

The AGE-RAGE Axis in Periodontitis – A Narrative Review

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Abstract Periodontitis is a chronic inflammatory disease influenced by microbial, metabolic, and molecular mechanisms, notably the AGE–RAGE axis. Advanced glycation end products (AGEs), formed via the Maillard reaction, accumulate in periodontal collagen, stiffening tissues and impairing repair. Binding to RAGE triggers oxidative stress and NF-κB–driven inflammation, promoting cytokine release, collagen breakdown, and bone resorption. Membrane RAGE amplifies damage, while soluble RAGE offers protection. Diabetes and periodontitis reinforce each other through AGE–RAGE signaling, with inflamed periodontal tissues acting as endogenous AGE sources. Risk factors include hyperglycemia, aging, smoking, and renal impairment. Therapy combines scaling with adjunctive antioxidants, AGE breakers, and RAGE inhibitors.

INTRODUCTION

Periodontitis is a chronic inflammatory disease of the supporting tissues of the teeth, characterized by gingival swelling, bleeding, pocket formation, and progressive alveolar bone loss.¹ It arises when bacterial biofilm triggers an exaggerated host immune response that damages connective tissue and bone rather than merely eliminating pathogens.² Beyond microbial factors, metabolic and molecular mechanisms play a crucial role in disease progression. One such mechanism involves advanced glycation end products (AGEs).¹

AGEs are stable compounds formed when sugars react non-enzymatically with proteins, lipids, or DNA. In periodontal collagen, which has slow turnover rate, it readily accumulates AGE crosslinks. This reduces tissue elasticity and repair capacity, leaving the periodontium more susceptible to damage.² AGEs accumulate in tissues and blood, where they bind to the receptor RAGE on immune and endothelial cells. This triggers ROS production and NF-κB activation, raising cytokines such as TNF-α and IL-6. The resulting inflammation contributes to complications like vascular damage, organ fibrosis, and nerve injury in diabetes and aging. Dietary AGEs and reduced clearance in kidney disease further increase the AGE burden, worsening systemic inflammation and oxidative stress.³

Clinical studies confirm a bidirectional relationship between periodontitis and diabetes, showing that periodontal therapy can reduce systemic inflammation and lower HbA1c by 0.29–0.48% within three months.⁴ On one side, periodontal inflammation elevates systemic cytokines such as TNF-α and IL-6, impairing insulin signaling and driving insulin resistance and hyperglycemia.⁵ On the other side, hyperglycemia accelerates AGE formation, and these AGEs bind to RAGE receptors on gingival and immune cells, triggering oxidative stress and NF-κB activation.⁶ This cascade amplifies cytokine release, collagen breakdown, and bone resorption, creating a cycle in which diabetes and periodontitis continually worsen each other through the AGE–RAGE axis.⁷

STRUCTURE OF AGEs

AGEs are heterogeneous molecules formed through the Maillard reaction, a sequence of non-enzymatic glycation steps.⁸ They accumulate in tissues with slow turnover, such as the periodontal ligament, altering structural integrity and repair capacity. The major types include:

- **Nε-carboxymethyl-lysine (CML):** a small, common AGE formed when a sugar fragment attaches to the side chain of lysine in a protein; it does not cross-link two proteins but marks the protein as “glycated.” CML is mainly a chemical marker that signals a protein has been sugar modified; pentosidine and glucosepane actually glue protein fibres together.⁹
- **Pentosidine:** a fluorescent cross-link that connects a lysine residue on one protein to an arginine residue on another, so it physically ties protein strands together. When cross-links form in long-lived collagen (like periodontal ligament collagen), the fibres become stiffer and less flexible, so the tissue cannot stretch, remodel, or heal as well after injury or infection.¹⁰
- **Glucosepane:** a non-fluorescent but abundant cross-link that links lysine and arginine residues within and between collagen molecules; it is estimated to account for the majority of AGE-mediated cross-links in human collagen.¹¹

Mechanism of Formation^{12,13,14}

AGEs form via the Maillard reaction:

