Archives of Oral Biology 93 (2018) 22–30

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

Review

Advanced glycation end products (AGEs) in oral pathology

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ARTICLE INFO

Keywords:
Advanced glycation end products - AGEs
Chronic inflammation
Diet-related disease
Oral pathology
Salivary biosensor

ABSTRACT

Objective: Maillard advanced glycation end products (AGEs) are connected with high dry temperature food processing, color and flavor modification of food products. Oral cavity pathology is strongly influenced by dietary intake. The aim of the present paper is to update current data regarding the sources and metabolism of AGEs, their impact on oral cavity tissues, to discuss and suggest new approaches for the early diagnosis and efficient treatment of AGEs-related oral pathology.

Design: This paper is a narrative review of the studies discussing AGEs and mainly the dietary AGEs (dAGEs) sources, metabolism, linkage to general diseases, and specifically the oral cavity pathology. The authors used "PUBMED" and MeSH for the finding of English written and published articles concerning AGEs. There were used the next keywords association: "advanced glycation end products- AGEs" AND "Maillard products", "AGEs" AND "diet-related disease, "AGEs" AND "salivary biosensor", "AGEs" AND "metabolic syndrome AGEs", "AGEs" AND "oral pathology", "AGEs" AND "dentin AGEs" OR "periodontal AGEs", "AGEs" AND "diagnosis and monitoring". The authors used free full-text articles to determine the etiology and physiopathology of AGEs, their association with general diseases and oral cavity disease, assessment methods used in biofluids and tissues, AGEs prevention and treatment approaches. Articles concerning AGEs etiology, metabolism and effect in the human body and specific implication in oral pathology were selected. There were no exclusion criteria in what concerns the study design. Studies in other language than English and articles abstracts were excluded.

Criteria of inclusion were free full-text articles written in English. Equally human and animal model studies were included. Regarding the date of publication, all subjects concerning glycation products after 1953 (first published article) were included.

Results: Evidence show that AGEs are responsible for inducing low intensity chronic inflammation and thereby, for initiating and/or aggravating chronic diseases. Nowadays, research has demonstrated a significant association between AGEs and dental or periodontal pathology. Moreover, salivary AGEs are consistent with the levels of AGEs in other biological fluids and are correlated with the general and oral pathology.

Conclusions: Assessment of salivary AGEs could be a reliable tool for early diagnosis and monitoring diet-related disease.

1. Introduction

Advanced glycation end products (AGEs) are final products of Maillard reaction. They were discovered by Louis-Camille Maillard in 1912, while he was trying to synthesize *in vitro* proteins by using a high temperature reaction between amino acids and sugars (Zhang, Ames, Smith, Baynes, & Metz, 2009). In 1953, John E. Hodge published an article in which he divided the reaction and in 1986, the formation of

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https://doi.org/10.1016/j.archoralbio.2018.05.013
Received 7 January 2018; Received in revised form 7 April 2018; Accepted 17 May 2018

reducing sugar-derived carbonyl products was added to the Maillard chain reaction (Hodge, 1953). It was associated with the flavor and pleasant scent of food, but also with oxidative stress production, local and general inflammation, and last but not least, mutagenic dicarbonyl compounds (Nagao, Takahashi, Yamanaka, & Sugimura, 1979).

In medical research, AGEs have been associated to ROS (reactive oxygen species) increase, with consequent generation of oxidative or carbonyl stress. Thus, ROS exert negative effects resulting in inflammatory, autoimmune, diet-related diseases. Comparing to the discovery of the Maillard reaction products, the hypothesis of the implication of AGEs in periodontitis and dental pathology was founded at a later time. Several studies have revealed a strong association between the accumulation of AGEs and the occurrence or worsening of metabolic diseases. However, the routine use of AGEs salivary levels for the diagnosis or monitoring the oral diseases has not been yet reported.

2. Material and method

The authors used "PUBMED" and MeSH for the finding of English written and published articles concerning AGEs. There were used the next keywords association: “advanced glycation end products- AGEs” AND “Maillard products”, “AGEs” AND “diet-related disease, “AGEs” AND “salivary biosensor”, “AGEs” AND “metabolic syndrome AGEs”, “AGEs” AND “oral pathology”, “AGEs” AND “dentin AGEs” OR “periodontal AGEs”, “AGEs” AND “diagnosis and monitoring”. The authors used free full-text articles to determine the etiology and physiopathology of AGEs, their association with general diseases and oral cavity disease, assessment methods used in biofluids and tissues, AGEs prevention and treatment approaches. Articles concerning AGEs etiology, metabolism and effect in the human body and specific implication in oral pathology were selected. There were no exclusion criteria in what concerns the study design. Studies in other language than English and articles abstracts were excluded.

