LIPUS In Periodontal Regeneration -A Comprehensive Review Article

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***Abstract*—Periodontitis is a chronic inflammatory disease characterized by progressive destruction of the supporting structures of the teeth, including the periodontal ligament, cementum, and alveolar bone. Although conventional periodontal therapies such as scaling and root planning, guided tissue regeneration (GTR), and bone grafting can control infection and limit disease progression, achieving predictable periodontal regeneration remains a major clinical challenge. Therefore, novel adjunctive therapeutic approaches that can enhance tissue healing and regeneration are being actively explored. Low-intensity pulsed ultrasound (LIPUS) is a non-invasive biophysical stimulation technique that has been widely used in orthopedics to accelerate fracture healing and bone repair. In recent years, its potential application in periodontal regeneration has attracted considerable interest. LIPUS exerts its therapeutic effects through mechanical stimulation that initiates Mechan transduction pathways within cells. These mechanical signals activate intracellular signaling cascades, including integrin-mediated pathways such as PI3K/Akt and MAPK, which promote osteoblast differentiation, extracellular matrix production, and angiogenesis. Additionally, LIPUS exhibits anti-inflammatory properties by suppressing pro-inflammatory cytokines through modulation of signaling pathways such as TLR4/NF-κB.**

Experimental studies have demonstrated that LIPUS enhances the migration and osteogenic differentiation of periodontal ligament stem cells (PDLSCs), particularly through the SDF-1/CXCR4 signaling pathway, thereby contributing to periodontal tissue repair and bone regeneration. Furthermore, LIPUS has been shown to improve the inflammatory microenvironment and promote alveolar bone formation, making it a promising adjunct to conventional regenerative procedures such as guided tissue regeneration and bone grafting.

Despite encouraging preclinical and emerging clinical evidence, limitations such as lack of standardized treatment parameters, small sample sizes, and limited long-term clinical studies remain challenges for its widespread clinical application. This review aims to summarize the current evidence regarding the biological mechanisms, therapeutic potential, and clinical implications of LIPUS in periodontal regeneration, while also highlighting existing limitations and future research directions for optimizing its use in periodontal therapy.

***Index Terms*—Low-intensity pulsed ultrasound (LIPUS); periodontal regeneration; periodontitis; periodontal ligament stem cells; Mechan transduction; alveolar bone regeneration; inflammation modulation.**

I. INTRODUCTION

Periodontitis is a chronic inflammatory condition that affects the supporting structures of the teeth, characterized by the progressive destruction of periodontal attachment and alveolar bone. It represents a leading cause of tooth loss and may contribute to systemic inflammation, making it a significant global health concern with substantial clinical and economic consequences. Although both non-surgical and surgical treatment approaches are available to control inflammation and limit disease progression, successful regeneration of periodontal tissues damaged by periodontitis remains a major challenge in contemporary dentistry [1].

Regenerative techniques such as guided bone regeneration (GBR) and guided tissue regeneration (GTR) are widely employed for periodontal reconstruction. However, persistent inflammation can

impair the regenerative potential of periodontal tissues, often leading to delayed healing and unpredictable outcomes, especially in posterior teeth with complex furcation defects. Consequently, there is growing interest in adjunctive therapies that can enhance tissue regeneration and accelerate periodontal healing [2].

However, most existing evidence is derived from in vitro experiments or small animal studies, which may not accurately reflect human periodontal conditions. Therefore, large animal models are necessary to better evaluate their clinical applicability. In the present study, a beagle dog model with furcation involvement was utilized to investigate the regenerative effects of LIPUS. Clinical, radiographic, and histological findings demonstrated that LIPUS, when used in combination with GTR, significantly enhances periodontal bone regeneration through anti-inflammatory and pro-angiogenic mechanisms, suggesting its potential as an adjunctive therapy in periodontal regenerative treatment [3].

