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Review Article

Regenerative Outcomes of Stem Cell-Based Therapies in Periodontal Intrabony Defects, Clinical Evidence and Biological Rationale: A Narrative Review

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Abstract

Periodontal intrabony defects are an irreversible consequence of periodontitis and although conventional therapy can arrest disease progression, it rarely achieves predictable regeneration. Stem cell-based approaches have therefore gained attention as a biologically driven strategy for rebuilding the lost attachment apparatus. This narrative review examines the biological rationale and clinical evidence supporting mesenchymal stem cell therapies in the management of intrabony defects. We discuss how defect morphology guides case selection, compare the periodontal potential of periodontal ligament, dental pulp, bone marrow and gingival stem cells and outline their mechanisms of action through differentiation, immunomodulation and paracrine signaling. Reported clinical outcomes, including clinical attachment gain, probing depth reduction and radiographic bone fill, are reviewed alongside the scaffolds used for cell delivery, with particular attention to platelet-rich fibrin. We also address the safety profiles and complications of these therapies, then outline the methodological gaps that limit clinical translation and the priorities for future research.

Keywords: Periodontal Intrabony Defects; Mesenchymal Stem Cells; Periodontal Regeneration; Platelet-Rich Fibrin; Paracrine Signaling; Safety

Introduction

Periodontitis is a chronic inflammatory disease of the tooth-supporting tissues that affects more than half of the adult population and remains a leading cause of tooth loss worldwide [1]. The condition begins as a dysbiotic, plaque-associated gingival inflammation that, in susceptible individuals, drives a host-mediated immune response capable of destroying the periodontal ligament, cementum and alveolar bone. When this destruction follows a vertical pattern, it produces intrabony defects, three-dimensional bony craters whose architecture has long been recognized as a determinant of healing potential and overall prognosis [2,3]. Non-surgical and surgical periodontal therapies are effective at controlling inflammation and halting attachment loss, yet they rarely reconstitute lost tissues. Healing after conventional treatment occurs largely through a long junctional epithelium rather than true regeneration and even established regenerative procedures such as guided tissue regeneration, bone grafting and the use of enamel matrix derivative produce outcomes that vary considerably from case to case [3]. This gap between disease control and genuine tissue reconstruction is precisely what has motivated interest in cell-based regenerative strategies [4].

Mesenchymal stem cells have emerged as a promising tool in this setting because they combine multilineage differentiation with potent immunomodulatory and trophic activity, enabling them to act on multiple arms of the regenerative cascade simultaneously [5]. Several systematic reviews and meta-analyses now report that the adjunctive use of stem cells can improve clinical attachment level, reduce probing pocket depth and increase radiographic bone fill compared with stem cell-free controls in carefully selected intrabony defects [6]. Early human trials using autologous cells have also supported the safety of these approaches, with low reported morbidity at the site of harvest [7].

Nevertheless, enthusiasm must be balanced against the heterogeneity of the available evidence. Studies differ widely in the stem cell source used, the scaffold that carries the cells, the way cells are processed and dosed and the outcomes reported, which makes it difficult to draw firm clinical recommendations [8]. Against this background, the present narrative review brings together the biological rationale and the clinical evidence for stem cell-based therapy in periodontal intrabony defects [9]. We first consider how defect morphology guides case selection, then compare the main stem cell sources, summarise their mechanisms of action, appraise reported clinical outcomes, examine the scaffolds used for delivery and finally discuss the safety profile and the methodological limitations and research priorities that will shape the field over the coming years [10].

The aim of this review is to critically synthesize the biological rationale and the current clinical evidence for mesenchymal stem cell-based therapy in periodontal intrabony defects, in order to clarify which factors, including defect morphology, cell source, mechanism of action, scaffold selection and safety, determine regenerative outcomes and to define the methodological requirements that must be met before these therapies can be recommended for routine periodontal practice.

