nerves due to their similarity to ECM on a nanoscale level [19, 20]. Table 1 represents a few examples of the significant

Table 1. Effects of nanoparticles in PNI Studies

Type of nanoparticle	Scaffold	Size of nanoparticles	Effects	References
Gold nanoparticles (AuNPs)	Polycaprolactone (PCL)/chitosan	mean diameter: 175 nm ± 69 nm	The inclusion of AuNPs notably boosted the conductivity of scaffolds. This enhancement promoted cell attachment and proliferation, particularly observed in Schwann cells.	[21]
Cerium oxide nanoparticles (CNPs)	Silk-fibroin (SF)/polycaprolactone (PCL)	N/A	As the concentration of CNPs increased, the optical density indicating viable cells also increased. Moreover, over time, the cellular growth rates on the surface of the fiber samples showed an upward trend.	[22]
zero-valent iron (Fe) nanoparticles	Electrospun poly(ε-caprolactone)	60-80 nm	Fe nanoparticles were found to stimulate astrocyte proliferation. Confocal imaging showed that conductive surfaces based on PCL may enhance adhesion and support neurite growth.	[7]
AuNPs coated with a thin layer of nano-sized reduced graphene oxide (RGO)	Polycaprolactone (PCL) based electrospun nanofiber scaffold	35 nm	The incorporation of RGO-AuNPs on PCL resulted in an approximately twofold increase in neurite length growth. Moreover, nanoparticles exhibited a beneficial impact on neuronal cell differentiation without inducing any toxic effects on the cells.	[23]
AuNPs	Polyvinylidene fluoride (PVDF)	10 to 25 nm	The heightened piezoelectricity and electroactivity of the nanofibers, attributed to the presence of Au nanoparticles, influenced cell signaling, ultimately resulting in enhanced cell adhesion and morphology.	[24]
Silver nanoparticles (AgNPs)	collagen type I and gelatin	N/A	The scaffold had a highly biomimetic structure with axially arrayed microtubules, which promoted directional growth in axons. Additionally, the presence of nanosilver particles in the scaffold imparted antibacterial properties, effectively inhibiting bacteria both in vitro and in vivo.	[25]
Zinc oxide (ZnO) and polyaniline/graphene (PAG)	Co-electrospun mats of polycaprolactone/polyvinylidene filled with gelatin-chitosan hydrogels	254 ± 36 nm for the PAG nanoparticles and 252 ± 39 nm for the ZnO nanoparticles	PAG nanoparticles enhance scaffold conductivity and mechanical properties, while ZnO nanoparticles prevent inflammation and contribute to piezoelectric properties. Both promote PC12 cell growth.	[26]

effects caused by different nanoparticles on PNS for the recovery of Peripheral Nerve Injury (PNI).

Gold Nanoparticles (AuNPs)

AuNPs are highly promising in the field of nanomedicine, with applications in drug delivery, photothermal therapy, diagnostics, and imaging. Their small size, compatibility with biological compounds, ease of synthesis, large surface area, and customizable functionalization make them ideal for various nanomedicine uses. Moreover, their unique physicochemical properties set them apart from traditional nanoparticles such as liposomes, polymeric NPs, and protein-based NPs [27].

Previous research has demonstrated that cells cultured on pristine scaffolds exhibited limited extension of neurites when exposed to nerve growth factor (NGF). In contrast, cells on AuNP scaffolds exhibited enhanced neurite outgrowth and formed preliminary neuronal networks. The presence of AuNPs improved the differentiation and maturation of PC12 cells, encouraging the development of mature neuronal characteristics and facilitating the formation of neuronal networks [28]. Additionally, AuNPs were found to enhance the behavior of Schwann cells on the scaffold [29]. It has been reported that AuNPs promote neurite outgrowth and elongation, especially when combined with NGF and electrical stimulation [30]. Jahromi et al. discussed the utilization of techniques for the controlled release of nanoparticles, indicating that in vivo testing showed a significant increase in axonal growth at the transplantation site [31].

Cytotoxicity mediated by AuNPs typically follows a dose-dependent pattern and is linked to membrane damage, leakage of cell contents, and the generation of reactive oxygen species (ROS) [32, 33]. Recent studies indicate that although standalone AuNPs may elevate ROS production, their incorporation into scaffolds has been shown to mitigate ROS levels [34]. Future directions in this field entail conducting thorough, long-term investigations that integrate in vivo and in vitro assays to establish standardized protocols. This includes defining optimal cell types, dosage of AuNPs, and relevant cytotoxicity assays to ensure safer and more effective applications [27].