- **Schiff base (initial stage):** When a reducing sugar such as glucose reacts with the ϵ -amino group of lysine on a protein, it forms a temporary compound called a Schiff base. This bond is unstable and reversible, representing the earliest step in non-enzymatic glycation.
- **Amadori rearrangement (stabilization):** The Schiff base undergoes a chemical rearrangement to produce a more stable ketoamine, known as an Amadori product. This intermediate is clinically relevant, as it is the basis for HbA1c measurement in diabetes.
- **Glycoxidation and fragmentation (irreversible stage):** Over time, Amadori products undergo oxidation and fragmentation, leading to the formation of irreversible advanced glycation end products (AGEs) such as N ϵ -carboxymethyl-lysine (CML), pentosidine, and glucosepane. Some of these AGEs create cross-links between collagen molecules, resulting in increased stiffness, reduced elasticity, and impaired tissue remodelling in periodontal structures.

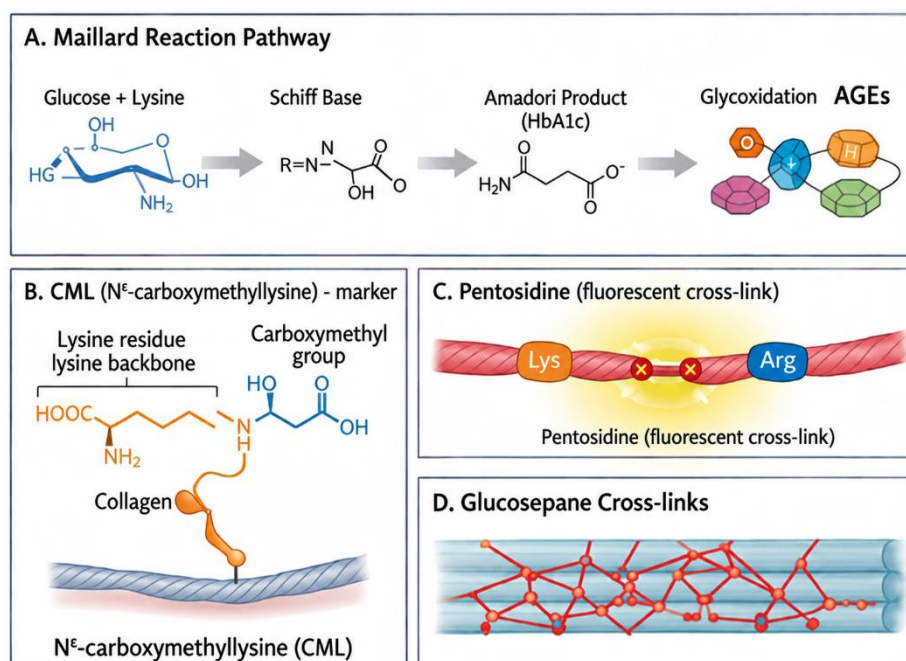


Figure 1. Schematic overview of AGE chemistry and representative AGE structures found in periodontal tissues. Panel A shows the three-step Maillard pathway from initial Schiff base formation to irreversible AGE products. Panels B–D illustrate common AGE modifications: CML (marker), pentosidine (fluorescent cross-link), and glucosepane (major non-fluorescent collagen cross-link). Color key: sugars blue; amino acids orange; cross-links red.

THE RECEPTOR FOR AGEs (RAGE)

RAGE is a 35-kDa transmembrane receptor belonging to the immunoglobulin superfamily, expressed at low levels in healthy tissues but markedly upregulated in diabetes and chronic inflammation, making it a central mediator of AGE-driven pathology.³ RAGE expression is detected across multiple cell types, including, gingival epithelial cells, fibroblasts, endothelial cells, osteoblasts, osteoclasts, and macrophages, where its activation triggers oxidative stress and NF- κ B-mediated inflammation, contributing to connective tissue breakdown and alveolar bone loss.^{8,9}

Importantly, RAGE exists in different structural forms (Isoforms) that determine how it influences disease progression:

- **mRAGE:** The full-length, membrane-bound receptor that transduces intracellular signals and activates oxidative and inflammatory pathways.⁵
- **sRAGE:** A soluble form that acts as a decoy receptor, binding circulating AGEs and preventing their interaction with mRAGE. Low serum sRAGE levels have been associated with severe periodontitis in type 2 diabetes.^{1,6}

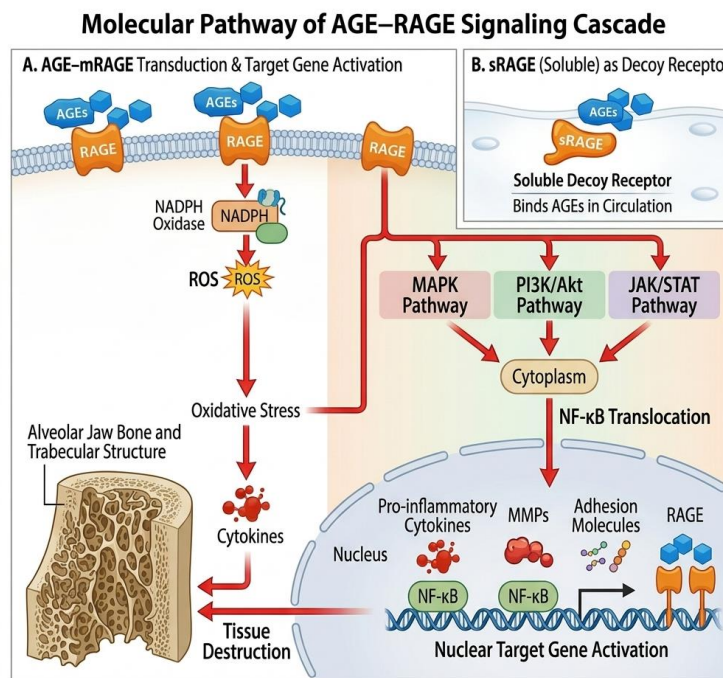


Figure 2. The role of RAGE isoforms (mRAGE and sRAGE) and the downstream molecular signaling cascade in alveolar bone destruction.

AGE-RAGE SIGNALING IN PERIODONTAL DESTRUCTION

AGEs exert their pathogenic effects primarily through binding to the receptor for advanced glycation end products (RAGE), a 35-kDa transmembrane receptor of the immunoglobulin superfamily.¹⁵ This interaction activates multiple intracellular pathways that amplify oxidative stress and inflammation.¹⁵

Molecular Pathway of AGE-RAGE

The mechanism of AGE-RAGE signaling operates through a well-defined cascade. Binding of AGEs to membrane-bound RAGE activates NADPH oxidase, generating ROS, and engages MAPK, PI3K/Akt, and JAK/STAT pathways that drive NF-κB translocation. Activated NF-κB then induces pro-inflammatory cytokines, MMPs, adhesion molecules, and RAGE itself, amplifying tissue destruction^{16,17}

Table no. 1: This table illustrates how AGE-RAGE activation alters cellular behaviour, leading to tissue destruction and impaired regeneration.

Cell type	Effect	Periodontal Outcome
Gingival fibroblast	↓ Collagen synthesis, ↑ apoptosis, ↑ MMPs	Loss of attachment, impaired healing
Osteoblast	↓ RUNX2 expression, ↑ apoptosis	Reduced bone formation
Osteoclast	↑ RANKL-mediated differentiation	Alveolar bone resorption
Endothelial cell	↑ Permeability, ↑ leukocyte adhesion	Edema, sustained inflammation
Macrophage	M1 polarization	Chronic inflammation