Methodology

This is a narrative review and was not registered as a systematic review. The literature was identified through PubMed/MEDLINE, Scopus, Web of Science and Google Scholar, using combinations of the terms periodontal intrabony defect, infrabony defect, mesenchymal stem cells, periodontal ligament stem cells, dental pulp stem cells, periodontal regeneration, scaffold and platelet-rich fibrin. Priority was given to randomized controlled trials, systematic reviews, meta-analyses and mechanistic studies published in English, supplemented by seminal earlier work where relevant. Reference lists of retrieved articles were manually screened to identify additional sources. Studies were selected for their relevance to the biological basis and clinical performance of stem cell-based therapies in intrabony defects rather than through a formal quality-scoring protocol. Classification and Morphological Characteristics of Intrabony Defects as Determinants of Regenerative Prognosis Intrabony defects are among the main clinical scenarios for regenerative periodontal therapy, since their three-dimensional architecture can, in favorable cases, support the reconstruction of the attachment apparatus [5,6]. These defects arise from localized periodontal destruction and present a range of anatomical configurations that directly shape healing potential. It is notable that systematic reviews and meta-analyses of stem cell-based therapy have predominantly enrolled defects with favorable morphology, which underlines how strongly defect anatomy influences regenerative outcomes [7,8].

Regenerative prognosis is governed in large part by the remaining alveolar bone walls. Based on the number of residual walls, defects are described as one-wall, two-wall or three-wall [9]. Three-wall defects generally show the greatest regenerative potential because the surrounding walls provide vascular supply, stabilize the blood clot, contain regenerative materials and preserve the space needed for new tissue to form [10,11]. One-wall defects, by contrast, offer less anatomical support and behave far less predictably [7]. Clinically, defects are identified through probing pocket depth and clinical attachment level, while periapical radiographs and Cone-Beam Computed Tomography (CBCT) allow assessment of their morphology and extent [8].

Among morphological features, the radiographic defect angle and the defect depth are considered the strongest prognostic indicators. Narrow, deep defects create a more contained, mechanically stable wound that limits apical epithelial migration and favors regeneration, whereas wide-angle defects are less predictable [12]. Greater baseline depth has been associated with larger absolute gains in clinical attachment and radiographic bone fill after regenerative surgery. These variables matter particularly for cell-based approaches, which depend on a stable microenvironment that supports cell retention, survival and tissue formation; this is why trials of periodontal stem cells, including periodontal ligament stem cells, have typically selected well-contained defects with favorable anatomy [7,8].

CBCT has become a valuable adjunct for three-dimensional evaluation of these defects. Unlike conventional radiographs, it allows the residual walls, depth, width and spatial configuration to be assessed more accurately, thereby improving case selection and surgical planning [10]. The 2018 classification of periodontitis further integrates intrabony defects into the staging system as a complexity factor, linking defect morphology to disease severity, treatment difficulty and prognosis [2].

Taken together, the evidence indicates that defect anatomy is a foundational determinant of regenerative success [13]. Careful morphological characterization enables clinicians to identify patients most likely to benefit from advanced biologic approaches and provides a rational basis for matching an appropriate stem cell source to a given defect [11]. Table 1 summarizes how wall configuration relates to radiographic features and expected regenerative potential.

Defect Type	Residual Walls	Radiographic Features	Regenerative Potential
Three-wall	3 bony walls	Deep, narrow, well-contained crater	High
Two-wall	2 bony walls	Intermediate width and containment	Moderate
One-wall	1 bony wall	Wide, shallow, poorly contained	Low to moderate
Combined	Variable	Mixed wall counts at different levels	Depends on the deepest contained component

Table 1: Morphological classification of intrabony defects and expected regenerative potential REF [10,11].

Stem Cell Sources with Periodontal Potential: A Comparative Biological Profile

The mechanisms of mesenchymal stem cells have been studied extensively, but clinical success depends just as much on the biological characteristics of the chosen cell source. Each population differs in proliferative capacity, osteogenic differentiation, immunomodulatory behavior and ease of harvest and these differences shape clinical applicability [11-12]. The most thoroughly investigated sources for periodontal regeneration are Periodontal Ligament Stem Cells (PDLSCs), Dental Pulp Stem Cells (DPSCs), Bone Marrow-Derived Mesenchymal Stem Cells (BMSCs) and Gingiva-Derived Mesenchymal Stem Cells (GMSCs) [13].

