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NONENZYMATIC GLYCOLISATION AND GINGIVAL TISSUES: A REVIEW

Angelina Bozhinov[1], Marija Nakova[1]
[1]International Balkan University, Skopje, R. of North Macedonia

Abstract

Periodontal diseases are multifactorial conditions caused by infection with pathogenic bacteria and inflammation of tissue. Nonenzymatic glycolisation play a key role in treatment of periodontitis because of the many scientific evidence that advanced-glycation end products can modify many metabolism pathways that can change way of gingival tissue inflammatory and tissue damages.

There is no direct evidence for the presence of AGEs in the periodontal ligament but, valuable results that are based on the studies in chronic periodontal patients support a potential role for protein glycation in the aetiology and severity of this disease.

This study highlights the need for further investigation on the presence of AGEs in the periodontal tissues and the pathogenic mechanisms underlying periodontal diseases in order to develop prevention and treatment modalities for this dysfunction.

Keywords: Nonenzymatic glycolisation, AGEs, RAGEs, Periodontitis, gingival tissue.

Introduction

Advanced-glycation end products (AGEs) are heterogeneous molecules derived from post-translational nonenzymatic modifications of macromolecules including proteins, lipids, and nucleic acids by glucose or other saccharides. AGE accumulation can cause metabolic burden such as hyperglycemia and hyperlipidemia, oxidative stress, inflammatory responses, and endothelial dysfunction after binding with (Receptors for advanced glycation end products) RAGEs [1].

Also this condition have correlation with periodontitis. Periodontitis is defined as an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both [2].

Also, recently, interest in periodontal disease has been increasing due to its complex interplay with systemic disorders such as cardiovascular and cerebrovascular diseases, immunodeficiency, chronic inflammation, microangiopathic damage and diabetes [3].

In addition to structural changes caused by the formation of AGEs, interaction of AGEs with RAGE have been shown to cause inflammation and oxidative stress both of which are important in the progression of periodontitis and diabetes. RAGE is constitutively or inducible expressed in a variety of cell types, including neurons, immune cells (neutrophils, monocytes, macrophages, lymphocytes and dendritic cells), smooth muscle cells and vascular endothelial cells [4, 5].

1. Glycation

Glycation products formed in the body are classified into three groups - MRPs in proteins (> 12 kDa), MRPs in peptides (<12 kDa) and free MRPs. The term MRPs (Maillard Reaction Products) is more general than the term AGEs and covers both early and advanced glycation products. Peptide MRPs are found mainly in portal vein plasma and urine and are considered to be degraded products of glycated proteins. Free MRPs are glycation products that are found in amino acids.

They may result from the hydrolysis of glycated proteins and peptides or from the endogenous glycation of the amino acids lysine and arginine. Free MRPs is thought to have limited physiological significance due to the relatively low concentration of free amino acids in the body compared to the concentration of the corresponding amino acid residues in proteins [6].

Cellular proteins, extracellular matrix proteins, and plasma proteins have a high fructosolysin content (0.1 to 1.8 mmol / mol lysine) and a wide range of AGEs (0.001 to 15 mmol / mol modified amino acid residue) depending on the site of formation, and the type of specific glycation end product. Hydroimidazolones are found in the largest amount compared to other AGEs.

For example, the concentrations of CML and CEL are 5 to 10 times, and those of pentosidine and imidazole crosslinks up to 1000 times lower than the concentration of hydroimidazolones. Hydroimidazolone AGEs are found in the highest concentrations in lens proteins (crystallines) in adults. For the methylglyoxal-derived hydroimidazolone MG-H1, this concentration is 1 to 2% of the total arginine residue content of these proteins.

The stable end product of CML glycation accumulates progressively with aging in the lens capsule, skin, and cartilage collagen, reaching a concentration of 6 mmol / mol lysine in the cartilage tissue of adults [7, 8].

The physiological significance of protein glycation is under intensive research. Glycation products accumulating in proteins affect their functions, especially when the affected amino acid residues are located in functionally important regions of proteins such as protein-protein sites, protein-DNA, enzyme-substrate, ligand-receptor interactions. Such modifications severely impair protein function.

An example is human serum albumin (HSA), the major protein in blood plasma. Approximately 10% of HSA albumin in the serum of healthy individuals is affected by glycation, mainly by ε-NH2 of lysine residue 525.

2. Receptors for advanced glycation end products-RAGE

Many cells in the human body have receptors for AGEs. Such receptors are p60 (AGE-R1), p90 (AGE-R2), galectin-3 (AGE-D3), type II macrophage receptor (ScR-II), OST-48, 80K-H and CD36 [9]. These different receptors are mainly involved in the disposal of AGEs by intracellular degradation (endocytosis).

The specific receptor for AGEs, known as RAGE (Receptor for Advanced Glycation End Products), is best characterized. This receptor is also thought to be involved in clearing glycated proteins from the body, but its main function is to unlock various signaling pathways. RAGE is a multiligand receptor that plays a key role in inflammatory processes. Its extracellular domain consists of three immunoglobulin-like regions: one of the "V" type and two of the "C" type [10].