ENDOGENOUS ROLE OF PERIODONTITIS ¹

In a systematic review registered by Chopra, A.; Jayasinghe, T.N.; Eberhard, J., included 13 observational studies were analyzed to evaluate the link between periodontitis and advanced glycation end products (AGEs). The collective evidence showed that individuals with periodontitis consistently showed higher levels of advanced glycation end products (AGEs) in their saliva, gingival crevicular fluid, and blood compared to those without periodontal disease. This increase was seen not only in individuals with diabetes but also in individuals who are otherwise healthy. In other words, inflamed periodontal tissues themselves can raise AGE levels, independent of blood sugar status. Inflamed periodontal tissues act as chronic infectious foci where pathogens such as *Porphyromonas gingivalis* and *Tannerella forsythia* activate host immune cells, leading to the release of reactive oxygen species (ROS) and proteolytic enzymes. These ROS enter systemic circulation, trigger mitochondrial stress, and promote non-enzymatic glycation of proteins and lipids, thereby elevating advanced glycation end products (AGEs). AGEs impair insulin receptor signaling, stimulate proinflammatory cytokines (TNF-α, IL-6, IL-17, CRP), and drive adipokine release and hyperlipidemia, all of which

worsen insulin resistance and hyperglycemia. Importantly, certain oral bacteria such as *Tannerella forsythia* are shown to produce methylglyoxal, a key precursor of AGEs, further exacerbating this process. Together, these findings highlight that periodontitis acts as an endogenous source of AGEs, helping explain the two-way relationship between Periodontal disease and diabetes.

FACTORS MODULATING AGEs ACCUMULATION

Systemic and local conditions significantly modulate the formation and deposition of advanced glycation end products (AGEs), thereby affecting periodontal tissue integrity. Hyperglycemia increases substrate availability for glycation and remains the principal mechanism in diabetes. Oxidative stress, particularly from reactive oxygen species generated during periodontal inflammation, accelerates the conversion of early glycation products into AGEs. Advancing age contributes through prolonged collagen turnover, permitting gradual accumulation within the periodontal ligament. Smoking introduces exogenous AGEs and enhances oxidative stress, compounding periodontal damage, especially in diabetic individuals. Renal impairment reduces clearance of circulating AGEs, expanding the systemic burden and intensifying periodontal inflammation. Collectively, these factors explain the elevated AGE load observed in periodontitis and its amplification in systemic disease states.¹⁸

DISCUSSION

Periodontal tissues, especially collagen, have slow turnover, making them prone to AGE accumulation. These AGE crosslinks stiffen the tissue, reduce healing, and increase fragility. When RAGE is upregulated, bacterial challenge is converted into persistent NF- κ B-driven inflammation, leading to connective tissue breakdown and accelerated bone loss¹⁹. This explains why diabetic patients often show faster periodontal destruction even with similar plaque levels.²⁰ Clinically, this manifests as poorer response to scaling and root planing (SRP) in uncontrolled diabetes, but also highlights how periodontal therapy can improve glycemic control.^{19,21,22} Together, these findings support the concept of host modulation, where targeting AGE–RAGE signaling could enhance treatment outcomes. However, longer-term biomarker studies and trials of RAGE inhibitors are needed before these approaches can be widely applied.

CLINICAL AND THERAPEUTIC IMPLICATIONS

1. **Screening:** The ADA and AAP recommend physicians screen diabetic patients for periodontitis and dentists screen severe periodontitis cases for dysglycemia, reinforcing the bidirectional link.⁶
2. **Glycemic control:** Maintaining HbA1c <7.0% reduces new AGE formation and limits periodontal damage.⁴
3. **Adjunctive therapy:** Agents such as antioxidants and emerging AGE-breakers or RAGE blockers may enhance outcomes when combined with SRP.^{23,24}
4. **Biomarkers:** GCF CML and serum sRAGE are under investigation as tools for risk stratification and personalized management.¹

CONCLUSION

The AGE–RAGE pathway is central to the link between diabetes and periodontitis. AGE buildup makes periodontal tissues structurally weak and highly reactive to inflammation, driving progressive destruction. Because diabetes and periodontitis worsen each other through this mechanism, coordinated medical and dental care is essential. Conventional therapy remains the foundation, but adjunctive strategies that block AGE–RAGE signaling may offer promising future directions for reducing both oral and systemic complications.

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