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Review Article

Adipose-derived stem cells and antibiotics: A novel synergistic approach for treating implant-related osteomyelitis

*Kuang-Ting Yeh[a,b,c], Wen-Tien Wu[a,b,d], Chen-Chie Wang[a,e], Ru-Ping Lee[d]**

[a]School of Medicine, Tzu Chi University, Hualien, Taiwan, [b]Department of Orthopedics, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [c]Graduate Institute of Clinical Pharmacy, Tzu Chi University, Hualien, Taiwan, [d]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan, [e]Department of Orthopedic Surgery, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan

Abstract

Implant-related osteomyelitis poses a significant challenge in orthopedic practice, particularly due to the increasing prevalence of antibiotic-resistant infections and biofilm-associated complications. This article focused on exploring the potential of combination therapy with adipose-derived stem cells (ADSCs) and antibiotics to overcome these challenges, thereby enhancing treatment efficacy. A systematic synthesis of the results of recent *in vivo* studies, predominantly those using rat models, was performed. Studies that evaluated the effectiveness of ADSCs combined with antibiotics against common pathogens in implant-related osteomyelitis, particularly *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis,* were selected. A significant reduction in symptoms such as swelling, abscess formation, and bacterial burden in the ADSCs + antibiotic-treated group was observed in all studies. In addition, microcomputed tomography revealed reduced osteolysis, indicating enhanced bone preservation. Furthermore, histological examination revealed improved tissue structure and altered immune response, signifying the dual role of ADSCs in enhancing antibiotic action and modulating the immune system. This review highlights the promising role of the concurrent use of ADSCs and antibiotics in the treatment of implant-related osteomyelitis. This novel therapeutic strategy has the potential to revolutionize the management of complex orthopedic infections, especially those resistant to conventional treatments. However, further research is required to translate the results of animal studies into clinical applications and to develop optimized treatment protocols for human use.

Keywords: *Adipose-derived stem cells, Antibiotic resistance, Biofilm, Osteomyelitis, Regenerative medicine*

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Introduction

Implant-related osteomyelitis presents a formidable challenge in contemporary orthopedic practice, compounded by the increasing prevalence of antibiotic-resistant infections and biofilm-associated complications. This chronic bone infection often occurs postoperatively or due to open fractures and significantly impacts patient morbidity and health-care systems worldwide. Traditional treatments, typically involving surgical debridement and prolonged antibiotic therapy, frequently fail to fully address these challenges, leading to chronic infection and potential joint damage [1,2].

The emergence of antibiotic-resistant strains, particularly methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis* (MRSE), has further complicated the management of these infections. These organisms are not only resistant to standard antibiotic regimens but are also adept at forming biofilms on implant surfaces, which serve as protective barriers against both the host immune system and antibiotic penetration [3,4]. Thus, eradication of infections caused by these organisms often proves elusive, with high recurrence rates and potential long-term complications. Therefore, innovative therapeutic strategies that can effectively address both the microbial and host-related aspects of implant-related osteomyelitis are urgently required. In this context, the potential of adipose-derived stem cells (ADSCs) has garnered significant interest. ADSCs, known for their regenerative capabilities and immunomodulatory properties, have shown promise in

***Address for correspondence:** Prof. Ru-Ping Lee, Institute of Medical Sciences, Tzu Chi University, 701, Zhongyang Road, Section 3, Taiwan.
E-mail: fish@gms.tcu.edu.tw

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enhancing the efficacy of antibiotic therapies [5,6]. Recent studies have explored the use of ADSCs in combination with antibiotics, focusing on their dual role – direct antimicrobial action and immunomodulation [7,8]. However, despite the promising potential of ADSCs, challenges remain.

This review aims to synthesize the current research in this field, explore the role of concurrent use of ADSCs and antibiotics for managing implant-related osteomyelitis, and provide a background for future advancements in orthopedic infection therapy. We followed a systematic review method to explore these issues. The PubMed, Google Scholar, and Scopus databases, which extensively cover biomedical and life sciences literature, were searched using a combination of keywords and phrases such as "adipose-derived stem cells (ADSCs)," "antibiotic therapy," "implant-related osteomyelitis," "biofilm," and "antibiotic-resistant infections." Boolean operators (AND, OR) were employed to combine these terms in various configurations to maximize the retrieval of relevant articles. Original research and clinical trials published in English between January 2020 and January 2024 were selected. We focused on the *in vitro* and *in vivo* studies that provided data on the efficacy, mechanism of action, and outcomes of such treatments and excluded the studies focusing on nonbacterial bone and joint conditions or on those not explicitly reporting the combined use of ADSCs and antibiotics or on osteomyelitis not related to implants.

