Dentistry 3000

Vol 14, No 1 (2026)
ISSN 2167-8677 (online)
DOI 10.5195/d3000/2026.1131

The Role of Advanced Glycation End Products in the Pathogenesis of Diabetes-Associated Periodontitis

Rafal Ali Salman, Batool Hassan Al-Ghurabi

College of Dentistry, University of Baghdad, Baghdad, Iraq

Abstract

Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of the tooth-supporting tissues and is also markedly affected by systemic conditions, especially diabetes mellitus. In diabetic patients, hyperglycemia leads to the formation and accumulation of advanced glycation end products in periodontal tissues. The binding of these products with their cellular receptor activates a proinflammatory signaling cascade, increases oxidative stress, and interferes with immune regulation. These mechanisms lead to enhanced periodontal inflammation, delayed healing, and increased alveolar bone loss. This review highlights evidence of the molecular, inflammatory, and microbial actions of advanced glycation end products in the pathogenesis of diabetes-associated periodontitis and their potential application in the diagnosis and treatment of periodontal disease in patients with diabetes.

Open Access

Citation: Salman RA et al. (2026) The Role of dvnced Glycation End Products in the Pathogenesis of Diabetes-Associated Periodontitis. Dentistry 3000. 1:a001 doi:10.5195/d3000.2026.1131
Received: December 30, 2025
Accepted: January 7, 2026
Published: February 16, 2026

Email: batoolamms@codental.uobaghdad.edu.iq

Introduction

Periodontitis (PD) is a multifactorial chronic inflammatory disease affecting the gingiva, periodontal ligament, cementum, and alveolar bone and is one of the major causes of tooth loss around the globe. PD is caused by a dysbiotic subgingival biofilm, and while initiated by bacteria, the host immune-inflammatory response determines the severity and progression of tissue destruction and is greatly impacted by systemic diseases like diabetes mellitus (DM) [1]. Epidemiological and clinical studies persistently show that patients with diabetes exhibit a higher prevalence, greater severity, and more rapid progression compared with non-diabetic individuals [2,3]. DM occurs due to chronic hyperglycemia because of improper insulin secretion or action. Prolonged hyperglycemia leads to oxidative stress, immunologic abnormalities, and low-grade chronic inflammation, which make periodontal tissues more vulnerable to destruction. Increased formation and deposition of advanced glycation end products (AGEs) appear to be a key pathogenic pathway among the molecular mechanisms connecting DM with periodontal disease [3]. AGEs are heterogeneous compounds induced by non-enzymatic reactions of reducing sugars with proteins, lipids, or nucleic acids; their formation is vastly accelerated by hyperglycemic conditions. In patients with diabetes-associated PD, increased levels of AGEs have been found in periodontal tissues and body fluids [4]. The biological action occurs through their action on the receptor for advanced glycation end products (RAGE), expressed on many different cell types found within periodontal tissues such as epithelial cells, fibroblasts, endothelial cells, and immune cells [5]. The AGE–RAGE axis activation induces intracellular signal transduction pathways, especially nuclear factor kappa B (NF-Kb), causing an enhanced release of pro-inflammatory cytokines and oxidative stress [6]. The aim of this review was to assess the contribution of AGEs in PD associated with DM.

Material and Methods

A comprehensive analysis of the electronic literature was carried out using the databases Google Scholar, Web of Science, and PubMed. Only studies published since 2020 were eligible for inclusion. The search strategy

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consisted of the following combinations: AGEs, periodontitis, diabetic periodontitis, diabetes mellitus, RAGE, methylglyoxal, and inflammation. Search results were narrowed using Boolean operators. The first search resulted in 94 records, with 63 studies meeting the eligibility criteria after the title, abstract, and full-text screening.

Inclusion Criteria

This review included studies that were published between 2020 and 2024 in English and were original research articles, systematic reviews, narrative reviews, or case-control studies that investigated AGE–RAGE signaling or other inflammatory mechanisms in periodontitis associated with diabetes mellitus.

Exclusion Criteria

Studies published before 2020, not written in English, conference abstracts, editorials, letters to the editor, animal-only studies, and articles not specifically addressing the relationship between advanced glycation end products, periodontitis, and diabetes mellitus were excluded (Figure 1).