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2.1. AGEs production sources, metabolic pathways and their effects on storage organs

There are both exogenous and endogenous sources of AGEs. Endogenous sources are generated by protein glycation by means of oxidative stress, conditions which imply hyperglycemia. Exogenous sources are represented by dietary compounds (especially carbohydrates and lipids), UV (ultraviolet) radiation, cigarette smoke, microwaves and ultrasounds. Microwaves are largely used in food heating, because they transform electromagnetic frequency into thermal energy. The type of diet influences to a great extent the amount of AGEs produced during the heating process (Contreras, Sevilla Garay, Wrobel, & Malacara, 2013).

The Western diet (carbohydrates-47%, fats-37%, proteins-16%) represents an important source of Dietary Advanced Glycation End Products (dAGEs) due to the Maillard reaction, which renders the food flavor and brown. Dietitians assessed CML (carboxymethyllysine) as an AGEs marker in 250 different types of food, focusing on meat, carbohydrates and fat groups that are cooked under boiling water (100 °C), fried (180 °C), broiled (225 °C), roasted (177 °C) or oven fried (230 °C) (Goldberg et al., 2004). CML values were the highest in the fat group, followed by meat and carbohydrates. The cooking methods related to the highest CML values were as follows: oven frying > deep frying/broiling > roasting > boiling.

Sugars are widely used in the food industry. Studies show that a high fructose diet with more than 100 g/day was associated with weight gain in the subjects (Sieveenpiper et al., 2010). In a healthy human organism, no more than 0.4% of glucose intake is transformed into methylglyoxal (Thornalley, 2003). This is one of the main AGEs compounds that interacts with arginine and lysine and thus alters DNA proteins, leading to apoptosis (Amicarelli et al., 2003).

Researchers who investigated the influence of dAGEs in diabetic wound healing noticed an indirect correlation between the healing time and AGEs circulating levels (Peppa et al., 2003). The high-AGEs diet fed mice presented a persistent and dense inflammatory cells infiltration and fibrous scars. Tessier and his colleagues evaluated the organ distribution of dAGEs by synthesis of the dCML-fortified protein using [13C2] glyoxylic acid to label CML, which made possible the differentiation between exogenous dCML and native CML (nCML) (Tessier et al., 2016). NCML is synthesized both from endogenous glycation and diet intake. The CML derivate synthesized by the research team was of dietary source only. Their results suggested that dCML spare into protein-bound and free CML, from which only the free form circulates and deposits. The authors also showed that dCML had no influence on organ weight and did not deposit in adipose tissue, maybe because of the differences between the hydrophilic lipids and hydrophobic proteins (Aris et al., 2010).

Another AGEs source is represented by cigarette smoke byproducts such as nicotine and nornicotine. Smoking AGEs, in contrast with other exogenous sources (UV, nutrients), are formed in a couple of hours (Cerami et al., 1997; Monnier, Kohn, & Cerami, 1984). Nicotine sourced AGEs bind to connective tissue collagen fibers increasing tissue hardness. Moreover, they bind to serum low-density lipoproteins (LDL) and alter their levels (Lee & Cerami, 1987). High serum ratio smoking AGEs activates cytokines and ROS production, resulting in noxious effects on the vessel endothelium, hence the strong association with the risk of atherosclerosis and coronary heart disease.

Unrelated to the source of glycation, the formation of AGEs takes place at the hepatic structures in several steps, which include reversible and irreversible reactions. The last step is irreversible; in weeks/months, after dehydrating and very stable cross-linking or non-cross-linking reactions have taken place, AGEs [pentosidine, CML, GOLD (glyoxal-lysine dimer), GLAP (glyceraldehyde-derived pyridinium compound), MOLD (methylglyoxal-lysine dimer)] are formed (Magalãsh, Appel, & Duarte, 2008).

In humans, approximately 90% of AGEs are eliminated through renal excretion, while the rest of 10% are accumulated in the biological fluids (serum, cerebrospinal fluid, and saliva), oral mucosa and skin, hard tissues (bone, teeth, joints), organs, nervous fibers, muscles, connective tissue, including pathological structures (Koschinsky et al., 1997). AGEs accumulation aggravates the existing diseases and increases the risk for the development of other pathologies.