PDLSCs are highly tissue-specific and can differentiate along osteogenic, chondrogenic, adipogenic, neurogenic and cardiomyogenic lineages. They secrete bioactive factors that regulate the local microenvironment, promoting proliferation, angiogenesis and osteogenesis while modulating inflammation [14]. Their low immunogenicity allows use with little risk of rejection and they show strong cementogenic and immunoregulatory capacity, expressing mesenchymal markers such as STRO-1, CD73, CD90 and CD105 [9-11]. These properties make them the most periodontally relevant source, although their harvest is limited by tissue availability [15].

DPSCs are attractive mainly because of their accessibility; they can be obtained from extracted third molars and other discarded teeth, thereby avoiding additional surgical morbidity [16]. They display high proliferative capacity, clonogenicity and multipotency, differentiating into odontoblasts, osteoblasts, adipocytes and neural-like cells and autologous harvesting during routine procedures is associated with few adverse events [12]. Their main drawback is lower specificity for periodontal tissues compared with PDLSCs.

BMSCs remain the gold standard for osteogenesis and are widely used because of their robust immunomodulatory and trophic properties. They proliferate readily and show multilineage differentiation *in-vitro* and *in-vivo* [13-14]. Their clinical use in periodontics is, however, constrained by an invasive, uncomfortable harvest and an age-related decline in regenerative capacity, even though their biological performance remains strong [17].

GMSCs reside in the gingival connective tissue around the necks of the teeth and can be obtained with minimal discomfort from tissue that would otherwise be discarded after crown lengthening, gingivectomy or flap surgery [18]. They respond to inflammatory stimuli, help maintain oral homeostasis and have shown value in autoimmune and graft-versus-host settings, while also supporting the healing of cementum and alveolar bone [16-17]. Their long-term clinical evidence for periodontal regeneration remains limited [19].

As summarized in Table 2, the four sources diverge meaningfully. PDLSCs offer the highest periodontal specificity and strong osteogenic differentiation; DPSCs are easier to obtain and retain good osteogenic potential but are less periodontally specific; BMSCs deliver very high osteogenic capacity at the cost of invasive harvesting; and GMSCs provide the greatest accessibility with a favorable anti-inflammatory profile [17]. Source selection should therefore be guided by the regenerative goal, defect characteristics, tissue availability and surgical feasibility [20]; further standardization of harvesting, expansion and delivery protocols will be essential to improve efficacy.

Cell Type	Tissue Source	Osteogenic Potential	Clinical Accessibility	Key Limitation
PDLSCs	Periodontal ligament	High	Moderate	Limited tissue availability; difficult harvest
DPSCs	Dental pulp	High	High	Lower periodontal tissue specificity
BMSCs	Bone marrow	Very high	Low	Invasive harvest; age-related decline
GMSCs	Gingival tissue	Moderate to high	Very high	Limited long-term clinical evidence

Table 2: Comparative profile of stem cell sources with periodontal regenerative potential REF [17-20].

Mechanisms of Action: Differentiation, Immunomodulation and Paracrine Effects

Stem cell-based therapies promote periodontal repair through several complementary mechanisms. Current evidence indicates that PDLSCs, DPSCs and other mesenchymal stem cells contribute to regeneration through direct differentiation, immunomodulation and paracrine signaling [21]. All three appear to participate, but recent work increasingly points to paracrine activity as the dominant driver of the outcomes seen *in-vivo* [18-20].

The most extensively studied mechanism is direct differentiation into osteoblasts, cementoblasts and periodontal ligament fibroblasts. *In-vitro* studies show that activation of the BMP, Wnt/beta-catenin and Runx2 pathways promotes osteogenic differentiation, extracellular matrix deposition and mineralized tissue formation [18,21,22]. Wnt signaling is a critical regulator of osteogenic commitment in PDLSCs, while Runx2 acts as a master transcription factor for osteoblast differentiation [21,22]. Cell-based bioactive constructs have regenerated alveolar bone, periodontal ligament and cementum in preclinical models [18,22]. Even so, robust evidence of long-term engraftment and true tissue replacement *in-vivo* remains limited, which is why claims of direct differentiation should be supported primarily by histological data [23].

