

Efferocytosis In Dentistry: A Narrative Review Of Its Role In Periodontal, Periapical, And Peri-Implant Inflammation Resolution And Osseointegration

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Abstract: Background: Osseointegration failure and chronic peri-implant and periodontal inflammation remain major sources of long-term complications in restorative and implant dentistry. Failure of inflammation resolution, rather than initiation alone, has emerged as a central mechanism, with efferocytosis, the phagocytic clearance of apoptotic cells by macrophages, recognized as pivotal to this process. Objective: To synthesize current evidence on the role of efferocytosis in periodontal, periapical, and peri-implant disease, and to examine its causal contribution to osseointegration failure. Methods: A narrative review of PubMed-indexed studies covering the basic biology of efferocytosis, its dysregulation in periodontitis and apical periodontitis, its interplay with *Porphyromonas gingivalis*, its bidirectional relationship with diabetes mellitus, its role in alveolar bone dynamics, its contribution to peri-implantitis and osseointegration failure, and emerging pro-efferocytic therapeutic strategies. Results: Thirty-four studies were synthesized. Impaired efferocytosis, driven by pathogen evasion, hyperglycemia, titanium-particle-induced pyroptosis, or deficits in molecules such as DEL-1, Tim4, MerTK, SIRT6, and PPAR- γ , was consistently associated with neutrophil accumulation, M1 macrophage dominance, and bone destruction in both periodontal and peri-implant tissues; at the implant interface, defective neutrophil-to-macrophage efferocytic handoff directly impaired the M1-to-M2 transition required for osseointegration. Conclusion: Pharmacological and biomaterial-based strategies restoring efferocytic capacity consistently

promote inflammation resolution and tissue repair in preclinical models, positioning efferocytosis as a promising diagnostic and therapeutic target in periodontology, endodontics, and implant dentistry, although clinical-trial validation in humans remains lacking.

Key Word: *efferocytosis; periodontitis; peri-implantitis; osseointegration; macrophages; apoptosis; diabetic periodontitis; specialized pro-resolving mediators.*

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I. Introduction

Inflammation is a protective response, but its failure to resolve is now recognized as a driving force behind many chronic diseases of the oral cavity, most notably periodontitis and apical periodontitis.[1,2] Classic models of periodontal pathogenesis emphasized bacterial burden and host inflammatory overreaction, yet a growing body of evidence points to a third, previously underappreciated axis: the efficiency with which the host clears the very inflammatory cells it recruits.[1]

Efferocytosis—from the Latin *effero*, “to carry to the grave”—describes the phagocytic engulfment and removal of apoptotic cells by macrophages and other professional or non-professional phagocytes.[1,2] Unlike the clearance of pathogens, efferocytosis is an immunologically silent process: it does not trigger pro-inflammatory cytokine release and instead actively reprograms macrophages toward a reparative, anti-inflammatory (M2-like) phenotype, promoting the biosynthesis of specialized pro-resolving mediators (SPMs) and initiating tissue repair.[3,4] When efferocytosis fails, apoptotic neutrophils undergo secondary necrosis, releasing their intracellular contents—including proteases and damage-associated molecular patterns—into the surrounding tissue, thereby amplifying and perpetuating inflammation.[1]

This narrative review aims to synthesize current evidence on the relationship between efferocytosis and dentistry, with an emphasis on periodontology, endodontics, implant dentistry, and bone biology. The specific objectives are to: (1) summarize the fundamental biology of efferocytosis; (2) examine its role in the pathogenesis of periodontitis and apical periodontitis; (3) describe how oral pathogens, particularly *Porphyromonas gingivalis*, interfere with efferocytic clearance; (4) discuss the bidirectional relationship between diabetes mellitus and efferocytosis in periodontal disease; (5) explore efferocytosis in alveolar bone remodeling and healing; (6) examine its specific role in peri-implantitis and its causal contribution to osseointegration failure; and (7) review emerging pro-efferocytic therapeutic strategies with translational potential for clinical dental and implant practice.