Periodontal Disease

Periodontal disease is a condition that affects the tissues that surround and support the teeth and includes a broad group of inflammatory diseases that cause PD [7]. Among these diseases, gingivitis, the mildest form, is reversible with improved oral care, but in the absence of early intervention, gingivitis progresses to PD, a chronic and irreversible inflammatory condition, with clinical signs of inflammation, such as bleeding on probing (BOP), gingival recession, and periodontal pocket development. There are several risk factors that influence these diseases, which are categorized as modifiable risk factors, e.g., smoking, or non-modifiable risk factors, e.g., genetic disorders [8]. Nevertheless, some of the signs of inflammation, such as BOP, are reduced in smokers compared to non-smokers [9]. For instance, many virulence factors of periodontopathic microbes including lipopolysaccharide, are stimulants of inflammatory responses from gingival tissues [10].

Periodontitis

Periodontitis is a chronic multifactorial inflammatory disease initiated by a dysbiotic subgingival biofilm but driven primarily by an inappropriate host immune response [11]. Continued stimulation of innate and adaptive immune pathways culminates in excessive secretion of pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and reactive oxygen species (ROS) that causes progressive loss of the ligament of the teeth and the alveolar bone [12]. PD is clinically defined by gingival inflammation, BOP, periodontal pocket depth, clinical attachment loss (CAL), and radiographic evidence of alveolar bone loss [13]. The 2017 World Workshop classification of PD categorizes it according to extent and severity. PD is classified based on severity as localized (≤30% of teeth involved) or generalized (>30% of teeth affected). Severity is staged based on the amount of interdental CAL and radiographic bone loss. Stage I and Stage II have been defined as having interdental CAL of 1–2 mm and radiographic bone loss of less than 15% and CAL of 3–4 mm and bone loss of between 15% and 33%, respectively; Stage III has CAL greater than 5 mm and radiographic bone loss extending to the middle third of the root, while Stage IV has CAL of ≥5 mm, radiographic bone loss beyond the middle third of the root, and loss of five or more teeth due to PD [14,15].

Certain modifying factors have been described to influence the severity and progression of disease, including poor oral hygiene, smoking, genetic predisposition, and systemic diseases, such as DM [16]. In addition to its local destructive effects, PD adds to systemic inflammatory burden, and studies have demonstratively linked PD to systemic diseases, most notably DM and cardiovascular disease, establishing PD as an oral and systemic inflammatory disease [17]. Pathologically, PD represents a failure of homeostasis between the subgingival microbiota and the host defense system. PD is now described as a dysbiosis-associated condition, not the result of specific pathogens alone, but rather, a state of altered biofilm composition and metabolic activity that creates a sustained inflammatory milieu. The dysbiotic environment is conducive to keystone pathogens that can modulate host immune responses, impair bacterial clearance, and ensure chronic inflammation [18]. Reduced resolution of inflammation is a hallmark of PD. Physiologically, inflammation associated with PD is conservatively regulated, mediated by specialized pro-resolving mediators [19]. Executing these pathways, however, leads to immune infiltration in tissues, and, common in PD, the resolution pathways are impaired. This could lead immune cells to stay longer in the tissues, causing tissue-destructive mediators to be released continuously. Such an ongoing dysregulated inflammatory response continues destruction of connective tissue and resorption of alveolar bone, even in the absence of further microbial challenges [20].

Interindividual variability is evident in clinical presentation and rate of progression in PD. Disease susceptibility and progression are ultimately dictated by host-related factors, including immune responsiveness, genetic polymorphisms, and the epigenetic regulation of inflammatory processes [21]. These biological differences explain why different clinical outcomes result from similar microbial challenges and form the biological underpinnings of disease grading within the present classification framework. Together these processes underpin PD as a chronic immune-mediated inflammatory disease and offer a very strong mechanistic basis for the association of PD with other systemic inflammatory diseases such as DM [22].