2.2. AGEs in dentin

Human dental tissues are represented by hard tissues: enamel and dentin, and soft tissues: the pulp, which contains cells, collagen fibers and intercellular matrix. Dental tissues receive nutrients from blood vessels and neural impulses through nervous fascicles along the root canals. Beside nutrients, damaging molecules, including AGEs, also reach dental tissues. AGEs cross-link collagen fibers and induce morphological and mechanical changes in dentin and pulp. Miguez, Pereira, Atsawasuwa, and Yamauchi, 2004 demonstrated that the concentrations of dihydroxylysinonorleucine and pyridinoline (two major enzymatic cross-links) in radicular dentin were higher than those in coronal dentin.

An *in vitro* study analyzed the degradation of dentine collagen under trypsin and pepsin action. After 10 weeks of incubation with glucose at 37 °C, the characteristic Maillard fluorescence 370/440 was observed (Kleter, Damen, Buijs, & Ten Cate, 1997). The authors stated that dentine collagen was degraded by pepsin- a carboxylic protease which is active in an acid medium, but not by trypsin which is active in an alkaline environment.

Furosine (an early Maillard reaction product) collagen cross-links

and oxidation were examined by fluorescence and HPCL in healthy and carious dentine (Kleter, Damen, Buijs, & Ten Cate, 1998). In the affected dentine the highest fluorescence was observed at 370/440 which was associated with the Maillard reaction. The authors found that dentine matrix was exposed to AGEs only after acid demineralization, and collagen cross-linking occurred in predentin area.

Greis et al. examined the correlation between age and AGEs fluorescent pentosidine in root dentine- healthy, diabetic, heated and storage. The authors suggested that age produced methylation and DNA posttranslational modification which generated AGEs and aspartic acid racemization- AAR, both measurable and quantified. Their results showed that carious and heated teeth presented high pentosidine levels. Storage conditions (−20 °C for up to 8 years) had no influence on teeth (Greis, Reckert, Fischer, & Ritz-Timme, 2017) Armstrong (1964) supposed that the Maillard reaction was responsible for the increased resistance of dentine collagen against collagenolytic breakdown and for browning of carious lesions. Based on its fluorescence property, *in vivo* fluorescence lifetime measurement (FLM) was used to show ribose incubation for 6–9 weeks to carious-free dentin collagen fibers. FLM decreased in young and aged dentin after incubation with ribose (Fukushima et al., 2015).

A study conducted by Miura et al. (2014) demonstrated high AGEs concentration in the intertubular collagenous matrix and along dentinal tubules in the predentin area. The high AGEs accumulation was related to the hardness and brown discoloration of dentin, associated with age. Glycation products not only contribute to the hardness of dental tissues, but also increase the risk of fracture. Shinno et al. (2016) demonstrated the role of pentosidine in diminishing flexural strength of both radicular and coronal dentin, by cross-linking collagen fibers.

Ganeko et al. investigated mandible and femoral bone mechanical strength and density using nanoindentations tests and 3-point bending tests, taking into consideration that collagen fiber strength and enzymatic cross-links increase the fibers strength, but non-enzymatic ones (AGEs) decrease bone strength (Karim & Vashishth, 2012). The results indicated that methionine-treated rabbits had increased primary strength, whereas AGEs implication lead to bone fragility (Ganeko et al., 2015).

Sakamoto et al. investigated *in vitro* osteoblasts activity under the simultaneous effect of AGEs and P. gingivalis in rat bone marrow culture (Sakamoto et al., 2016). In their paper, it was stated that AGEs could act from the gingival tissue on the alveolar bone surface by the opposite effect of osteoclast activation and osteoblast inhibition. The *in vitro* study results showed that AGEs addition in culture led to a decrease in alkaline phosphatase activity and bone nodule formation; by contrast, increased levels of IL-1 and S100A8 inflammatory markers were observed.

Several studies investigated the *in vitro* modulation of osteoclasts activity and osteoclastogenesis by AGEs were (Valcourt et al., 2007). Previous publications suggested that AGEs accumulation was higher in tissues with low turnover, such as bone, cartilage, tendons, affecting the mechanical properties (Bartolucci & Parks, 1981). In cortical calve bone incubated in D-ribose at 37 °C for 3 months, high pentosidine concentration, along with the coloration in brown of the intercellular matrix were observed. Therefore, AGEs accumulation in bone and dentine decreased matrix resorption, probably because of the collagen fiber strengthen (Fig. 1).