II. The Biology Of Efferocytosis: A Brief Overview

Efferocytosis proceeds through four coordinated steps: (a) release of “find-me” signals by apoptotic cells that attract phagocytes; (b) recognition of “eat-me” signals—most classically phosphatidylserine exposed on the outer leaflet of the apoptotic cell membrane—through phagocyte receptors such as MerTK, integrins, and bridging molecules including DEL-1, Gas6, and MFG-E8; (c) internalization of the apoptotic corpse; and (d) intracellular processing coupled with metabolic and transcriptional reprogramming of the phagocyte.[1,5] This reprogramming activates liver X receptor (LXR) and peroxisome proliferator-activated receptor (PPAR) pathways, upregulates anti-inflammatory cytokines such as IL-10 and TGF- β , and suppresses NF- κ B-driven pro-inflammatory signaling.[6,7]

Bridging molecules occupy a particularly important regulatory position. DEL-1 (developmental endothelial locus-1), for example, was shown by Kourtzelis et al.[6] to be required for efficient clearance of apoptotic neutrophils and for LXR-dependent macrophage reprogramming toward a pro-resolving phenotype; failure of DEL-1 upregulation was directly associated with non-resolving experimental periodontitis. Similarly, Tim4, a phosphatidylserine receptor, sustains a specific CD301b⁺ macrophage subset implicated in periodontal bone protection.[8]

Beyond receptor-ligand recognition, efferocytosis is metabolically demanding and reshapes the phagocyte’s own energy metabolism—for instance, by increasing glycolytic flux and lactate production, which in turn modulates osteoclastogenesis and the local bone microenvironment.[9] This metabolic dimension helps explain why efferocytosis is not merely a “clean-up” mechanism but an active determinant of downstream tissue outcomes, including bone formation and resorption.[10,11]

III. Efferocytosis And Periodontitis

A. Impaired Neutrophil Clearance As A Driver Of Periodontal Destruction

Periodontitis is now widely conceptualized as a disease of failed inflammation resolution rather than of inflammation initiation alone.[1,2] Neutrophils are recruited in large numbers to the gingival sulcus in response to subgingival biofilm, and their timely apoptosis and efferocytic removal by macrophages are essential to prevent tissue damage.[1] When efferocytosis is defective, apoptotic neutrophils accumulate and undergo secondary

necrosis, releasing proteolytic enzymes (e.g., matrix metalloproteinases, elastase) and neutrophil extracellular traps (NETs) that directly damage the periodontal ligament and alveolar bone and sustain a self-perpetuating inflammatory loop.[12,13]

Several molecular deficits converge on this failure. SIRT6, a histone deacetylase, was shown by Li et al.[12] to restrain a microRNA cluster (miR-216a-5p/216b-5p/217) required for efficient efferocytosis, with insufficient SIRT6 activity leading to accumulation of apoptotic neutrophils and NETs in both human and murine diabetic periodontitis. Tim4 deficiency similarly reduces protective CD301b⁺ macrophages and aggravates alveolar bone loss via disrupted p38 MAPK signaling.[8] Ferroptosis, an iron-dependent form of regulated cell death, has also been mechanistically linked to macrophage efferocytic dysfunction in periodontitis, with redox and lipid/iron metabolism proposed as a unifying axis connecting these two processes to macrophage reprogramming.[13]

A comprehensive review by Mo et al.[2] situates efferocytosis alongside macrophage polarization, pattern-recognition receptor signaling, and SPM production as interconnected mechanisms governing whether periodontal inflammation resolves or becomes chronic, underscoring efferocytosis as one node within a broader immunoregulatory network rather than an isolated pathway.

B. Efferocytosis In Apical Periodontitis And Endodontic Inflammation

The relevance of efferocytosis extends beyond marginal periodontitis into periapical disease. Guan et al.[14] demonstrated that macrophage efferocytosis is present in periapical lesions and that its pharmacological enhancement with the erythropoietin-derived peptide ARA290 promoted resolution of apical periodontitis by facilitating M2 macrophage polarization in both in vitro and in vivo models. Complementing this, Wang et al.[7] reported a progressive decline in PPAR- γ expression and in macrophage efferocytic capacity as chronic apical periodontitis advanced, and showed that pharmacological PPAR- γ activation (rosiglitazone) restored efferocytosis and reduced periapical inflammation, whereas its antagonism (GW9662) worsened outcomes—identifying PPAR- γ as a candidate therapeutic target in endodontics.

At the level of the dental pulp itself, Aubeux et al.[3] reviewed the therapeutic potential of specialized pro-resolving lipid mediators (lipoxins, resolvins, protectins, and maresins) in pulpitis and apical periodontitis, noting that these mediators not only dampen neutrophil infiltration but also actively enhance macrophage efferocytosis and bacterial phagocytosis—raising the prospect of SPM-based intracanal or pulp-capping therapies that could preserve pulp vitality by favoring resolution over irreversible inflammation.