Low-intensity pulsed ultrasound (LIPUS) is a non-invasive therapy approved by the U.S. FDA and commonly used in orthopedics to promote fracture healing. It exerts biological effects by stimulating osteoblast differentiation, extracellular matrix remodeling, and angiogenesis through mechanical signaling. Recent evidence suggests that LIPUS may also promote periodontal regeneration under inflammatory conditions by enhancing the osteogenic potential of human periodontal ligament stem cells and suppressing the expression of inflammatory cytokines through modulation of the NF-κB signaling pathway.

II. MECHANISMS OF LIPUS TREATMENT

Low-intensity pulsed ultrasound (LIPUS) has potential applications in several therapeutic areas, including bone repair, soft-tissue regeneration, modulation of inflammatory responses, and neuromodulation. The high frequency pressure waves generated by LIPUS provide mechanical stimulation to targeted tissues, thereby initiating biochemical processes involved in tissue healing and regeneration. Although the precise mechanisms underlying LIPUS-induced tissue repair are not fully understood, mechanical stress and fluid microstreaming are considered to play important roles in its biophysical effects [4]. These mechanical stimuli interact with the cell plasma membrane, triggering intracellular signal transduction pathways that subsequently regulate gene transcription.

III. LIPUS IN BONE REGENERATION THERAPY

Bone is an active and dynamic tissue that undergoes continuous remodeling in response to biochemical and mechanical stimuli. Appropriate mechanical stimulation is essential for maintaining bone volume and structural integrity. Mechanical loading promotes bone remodeling by regulating the activity and metabolism of osteoblasts and osteoclasts. In addition, mechanical signals stimulate several cellular processes, including cell proliferation, differentiation, gene expression, and protein synthesis [5].

Since the U.S. FDA approved the first low-intensity pulsed ultrasound (LIPUS) device for bone healing in 1994, extensive research has demonstrated its beneficial effects on fracture repair. A retrospective observational study reported successful radiological union in 12 of 18 patients with delayed union or non-union fractures following LIPUS therapy. Similarly, a retrospective cohort study evaluating distal upper-limb non-unions treated with LIPUS either alone or combined with surgery showed an overall union rate of 62% when patients received low-intensity pulsed ultrasound (30 mW/cm²) for 20 minutes daily for at least three months [6]. These findings provided a strong basis for further investigations into the role of LIPUS in bone regeneration.

LIPUS appears to facilitate fracture healing across multiple stages of the repair process, including modulation of inflammation, enhancement of angiogenesis, promotion of ossification, and stimulation of bone remodeling. Its influence on different stages of bone healing suggests that LIPUS acts through multiple biological mechanisms. In vitro studies have shown that LIPUS upregulates the expression of several osteogenic genes, including Runx-2, osteocalcin, transforming growth factor-β (TGF-β), collagen types I and X, alkaline phosphatase (ALP), aggrecan, insulin-like growth factor-1 (IGF-1), and bone sialoprotein. Furthermore, LIPUS has been

reported to enhance protein synthesis and calcium uptake in various osteoblast cell lines.

Mechanotransduction has been proposed as the primary mechanism by which LIPUS converts mechanical stimuli into biological signals. This process occurs through mechanosensitive cells within bone tissue, particularly osteocytes, which play a central role in sensing mechanical forces and regulating bone homeostasis. Osteocytes regulate local calcium balance and indirectly control osteoblast and osteoclast activity through the secretion of regulatory factors [7].

Studies have also shown that LIPUS stimulation alters gene expression in osteoblasts. Specifically, LIPUS promotes fracture healing by regulating transcription factors such as early growth response proteins (Egr1 and Egr2), forkhead box Q1 (FoxQ1), JunB, and nuclear factor of activated T-cells c1 (NFATc1). Mechanical stimulation produced by LIPUS induces fluid shear stress around osteocytes, activating mechanosensory such as integrins and kinase signaling pathways, which initiate a cascade of intracellular responses.