Silver Nanoparticles (AgNPs)

Nanosilver has been proven to have significant medicinal value due to its antibacterial [35], antifungal [36], antiviral [37], antiprotozoal [38], and anticancer [39] characteristics. The creation of antimicrobial structures is crucial for medical applications as they can effectively prevent biofilm formation, reduce hospital-acquired infections, and decrease related fatalities. The dosage of AgNPs is a critical factor as it can be harmful to cells. Koudehi et al. determined that a concentration of 0.0007 µL of silver was an appropriate sample for subsequent experiments in neural scaffolds, as higher silver content may lead to cytotoxic effects [40]. Another study showed that RGO_Ag acts as an effective filler to enhance modulus, provide electrical conductivity, and exhibit outstanding antibacterial properties without causing cytotoxicity or compromising cellular function [41]. There is controversy surrounding the ability of AgNPs to promote neurogenesis, and concerns about their toxicity and safety. AgNPs have been found to serve as favorable anchoring sites for neuroblastoma cells, promoting neurite outgrowth. The production of ROS by nanoparticles or Ag+ ions plays a crucial role in cell proliferation and differentiation [42].

Exposing embryonic stem cell-derived neurons and astrocyte networks to AgNPs has been shown to decrease neurite outgrowth and induce neurotoxicity through the activation of AKT/GSK-3/caspase-3 signaling pathways [43]. The authors observed that coating the substrate with AgNPs provides anchoring sites for neurite adhesion, leading to the induction of tensile forces along the neurites upon attachment to the AgNPs. This promotes their stabilization and the formation of highly straightened neurites [19].

Zinc Oxide Nanoparticles (ZnO NPs)

The rapid advancement of nanotechnology has led to the production of various metal oxide nanoparticles, including ZnO NPs [44], which are used in the biomedical, drug, and construction industries. ZnO NPs are engineered white materials that exhibit thermal resistance and find application in diverse fields such as cosmetics, electronic devices, food additives, cement, rubber, plastics, and biosensors [45].

The impact of ZnO on nerve cells and neurite growth seems to produce conflicting results across different studies. Liu et al. observed that nano-ZnO could disrupt neuronal structure by affecting cytoskeleton proteins (tubulin-α, tubulin-β, and NF-H), thereby interrupting connections between nerve cells and potentially impairing nervous system function. On the other hand, nano-ZnO was found to induce disorders

in neuronal repair and regeneration by affecting the growth-related protein GAP-43, and it also showed delayed neurotoxicity by interfering with the calcium/calcium-regulated kinase (CAMK2A/CAMK2B protein) signaling pathway [46]. Even at noncytotoxic concentrations, ZnO nanoparticles have been found to cause neurite shortening and degeneration in differentiated PC12 cells [45, 47]. The piezoelectric properties of ZnO hold significant potential in biomedical applications, especially in the treatment of peripheral nerve injuries. Recent empirical studies have demonstrated the effectiveness of ZnO-incorporated scaffolds in nerve repair processes. These scaffolds have been shown to promote the growth of Schwann cells (SCs), which play a crucial role in peripheral nerve regeneration. Furthermore, the presence of ZnO has been associated with the enhancement of SC-mediated axonal extension, suggesting a synergistic interplay between the piezoelectric properties of ZnO and the cellular mechanisms involved in nerve repair [48, 49]. An animal study has shown the reconstruction of a 10 mm sciatic nerve defect using a chitosan zinc oxide nanocomposite conduit (CZON) [50]. This variation in results may be due to differences in nanoparticle concentration, size, the creation of different physical and piezoelectric properties on the scaffolds, and the duration of the experiment.