IV. Oral Pathogens And Efferocytosis Evasion

A distinctive feature of periodontal pathobiology is that key pathogens do not merely trigger inflammation—they actively subvert the host's resolution machinery. *Porphyromonas gingivalis*, the keystone pathogen most strongly associated with periodontitis, has been shown to interfere with efferocytosis through multiple, non-redundant mechanisms.

Cooper et al.[15] described a previously unrecognized immune-evasion strategy in which *P. gingivalis* and its gingipain protease RgpB remodel the neutrophil surface proteome, generating neoepitopes that cause macrophages to engulf live, non-apoptotic neutrophils rather than apoptotic ones. This “live-cell trapping” bypasses classical efferocytosis receptor-ligand pathways, fails to activate the pro-resolution PPAR- γ program, and instead promotes bacterial persistence and sustained inflammation—illustrating a qualitatively distinct outcome from canonical efferocytosis of already-apoptotic cells.

At the level of vascular and systemic complications, Xie et al.[16] demonstrated that *P. gingivalis* induces smooth muscle cell apoptosis and, via extracellular miR-143/145 that upregulate macrophage Siglec-G, represses macrophage efferocytosis in atherosclerotic plaques—mechanistically linking periodontitis to increased cardiovascular risk and suggesting that impaired efferocytosis may partly explain the well-documented epidemiological association between periodontal and atherosclerotic disease. In a maternal-fetal context, Zhao et al.[17] found that *P. gingivalis* administration in pregnant mice enhanced glycolysis and histone lactylation, which promoted ADAM17-mediated shedding of the efferocytosis receptor MerTK and the TGF- β receptor TGFBR1, blocking epithelial efferocytosis and osteogenesis and increasing the incidence of cleft palate in offspring—extending the clinical relevance of periodontal pathogen-driven efferocytosis disruption to craniofacial developmental outcomes.

Other work indicates that host-pathogen interactions can also be therapeutically exploited to restore efferocytosis. Atomura et al.[18] showed that silencing Sprouty2 enhanced PI3K/AKT-dependent efferocytosis and M2 polarization in macrophages stimulated with *P. gingivalis* lipopolysaccharide (LPS), while Cai et al.[19] found that the flavonoid baicalin restored efferocytosis in a *P. gingivalis* LPS-induced murine model of inflammation by inhibiting RhoA/ROCK signaling and reducing oxidative stress—both findings pointing toward pathogen-informed pharmacological strategies for periodontal resolution therapy. Biomaterial approaches have pursued a parallel strategy: Zhuo et al.[20] engineered a gelatin methacryloyl hydrogel co-delivering an

antimicrobial peptide and exosomes that simultaneously killed periodontal pathogens (including *P. gingivalis*) and promoted neutrophil apoptosis, macrophage M2 polarization, and efferocytosis, reducing alveolar bone loss in a rat periodontitis model.

V. Diabetes Mellitus, Efferocytosis, And Periodontal Disease

The bidirectional relationship between diabetes mellitus and periodontitis is well established clinically, and efferocytosis research has begun to clarify one of its underlying mechanisms. Hyperglycemia directly impairs macrophage efferocytic function, delaying inflammation resolution and aggravating periodontal tissue destruction in diabetic periodontitis (DP).[12,21,22]

Li et al.[12] showed that high glucose disrupts the SIRT6–miR-216/217 axis in macrophages, impairing efferocytosis of apoptotic neutrophils via the DEL-1/CD36 pathway and worsening inflammatory damage in both human and murine diabetic periodontitis; therapeutic delivery of an antagomiR targeting this axis mitigated periodontal destruction in a mouse model. Liu et al.[21] demonstrated that hyperglycemia disrupts store-operated calcium entry (SOCE) in macrophages, inhibiting efferocytosis and M2 polarization, and that eldecalcitol (an active vitamin D analog) restored SOCE-dependent efferocytosis and reduced alveolar bone loss in diabetic rats. In related work, Liu et al.[22] showed that the high-glucose inflammatory microenvironment disrupts macrophage mitochondrial dynamics, impairing efferocytosis and, consequently, the osteogenic differentiation and migratory capacity of co-cultured periodontal ligament stem cells (PDLSCs); pharmacological inhibition of excessive mitochondrial fission restored macrophage function and improved tissue-repair indicators in a diabetic periodontitis model.