Activation of integrins leads to the formation of focal adhesions composed of proteins such as talin, paxillin, focal adhesion kinase (FAK), p130Cas, and vinculin (Stewart et al., 2020). LIPUS has been shown to induce phosphorylation of FAK, which subsequently activates phosphoinositide-3-kinase (PI3K) and protein kinase B (Akt), triggering the integrin/PI3K/Akt signaling pathway. Activation of this pathway stimulates cyclooxygenase2 (COX-2) expression, leading to increased production of prostaglandin-E2 (PGE2), which enhances osteoblast mineralization [8]. In addition to these effects, LIPUS also promotes angiogenesis during bone healing by upregulating vascular endothelial growth factor (VEGF) expression.

IV. LIPUS-INDUCED ANTI-INFLAMMATORY EFFECTS

Inflammation plays a critical role in tissue repair by initiating protective responses and facilitating healing. However, prolonged or excessive inflammation can lead to tissue damage and impaired regeneration. In recent years, physical therapy approaches have been explored not only for rehabilitation but also for their potential anti-inflammatory effect [9]. Low-intensity pulsed ultrasound (LIPUS) has been reported to regulate inflammatory responses by influencing the activity of various cell types involved in tissue repair.

Leukocytes are key mediators of the inflammatory response during wound healing. Following tissue injury, leukocytes migrate to the affected site to remove debris and prevent infection, thereby supporting subsequent tissue regeneration. Mechanical stimulation, such as LIPUS, can modulate this process by regulating leukocyte infiltration. Interestingly, LIPUS exhibits a bidirectional effect on leukocytes. It enhances leukocyte infiltration during the early stages of inflammation to facilitate wound cleaning, while reducing leukocyte accumulation during later stages to prevent excessive inflammation and tissue destruction [10].

Experimental studies further support the anti-inflammatory potential of LIPUS. In a rat model of post-traumatic osteoarthritis, LIPUS significantly reduced synovial leukocyte infiltration and decreased interleukin-1β (IL-1β) levels in joint fluid. Additionally, LIPUS has been shown to influence macrophage polarization by reducing proinflammatory M1 macrophages and promoting anti-inflammatory M2 macrophages, thereby supporting tissue repair [11].

Furthermore, LIPUS suppresses lipopolysaccharide (LPS)-induced inflammatory responses by inhibiting proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8 through modulation of signaling pathways including TLR4/NF-κB and MAPK [12]. Collectively, these findings suggest that LIPUS may serve as a promising therapeutic approach for controlling inflammation and enhancing tissue regeneration.

V. SOFT-TISSUE REGENERATION

Low-intensity pulsed ultrasound (LIPUS) has been reported to accelerate the regeneration of various soft tissues, including tendons, ligaments, cartilage, and intervertebral discs. These tissues are subjected to significant mechanical loading in the body, and LIPUS provides beneficial mechanical stimulation that supports tissue healing and development. Studies have demonstrated that LIPUS enhances bone–tendon healing by promoting fibroblast activity, collagen synthesis, and angiogenic, chondrogenic, and osteogenic processes [13].

VI. THE MECHANISMS OF LIPUS IN TREATING EXPERIMENTAL PERIODONTITIS:

LIPUS induces stem cell migration:

Mechanical stimulation plays a crucial role in bone remodeling by maintaining a balance between bone formation and resorption through the process of Mechan transduction. In periodontal regeneration, Mechan transduction influences several cellular processes, including cell migration, proliferation, differentiation, and the regulation of inflammatory responses. Among these processes, cell migration is essential for periodontal tissue repair. Mesenchymal stem cells (MSCs) contribute to tissue healing by migrating to sites of injury, where they differentiate into osteoblasts and support bone regeneration [14]. Similarly, the mobilization of MSCs is important for maintaining periodontal tissue homeostasis.