Pathogenesis of Periodontitis

The oral microenvironment has a significant influence on the composition of the oral microbiome. Therefore, changes in the local environment can disturb the interactions in the oral communities and change the host–microbiome relationship from symbiosis to dysbiosis, rendering the host susceptible to periodontal disease. In the presence of health, the microbial communities are in a balance driven, as described above, by competition between species and regulation by the host [23]. The inflammation and enlargement of soft tissues because of gingivitis creates the periodontal pockets, which have a decreased oxygen tension, creating an anaerobic microenvironment. Gingival bleeding releases tissue breakdown products, plasma proteins, and hemoglobin, creating an environment that makes it favorable for anaerobic Gram-negative proteolytic bacteria to grow [24]. This in turn alters microbial homeostasis, leading to the overgrowth of species of the polymicrobial biofilm at the expense of other species. Such change propels the microbial community to a state of dysbiosis that correlates remarkably with periodontal inflammation. Finally, and crucially, dysbiosis is not an epiphenomenon of inflammation but rather a precursor of additional tissue damage by maintaining a self-perpetuating feed-forward loop that facilitates disease progression [25]. It has been shown through longitudinal studies that the mere presence of bacterial buildup is both a necessary and an insufficient factor in the development of periodontal disease. Subsequently, it is the unbalanced immune response of the host, leading to chronic, unregulated inflammatory mediators, which leads to the connective tissue destruction and alveolar bone loss associated with PD [26]. It is characterized by uncontrolled production

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of pro-inflammatory cytokines, dysregulation of bone homeostasis, and progressive damage of periodontal supporting structures [27]. Cytokines are important signaling molecules in periodontal tissues, as they represent mediators of host defense during periodontal destruction and regulators of periodontal homeostasis in the normal, healthy context. The role of several key cytokines in periodontal pathogenesis, such as tumor necrosis factor-alpha (TNF-α), in addition to interleukins (ILs), including IL-1, IL-6, IL-7, IL-8, IL-11, IL-15, IL-17, IL-23, IL-34, and receptor activator of NF-Kb ligand (RLANKL). High levels of TNF-α and IL-1β in PD not only stimulate osteoclastogenesis but also trigger a general inflammatory cascade that threatens the structure of periodontal tissues [28]. Chronic inflammation seen in PD represents ongoing immune dysfunction which exacerbates destruction of tissues and inhibits mechanisms for repair while limiting bone formation. The processes become worse due to cytokines such as TNF-α, IL-1β, and IL-6 that are pro-inflammatory in nature by disrupting pathways of remodeling relevant for periodontal homeostasis. This continued activity creates an unfavorable environment tilting the balance between bone formation and bone resorption from osteoblasts and osteoclasts, favoring the loss of bone over repair [29, 30].

Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disease characterized by chronic hyperglycemia due to lack of insulin secretion, insulin action, or both, and associated with widespread microvascular and macrovascular complications [31]. Insulin resistance in peripheral tissues and increasing pancreatic β-cell dysfunction are the hallmarks of type 2 diabetes mellitus (T2DM), the most prevalent form of the disease. Severe cellular and metabolic disruptions brought on by persistent hyperglycemia are essential to the development of complications and the advancement of the disease. The availability of excess glucose facilitates oxidative stress by increased production of ROS, exacerbates derangements in immune regulation, and promotes protein and lipid non-enzymatic glycation, resulting in overproduction and accumulation of AGEs [32]. DM is being recognized as a chronic low-grade inflammatory disease in which continuous increases in circulating levels of the pro-inflammatory cytokines, including TNFα, IL-1β, and IL-6, also play a major role in the pathogenesis of insulin resistance and metabolic disturbances. Chronic hyperglycemia links the various pathogenic pathways at the molecular level, such as increased flux through the polyol and hexosamine pathways, activation of protein kinase C, and accelerated AGE formation [33]. When AGEs bind to RAGE, however, they trigger intracellular signaling pathways, most notably the NF-kB pathway, that result in sustained transcription of genes associated with adhesion molecules, inflammatory mediators, and oxidative stress. These pathways have a synergistic effect resulting in the following: Inducing endothelial dysfunction; Impairing immune cells functioning; Aberrant tissue repair Thus, sustaining a state of systemic inflammation stimulates the stages of development of diabetic complications [34].