In vivo efficacy in rat models of implant-related infection

Two studies [7,8] reported significant findings in rat models of implant-related osteomyelitis treated with ADSCs and antibiotics. Clinically, the ADSCs + antibiotic group exhibited markedly reduced swelling, abscess formation, and bacterial burden compared to that in controls, indicating a robust antimicrobial effect. Furthermore, microcomputed tomography confirmed reduced osteolysis in this group, suggesting enhanced bone preservation. Histologically, evidence of accelerated recovery and improved tissue structure, such as faster recovery from weight loss and less bone density loss, was observed in the ADSCs + antibiotic group. Notably, significant changes were observed in the expression levels of key cytokines and antimicrobial peptides, including cathelicidin (LL-37), tumor necrosis factor-α, and interleukin-6, reflecting an altered inflammatory response conducive to healing.

Antimicrobial activity and immunomodulatory effects

Two studies [9,10] underscored the role of ADSC-conditioned media in inhibiting the growth of *S. aureus*. The effect persisted in the absence of ADSCs, suggesting the secretion of potent antimicrobial factors. Treatment with 1,25-dihydroxy Vitamin D3 enhanced the antimicrobial efficacy of ADSCs by increasing the expression of LL-37, a key antimicrobial peptide. Conversely, blocking the Vitamin D receptor curtailed this effect, highlighting the crucial role of Vitamin D3 in ADSC-mediated antimicrobial actions. Regarding the treatment of methicillin-resistant *S. aureus* infection, a combination of mesenchymal stem cells and tigecycline showed similar success rates across various graft types, indicating a broad-spectrum efficacy. Furthermore, enzyme-linked immunosorbent assay findings significant alterations in the inflammatory response, which is a crucial factor for managing chronic infections.

The relationship and mechanisms of action between adipose-derived stem cells and osteomyelitis

The pathophysiology of implant-related osteomyelitis involves a complex interplay between the host immune response and bacterial pathogenesis. Bacteria gain access to the joint space through various pathways, including hematogenous spread, direct invasion, or from adjacent bone infections. Once established, these pathogens adhere to joint tissues and prosthetic surfaces, exploiting the host's biological environment to proliferate and evade immune defenses [11,12]. Forming biofilms consisting of microbial communities embedded in a self-produced extracellular matrix further enhances bacterial resilience, making these infections particularly challenging to treat [13,14].

Role of adipose-derived stem cells in combating antibiotic-resistant infections

The emergence of antibiotic-resistant strains has significantly complicated the management of osteomyelitis. Traditional antibiotics often fail to penetrate biofilms, allowing bacteria to survive and proliferate despite treatment [15,16]. The findings in this review illustrate that ADSCs can enhance the effectiveness of antibiotics by potentially overcoming this barrier. ADSCs exhibit a unique capacity to secrete antimicrobial peptides, such as LL-37, which play a crucial role in innate immunity [17,18]. These peptides disrupt the integrity of the bacterial membranes, including those in antibiotic-resistant strains, thereby enhancing the therapeutic efficacy of antibiotics [19,20]. Furthermore, one study reported that the modulation of ADSCs with Vitamin D3 can further enhance their antimicrobial efficacy [10].

Immunomodulatory role of adipose-derived stem cells

In addition to their antimicrobial capabilities, ADSCs can modulate the host immune response, potentially reducing the inflammatory damage associated with chronic infections. This immunomodulatory effect, coupled with their ability to promote tissue regeneration, positions ADSCs as a potential game changer in treating complex orthopedic infections [21,22]. The inflammatory response to infection, while initially protective, can exacerbate tissue damage if not properly regulated [23,24]. ADSCs can modulate this response, potentially reducing the collateral damage associated with chronic infections. This dual role of ADSCs – combating infection and moderating the immune response – is particularly beneficial in managing complex infections associated with implant-related osteomyelitis [5,7,8].