Iron Oxide Nanoparticles (Fe3O4 NPs)

Iron oxide nanoparticles in the Fe3O4 form have received approval for clinical applications due to their exceptional biocompatibility [51]. There is a need for novel in vitro tools to assess the neurotoxicity caused by nanoparticle translocation to the brain and their impact on the central nervous system (CNS). De Simone et al. developed CNS spheroids using human astrocyte-like and neuronal-like cells to evaluate the neurotoxic effects of Fe3O4NPs. Short-term exposure resulted in cytotoxicity at 10 µg/mL in astrocytes and 25 µg/mL in neurons. Long-term exposure revealed concentration- and time-dependent cell mortality, with neurons being more susceptible compared to astrocytes [52]. Superparamagnetic Fe3O4 NPs, which are widely used in magnetic resonance imaging, have also garnered approval for clinical applications due to their exceptional biocompatibility. They are commonly used in various applications, including magnetic field guidance to enhance the therapeutic effect of Fe3O4@PDA-labeled MSCs on the spinal cord and chronic compression sciatic nerve injury. This approach has shown to decrease spinal nerve demyelination and c-Fos expression (a pain molecule), as well as inhibit microglia and astrocyte activation [51]. In another study, a magnetic NGC utilizing magnetite nanoparticles modified by citric acid (Fe3O4–CA) was used to bridge damaged sciatic nerves in rats. These conduits demonstrated the absence of acute inflammation and exhibited a barrier function that facilitated nerve regeneration [53]. These nanoparticles are employed in medicinal treatments to enhance the regeneration of peripheral nerves, such as serving as carriers for omega-3 to promote the regeneration of the sciatic nerve [54].

Applications of Nanoparticles in Nerve Tissue Engineering

Various nanoparticles are used in nerve tissue engineering for different applications. Table 2 lists some of the applications of nanoparticles in neural studies. One application of nanoparticles in neurological studies is their use as a tool for diagnosis and imaging. Polyethyleneimine (PEI) copolymers conjugated to poly (glycidyl methacrylate) have previously been investigated as a magnetic resonance contrast agent in MRI. However, when these superparamagnetic Fe3O4 nanoparticles were administered through intramedullary or intravitreal routes, it was observed that the majority of the nanoparticles remained near the injection site. Only a small quantity of the nanoparticles was able to penetrate the axons and be transported to neuronal somata [55]. To address the issue of blood-brain barrier (BBB) impermeability, PS 80-poly(methacrylic)acid nanoparticles have been used to deliver imaging agents like gadolinium. MRI studies have shown that these Gd-nanoparticles can effectively cross the BBB and enter the brain in healthy mice. Additionally, it is hypothesized that PS 80 may play a crucial role in facilitating the transport of nanoparticles across the BBB, enabling their entry into the central nervous system (CNS) [56]. Nanoparticles can also affect the physical properties of the scaffold, such as conductivity, biocompatibility, and strength Research has indicated that nanoparticles have the potential to deliver and extend the activity of various growth factors, such as nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), and basic fibroblast growth factor (FGF-2). Furthermore, magnetic nanoparticles offer the added benefit of being guided by magnetic fields at a distance. This capability could prove to be exceptionally advantageous, as in the natural physiological process of nerve regeneration, cells migrate,

Table 2. Different applications of nanoparticles

Type of nanoparticle	Application	Results	References
iron oxide (SPIO)-gold (Au)	Delivery of nerve growth factor (NGF)	The promotion of neuronal growth and orientation was observed. The elongation of neurite length increased by 63%.	[59]
chitosan-graft-polyethyleneimine (RCP)	Gene vectors for c-Jun	The use of a scaffold with c-Jun plasmids facilitated nerve repair by maintaining the sustained release of essential growth factors such as NGF, BDNF, and VEGF from Schwann cells. This approach resulted in enhanced nerve regeneration, myelination, and microvascular growth.	[60]
Polyethyleneimine (PEI)	Delivery of pDNA encoding for NGF, glial derived neurotrophic factor (GDNF) or the transcription factor c-Jun.	All three genes exhibited therapeutic potential by enhancing neurotrophic cytokine production and promoting neurite outgrowth. However, the delivery of the gene encoding for c-Jun demonstrated the highest capacity to enhance regenerative cellular processes in vitro.	[61]
PAMAM dendrimer	Delivery of corticosteroid, methylprednisolone (MP)	MP diffused broadly throughout the healthy rat brain following administration into the cerebrospinal fluid (CSF). Incorporating MP into a dendrimer formulation was responsible for modulating the metabolic activity of microglia.	[62]
iron oxide nanoparticles	CNS tumor imaging	The results demonstrate the safety and efficacy of iron oxide-based MRI contrast agents in brain tumor models.	[63]
Poly (ethylene glycol)- poly(3-caprolactone) (MPEG-PCL)	Drug delivery of XMU-MP-1 (4-((5,10-dimethyl-6-oxo-6,10-dihydro-5H-pyrimido[5,4-b]thieno[3,2-e][1,4]diazepin-2-yl)amino) benzenesulfonamide)	The nerve conduit efficiently induced the recovery of sciatic injuries in morphology, histopathology, and functions in vivo.	[64]
ZnO	Create a biomimetic electrically conductive microenvironment	The ZnO/PCL scaffold was suitable for Schwann cell proliferation and attachment. Additionally, the scaffold increased angiogenesis due to low ROS production.	[49]

proliferate, and infiltrate from both ends of the damaged nerve towards the center [57].