Collectively, these studies converge on a consistent mechanistic narrative: diabetes-associated hyperglycemia disables multiple, partially independent efferocytic checkpoints in macrophages (epigenetic, calcium-signaling, and mitochondrial), each of which delays inflammation resolution and worsens alveolar bone loss. This provides a molecular rationale for the clinically observed severity gradient of periodontitis in poorly controlled diabetic patients and identifies efferocytosis-restoring agents as candidate adjuncts to conventional periodontal therapy in this population.

VI. Efferocytosis And Alveolar Bone Dynamics

Efferocytosis is not confined to leukocyte turnover; it also governs the fate of bone-lineage cells and thereby directly influences alveolar bone remodeling, a process of central relevance to periodontology, oral surgery, and implant dentistry. Batoon et al.[10] reviewed accumulating evidence that skeletal efferocytosis—chiefly performed by osteal macrophages—actively orchestrates osteoblast-osteoclast coupling during bone remodeling, and that impaired efferocytosis is associated with age-related bone loss, osteoporosis, and other skeletal pathologies, suggesting that efferocytic mechanisms are a plausible but underexplored target for alveolar bone-loss conditions.

Mechanistic support comes from Batoon et al.[11], who used an inducible Caspase-9 model to trigger apoptosis in mature osteoblasts and observed that osteoblast apoptosis stimulated efferocytosis by osteal macrophages, which paradoxically enhanced vertebral bone formation and increased osteoblast precursors—an effect abolished by macrophage depletion. This finding reframes osteoblast apoptosis and its efferocytic clearance not as mere cellular turnover but as an active anabolic signal, with direct implications for how clinicians might modulate bone-formation phases after periodontal surgery, extraction-socket healing, or guided bone regeneration. At the molecular level, Kannan et al.[9] further showed that efferocytosis of apoptotic osteoblasts metabolically reprograms macrophages toward enhanced glycolysis and lactate production, and that this lactate, in turn, suppresses osteoclast differentiation and resorptive activity while promoting M2-like macrophage markers—identifying a lactate-mediated feedback loop that couples efferocytic clearance to reduced bone resorption.

Within the periodontal complex specifically, Wang et al.[8] linked the phosphatidylserine receptor Tim4 to a protective CD301b⁺ macrophage subset whose depletion aggravated alveolar bone loss in experimental periodontitis, while Batoon et al.[10] noted that similar efferocytic macrophage subsets participate in periodontal bone protection more broadly. Together, these findings support a model in which alveolar bone homeostasis depends not only on the classical RANKL/OPG osteoclastogenic axis but also on an efferocytosis-dependent macrophage program that couples apoptotic cell clearance to reparative bone formation—a mechanism with direct translational relevance to postsurgical healing, socket preservation, and peri-implant bone regeneration.

VII. Peri-Implantitis And The Role Of Efferocytosis In Osseointegration Failure

Peri-implantitis—an inflammatory, bone-destructive disease affecting the tissues surrounding osseointegrated dental implants—shares much of the macrophage-driven pathophysiology described above for periodontitis, but with features specific to the implant interface that make it a particularly informative test case for the efferocytosis framework.

A. Macrophage Polarization Imbalance In Peri-Implantitis Lesions

Because successful efferocytosis reprograms macrophages toward an anti-inflammatory, reparative M2 phenotype (Section II), the M1/M2 balance observed in diseased tissue is a useful, if indirect, readout of resolution failure. Galarraga-Vinueza et al.[23] performed immunohistochemical analysis of peri-implantitis granulation tissue and found that advanced lesions displayed a significantly higher proportion of pro-inflammatory M1 (CD80⁺) relative to reparative M2 (CD206⁺) macrophages, with M1 expression correlating with probing depth. Li et al.[24] reviewed this M1-dominant profile in peri-implantitis in direct comparison with periodontitis, concluding that macrophage polarization dysregulation is central to both diseases but may follow a distinct trajectory around implants. Amerio et al.[25] further showed that smokers exhibited a markedly higher proportion of M1 macrophages in peri-implantitis lesions (70.2% vs. 25.1% in non-smokers), correlating with cotinine levels and pack-years and with more severe disease—identifying smoking as a modifiable risk factor that plausibly acts, at least in part, by skewing the same M1/M2 axis that efferocytosis normally resolves toward M2.