Links Between Diabetes Mellitus and Periodontitis

Diabetes mellitus, a chronic disease characterized by high blood sugar levels, and PD, a chronic inflammatory disease caused primarily by infection of the periodontium tissue, are interrelated diseases, in part due to common pathogenic mediators. Hyperglycemia causes oxidative stress associated with impaired neutrophil function, and dysregulated cytokine production, which leads to impaired periodontal immune surveillance and a mitochondrial dysfunction that enhances tissue destruction [35]. Overproduction and deposition of AGEs are an important molecular bridge between DM and PD. These compounds are sequestered in periodontal tissues and bind to RAGE expressed on epithelial cells, fibroblasts, endothelial cells, osteoblasts, osteoclasts, and immune cells. AGE-RAGE signaling activates NF-κB and subsequently increases expression of pro-inflammatory cytokines, including TNFα, IL-1β, and IL-6, thereby magnifying periodontal inflammation and redescribing osteoclastogenesis [36]. Apart from their proinflammatory action, AGEs contribute to the dysregulation of bone metabolism in PD related to diabetes. Increased AGE-RAGE activation promotes expression of RANKL and reduced expression of osteoprotegerin, resulting in an imbalance favoring osteoclast differentiation and activation. Such shift promotes alveolar bone resorption and subsequently aggravates periodontal bone loss. At the same time AGE also hampers osteoblast differentiation and mineralization, which aggravates the imbalance between bone resorption and bone formation [37].

Methylglyoxal (MGO) is a highly reactive dicarbonyl compound formed mainly as a glycolytic by-product from the non-enzymatic degradation of the triose phosphate intermediates glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. The glyoxalase system detoxifies MGO effectively under physiological conditions, but metabolic stress and elevated glycolytic activity cause a dramatic increase in MGO production, resulting in dicarbonyl stress and AGE accumulation [38].

Upon comparison to the slower glycation that is mediated by glucose, it has been found that MGO reacts quickly with arginine and lysine on proteins, generating extremely potent MGO-derived AGEs, including MGO-derived hydroimidazolone and Nε-carboxyethyl-lysine (CEL). These AGEs account for a considerable part of the tissue AGE load, and because they are generated rapidly and are very reactive, they have greater biological activity than glucose-derived AGEs [39]. MGO-derived AGEs accumulation have a profound effect on protein dysfunction, active impairment, and cellular signaling pathways. Moreover, AGEs from MGO are ligands for RAGE, thus triggering the downstream pro-inflammatory and oxidative stress pathway. Activation of the AGE–RAGE axis drives high levels of ROS production and persistent NF-κB activation, which amplify the inflammatory response and mediate cellular injury [40]. Notably, the impairment of the glyoxalase detoxification pathway worsens MGO accumulation, thus creating a vicious cycle of dicarbonyl stress and AGEs. This mechanism urges us to consider MGO not only as a metabolic waste but rather as the major instrument for AGE-related tissue injury and chronic inflammation. However, formation of AGEs, induced by MGO, represents a significant molecular bridge between metabolic stress, oxidative damage, and AGE-RAGE–dependent pathological pathways [41]. The DM is also responsible for quantitative and qualitative alterations of subgingival microbiota, leading to the overgrowth of pathogenic anaerobic bacteria. During a longitudinal study of PD, *Tannerella forsythia (T. forsythia)* which is a primary member of the red complex, was found to be highly associated with the severity of periodontal disease, particularly in diabetics having poor glycemic control [42]. Enrichment for AGEs in the periodontal microenvironment activates host inflammatory responses to the bacterial challenge instead of merely increasing the bacterial load. As discussed above, activation of immune cells by AGE–RAGE signaling in those tissues may predispose them to overreact to the presence of pathogens like *T. forsythia,* resulting in an enhanced release of cytokines that perpetuates inflammation, the destruction of connective tissue, and the resorption of the alveolar bone [43].