Recent evidence suggests that the homing of periodontal ligament stem cells (PDLSCs) may represent a key mechanism underlying LIPUS-mediated periodontal regeneration. PDLSCs are mechanosensitive cells involved in tissue repair and homeostasis. Studies have shown that LIPUS stimulation enhances the expression of stromal cell-derived factor-1 (SDF-1), a chemokine essential for stem cell homing, thereby promoting PDLSC migration through the SDF-1/CXCR4 signaling pathway [15]. Further investigations demonstrated that twist family bHLH transcription factor-1 (TWIST1) acts as a mechanosensitive regulator that upregulates SDF-1 expression in response to mechanical stimulation. Activation of TWIST1 under LIPUS treatment promotes PDLSC migration and enhances periodontal bone regeneration.

However, the migration of periodontal ligament cells is not completely inhibited by TWIST1 blockade, indicating the presence of additional regulatory mechanisms. Other chemokine receptors, including CCR1, CCR4, and CCR7, may also contribute to MSC migration. Therefore, further research is required to fully elucidate the mechanisms by which LIPUS regulates stem cell mobilization in periodontal tissues [16].

LIPUS modulates inflammatory response in periodontitis:

Dental plaque biofilm is the primary etiological factor in periodontitis. The host immune and inflammatory responses to microorganisms within the biofilm create a subgingival environment characterized by hypoxia and ischemia, favoring the growth of anaerobic pathogens such as Porphyromonas gingivalis, a key bacterium associated with severe periodontitis. Lipopolysaccharide (LPS), a major virulence factor of P. gingivalis, activates Toll-like receptor-4 (TLR4) and triggers inflammatory signaling pathways, particularly the nuclear factor-κB (NF-κB) pathway, leading to the release of pro-inflammatory cytokines and chemokines [17]. Persistent activation of this pathway impairs osteogenic differentiation of periodontal ligament stem cells (PDLSCs), increases osteoclast activity, and contributes to alveolar bone loss.

The inflammatory microenvironment also induces oxidative stress and endoplasmic reticulum stress (ERS), both of which reduce the regenerative potential of periodontal cells [18]. ERS activates the unfolded protein response (UPR) through transmembrane sensors such as PERK, ATF6, and IRE1, further inhibiting osteogenic differentiation of PDLSCs.

Low-intensity pulsed ultrasound (LIPUS) has been shown to counteract these pathological mechanisms. Studies indicate that LIPUS suppresses LPS-induced inflammatory responses by interfering with the TLR4/MyD88/NFκB signaling pathway, thereby reducing the expression of inflammatory cytokines such as IL-6 and IL-8 and improving osteogenic differentiation of periodontal ligament cells [19]. Additionally, LIPUS decreases oxidative stress by activating the PI3K/Akt-mediated nuclear factor erythroid-2–related factor-2 (Nrf2) pathway, which enhances antioxidant gene expression and protects alveolar bone.

Furthermore, LIPUS reduces ERS and downregulates UPR-related genes such as IRE1α, GRP78, and ATF4, thereby promoting osteogenic differentiation markers, including RUNX2 and ALP. LIPUS also stimulates autophagy-related proteins, such as LC3 and Beclin-1, which contribute to its anti-inflammatory effects and enhance PDLSC survival under inflammatory conditions [20].

VII. CLINICAL IMPLICATIONS

Furthermore, LIPUS may accelerate postoperative healing and enhance periodontal regeneration in advanced conditions such as severe periodontitis or peri-implantitis, where conventional therapies may have limited effectiveness. It may also be incorporated into non-surgical periodontal management strategies for high-risk patients, including individuals with diabetes or immunosuppressive disorders. However, standardization of treatment parameters such as application duration, frequency, and intensity is necessary to optimize clinical outcomes and ensure consistent results across different patient populations [23,24].