Beyond differentiation, these cells exert immunomodulatory effects that are especially relevant in the inflamed periodontal pocket. PDLSCs can dampen both innate and adaptive responses; they inhibit T-lymphocyte proliferation, reduce pro-inflammatory cytokines such as IL-1 beta and TNF-alpha and shift macrophages toward the anti-inflammatory M2 phenotype [23]. These actions help resolve chronic inflammation and create a microenvironment more conducive to repair [24,25].

The third and increasingly favored mechanism is paracrine signaling. Rather than physically replacing lost tissue, transplanted cells release a broad secretome that includes Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor 2 (FGF-2), Insulin-like Growth Factor 1 (IGF-1), cytokines, chemokines, extracellular vesicles and exosomes [25]. These factors stimulate angiogenesis, recruit endogenous progenitor cells, remodel the extracellular matrix and support the survival and proliferation of resident periodontal cells [26]. The observation that meaningful regeneration often occurs despite poor long-term survival of the transplanted cells supports the view that secreted factors, rather than the cells themselves, are primarily responsible for repair *in-vivo* [19-20].

In summary, periodontal regeneration mediated by stem cells reflects an interplay of differentiation, immunomodulation and paracrine activity. Direct differentiation occurs under specific conditions and should be documented histologically, but the current evidence points to paracrine signaling as the predominant regenerative mechanism *in-vivo* [18]. This shift in understanding has practical consequences, since it suggests that cell-free, secretome-based products may eventually reproduce much of the benefit currently attributed to live-cell transplantation [27].

Clinical Outcomes: Clinical Attachment Gain, Probing Depth Reduction and Radiographic Bone Fill

The clinical management of intrabony defects requires a balance between eliminating inflammation and rebuilding the periodontal ligament, cementum and alveolar bone [28]. Recent trials have sought to improve regenerative outcomes using biological concentrates and bone substitutes, which provide a useful benchmark against which cell-based approaches can be judged [25].

Platelet-Rich Fibrin (PRF) combined with bone graft materials has produced favorable results in intrabony defects. In a split-mouth randomized trial, the addition of decortication to a PRF and NovaBone protocol further improved both clinical attachment gain and radiographic bone fill, suggesting that intramarrow penetration can enhance the regenerative response [25]. Comparative work on nanocrystalline hydroxyapatite grafts has likewise shown meaningful soft-tissue healing and bone fill, with some formulations performing better than others on attachment gain and probing depth reduction [29,30]. Representative outcomes are summarized in Table 3.

Strategy	Study Type	PPD Reduction (mm)	CAL Gain (mm)	Radiographic Bone Fill
PRF + NovaBone	RCT (split-mouth)	3.86	2.66	20.93%
Decortication + PRF + NovaBone	RCT (split-mouth)	4.60	3.04	27.26%
Sybograf (nanocrystalline HA)	RCT	4.20	4.30	33.1%
Ostin	RCT	Lower than Sybograf	Lower than Sybograf	25.5%

Table 3: Reported clinical and radiographic outcomes of selected regenerative strategies in intrabony defects [25,29,30].

Mesenchymal stem cells represent a complementary and more biologically ambitious route to the same endpoints. DPSCs, BMSCs and PDLSCs are the principal sources studied for periodontal and alveolar repair, with the periosteum and buccal fat pad serving as additional reservoirs for larger bone defects [30]. Human trials report that these cells are safe and associated with low harvest-site morbidity, with encouraging gains in clinical attachment and reductions in probing depth across both contained periodontal defects and more extensive craniofacial defects [6,30]. Autologous periodontal ligament cell sheets, for example, were safely applied in a first-in-human series, with stable medium-term results [26,31].

That said, the cell-based literature is difficult to pool. Systematic reviews repeatedly highlight heterogeneity in defect morphology, cell source, scaffold and outcome reporting, which prevents identification of a single preferred protocol [32]. Several trials nonetheless report sustained benefit and an absence of major adverse events at mid- to long-term follow-up, which is reassuring for the management of defects that conventional therapy addresses poorly [26,28]. PRF has also been shown to add value in related indications such as grade II furcation defects, reinforcing its role as an accessible biological adjunct and narrative syntheses of oral-cavity stem cells continue to support their osteogenic promise [27,31,33]. On balance, the standardized handling of regenerative materials, scaffold choice and defect containment all influence results and larger multicentre studies with histological validation are still needed to confirm any clear superiority over the current standard of care [25,28,34].

