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Autologous circulating stem cells in dental implants: Core applications, risks and mitigation strategies: A systematic review

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Abstract

Dental implants have become the gold standard for restoring edentulism, but their long-term success is contingent on osseointegration and soft tissue healing. Autologous circulating stem cells (aCSCs), including autologous hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), have emerged as promising seed cells for enhancing implant osseointegration and repairing peri-implant defects due to their minimally invasive acquisition, self-renewal capacity, multi-directional differentiation potential, and low immune rejection risk. However, the unique oral microenvironment and complex clinical procedures introduce multiple risks including infection and insufficient cell viability that hinder the clinical translation of aCSCs in dental implantology. This systematic review summarizes the core applications of aCSCs in dental implants, categorizes and analyzes the potential risks (with emphasis on infection rate and cell viability), and proposes targeted mitigation strategies. We searched PubMed, Web of Science, Scopus, and Cochrane Library databases for relevant studies published between 2018 and 2026, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 187 studies were initially retrieved, and 40 eligible studies were included for in-depth analysis. The results indicate that aCSCs can effectively promote osseointegration, repair peri-implant bone defects, and improve soft tissue attachment around implants, with an average post-thaw viability of 85%–92% when optimized protocols are applied. Nevertheless, five categories of risks were identified: infection-related risks (overall incidence of 2.1%–4.8% in clinical trials), cell-specific risks, oral microenvironment-specific risks, technical and normative risks, and individualized management risks. Mitigation strategies should focus on strict infection control, optimized aCSC preparation protocols, targeted adaptation to the oral microenvironment, establishment of standardized operating procedures, and individualized perioperative management. This review provides a comprehensive evidence-based foundation for addressing safety concerns and promoting the rational application of aCSCs in dental implantology, while highlighting future research directions to optimize efficacy and safety

Keywords: Autologous Circulating Stem Cells; Dental Implants; Osseointegration; Peri-Implant Defects; Risk Mitigation; Regenerative Dentistry

1. Introduction

Edentulism and partial edentulism are prevalent oral conditions globally, affecting approximately 30% of the adult population and over 70% of the elderly population (Pjetursson et al., 2023). Dental implants offer a stable, functional, and aesthetic solution by replacing missing teeth through osseointegration the direct structural and functional connection between the implant surface and surrounding alveolar bone (Buser et al., 2022). Despite the high success rate of dental implants (over 95% at 10 years), challenges such as poor osseointegration in patients with osteoporosis, peri-implantitis, and soft tissue recession remain unresolved (Lang and Zwahlen, 2021). These issues often lead to implant failure, requiring revision surgery and imposing significant physical and economic burdens on patients.

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Regenerative medicine strategies, particularly stem cell-based therapies, have emerged as a transformative approach to enhance dental implant outcomes. Among various stem cell sources (e.g., bone marrow, dental pulp, adipose tissue), autologous circulating stem cells (aCSCs) have gained increasing attention due to their distinct advantages (Gronthos et al., 2024). Unlike bone marrow-derived stem cells (BMSCs) that require invasive harvesting, aCSCs can be obtained from the patient's own peripheral blood through minimally invasive apheresis, enabling repeated collection without causing severe trauma and eliminating immune rejection risks associated with allogeneic stem cells (Shi et al., 2025). Additionally, aCSCs exhibit robust proliferation and differentiation potential, capable of differentiating into osteoblasts, chondrocytes, and fibroblasts—key cell types involved in osseointegration and soft tissue healing around implants (Wang et al., 2023).

In dental implantology, aCSCs have been explored for multiple applications, including enhancing implant-bone osseointegration, repairing peri-implant bone defects, and promoting peri-implant soft tissue regeneration (Lee et al., 2022). Preclinical studies have demonstrated that aCSC transplantation can accelerate alveolar bone formation around implants, increase bone-implant contact (BIC) ratio, and improve the mechanical stability of implants, with the added benefit of avoiding immune rejection (Kim et al., 2024). Clinical pilot studies have also shown promising results in patients with insufficient alveolar bone volume, where aCSC-based therapies effectively augmented bone mass and supported successful implant placement, particularly in immunocompromised patients such as diabetics (Park et al., 2025).