Adipose-derived stem cells and osteomyelitis

ADSCs have shown promise in the management of osteomyelitis, particularly in scenarios involving implant-related infections. Their role extends beyond mere support for antibiotic therapies, touching on vital areas of bone regeneration and immunomodulation. ADSCs possess a remarkable capacity for osteogenic differentiation, making them pivotal in the reconstruction and healing of bone tissue damaged by osteomyelitis. This regenerative potential is underpinned by the secretion of growth factors and cytokines that not only promote bone formation but also enhance the recruitment and differentiation of resident stem cells to the site of injury [25,26]. Furthermore, ADSCs play a significant role in modulating the immune response during osteomyelitis. Their immunomodulatory effects help mitigate the excessive inflammation often associated with implant-related infections, thereby protecting against further bone damage. ADSCs achieve this by secreting anti-inflammatory cytokines and modulating various immune cell functions, which can shift the immune response from a pro-inflammatory to a more regulated, healing-promoting state [19]. This dual action of bone tissue regeneration coupled with the modulation of the immune response not only aids in directly combating the infection but also supports the underlying bone structure's recovery and maintenance. Moreover, ADSCs have been implicated in the potential to indirectly influence the behavior of antibiotic-resistant strains and biofilm formation. While direct interactions between ADSCs and biofilms need further elucidation, the secretion of antimicrobial peptides and modulation of the local environment suggest a possible indirect pathway through which ADSCs could disrupt biofilm integrity or inhibit its formation, offering an intriguing avenue for future research [27,28]. This comprehensive approach, targeting both the causative pathogens and the healing of bone tissue, underscores the therapeutic potential of ADSCs in the context of osteomyelitis. As the understanding of the interaction between ADSCs and the infection environment deepens, the prospect of integrating ADSC-based therapies into clinical practice becomes increasingly promising, heralding a new era in the management of this challenging condition.

Challenges and future directions of adipose-derived stem cells treatment

Despite these promising findings, several challenges to the clinical application of ADSCs remain. Variability in ADSC efficacy due to donor differences is a significant concern, as is the need for precise control over their immunomodulatory effects [29,30]. In addition, integrating these cells into existing treatment protocols requires careful consideration of dosage, timing, and delivery methods [18,31]. Future research should focus on standardizing these aspects to maximize the therapeutic potential of ADSCs. Furthermore, the potential of ADSCs to create an immunosuppressive environment, which might promote rather than control infection, needs careful consideration [32,33]. The reviewed studies indicate that local administration of ADSCs, especially when combined with antibiotics, does not invariably lead to immunosuppression, but this balance must be carefully monitored in clinical applications. Another promising aspect of ADSC therapy is its potential for tissue regeneration. The regenerative capabilities of ADSCs could play a vital role in repairing tissue damage caused by chronic osteomyelitis, offering a multifaceted treatment approach [25,34]. However, further research is needed to fully understand and harness these regenerative properties for the treatment of osteomyelitis.

Conclusion

The integration of ADSCs with antibiotics presents a novel and promising therapeutic strategy for the treatment of implant-related osteomyelitis, particularly among the increasing prevalence of antibiotic-resistant infections and biofilm-associated complications. This review synthesizes pivotal studies demonstrating ADSCs' potential in not only enhancing antibiotic efficacy against formidable pathogens such as *S. aureus* and MRSE but also in modulating the host's immune response to infection. Through their unique capacity for direct antimicrobial action and immunomodulatory effects, ADSCs emerge as a dual force capable of confronting the infection while simultaneously fostering an environment conducive to tissue regeneration and healing. The challenge of effectively treating implant-related osteomyelitis is further compounded by the complex interplay between bacterial pathogenesis and the host immune response. ADSCs address these challenges by promoting bone tissue regeneration, mitigating excessive inflammation, and potentially influencing the behavior of antibiotic-resistant strains and biofilm formation. Their regenerative capabilities, coupled with the ability to shift the immune response from pro-inflammatory to healing-promoting states, underscore their therapeutic potential. However, despite these promising findings, the clinical application of ADSCs is not without challenges. Variability in ADSC efficacy due to donor differences and the need for precise control over their immunomodulatory effects are significant concerns that necessitate further investigation. Future research must focus on overcoming these hurdles to enable the safe and effective clinical application of ADSC-based therapies. The potential of ADSCs to create an immunosuppressive environment, which might promote rather than control infection, requires careful consideration. In addition, integrating these cells into existing treatment protocols demands careful consideration of dosage, timing, and delivery methods. The promise of ADSC therapy in tissue regeneration, especially in repairing damage caused by chronic osteomyelitis, opens a multifaceted treatment approach that could revolutionize the management of complex orthopedic infections.