Safety Profile, Complications and Repercussions

Although stem cell-based therapy for intrabony defects has a reassuring safety record, a balanced appraisal must set out its potential complications and repercussions, since these shape informed consent and case selection. Across periodontal clinical studies the intervention has been well tolerated, with no treatment-related serious adverse events reported and only the local effects expected of any regenerative surgery, such as transient pain and swelling, postoperative sensitivity and occasional angular cheilosis, all of which resolve within a few weeks without tooth loss [7,28]. The most consistent repercussions are procedural rather than biological and they follow the cell source. Autologous harvesting adds a second surgical site: bone marrow aspiration is invasive and uncomfortable and its regenerative yield declines with age, whereas dental pulp, gingival and periodontal ligament sources carry lower morbidity but are constrained by limited tissue availability [15,17]. In the reported periodontal trials, harvest-site morbidity has been low and healing uneventful [26,35].

Additional considerations arise from cell processing rather than from the periodontal procedure itself. General reviews of mesenchymal stromal cell therapy note that prolonged *in-vitro* expansion can lead to accumulation of chromosomal abnormalities, that inadequate culture control carries a risk of microbial or mycoplasma contamination and that thromboembolic events and ectopic or fibrotic tissue formation have been reported after systemic administration in other medical fields [36]. These events have not been observed with the small, locally delivered autologous cell doses used in periodontal regeneration, but they justify strict manufacturing standards, quality control and their inclusion in patient consent [36].

A further repercussion is clinical rather than physical. Because benefit has not been consistently demonstrated over graft or biologic controls in every trial and because protocols remain unstandardized, patients may be exposed to the added cost and complexity of a cell-based procedure without a guaranteed incremental gain [28,35]. Weighing this uncertainty against the low risk of harm is central to responsible case selection until larger, histologically validated trials are available [34].

Carrier Systems and Scaffolds for Stem Cell Delivery at the Periodontal Site

The success of cell-based periodontal regeneration depends not only on the biology of the cells but also on how effectively they are delivered and retained within the defect [32]. Carrier systems and scaffolds provide a three-dimensional microenvironment that supports cell survival, migration, proliferation and differentiation, while shielding the cells from the hostile inflammatory conditions of the periodontal wound. Many of these biomaterials also actively contribute to healing by providing structural support and, in some cases, releasing bioactive signals [34].

Collagen-based scaffolds are among the most widely used, owing to their biocompatibility and close resemblance to the native extracellular matrix. They provide transient structural support while promoting adhesion, proliferation and migration and collagen membranes are routinely employed in guided tissue and guided bone regeneration as barriers against epithelial downgrowth [37]. Their main weaknesses are rapid degradation and limited mechanical strength, which have driven the development of hybrid constructs that combine collagen with synthetic polymers or other biomaterials [33].

Platelet-rich fibrin and fibrin gels are particularly appealing because they are autologous, biologically compatible and inherently regenerative. PRF forms a three-dimensional fibrin network that serves as both a scaffold and a reservoir of growth factors, including Platelet-Derived Growth Factor (PDGF), VEGF and Transforming Growth Factor beta (TGF-beta) [38]. The gradual release of these molecules promotes angiogenesis, cell migration, proliferation and wound healing, while improving cell retention within the defect. Because PRF is inexpensive, simple to prepare and supported by extensive clinical experience, it is one of the most clinically relevant scaffolds currently in use [34,37].

Hydroxyapatite-based scaffolds and decellularised matrices add osteoconductive value. Hydroxyapatite mimics the mineral phase of bone and provides an architecture that favors cell attachment and new bone formation, while decellularised matrices retain extracellular matrix cues that can guide cell differentiation and tissue organization [39]. Both aim to recreate a biomimetic environment and their regenerative capacity is typically enhanced when combined with cells, growth factors or other bioactive delivery systems [38].

The physicochemical properties of a scaffold strongly influence cell behavior. Porosity should permit cell infiltration, vascularisation and nutrient diffusion; the degradation rate should match the pace of new tissue formation; and stiffness modulates cell fate through mechanotransduction pathways governing adhesion, proliferation and differentiation [40]. Optimizing these parameters is therefore central to designing scaffolds that genuinely support regeneration [32,34].