Nanoparticles can be combined with other treatments, such as stem cell therapy, to potentially enhance the synergistic effects and improve the outcomes of nerve regeneration [58].

Challenges and Limitations in Current Researches

Nanoparticles have shown great potential in various tissue engineering applications. They can enhance biological, mechanical, and electrical properties, provide antimicrobial effects, facilitate gene delivery, and aid in the construction of engineered tissues. However, there are several challenges that need to be addressed for their widespread clinical use.

Firstly, there is an urgent need for improved tools and methods to assess the toxicity, carcinogenicity, and teratogenicity of nanoparticles. Additionally, adverse effects are highly dependent on the dosage and exposure duration. Although nanoparticles are typically used below harmful concentrations, their accumulation in the body over time may lead to toxicity, cancer induction, or reproductive harm. Despite the availability of numerous nanoparticle-containing products,

there are still gaps in understanding the specific hazards associated with nanomaterials, and there are no internationally recognized standards for nano-specific risk assessments. Manufacturers are responsible for assessing the safety of their nanoparticle-based products, but the regulatory tools available are not tailored to nanomaterials. Therefore, precautionary measures are necessary in nanoparticle applications where chronic bioaccumulation is possible [65, 66].

In the context of nerve tissue engineering, addressing nanoparticle challenges is crucial for promoting nerve regeneration and functional recovery in individuals with neurological injuries or disorders. These challenges include overcoming the blood-brain barrier for effective nanoparticle delivery, promoting neural regeneration using nanoparticle-based scaffolds and bioactive molecules, ensuring biocompatibility to prevent adverse reactions, achieving targeted delivery to specific neural cells or regions, facilitating integration with host tissue, maintaining long-term stability within the neural environment, enhancing functional recovery through controlled release of growth factors, and ensuring safety by minimizing cytotoxic effects and inflammatory responses. By addressing these challenges, researchers can pave the way for the successful application of nanoparticles in nerve tissue engineering, ultimately improving outcomes for patients.

CONCLUSION

The use of nanoparticles in peripheral nerve repair and tissue engineering shows great promise for improving therapeutic outcomes. Nanoparticles possess versatile properties that enhance biological, mechanical, and electrical aspects essential for nerve regeneration. They facilitate cellular processes such as proliferation, differentiation, and adhesion, while also providing antimicrobial effects and assisting in gene delivery. The best nanoparticles for nerve tissue engineering depend on the specific application and desired outcomes. For instance, if the goal is to deliver growth factors to promote neural regeneration, biodegradable polymeric nanoparticles might be the best choice [67]. If the objective is to guide neurite outgrowth, carbon nanotubes or magnetic nanoparticles could be more suitable [68, 69]. However, despite their potential benefits, nanoparticle-based therapies face challenges regarding toxicity, carcinogenicity, and regulatory standards. Further research is necessary to develop comprehensive assessment tools and standardized protocols to ensure the safe and effective clinical translation of nanoparticle-based interventions. By addressing these challenges, nanoparticles have the potential to revolutionize the field of peripheral nerve repair and tissue engineering, opening up new avenues for enhancing patient outcomes and quality of life. Specifically, AuNPs and Fe_3O_4 NPs are likely the most promising options for nerve tissue engineering, with AuNPs generally being more favored due to their low toxicity and excellent functionalization capabilities.

ACKNOWLEDGEMENTS

We are grateful to all those who helped us in conducting this study.

ETHICAL APPROVAL

Not applicable

FUNDING

Not applicable

DECLARATION OF ORIGINALITY

We hereby declare that the content presented in this article is original and has been created by us. Any references or sources used have been properly cited and acknowledged.

CONFLICT OF INTEREST

We do not have any conflicts of interest, financial or nonfinancial, that could influence the content or bias the findings presented in this article.

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