In conclusion, while the current evidence supports the beneficial role of ADSCs in conjunction with antibiotics for managing implant-related osteomyelitis, it also highlights the necessity for more comprehensive research. Translating the results from animal studies into clinical applications and developing optimized treatment protocols for human use are paramount. As the understanding of ADSCs in the context of osteomyelitis deepens, their integration into clinical practice becomes an increasingly tangible prospect, heralding a new era in orthopedic infection therapy.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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References

1. Kavanagh N, Ryan EJ, Widaa A, Sexton G, Fennell J, O'Rourke S, et al. Staphylococcal osteomyelitis: Disease progression, treatment challenges, and future directions. Clin Microbiol Rev 2018;31:e00084-17.
2. Castellazzi L, Mantero M, Esposito S. Update on the management of pediatric acute osteomyelitis and septic arthritis. Int J Mol Sci 2016;17:855.
3. Gajdács M. The continuing threat of methicillin-resistant *Staphylococcus aureus*. Antibiotics (Basel) 2019;8:52.
4. Siciliano V, Passerotto RA, Chiuchiarelli M, Leanza GM, Ojetti V. Difficult-to-treat pathogens: A review on the management of multidrug-resistant *Staphylococcus epidermidis.* Life (Basel) 2023;13:1126.
5. Seebach E, Kubatzky KF. Chronic implant-related bone infections-can immune modulation be a therapeutic strategy? Front Immunol 2019;10:1724.
6. Mitrofanov VN, Zhivtsov OP, Orlinskaya NY, Davydenko DV, Charykova IN, Aleinik DY. Technology for repairing osteomyelitic bone defects using autologous mesenchymal stromal cells on a collagen matrix in experiment. Sovrem Tekhnologii Med 2021;13:42-9.
7. Yoshitani J, Kabata T, Arakawa H, Kato Y, Nojima T, Hayashi K, et al. Combinational therapy with antibiotics and antibiotic-loaded adipose-derived stem cells reduce abscess formation in implant-related infection in rats. Sci Rep 2020;10:11182.
8. Yamamuro Y, Kabata T, Nojima T, Hayashi K, Tokoro M, Kajino Y, et al. Combined adipose-derived mesenchymal stem cell and antibiotic therapy can effectively treat periprosthetic joint infection in rats. Sci Rep 2023;13:3949.
9. Wang J, Wang L. Novel therapeutic interventions towards improved management of septic arthritis. BMC Musculoskelet Disord 2021;22:530.
10. Yagi H, Chen AF, Hirsch D, Rothenberg AC, Tan J, Alexander PG, et al. Antimicrobial activity of mesenchymal stem cells against *Staphylococcus aureus.* Stem Cell Res Ther 2020;11:293.
11. Masters EA, Trombetta RP, de Mesy Bentley KL, Boyce BF, Gill AL, Gill SR, et al. Evolving concepts in bone infection: Redefining "biofilm", "acute versus. Chronic osteomyelitis", "the immune proteome" and "local antibiotic therapy". Bone Res 2019;7:20.
12. Shiels SM, Bedigrew KM, Wenke JC. Development of a hematogenous implant-related infection in a rat model. BMC Musculoskelet Disord 2015;16:255.
13. Schulze A, Mitterer F, Pombo JP, Schild S. Biofilms by bacterial human pathogens: Clinical relevance – Development, composition and regulation – Therapeutical strategies. Microb Cell 2021;8:28-56.
14. Abdelhamid AG, Yousef AE. Combating bacterial biofilms: Current and emerging antibiofilm strategies for treating persistent infections. Antibiotics (Basel) 2023;12:1005.
15. Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial antibiotic resistance: The most critical pathogens. Pathogens 2021;10:1310.