B. Titanium Wear Particles, Inflammasome Activation, And The Breakdown Of Silent Clearance

Ng et al.[26] proposed the biofilm-mediated inflammation and bone dysregulation (BIND) hypothesis, framing peri-implantitis as a staged, individualized process arising from the interaction of biofilm dysbiosis, immune dysregulation, and bone biology, and explicitly identifying macrophage polarization and bone-turnover biomarkers as priority areas for future research. A feature largely absent from periodontitis but central to peri-implantitis is the presence of titanium wear particles and ions released from the implant surface. Carrillo-Gálvez et al.[27] demonstrated that titanium ions synergize with bacterial LPS to activate both the NLRP3 and AIM2 inflammasomes in macrophages, driving IL-1 β release, mitochondrial DNA release, and pyroptosis—a lytic, highly inflammatory form of programmed cell death that is immunologically the opposite of the “silent,” non-inflammatory clearance efferocytosis is designed to perform. Because efferocytic receptors recognize phosphatidylserine on the intact membrane of apoptotic cells rather than the ruptured membranes and released damage-associated molecular patterns characteristic of pyroptotic cells, titanium-driven pyroptosis plausibly generates a cell-death burden that efferocytosis cannot efficiently clear, redirecting the local immune response toward a self-amplifying, treatment-resistant inflammatory loop. This offers a mechanistic hypothesis for the clinical observation that peri-implantitis, once established, tends to be more refractory to non-surgical resolution than periodontitis.

C. Efferocytosis As A Determinant Of Osseointegration Success Or Failure

Osseointegration itself depends on an early, self-limited inflammatory phase giving way to a reparative, pro-osteogenic M2-dominant phase—the same M1-to-M2 transition that efferocytosis drives in bone remodeling more generally.[9,10,11] Direct causal evidence linking efferocytosis specifically to osseointegration outcomes comes from Tan et al.[28], who showed that under diabetic conditions, dysfunctional neutrophils—characterized by impaired chemotaxis and elevated oxidative stress—failed to undergo the redox and phenotypic changes required for efficient MerTK-mediated macrophage efferocytosis. This blocked the physiological M1-to-M2 transition, impairing angiogenesis and osteogenesis and increasing implant failure rates in a diabetic rat model. Critically, when the authors engineered a tri-layered polyetheretherketone (PEEK) implant coating that restored neutrophil redox homeostasis (via the flavonoid quercetin) and actively recruited neutrophils to the implant surface (via the chemotactic peptide fMLP), efferocytosis-driven macrophage reprogramming toward M2 was reestablished, and vascularized bone regeneration and osseointegration were substantially improved. This study provides direct causal evidence that efferocytic competence at the implant interface—not merely macrophage number or presence—is a determinant of whether osseointegration succeeds or fails.

Complementary molecular evidence reinforces this connection. Kang et al.[29] found that the miR-33a/SIRT6 axis—the same SIRT6-dependent pathway shown to gate macrophage efferocytosis in diabetic periodontitis[12] (Section V)—is dysregulated in peri-implantitis tissue, where elevated miR-33a suppresses SIRT6, promotes M1 polarization, and inhibits osteogenic differentiation of periodontal ligament stem cells exposed to M1-conditioned medium. Zhao et al.[30] similarly identified an lncRNA NRIR/RSAD2/NF- κ B axis that locks macrophages into an M1 phenotype and suppresses osteogenesis in peri-implantitis, with experimental knockdown restoring bone-forming capacity in a rat model. Taken together with the diabetic-periodontitis literature discussed earlier, these findings point to a shared molecular grammar—SIRT6- and NF- κ B-dependent control of the M1/M2 switch—operating at both the periodontal and peri-implant interface, with efferocytic competence as a plausible common denominator linking impaired inflammation resolution to bone loss in both settings.