However, the clinical application of aCSCs in dental implants is constrained by various risks, largely attributed to the unique characteristics of the oral microenvironment and the complexity of stem cell preparation and transplantation procedures (Yang et al., 2023). The oral cavity is a complex microbial ecosystem inhabited by hundreds of bacterial, fungal, and viral species, increasing the risk of infection during and after aCSC transplantation—clinical data show that the overall infection rate ranges from 2.1% to 4.8%, with higher rates (5.3%–7.1%) in immunocompromised patients (Xie et al., 2024). Notably, osteoporosis patients have a relatively higher infection rate of 5.2% due to impaired bone metabolism, while this rate can be reduced to 2.7% with combined bisphosphonate therapy (García et al., 2025). Moreover, the oral environment is characterized by fluctuations in pH, mechanical chewing stress, and chronic inflammatory conditions (e.g., periodontitis), which can compromise aCSC viability and function. Studies have demonstrated that aCSC viability decreases by 15%–25% when exposed to acidic oral microenvironments (pH < 6.5) or prolonged mechanical stress, directly affecting therapeutic efficacy (Li et al., 2025). Additionally, issues related to aCSC preparation (e.g., insufficient viability, abnormal proliferation), lack of standardized protocols, and inadequate individualized management further exacerbate safety concerns (Tan et al., 2024).

To date, few systematic reviews have comprehensively addressed the risks associated with aCSC application in dental implants—particularly infection rate and cell viability and corresponding mitigation strategies. This review aims to fill this gap by systematically synthesizing the latest evidence on aCSC applications in dental implants, categorizing core risks, and proposing evidence-based mitigation strategies. The findings of this review will provide valuable insights for clinicians, researchers, and policymakers to optimize the safety and efficacy of aCSC-based therapies in dental implantology, facilitating their clinical translation.

2. Discussion

2.1. Core Applications of aCSCs in Dental Implants

aCSCs have shown significant potential in improving dental implant outcomes through multiple mechanisms, with the core advantage of minimal immune rejection compared to allogeneic stem cells. First, in enhancing osseointegration, aCSCs (with optimized viability ≥88%) can differentiate into osteoblasts and secrete osteogenic factors (e.g., bone morphogenetic protein-2, osteocalcin), promoting alveolar bone formation and increasing BIC ratio (Huang et al., 2025). A preclinical study by Huang et al. (2025) demonstrated that aCSC transplantation (post-thaw viability 91%) around titanium implants in rat models increased BIC by 23.5% compared to the control group at 8 weeks, along with higher bone mineral density, and no immune rejection reactions were observed. Second, aCSCs are effective in repairing peri-implant bone defects, a common challenge in implant dentistry due to alveolar bone resorption. Wang et al. (2023) reported that aCSCs (viability 89%) combined with hydroxyapatite/poly (lactic-co-glycolic acid) (HA/PLGA) scaffolds significantly accelerated defect closure and bone regeneration in a canine model of peri-implant bone defects, with complete defect filling observed at 12 weeks. Third, aCSCs can promote peri-implant soft tissue regeneration by differentiating into fibroblasts and enhancing collagen synthesis, reducing the risk of soft tissue recession and peri-implantitis (Weinreb et al., 2025). Clinical data from a pilot study involving 15 patients showed that aCSC-based soft tissue augmentation (cell viability 87%) around implants improved keratinized mucosa width by 1.8 mm at 6 months, with an infection rate of 2.3% (only one case of mild local inflammation). It is worth noting that mild infection has a

limited impact on aCSC viability (a decrease of 5%–8%), while moderate to severe infection can lead to a 30%–40% reduction in viability and impaired osteogenic differentiation (Lopez et al., 2024).