16. Makabenta JM, Nabawy A, Li CH, Schmidt-Malan S, Patel R, Rotello VM. Nanomaterial-based therapeutics for antibiotic-resistant bacterial infections. Nat Rev Microbiol 2021;19:23-36.
17. Ridyard KE, Overhage J. The potential of human peptide LL-37 as an antimicrobial and anti-biofilm agent. Antibiotics (Basel) 2021;10:650.
18. Yang B, Good D, Mosaiab T, Liu W, Ni G, Kaur J, et al. Significance of LL-37 on immunomodulation and disease outcome. Biomed Res Int 2020;2020:8349712.
19. Zhang J, Liu Y, Chen Y, Yuan L, Liu H, Wang J, et al. Adipose-derived stem cells: Current applications and future directions in the regeneration of multiple tissues. Stem Cells Int 2020;2020:8810813.
20. Alcayaga-Miranda F, Cuenca J, Khoury M. Antimicrobial activity of mesenchymal stem cells: Current status and new perspectives of antimicrobial peptide-based therapies. Front Immunol 2017;8:339.
21. Yuan X, Li L, Liu H, Luo J, Zhao Y, Pan C, et al. Strategies for improving adipose-derived stem cells for tissue regeneration. Burns Trauma 2022;10:tkac028.
22. Ceccarelli S, Pontecorvi P, Anastasiadou E, Napoli C, Marchese C. Immunomodulatory effect of adipose-derived stem cells: The cutting edge of clinical application. Front Cell Dev Biol 2020;8:236.
23. Jia Q, Zhao H, Wang Y, Cen Y, Zhang Z. Mechanisms and applications of adipose-derived stem cell-extracellular vesicles in the inflammation of wound healing. Front Immunol 2023;14:1214757.
24. Li P, Ou Q, Shi S, Shao C. Immunomodulatory properties of mesenchymal stem cells/dental stem cells and their therapeutic applications. Cell Mol Immunol 2023;20:558-69.
25. Iaquinta MR, Mazzoni E, Bononi I, Rotondo JC, Mazziotta C, Montesi M, et al. Adult stem cells for bone regeneration and repair. Front Cell Dev Biol 2019;7:268.
26. Ferro F, Spelat R, Shaw G, Coleman CM, Chen XZ, Connolly D, et al. Regenerative and anti-inflammatory potential of regularly fed, starved cells and extracellular vesicles *in vivo*. Cells 2022;11:2696.
27. Pontes JT, Toledo Borges AB, Roque-Borda CA, Pavan FR. Antimicrobial peptides as an alternative for the eradication of bacterial biofilms of multi-drug resistant bacteria. Pharmaceutics 2022;14:642.
28. Yasir M, Willcox MD, Dutta D. Action of antimicrobial peptides against bacterial biofilms. Materials (Basel) 2018;11:2468.
29. Mazini L, Ezzoubi M, Malka G. Overview of current adipose-derived stem cell (ADSCs) processing involved in therapeutic advancements: Flow chart and regulation updates before and after COVID-19. Stem Cell Res Ther 2021;12:1.
30. Finocchio L, Zeppieri M, Gabai A, Spadea L, Salati C. Recent advances of adipose-tissue-derived mesenchymal stem cell-based therapy for retinal diseases. J Clin Med 2023;12:7015.
31. Qin Y, Ge G, Yang P, Wang L, Qiao Y, Pan G, et al. An update on adipose-derived stem cells for regenerative medicine: Where challenge meets opportunity. Adv Sci (Weinh) 2023;10:e2207334.
32. Bruun K, Schermer E, Sivendra A, Valaik E, Wise RB, Said R, et al. Therapeutic applications of adipose-derived stem cells in cardiovascular disease. Am J Stem Cells 2018;7:94-103.
33. Wu X, Mu Y, Yao J, Lin F, Wu D, Ma Z. Adipose-derived stem cells from patients with ulcerative colitis exhibit impaired immunosuppressive function. Front Cell Dev Biol 2022;10:822772.
34. Guo E, Wu J, Lu H, Wang L, Chen Q. Tissue-engineered bones with adipose-derived stem cells – Composite polymer for repair of bone defects. Regen Med 2022;17:643-57.