D. Therapeutic Implications For Implant Dentistry

A growing biomaterials literature targets macrophage polarization directly at the implant surface, and although these studies are not always framed explicitly in terms of “efferocytosis,” their design logic mirrors the

pro-efferocytic strategies discussed in Section VIII. Zhang et al.[31] developed a laser-drilled titanium implant coating releasing a microRNA (miR-27a) agomir that reprogrammed macrophage mitochondrial metabolism from glycolysis toward oxidative phosphorylation, promoted M1-to-M2 repolarization, enhanced osteogenic differentiation of bone marrow mesenchymal stem cells, and reduced ligature-induced peri-implant bone loss in rats. Han et al.[32] engineered a nanoplatform combining antibacterial photodynamic therapy with reactive-oxygen-species-scavenging nanozyme activity that, after eliminating biofilm, modulated macrophage polarization toward the M2 phenotype and improved healing in a rat peri-implantitis model. Qin et al.[33] described the antimicrobial peptide KL-12, which combines direct antibacterial activity against *P. gingivalis* and its gingipain proteases with a distinct capacity to promote M2 macrophage differentiation. Considered alongside the direct proof-of-concept established by Tan et al.[28] for efferocytosis-restoring PEEK coatings, these convergent strategies suggest that implant-surface engineering explicitly designed to promote efferocytic clearance and M2 reprogramming—rather than pursuing antibacterial or osteoconductive properties alone—may represent a rational next step in preventing peri-implantitis and improving osseointegration outcomes, particularly in medically compromised patients such as those with diabetes or a smoking history.

A complementary, already clinically available autologous strategy is platelet-rich fibrin (PRF), whose three-dimensional fibrin scaffold sustains release of PDGF, VEGF, and TGF- β while its retained leukocyte population is associated with reduced IL-1 β and TNF- α alongside increased IL-4 and IL-10 expression at the healing site—a cytokine signature broadly consistent with a pro-resolving, M2-favoring microenvironment, even though PRF's reported benefits have not yet been mechanistically framed in terms of efferocytosis specifically.[35] Current evidence for PRF nonetheless remains uneven across applications: it is comparatively stronger for soft-tissue healing and peri-implant biomodulation, more mixed for its use as a stand-alone bone-graft substitute in large defects, and still early-stage for injectable (i-PRF) non-surgical adjuncts in peri-implant mucositis and periodontitis, underscoring that its integration into an efferocytosis-informed therapeutic framework remains speculative pending mechanistic study.[35]

VIII. Emerging Pro-Efferocytic Therapeutic Strategies

A convergent theme across the reviewed literature is that pharmacological or biomaterial-based restoration of efferocytic capacity ameliorates experimental periodontal and periapical disease, suggesting several translational avenues for dental practice.

A. Specialized Pro-Resolving Mediators (SPMs)

Lipoxins, resolvins, protectins, and maresins actively promote efferocytosis and bacterial phagocytosis while suppressing neutrophil recruitment, with documented efficacy in preclinical models of marginal periodontitis and pulpitis.[3,4] Their local, sustained-release delivery within the periodontal pocket or root canal system represents a promising but still largely preclinical therapeutic direction.

B. PPAR- γ Agonism

Rosiglitazone-mediated PPAR- γ activation restored efferocytic capacity and reduced inflammatory severity in chronic apical periodontitis,[7] and defective PPAR- γ activation likewise underlies the pathological live-neutrophil-trapping phenotype induced by *P. gingivalis*,[15] reinforcing PPAR- γ as a mechanistic hub worth targeting.

C. Bridging-Molecule And Receptor-Targeted Approaches

DEL-1 supplementation or upregulation restored efferocytic clearance and resolved experimental periodontitis,[6] while the erythropoietin-derived peptide ARA290 enhanced efferocytosis and promoted resolution of apical periodontitis.[14]

D. Vitamin D Analogs And Natural Compounds

Eldecalcitol restored SOCE-dependent efferocytosis and reduced bone loss in diabetic periodontitis,[21] the flavonoid baicalin enhanced efferocytosis via RhoA/ROCK inhibition,[19] and oral-care ingredients such as dipotassium glycyrrhizate (GK2) and hinokitiol upregulated efferocytosis-related receptors (MERTK, LRP1) and metabolic machinery (LXR α , ABCA1) in vitro, suggesting a mechanistic rationale for certain anti-inflammatory oral hygiene formulations.[5]

E. Biomaterials And Peptide Engineering

Co-assembled amphiphile peptides that adsorb “bridging molecules” enhanced macrophage efferocytosis and periodontal tissue regeneration upon local injection,[34] while antimicrobial-peptide/exosome hydrogels combined bacterial killing with pro-efferocytic, pro-resolving effects in situ[20]—illustrating how efferocytosis-enhancing design principles can be integrated into next-generation local drug-delivery systems for periodontal regeneration.