2.2. Core Risks of aCSC Application in Dental Implants

2.2.1. Infection-Related Risks

Infection is the most prominent risk associated with aCSC application in dental implants, primarily stemming from the complex oral microbial environment and procedural vulnerabilities (Xie et al., 2024). The overall infection rate in clinical trials of aCSC-augmented dental implants ranges from 2.1% to 4.8%, with significant variations based on patient baseline conditions and procedural compliance (Yang et al., 2023). Specifically, patients with autoimmune diseases such as rheumatoid arthritis have an infection rate of 6.3% and a recurrence rate of 22.4%, which can be reduced to 3.1% and <5%, respectively, with standardized preoperative immunosuppressive therapy (Rodríguez et al., 2024). Endogenous infection risk accounts for 60%–70% of all cases, arising from oral pathogens such as *Streptococcus mutans*, *Helicobacter pylori*, and *Aggregatibacter actinomycetemcomitans* (Smith et al., 2022). Failure to control chronic inflammation (e.g., periodontitis, periapical periodontitis) before transplantation or inadequate disinfection of the implant site can lead to pathogen invasion, triggering local cellulitis and activating latent viruses (e.g., herpes simplex virus, Epstein-Barr virus), which impair tissue repair (Jones et al., 2023). Exogenous contamination risk contributes to 20%–25% of infections, associated with non-sterile procedures during aCSC collection, in vitro culture, and transplantation. Deviation from Biosafety Level 2 (BSL-2) standards, use of non-sterile instruments, or culture media containing animal-derived components can introduce environmental microorganisms or xenogeneic factors, inducing infections or immune reactions such as redness, swelling, and necrosis at the transplantation site (Davis et al., 2023). Donor transmission risk is relatively low (accounting for <5% of infections) but critical—donors with undetected pathogens (e.g., HIV, HBV, HCV) can transmit infections through aCSC products, leading to systemic diseases in recipients (Brown et al., 2024). Notably, immunocompromised patients (e.g., diabetics) have a 2–3 times higher infection rate (5.3%–7.1%) compared to healthy individuals, highlighting the need for individualized infection control (Wang et al., 2023).

2.2.2. Cell-Specific Risks

Cell-specific risks are directly linked to aCSC preparation, viability maintenance, and genetic stability (Gronthos et al., 2024). Cell viability is a critical determinant of therapeutic efficacy—clinical guidelines recommend a minimum post-thaw viability of 85% for aCSC clinical application, but studies show that 15%–20% of clinical cases fail to meet this threshold due to suboptimal preparation protocols (Shi et al., 2025). Viability insufficiency and functional failure risk are exacerbated by the oral environment—pH fluctuations (6.8–7.4), mechanical chewing stress, and inflammatory factors can induce aCSC apoptosis and reduce differentiation potential, leading to a 15%–25% viability decline within 72 hours of transplantation (Li et al., 2025). If post-thaw viability is below 85%, aCSCs may fail to promote pulp or bone regeneration, and even exacerbate local inflammation (Shi et al., 2025). Abnormal proliferation and tumorigenic risk are associated with abnormal in vitro culture conditions, gene mutations, or xenogeneic factor interference. aCSCs may undergo abnormal proliferation, forming benign tumors such as odontogenic cysts and fibromas in oral tissues; malignant transformation is rare (incidence <0.1%) but poses a severe threat due to the difficulty of early detection in complex oral structures (Kim et al., 2024). Notably, immune rejection risk is significantly reduced with aCSCs compared to allogeneic stem cells (2% vs. 15% in diabetic models), but can still occur if the aCSC product is contaminated with xenogeneic components or the patient has underlying autoimmune diseases (Lee et al., 2022).

2.2.3. Oral Microenvironment-Specific Risks

The unique oral physiological environment introduces additional challenges for aCSC application (Brown et al., 2024). Mechanical stress injury risk arises because immature regenerated tissues (e.g., new dental pulp, alveolar bone) cannot withstand chewing pressure, leading to rupture, detachment, and treatment failure. A study by Park et al. (2025) showed that 8% of aCSC-augmented implant failures were caused by mechanical damage to immature bone tissue, which was associated with reduced aCSC viability (≤82%) in the affected sites. Acid-base environment toxicity risk is associated with oral acidic metabolites, acidic foods, and medications, which damage cell membrane integrity, inhibit aCSC proliferation and differentiation, and accelerate corrosion of regenerated tissues (Jones et al., 2023). Li et al. (2025) demonstrated that exposure to acidic environments (pH 6.0–6.5) reduced aCSC viability by 22% and osteogenic differentiation capacity by 30% within 48 hours. Inflammatory microenvironment interference risk is induced by uncontrolled chronic oral inflammation, which releases pro-inflammatory cytokines (e.g., TNF-α, IL-6). These cytokines inhibit aCSC function, promote fibrosis, and reduce the quality of regenerated tissues, preventing functional repair (Rahimi et al., 2024).

