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Potential role of ferroptosis in diabetic periodontitis: current evidences and clinical implications - A review

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Abstract:

Diabetic periodontitis is driven by hyperglycaemia and periodontal inflammation through a bidirectional relationship. Ferroptosis, an iron-dependent form of regulated cell death, has emerged as a key mechanism in both diseases. It promotes oxidative stress, inflammation and alveolar bone loss under hyperglycaemic conditions. Dysregulation of GPX4, SLC7A11 and transferrin receptor supports ferroptosis as a mechanistic link. Thus, ferroptosis is a promising mechanistic and therapeutic target for diabetic periodontitis.

Keywords: Ferroptosis, diabetic periodontitis, lipid peroxidation, glutathione peroxidase 4 (GPX4), oxidative stress, iron metabolism, alveolar bone resorption, periodontal disease

Background:

Periodontitis is a chronic inflammatory disease of the supporting structures of the teeth, representing one of the most prevalent oral conditions globally and a recognised complication of diabetes mellitus. The coexistence of hyperglycaemia and periodontal infection creates a self-reinforcing cycle of systemic and local tissue damage, with advanced glycation end-products (AGEs) and reactive oxygen species (ROS) playing central roles in disease amplification [1]. The precise cellular mechanisms by which diabetic metabolic derangements intensify periodontal destruction, however, remain an active area of investigation [2]. Ferroptosis is a recently characterised, iron-dependent form of regulated cell death distinct from apoptosis, necrosis and autophagy. It is driven primarily by the accumulation of lipid peroxides on cellular membranes, a process normally suppressed by the glutathione peroxidase 4 (GPX4) axis. Perturbations in iron homeostasis and glutathione metabolism, both of which are significantly altered in diabetic states, create conditions highly permissive for ferroptotic cell death [3]. Recent studies have begun to document ferroptotic signatures within periodontal tissues, suggesting that this pathway may constitute a critical but previously unrecognised mechanism of periodontal cell loss in diabetes [4]. In diabetic periodontitis, the convergence of elevated intracellular iron, depleted antioxidant defences and heightened inflammatory mediator production creates an environment where ferroptosis may be preferentially activated in periodontal ligament cells, gingival fibroblasts and osteoblasts [5]. The destruction of these cell populations, compounded by impaired regenerative capacity inherent to the diabetic milieu, may account for the accelerated attachment loss and bone resorption clinically observed in diabetic patients [6]. Therefore, it is of interest to examine the current evidence linking ferroptosis to diabetic periodontitis, elucidate the underlying molecular mechanisms and explore the translational implications for clinical periodontal management.

Ferroptosis:**Molecular mechanisms and key regulators:**

Ferroptosis was first formally described by Dixon *et al.* in 2012 [9] as a non-apoptotic, iron-dependent cell death mechanism

characterised by the lethal accumulation of lipid hydroperoxides. The central executor of ferroptosis is the depletion or inactivation of GPX4, the primary enzyme responsible for reducing phospholipid hydroperoxides to non-toxic alcohols using glutathione (GSH) as a cofactor [7]. When GPX4 activity is compromised, poly-unsaturated fatty acid-containing phospholipids on cellular membranes undergo iron-catalysed Fenton reactions, generating cytotoxic lipid radicals that ultimately breach membrane integrity [8]. Several upstream regulators modulate ferroptotic sensitivity. The system Xc⁻ transporter, encoded by SLC7A11, imports cystine for intracellular GSH synthesis and is a major determinant of ferroptotic resistance. Reduced expression of SLC7A11 limits cystine availability, depleting GSH and rendering cells vulnerable to lipid peroxidation [9]. Transferrin receptor 1 (TfR1) and ferritin govern cellular iron uptake and storage respectively; dysregulation of these proteins elevates the labile iron pool, accelerating Fenton chemistry and lipid radical generation. The CoQ10-FSP1 axis has been identified as a parallel, GPX4-independent defence against ferroptosis, further underscoring the complexity of its regulation [10].

Diabetes mellitus and ferroptotic susceptibility:

Diabetes mellitus induces systemic alterations in iron metabolism, redox balance and inflammatory signalling that collectively heighten ferroptotic susceptibility. Hyperglycaemia promotes the overproduction of ROS via mitochondrial dysfunction, NADPH oxidase activation and AGE-RAGE signalling, depleting intracellular GSH and impairing GPX4 function [11]. Elevated serum ferritin and disrupted hepcidin regulation observed in type 2 diabetes increase the labile iron pool within peripheral tissues, priming cells for iron-dependent lipid peroxidation [12]. Ferroptotic cell death has been documented in multiple diabetic target organs, including the kidney, retina, peripheral nerves and myocardium, where GPX4 down regulation and lipid peroxide accumulation correlate with the severity of end-organ damage [13]. Importantly, AGEs have been shown to directly suppress SLC7A11 expression through NF-κB-mediated transcriptional repression, creating a mechanistic bridge between the hyperglycaemic milieu and

impaired ferroptotic defence [14]. These findings establish diabetes as a condition of heightened systemic ferroptotic vulnerability, with implications extending to the periodontium.