RAGE is poorly expressed in normal, pathologically unaffected tissues, but its concentration increases in places where its ligands accumulate. Characteristic of RAGE is that it recognizes tertiary structures rather than amino acid sequences, a feature that gives it some of the properties of PRR (Pattern Recognition Receptor),which recognizes repetitive antigenic motifs such as PAMPs (Pathogen-Associated Molecular Patterns).

In addition to AGEs, RAGE ligands have been shown to be pro-inflammatory cytokine-like mediators of the S100 / calgranulin family [11] and amphoterin, also known as HMGB1 (High Mobility Group B1), a nuclear protein that is released in cell necrosis and also causes inflammatory reactions (12). AGEs, S / 100 calgranulins, and HMGB1 bind to RAGE on endothelial cells, neurons, smooth muscle, and immune cells and activate a wide range of signaling pathways, including NF-κB expression, a transcription factor that plays a key role in regulating the immune response. [13].

RAGE may also be involved in attracting immune cells to foci of inflammation. For example, RAGE on endothelial cells can function as an adhesive receptor that interacts directly with leukocyte β2-integrins [14].

3. Periodontitis

Periodontitis is serious condition that is connected with different chronic deceases, so we should pay attention to patient especially younger ones when there are symptoms and conditions that can be prevented.

One etiopathogenic mechanism could involve the presence of bacteria or their products, such as lipopolysaccharides, in the periodontal connective tissue.

They may induce an immune response with production of interleukins and tumor necrosis factor (TNF), which play an important role in the regulation of inflammatory processes.

This inflammation stimulates the production of secondary mediators, which amplify the inflammatory response. Simultaneously, the presence of these cytokines reduces the ability to repair damaged tissue by cells such as fibroblasts, and finally, bacterial products and this inflammatory cascade stimulate osteoclastogenesis, leading to alveolar bone destruction [15].

It is well known that periodontitis, as a consequence of low-grade systemic inflammation, is a phenomenon associated with a higher risk of glycosylated haemoglobin (HbA1c) progression and diabetes [16].

4. Periodontitis and AGEs

Given the high prevalence of neutrophils in periodontitis and indeed the dysregulation of neutrophil recruitment and function associated with both diabetes and periodontitis, AGE/RAGE interactions on these cells have the potential to cause increased local inflammatory responses. Upon AGE binding to RAGE, expression of inflammatory mediators (such as IL-1β, TNF-α and IL-6) are up-regulated [17].

Furthermore, AGE is associated with increased levels of ROS and oxidative stress (causing endothelial cell changes and vascular injury), impairment of bone formation and repair (potentially impacting bone resorption in periodontitis), a decrease in ECM production and decrease in collagen strength and turnover, all of which may impact periodontal health and the progression of diabetic complications [18].

Linking diabetes to periodontitis, increased serum AGE in diabetics with a positive correlation to increased periodontitis-associated attachment loss has been demonstrated [19].

Furthermore, immunohistochemical analysis of gingival tissues from diabetics indicated a higher percentage of AGE on cells (epithelium, blood vessels and fibroblasts) in diabetes with periodontitis compared with healthy tissues [20].

On the other hand, studies have also demonstrated increased RAGE expression in gingival tissues of diabetics with periodontitis in human studies [21].

Also is shown that gingival fibroblasts exposed to AGE modified human serum albumin had decreased cell viability and impairment of intracellular collagen I and collagen III synthesis and expression. This suggests AGE dysregulates collagen turnover which may exacerbate periodontitis tissue destruction.

Studies have shown how chronic hyperglycemia produces AGEs that can bind to specific receptors (RAGE) on different cells such as fibroblast, endothelial cells and macrophages [22].

Thereby, macrophages are transformed into hypereactive cells that produce pro-inflammatory cytokines such as interleukins 1β and 6 (IL-1β, IL-6) and TNF-α. AGEs can also alter endothelial cells which will become hyper-permeable and hyper-expressive for adhesion molecules, while fibroblasts will show decreased collagen production [23].

Therefore, AGEs produced by chronic hyperglycemia can produce hyper inflammatory responses, vascular modifications, altered healing and increased predisposition to infections. Other researchers supported the hypothesis that the activation of RAGE contributes to pathogenesis of periodontitis in diabetic patients.

Increased accumulation of AGEs and their interaction with RAGE in diabetic gingiva leads to hyper production of pro-inflammatory cytokines, vascular dysfunction, and loss of effective tissue integrity and barrier function. [24].

Conclusion

With this review we are highlighting the correlation between nonenzymatic glycation and AGEs to many diseases and immune response to them, especially to gingival changes in periodontitis.

That is why we are proposing multidisciplinary approach to treatment of periodontitis, including the qualitative and quantitative establishment of AGEs in the periodontal tissue and the study of the effectiveness of anti-AGE pharmacological treatments.

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