Advanced Glycation End Products

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Advanced glycation end products is a chemically heterogeneous group formed by non-enzymatic glycation and oxidation reactions leading to irreversible adducts. They are formed through the Maillard reaction, starting with the unstable Schiff base intermediates, followed by Amadori rearrangement products and then oxidative and cross-linking reactions that lead to stable AGEs structures [44]. Examples of structurally characterized AGEs include non-fluorescent (Nε-(carboxymethyl)lysine and Nε -CEL) and fluorescent cross-linking (pentosidine) compounds. Main characteristic of many of these products is their ability to form intra- and intermolecular covalent cross-links in long-lived extracellular matrix proteins, in particular collagen. AGEs may also increase cross-linking in collagen, leading to increased tissue stiffness, decreased solubility, and increased resistance to proteolytic degradation, consequently impairing normal connective tissue turnover and repair [45].
Direct harmful effects of AGEs on periodontal fibroblasts responsible for the maintenance of extracellular matrix are exerted. AGE is accumulated, which leads to senescence and apoptosis of fibroblasts, inhibition of collagen synthesis, and failure of restoration of homeostatic tissue architecture. Such changes reduce the elasticity and regenerative potential of the periodontal ligament, and under diabetic conditions periodontal tissues are extremely susceptible to irreversible damage. This can also explain the higher sensitivity of periodontal tissues to damage caused by AGEs, given their high collagen content and rapid remodeling rate [46]. Besides their structural impact, AGEs have profound biological actions via RAGE, a multiligand pattern-recognition receptor. Chronic RAGE stimulation potentiates RAGE-mediated inflammatory signaling through NF-κB, mitogen-activated protein kinases, and Janus kinase/signal transducer and activator of transcription pathways causing steady cytokine secretion, oxidative stress, and immune dysregulation [47]. AGE-RAGE signaling is pivotal for maintaining chronic inflammation and a rhythmic cycle of alveolar bone loss during diabetes-associated PD. Moreover, disease progression is exacerbated by microbial factors, especially *T. forsythia in* an AGE-enriched periodontal microenvironment [48]. Our integrated approach for GDM and its periodontal implications distinguishes novel interconnected mechanisms that promote not only the maintenance of systemic disease predisposing AGEs but also the idea of targeting specific pathways, potentially improving periodontal and overall outcomes in patients with DM.

Impact of Advanced Glycation End Products in Periodontitis

These PD-associated AGEs exert direct effects on periodontal tissues and indirect effects on associated inflammatory responses, making them essential contributors to the pathogenesis and progression of the disease. Accumulation of AGEs in Gingival Connective Tissue, Periodontal Ligament and Alveolar Bone AGEs accumulate in gingival connective tissue, periodontal ligament, and alveolar bone within the context of a vicious cycle of chronic inflammation, oxidative stress, and pathological tissue remodeling. This local accumulation causes structural changes in the tissue and, furthermore, can amplify destructive inflammatory pathways that characterize PD [49]. Finally, in periodontal tissues, one of the main collateral effects of AGEs is to modify some components of the elastic systems either inextricably associated with them (such as in the case of collagen) or even removed from them. The AGEs-mediated collagen cross-linking leads to a stiffer matrix that is more resistant to further normal enzymatic degradation, and it thus supersedes the normal physiological collagen turnover. This alteration in collagen structure leads to disorganization of the periodontal tissue and mechanical failure of the periodontal ligament. These changes weaken tissue and increase susceptibility to chronic connective tissue damage [50]. The periodontal fibroblast is an important connective tissue cell responsible for maintaining and healing the connective tissue and is also negatively influenced by AGE. AGEs adversely affect fibroblasts, which include the alteration of attachment, transit, and growth and the promotion of cellular aging and apoptosis. This results in a destruction of collagen production and a disruption of normal healing in periodontal tissues. Such fibroblast dysfunction leads to loss of periodontal ligament integrity and impaired regeneration upon tissue injury [51].
In addition to these structural effects, AGEs can act as biological mediators and interact with RAGE on endothelial cells, osteoblasts, osteoclasts, and immune cells. AGE-RAGE axis activation promotes autofeedback amplification of local inflammatory signaling. Cytoplasmic AGE-RAGE binding induces NF-κB activation, leading to up-regulation of pro-inflammatory cytokines. This chronic inflammatory response allows for a prolonged elevation of immune cell infiltration and activity in periodontal tissues [52]. Alteration of alveolar bone metabolism due to AGE-RAGE signaling. Elevated levels of pro-inflammatory cytokines and osteoclastogenic mediators up-regulate osteoclast differentiation and activity. At the same time, the reaction processes also inhibited the osteoblast functions and osteogenic capacities. PD progression is characterized by an excess of bone resorption over bone formation with an increased rate of alveolar bone loss [53]. Moreover, AGEs induce the unnecessary oxygen radical species (ROS) in periodontal tissues, leading to oxidative stress. Increased oxidative stress leads to more cell injury, interference with intracellular signaling, and activation of more inflammatory pathways. This initiates a cycle of inflammation and tissue destruction that perpetuates disease chronicity [54]. AGEs accumulation also negatively influences periodontal wound healing. AGEs block angiogenesis, decrease fibroblast survival, and inhibit the actions of growth factors involved in tissue repair. Consequently, this leads to a diminished capacity of periodontal tissues for healing and regeneration following any mechanical or inflammatory insult. This deficiency leads to apoptosis of these tissues and increases the futility of periodontal therapy [55]. AGEs are major mediators of periodontal tissue degeneration since they merge oxidative stress, the amplification of inflammation, structural matrix modification, and processes of impaired regeneration. They have localized accumulation within periodontal tissues that highlights their key role in sustaining chronic inflammation, connective tissue degradation, and alveolar bone loss in PD [56].