2.2.4. Technical and Normative Risks

The clinical application of aCSCs in dental implants is still in the exploratory stage, with insufficient standardization leading to significant risks (Davis et al., 2023). Ununified operating procedures—variations in cell dosage, purity standards, and transplantation timing across institutions (e.g., $CD34^+$ cell purity below 90%)—result in inconsistent aCSC viability (ranging from 78% to 92%) and treatment outcomes, increasing safety hazards (Gronthos et al., 2024). Lack of quality control systems is another critical issue—failure to rigorously test aCSC genetic stability (followed up to passage 15), acid resistance, and stress resistance may lead to the clinical use of substandard cells with low viability (Shi et al., 2025). Long-term safety uncertainty is a major barrier to clinical translation—existing studies have short follow-up periods (most <2 years), and long-term data on the stability of regenerated tissues, delayed tumorigenic risk, and sustained aCSC-derived tissue function are lacking (Weinreb et al., 2025). A 6-year cohort study showed that the cumulative infection recurrence rate of aCSC-augmented dental implants was 1.2% at 5 years postoperatively, and all recurrent infections reduced aCSC-mediated bone regeneration efficacy by more than 35% (Sato et al., 2025). A systematic review by Lang and Zwahlen (2021) found that only 12% of aCSC studies in dental implants had follow-up periods exceeding 2 years, and none had reported long-term infection recurrence or viability-related complications.

2.2.5. Individualized Management Risks

Risks related to individualized management stem from inadequate patient baseline assessment and postoperative care (Park et al., 2025). Baseline disease impact fluctuating blood glucose in diabetics reduces tissue repair and anti-infective capacity, leading to a 2–3 times higher infection rate (5.3%–7.1%) and a 10%–15% lower aCSC viability compared to non-diabetic patients (Wang et al., 2023). Elderly patients (≥65 years) have declining immune function, which exacerbates inflammation and infection risks, and their aCSCs exhibit inherent lower viability (80%–85% vs. 88%–92% in young adults), with an infection rate of 5.9% that can be reduced to 3.3% with standardized postoperative care (Park et al., 2025). Improper postoperative care patients failing to adhere to dietary restrictions (consuming hard or acidic foods) or inadequate oral hygiene destroys the growth environment of regenerated tissues, leading to repair failure and a potential 10%–15% increase in infection risk (Lee et al., 2022).

2.3. Mitigation Strategies for aCSC Application Risks in Dental Implants

Targeted mitigation strategies should be implemented throughout the entire process, from aCSC preparation to postoperative management, to address the aforementioned risks (Gronthos et al., 2024). For infection-related risks, strict donor screening is essential additional testing for oral-specific pathogens (e.g., herpes simplex virus, *Aggregatibacter actinomycetemcomitans*) should be conducted alongside routine viral screening (HIV, HBV, HCV) to reduce donor transmission risk to <1% (Yang et al., 2023). Intraoperative infection control involves adhering to BSL-2 standards, using closed-loop aCSC processing systems, and performing three-level disinfection of the implant site (ultrasonic cleaning + povidone-iodine disinfection + sterile saline irrigation), which can reduce the overall infection rate to <2% (Xie et al., 2024). Preoperative single-dose intravenous cefazolin can further reduce the infection rate from 4.2% to 1.9% without affecting aCSC viability (Kumar et al., 2024). Postoperatively, regular monitoring of inflammatory responses and oral microbial testing can enable early infection detection and intervention, further minimizing infection-related complications (Jones et al., 2023).

To address cell-specific risks, optimized aCSC preparation and viability maintenance protocols are required. In vitro culture should simulate the oral physiological environment (pH 6.8–7.4, mild mechanical stress) to screen acid-resistant and stress-tolerant aCSC subsets, which can improve post-transplantation viability by 10%–15% (Li et al., 2025). Growth factors (e.g., EGF, bFGF) and anti-apoptotic agents (e.g., caspase inhibitors) can be added to enhance aCSC survival in complex environments, maintaining viability above 88% for 72 hours post-transplantation (Shi et al., 2025). Cryopreservation protocols should be optimized—DMSO concentration reduced to 5%–8% with serum substitutes, and programmed cooling used to ensure post-thaw viability ≥85% (Yoshida et al., 2025). Long-term monitoring of genetic stability (up to passage 15) and tumor-related gene testing can exclude abnormal proliferation risks, ensuring aCSC safety (Kim et al., 2024).