Evidence for ferroptosis in periodontal disease:

A growing body of experimental evidence has begun to implicate ferroptosis in the pathogenesis of periodontitis. Transcriptomic analyses of gingival tissues from periodontitis patients have revealed significant up regulation of ferroptosis-associated genes, including ACSL4, LPCAT3, NOX2 and TfR1, alongside down regulation of GPX4 and SLC7A11, compared with periodontally healthy controls [19]. Elevated malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), surrogate markers of lipid peroxidation and ferroptosis, have been detected in gingival crevicular fluid and biopsy specimens from periodontitis sites [15]. *In vitro* studies using human periodontal ligament cells exposed to *Porphyromonas gingivalis* lipopolysaccharide have showed increased intracellular iron accumulation, GSH depletion and mitochondrial membrane shrinkage consistent with ferroptotic morphology. Ferroptosis inhibitors such as ferrostatin-1 and deferoxamine partially rescued cell viability in these models, providing direct mechanistic evidence for ferroptotic cell death in a periodontitis-relevant context [16]. Furthermore, osteoblasts and osteoclasts within the alveolar bone microenvironment have been shown to be sensitive to ferroptotic stimuli, with ACSL4-mediated phospholipid peroxidation promoting osteoblast apoptosis and enhancing osteoclastogenesis through NF- κ B and RANKL pathways [17].

Ferroptosis at the intersection of diabetes and periodontitis:

The diabetic periodontal microenvironment presents a uniquely permissive setting for ferroptosis. Hyperglycaemia-induced oxidative stress impairs the antioxidant defences of gingival fibroblasts and periodontal ligament cells, reducing GSH availability and GPX4 activity below thresholds required to suppress lipid peroxidation [18]. Simultaneously, the AGE-mediated downregulation of SLC7A11 limits cystine import, further constraining GSH biosynthesis and amplifying ferroptotic vulnerability in the periodontal compartment. Animal models of streptozotocin-induced diabetic periodontitis have showed significantly greater ferroptotic cell death in periodontal tissues compared with non-diabetic periodontitis controls, with histological evidence of increased lipid peroxidation products, reduced GPX4 immunostaining and enhanced alveolar bone loss [19]. Ferroptosis also intersects with the inflammatory amplification loop characteristic of diabetic periodontitis: lipid peroxidation products activate macrophages to produce IL-1 β , TNF- α and IL-6, cytokines that in turn suppress GPX4 expression and promote further ferroptotic susceptibility, creating a self-sustaining cycle of tissue destruction [20].

Clinical implications and therapeutic perspectives:

The identification of ferroptosis as a pathological mechanism in diabetic periodontitis opens several avenues for therapeutic

intervention. Pharmacological strategies targeting the GPX4-GSH axis, including N-acetylcysteine (NAC) supplementation to replenish GSH and small-molecule GPX4 activators, have shown efficacy in preclinical ferroptosis models and may hold potential as adjuncts to conventional periodontal therapy in diabetic patients [21]. Iron chelation therapy using deferoxamine or deferrioxime has demonstrated capacity to reduce the labile iron pool, attenuate lipid peroxidation and preserve periodontal tissue architecture in experimental diabetic periodontitis [22]. Nutraceutical approaches including vitamin E (α -tocopherol) and omega-3 fatty acids, which competitively inhibit PUFA peroxidation and Nrf2-activating compounds such as sulforaphane, which transcriptionally upregulate GPX4 and SLC7A11, represent accessible, low-risk strategies that warrant clinical investigation in the diabetic periodontitis population [23]. From a diagnostic standpoint, gingival crevicular fluid MDA and 4-HNE levels may serve as novel biomarkers of ferroptotic activity and periodontal disease severity in diabetic patients, enabling more precise monitoring of treatment response. From a practice standpoint, these findings support incorporating ferroptosis-related risk assessment into the periodontal management of diabetic patients, particularly those with poor glycaemic control, who may represent a subgroup most likely to benefit from adjunctive antioxidant or iron-modulating strategies alongside conventional scaling and root planing. Stratifying patients by markers of ferroptotic activity, such as gingival crevicular fluid MDA or 4-HNE could in principle help clinicians identify cases of disproportionately severe attachment loss relative to plaque burden and tailor maintenance intervals or adjunctive therapy accordingly [24]. Importantly, ferroptosis-targeted adjuncts are unlikely to be effective in isolation, since hyperglycaemia itself is the principal upstream driver of ferroptotic susceptibility in periodontal tissue; effective management therefore requires close collaboration between periodontists and physicians managing glycaemic control, with antioxidant or iron-chelating adjuncts positioned as complements to, rather than substitutes for, glycaemic optimisation and standard periodontal therapy. Translating these mechanistic insights into clinical practice will require well-designed randomized controlled trials, since current evidence for ferroptosis-targeted adjuncts in diabetic periodontitis rests almost entirely on preclinical and *in vitro* models [25]. Practical considerations also warrant attention before clinical adoption, including the systemic safety profile of iron chelators such as deferoxamine and deferrioxime outside their established indications, appropriate dosing of nutraceutical adjuncts such as N-acetylcysteine and sulforaphane in periodontal populations and the cost and feasibility of incorporating ferroptosis biomarker testing into routine periodontal diagnostics. Addressing these questions will be essential to determine whether ferroptosis-targeted strategies can move from a promising mechanistic concept to a validated component of periodontal care in diabetic patients [26-28].

Conclusion:

Ferroptosis may contribute to accelerated periodontal destruction in diabetic periodontitis. Iron dysregulation,

glutathione depletion, and lipid peroxidation may promote ferroptotic tissue injury. Targeting ferroptosis may provide a promising adjunctive therapeutic approach.

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