Clinically, resorbable collagen membranes and autologous PRF-based matrices dominate practice and have shown favorable results for wound healing, soft-tissue integration and periodontal regeneration. More advanced technologies, including injectable hydrogels, growth factor-loaded matrices, exosome-based delivery systems and multifunctional scaffolds, show strong preclinical promise but await robust clinical validation and protocol standardization [40-41]. PRF, by virtue of its dual role as carrier and active biological participant, remains among the most promising scaffold systems for periodontal regenerative therapy and is likely to anchor future combination approaches [35].

Methodological Limitations and Future Directions

Interpreting the evidence on stem cell-based periodontal therapy requires honesty about its methodological constraints. Although these therapies have improved clinical attachment level, probing pocket depth, gingival recession and radiographic measures such as the cementoenamel junction-to-defect base and bone crest-to-defect base distances, several limitations restrict the extent to which the findings can be generalized [35]. Periodontitis affects more than half of adults and causes progressive, irreversible tissue loss, so the stakes for getting these protocols right are high [4,42].

The first limitation is the small body of high-quality evidence. Rigorous quality appraisal leaves only a handful of randomized controlled trials and these vary considerably in stem cell source, scaffold and treatment protocol. In a representative meta-analysis, Sun and colleagues pooled just seven clinical studies and reported significant gains in attachment, probing depth and bone fill, yet cautioned that heterogeneity precluded direct comparison between investigations [4,43]. Vallabhaneni and colleagues similarly reported a mean attachment gain of about 2.0 mm, a probing depth reduction of about 2.7 mm and roughly 46% bone fill, while again noting small sample sizes, heterogeneous protocols and short follow-up [35].

A second limitation is the dominance of *in-vitro* and preclinical data, with limited insight into long-term *in-vivo* behavior. Liang and colleagues, for instance, showed that scaffold-free cell pellets from periodontal ligament and bone marrow stem cells had osteogenic potential in a rodent defect model, yet emphasized that standardized protocols are still needed to define their distinct advantages [44]. Across the literature, study designs range from randomized trials to case reports; follow-up periods are often shorter than 12 months; and histological confirmation of true periodontal regeneration is frequently absent. There is also no consensus on the minimum effective cell dose, the optimal timing of delivery or the most appropriate scaffold [45,46].

These gaps have direct clinical consequences. Without agreed-upon guidance on cell source, dose, culture conditions, delivery and scaffold selection, outcomes vary across studies and settings, results are difficult to reproduce and evidence-based recommendations remain difficult to formulate [47]. Greater standardization is therefore a prerequisite for routine clinical adoption.

Rather than viewing these issues solely as shortcomings, they are best framed as a concrete research agenda. Future trials should adopt reporting standards such as CONSORT for clinical studies and ARRIVE for animal work, enroll larger multicentre samples, extend follow-up well beyond a year and incorporate histological endpoints to confirm genuine regeneration [48]. Clinically relevant models that integrate chronic inflammation and systemic comorbidities, together with advances in biomimetic scaffolds, organoids, secretome-based products and gene-editing strategies, offer a realistic path toward predictable, reproducible therapy [1,12]. With that level of methodological rigor, stem cell-based regeneration can move from a promising experimental approach toward a dependable part of periodontal care [49].

Conclusion

Stem cell-based therapy is one of the most promising avenues in regenerative dentistry for treating periodontal intrabony defects. Defect morphology remains a decisive factor in case selection and the choice of cell source, whether periodontal ligament, dental pulp, bone marrow or gingival stem cells, should be tailored to the clinical situation. Current evidence positions paracrine signaling and immunomodulation, rather than direct differentiation alone, as the principal mechanisms of repair and identifies the scaffold, with platelet-rich fibrin as a leading example, as an active participant in regeneration rather than a passive carrier. Reported gains in clinical attachment, probing depth and bone fill are encouraging and the safety profile is favorable, but heterogeneity, short follow-up and the scarcity of histological confirmation continue to limit firm recommendations. Standardized protocols, larger multicentre trials and longer, histologically validated follow-up will be essential to translate this potential into routine periodontal practice.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Ethical Statement
The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Not applicable.

Authors' Contributions
All authors contributed equally to this paper.

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