These findings suggest that low-intensity pulsed ultrasound (LIPUS) may serve as a valuable adjunct to conventional periodontal therapy, particularly in cases requiring enhanced bone regeneration and tissue healing. Due to its non-invasive nature, LIPUS may be especially beneficial for patients who are not suitable candidates for surgical periodontal procedures. Its ability to stimulate osteoblastic activity, reduce inflammation, and promote extracellular matrix production indicates that LIPUS could improve clinical outcomes when combined with traditional treatments such as scaling and root planing, guided tissue regeneration (GTR), and bone grafting [21,22].

VIII. LIMITATIONS AND FUTURE DIRECTIONS

Despite the promising potential of low-intensity pulsed ultrasound (LIPUS) in periodontal regeneration, several limitations exist in the current literature. One major challenge is the lack of standardized treatment parameters, including variations in frequency, intensity, and duration of application, which leads to inconsistent outcomes and makes it difficult to establish clear clinical guidelines. Additionally, many existing clinical studies involve small sample sizes and short follow-up periods, limiting the generalizability of the findings and preventing definitive conclusions regarding the long-term effectiveness of LIPUS therapy [25].

Although preclinical studies provide valuable insights into the biological mechanisms of LIPUS, further validation through large-scale, multicenter randomized controlled trials is necessary before widespread clinical adoption. Moreover, only a limited number of studies have evaluated the long-term stability of periodontal regeneration induced by LIPUS, leaving uncertainty about the durability of treatment outcomes beyond the initial healing phase. Cost-effectiveness analyses are also scarce, making it difficult to assess the financial feasibility of incorporating LIPUS into routine periodontal therapy [26]. Future research should focus on well-designed randomized controlled trials with standardized treatment protocols to optimize LIPUS application parameters. Long-term clinical studies with extended follow-up periods are essential to evaluate the stability of regenerative outcomes. Furthermore, investigating the synergistic effects of LIPUS with biomaterials, growth factors, and stem cell-based therapies may enhance periodontal regeneration and improve clinical outcomes [27,28].

This systematic review and meta-analysis provide evidence supporting the potential effectiveness of low intensity pulsed ultrasound (LIPUS) in periodontal regeneration. The findings indicate that LIPUS contributes to improvements in clinical attachment level (CAL), reduction in probing depth (PD), and enhanced alveolar bone healing. Mechanistically, LIPUS promotes angiogenesis, stimulates osteoblastic activity, and modulates inflammatory responses, thereby creating a favorable environment for periodontal tissue regeneration. However, the absence of standardized treatment protocols and limited long-term clinical data highlight the need for further high-quality research to confirm its clinical effectiveness.

Due to its non-invasive nature and regenerative capabilities, LIPUS may serve as a valuable adjunct to conventional periodontal therapy. Future studies should focus on optimizing treatment parameters, evaluating long-term treatment stability, and assessing cost-effectiveness. With further validation through well-designed clinical trials, LIPUS has the potential to become an effective and patient-friendly approach for improving periodontal regeneration and overall periodontal health outcomes.

IX. CONCLUSION

Low-intensity pulsed ultrasound (LIPUS) has emerged as a promising non-invasive therapeutic modality for enhancing periodontal regeneration. Evidence from experimental and clinical studies suggests that LIPUS

promotes bone formation, stimulates angiogenesis, enhances extracellular matrix synthesis, and modulates inflammatory responses through multiple cellular and molecular pathways. In periodontal tissues, LIPUS improves osteogenic differentiation, promotes periodontal ligament stem cell migration, and suppresses inflammatory signaling pathways such as NF-κB, thereby creating a favorable microenvironment for tissue regeneration. These biological effects indicate that LIPUS may significantly enhance the outcomes of conventional periodontal therapies when used as an adjunctive treatment. However, despite encouraging findings, current evidence is limited by variations in treatment protocols, small sample sizes, and insufficient long-term clinical data. Therefore, further well-designed randomized controlled trials with standardized parameters are essential to validate its clinical effectiveness and establish clear treatment guidelines. With continued research and technological advancements, LIPUS has the potential to become an effective and patient-friendly approach for improving periodontal regeneration and overall periodontal health.

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