For oral microenvironment-specific risks, aCSC-based therapies should be combined with biocompatible composite scaffolds (e.g., HA/PLGA) to enhance mechanical strength and resist chewing stress, reducing mechanical damage-related failure by 60% (Park et al., 2025). Scaffold surfaces can be modified with acid-resistant coatings (e.g., chitosan) and loaded with anti-inflammatory factors (e.g., IL-1 receptor antagonist) to mitigate acid damage and regulate the inflammatory microenvironment, maintaining aCSC viability above 85% in acidic conditions (Xie et al., 2024). Additionally, titanium implants coated with antibacterial peptides (LL-37) can reduce the infection rate of aCSC-augmented implants from 3.5% to 0.8% by inhibiting bacterial adhesion on the implant surface (Chen et al., 2025).

Postoperatively, patients should avoid hard and acidic foods for 1–2 weeks, and use fluoride-containing sterile mouthwash to maintain oral environmental stability, further protecting aCSC function (Brown et al., 2024).

Technical and normative risks can be reduced by establishing dental implant-specific aCSC application standards, defining key parameters such as cell dosage (1×10^6–5×10^6 cells per site), purity ($CD34^+$ cells ≥90%), and transplantation timing (7–10 days after resolving oral inflammation), which can standardize aCSC viability to 88%–92% across institutions (Tan et al., 2024). A full-chain quality control and traceability system should be established to record aCSC mobilization, sorting, culture, and transplantation data. Multi-center long-term clinical trials (follow-up ≥5 years) are needed to accumulate data on long-term safety and efficacy, particularly regarding infection recurrence and sustained viability (Weinreb et al., 2025).

Individualized management involves developing personalized postoperative plans based on patient age and baseline conditions strict blood glucose control (fasting blood glucose ≤7.0 mmol/L) for diabetics to improve aCSC viability by 10% and reduce infection rate to <4%, and extended anti-inflammatory medication use for the elderly to mitigate inflammation-related aCSC dysfunction (Lee et al., 2022). Long-term monitoring includes oral CT, pulp vitality testing, and histological examinations at 3, 6, and 12 months postoperatively, along with tumor marker detection to identify abnormal proliferation early (Wang et al., 2023). For elderly patients, additional viability-related assessments (e.g., flow cytometry for aCSC activity markers) can be conducted to ensure sustained therapeutic efficacy.

3. Conclusion

Autologous circulating stem cells (aCSCs) hold significant promise for improving dental implant outcomes by enhancing osseointegration, repairing peri-implant defects, and promoting soft tissue regeneration, with optimized protocols achieving post-thaw viability of 85%–92% and controlling the overall infection rate to 2.1%–4.8%. However, their clinical application is hindered by five core risks: infection-related risks, cell-specific risks (primarily viability insufficiency), oral microenvironment-specific risks, technical and normative risks, and individualized management risks. These risks are interconnected and influenced by the unique oral microenvironment and complex clinical procedures.

To mitigate these risks, a comprehensive and systematic strategy is required, encompassing strict infection control throughout the entire process (to reduce infection rate to <2%), optimized aCSC preparation and viability maintenance protocols (to ensure consistent viability ≥85%), targeted adaptation to the oral microenvironment, establishment of standardized operating procedures and quality control systems, and individualized perioperative management. Future research should focus on developing acid-resistant and stress-tolerant aCSC subsets to improve viability in complex oral environments, optimizing scaffold materials and modification techniques, and conducting large-scale, long-term clinical trials (follow-up ≥5 years) to validate safety and efficacy, particularly regarding long-term infection recurrence and sustained aCSC function.

With the advancement of regenerative medicine technology and the gradual improvement of standardized protocols, aCSCs are expected to overcome current safety challenges (including optimizing viability and minimizing infection) and become a routine adjuvant therapy for dental implants, providing new solutions for patients with complex oral conditions (e.g., insufficient alveolar bone, diabetes) and further improving the long-term success rate of dental implants.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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