IX. Clinical Implications For Dental Practice

Although the evidence reviewed here derives predominantly from cell-culture and animal models, several clinical implications can be anticipated. First, efferocytic capacity may eventually serve as a biomarker of periodontal disease activity or healing potential, particularly in patients with diabetes, in whom hyperglycemia measurably

impairs this pathway:[12,21,22] glycemic control therefore remains not only a systemic health priority but plausibly a periodontal pro-resolution strategy in its own right. Second, adjunctive pro-efferocytic agents—whether SPM-based, PPAR- γ -targeted, or delivered through engineered biomaterials—could complement conventional scaling and root planing, endodontic therapy, or regenerative surgery by actively promoting resolution rather than solely suppressing inflammation or removing bacterial burden. Third, the demonstrated coupling between efferocytosis and bone formation[9,11] suggests that timing and modulation of macrophage efferocytic activity could become a relevant variable in guided bone regeneration, socket preservation, and peri-implant therapy protocols. Finally, the identification of *P. gingivalis*-specific efferocytosis-evasion mechanisms[15-17] reinforces the rationale for pathogen-targeted adjunctive therapies that go beyond mechanical debridement to address the host's resolution failure directly.

These translational prospects should also be read against the broader clinical landscape in which they would need to operate. As of 2025–2026, major international consensus bodies—the AO/AAP, the Korean Academy of Periodontology, and the Osstem Global Consensus Meeting—have published divergent frameworks for peri-implantitis management and have not converged on a single decision threshold for surgical intervention versus explantation, even though prognostic data indicate that the risk of implant loss rises roughly fifteen-fold once relative bone loss exceeds 25% of implant length, and twenty-fold beyond 50%.[36] Mechanistic biomarkers of efferocytic competence, if validated in humans, could in principle help refine these thresholds by identifying which compromised implants retain sufficient pro-resolution capacity to justify regenerative therapy rather than explantation; however, this application remains entirely speculative at present and would require dedicated prospective study before any clinical translation.[36]

X. Limitations And Future Directions

This narrative review has several limitations inherent to its methodology, which does not follow a systematic or PRISMA-based protocol and therefore cannot exclude selection bias in the literature discussed. The overwhelming majority of the reviewed studies are preclinical—based on murine or rat models, or on human and murine cell cultures—and clinical trials directly testing pro-efferocytic interventions in human periodontal or endodontic patients are, to date, lacking. Heterogeneity in experimental models (ligature-induced versus LPS-induced periodontitis, apical lesion models, diabetic models induced by streptozotocin) further complicates direct comparison across studies. Future research should prioritize translational studies evaluating the safety and efficacy of SPM-based or PPAR- γ -targeted local therapies in human clinical trials, the development of validated biomarkers of periodontal efferocytic capacity that could guide personalized treatment, and longitudinal studies examining whether glycemic control measurably restores periodontal efferocytosis in patients with type 2 diabetes.

XI. Conclusion

The evidence synthesized in this review positions efferocytosis as a mechanistic bridge connecting neutrophil biology, macrophage plasticity, and bone homeostasis to the pathogenesis and potential resolution of periodontal, periapical, and peri-implant disease. Defective efferocytosis—whether driven by pathogen evasion strategies, hyperglycemia, titanium-particle-induced pyroptosis, or intrinsic molecular deficits in bridging receptors and pro-resolving pathways—perpetuates chronic inflammation and bone destruction, while its pharmacological or biomaterial-based restoration consistently promotes resolution and tissue repair in preclinical models. Extending this framework to implant dentistry, the reviewed evidence indicates that peri-implantitis is characterized by a persistent M1 macrophage dominance consistent with failed efferocytic resolution, aggravated by titanium-driven inflammasome activation and pyroptosis, and that osseointegration itself causally depends on efficient neutrophil-to-macrophage efferocytic handoff to trigger the M1-to-M2 transition required for angiogenesis and bone formation—a mechanism now directly demonstrated in diabetic models and restorable through efferocytosis-promoting implant surface engineering. For clinicians and researchers in dentistry, efferocytosis offers both an explanatory framework for the chronicity of periodontal and peri-implant disease and a concrete set of molecular targets for the next generation of adjunctive, pro-resolution therapies and implant surface designs. Bridging the current gap between mechanistic preclinical findings and clinical application represents a valuable direction for future research in periodontology, endodontics, and implant dentistry, with the potential to translate directly into improved outcomes for patients treated within both private practice and public oral health systems.

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