Role of Advanced Glycation End Products and AGE–RAGE Signaling in Diabetes Mellitus

The primary molecules that connect chronic hyperglycemia to metabolic disturbance and tissue injury in the context of DM are AGEs. A cycle of repeated episodes of hyperglycemia promotes chronic glycation resulting in tissue accumulation of AGEs in plasma proteins, as well as intracellular and extracellular matrix. The systemic and progressive nature of diabetic complications has much to do with the accumulation of AGEs, which correlates well with disease duration as well as poor glycemic control [57]. AGEs induce metabolic imbalance through a series of both interconnected structural and biochemical mechanisms. AGE modification specifically impacts the structural composition of plasma proteins, and it alters the stability, biological activity, and turnover rates of plasma proteins and extracellular matrix constituents. The overall acceleration of protein cross-linking alters the fundamental molecular links and rigidity in the tissue, primarily within connective tissue and the vasculature. Such changes drive microvascular dysfunction, increased stiffness, and basement

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membrane thickening, which is a signature of DM [58].

On a cellular level, AGEs hamper the insulin signaling pathways. In the case of AGEs, they also promote the production of ROS, and the accumulation of AGEs will induce oxidative stress, which in turn disrupts the phosphorylation of the insulin receptor and downstream signaling for glucose uptake and utilization. This vicious cycle exacerbates the existing state of peripheral insulin resistance, sustains hyperglycemia, and thus continues to promote the endogenous pool of AGEs. The glycation of metabolic enzymes and transport proteins inhibit activity further increasing an already disturbed glucose and lipid metabolism [59]. AGEs have both classical metabolic manifestations (largely attributed to their formation by oxidative stress and advanced glycation) and damaging effects (largely, to some extent, via interaction with RAGE since AGEs can be regarded as proinflammatory molecules). RAGE is overexpressed in tissues that are intimately involved in its complications including vascular endothelium, kidneys, peripheral nerves, and immune cells. Activation of the AGE-RAGE signaling pathway then initiates a cascade of intracellular signaling pathways, including the signal transduction pathways of mitogen-activated protein kinases, NF-Kb, and phosphoinositide-dependent pathways. These signaling events result in prolonged transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, and mediators of oxidative stress [60].

Perhaps the hallmark of diabetic vascular disease is persistent AGE–RAGE crosstalk, at least in the vessels. Chronic involvement of RAGE in endothelial cells also increases vascular permeability, leukocyte adhesion, and nitric oxide consumption, leading to endothelial cell dysfunction and impaired microcirculation. Such alterations favor atherosclerotic processes and result in micro- and macrovascular complications of DM [61]. There are also important effects of the AGE–RAGE signaling pathway on immune regulation and cellular stress responses. RAGE chronic activation incites immune cells towards a pro-inflammatory phenotype, down-modulates intrinsic antioxidant defenses, and deranges cytoprotective stress-response pathways. Low-grade chronic inflammation, which is associated with increased risk of metabolic stress to cells [62], sustains the state of imbalance. Furthermore, chronic activation of the AGE−RAGE axis provides a persistent epigenetic signature to the cells, regulating metabolic memory. Chronic inflammatory signaling leads to epigenetic modifications and stable changes in cytokine gene expression that may endure after restoration of good glycemic control, thereby contributing to the enduring effects of acute hyperglycemia on diabetic complications. Collectively, AGEs and AGE-RAGE signaling integrate metabolic stress, oxidative injury, inflammation, and epigenetics as critical drivers of the chronic evolution of DM [63].

Conclusion

Advanced glycation end products represent a mechanistic link between DM and PD. In PD, chronic hyperglycemia in DM promotes accumulation of AGEs in periodontal tissues and promotes modification of extracellular matrix in addition to increased inflammation and the acceleration of alveolar bone loss. AGE-RAGE signaling pathway activation keeps oxidative stress and pro-inflammatory responses continuous, and reactive intermediates like MGO lead to an additional AGEs load. These mechanisms together highlight the importance of AGEs in the pathology of diabetes-associated PD.

Conflict of Interest

The authors declare no conflicts of interest.

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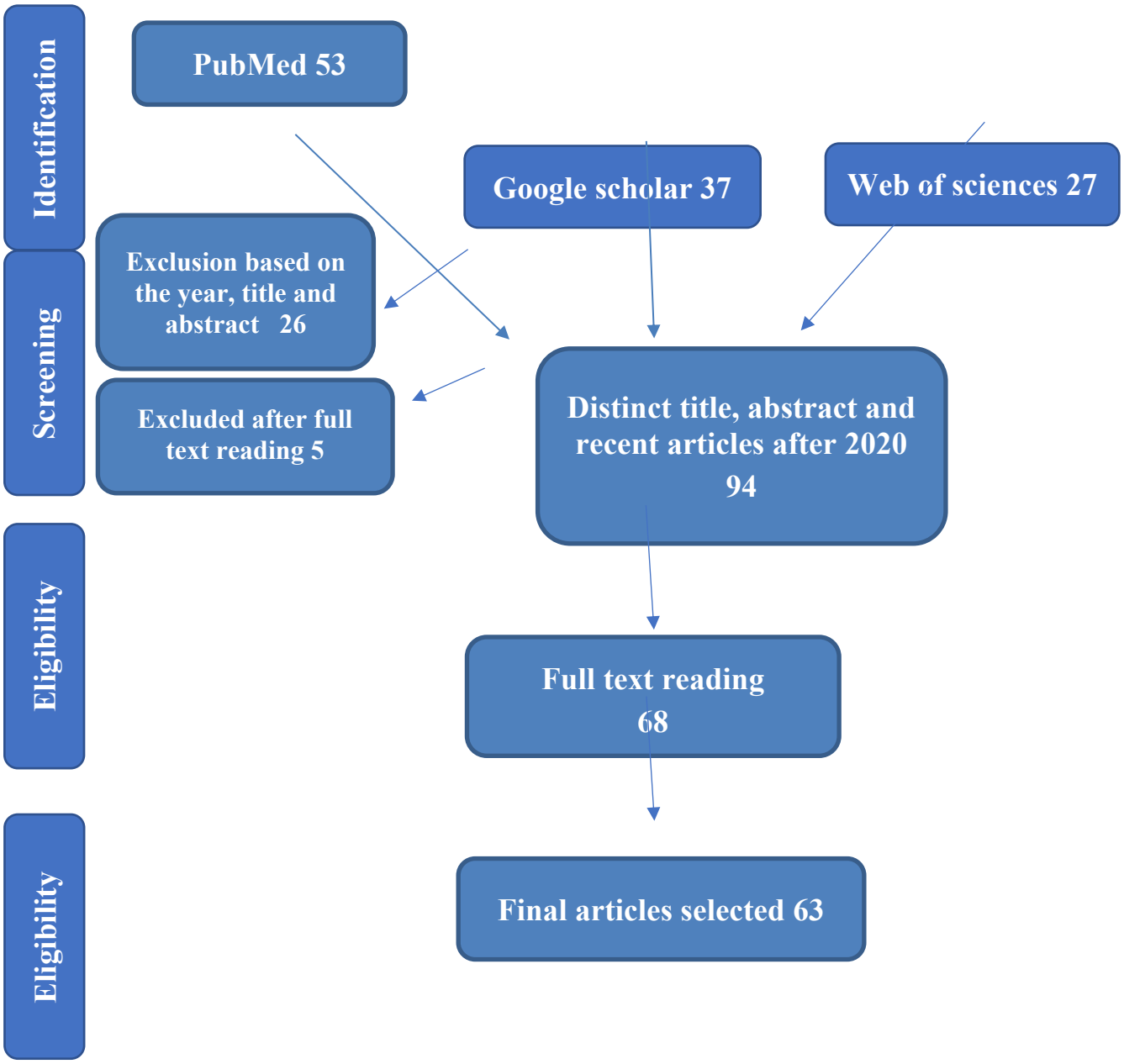

Figure 1. Flow of the search and selection process.