2.3. AGEs in dental pulp

AGEs create a neutrophilic condition, due to their chemotactic effect on inflammatory markers, increasing ALP and CRP, all together leading to ROS production, membrane hyperpermeability, collagen and fibroblast production (Vlassara, Brownlee, Manogue, Dinarello, & Pasagian, 1988). *In vitro* studies on rat dental pulp cell culture (Nakajima, Inagaki, Hiroshima, Kido, & Nagata, 2013; Nakajima, Inagaki, Kido, & Nagata, 2015) showed AGEs-stimulated release of inflammatory Interleukine-1 β (IL-1 β), S100A8, S100A9 (calcium regulators), osteopontin and osteocalcin leading to intrapulpal calcifications. By the same mechanism, but more abundantly, AGEs accumulate in the carious dentin area (Matsuda et al., 2016). When RAGE connected to S100 protein, the NF-kB pathway was activated, resulting in increased proinflammatory response (Takeichi et al., 2011).

During pulpitis, RAGE is intensely expressed in odontoblastic and subodontoblastic cells, in the predentin area, extracellular pulp matrix and fibroblasts (Tancharoen et al., 2014). Under normal conditions, high mobility group box 1 protein (HMGB1) is located in the nuclei, but in pulpitis and periodontal disease, it moves out into the cytoplasm and intercellular matrix (Parks et al., 2004). Inflamed pulp tissues express high levels of RAGE and HMGB1, which stimulate the activity of IL-1, IL-6, IL-8, IL-10 and Tumor Necrosis Factor- α (TNF-α) and dental pulp fibroblast migration. Depending on their concentration, receptors can exert a positive or negative effect on cell differentiation, by damaging the cellular matrix (Zhang et al., 2014). A previous study showed that the absence of RAGE in periapical granulomas led to a decrease in cortical bone resorbtion an in increased bone density (Zhou et al., 2006).

ROS occur as byproducts of cell normal metabolism. On one hand, beneficial redox signaling regulates cell differentiation and tissue regeneration and also prevents aging. On the other hand, high ROS levels expressed in immune cells have a noxious effect by altering cellular structure and function and by activating the inflammatory response (Schieber & Chandel, 2014).

Nitric oxide synthase (NOS) is known to generate free radical cytotoxic nitric oxide (NO) in inflammatory environment. Hama et al. examined the interrelation between RAGE and an inducible form of NOS (iNOS) in periapical granulomas. (Hama, Takeichi, Saito, & Ito, 2007). Their study showed that in granulomas, the inflammatory cells such as macrophages, PMN, lymphocytes and endothelial cells express on their surface the AGEs receptor, RAGE, while plasma cells do not express RAGE. Another study assessed the synergic activity between RAGE and S100 protein in periapical granulomas. The endothelial cells in granulomas present all of the three AGE, RAGE and S100 proteins on their surface, and the AGE interaction with RAGE is stronger than with S100. Moreover, the AGEs formation in the tissues induces the secretion of adhesion molecules, leading o the recruitment of inflammatory cells to the site of inflammation (Takeichi et al., 2011).

Lalla et al. found that RAGE is the cell-expressed receptor for extracellulary newly identified RAGE (EN-RAGE) binding proteins and S100 proinflammatory cytokines (Lalla et al., 2000). They analyzed in a murine model the effect of AGEs-RAGE and RAGE-EN-RAGE in diabetes-associated disease. Their study showed that RAGE inhibition reduced the alveolar bone destruction and decreased the gingival levels of matrixmetalloproteinases (MMPs) and AGEs. In the same study, intraperitoneal soluble RAGE (sRAGE) administered intraperitoneal to normoglycemic mice did not induce alveolar bone resorption.

Moreover, low levels of sRAGE in crevicular fluid and serum were associated with high TNF-α in type 2 diabetic patients with periodontal disease, suggesting the active inflammatory environment, both local and systemic. (Singhal, Pradeep, Kanoriya, & Garg, 2016). These data and previous ones prove that sRAGE has a positive competitive effect in AGE-RAGE interaction, and thus inhibits the proinflammatory pathways activated by glycation compounds (Singhal et al., 2016). The above presented studies and not only, show the importance of RAGE presence and influence in the maintenance and modulation of the inflammatory state.

Regardless of the source, AGEs reach the dental pulp by the blood flow, and by diffusion from dental support structures and gingival crevicular fluid. AGEs act through an AGE-RAGE inflammatory mechanism and induce membrane hyperpermeability, with a negative effect on collagen fibers, down-regulation of osteoblasts discharge, color and hardness of dental tissues. From the dental pulp, AGEs penetrate into the dentinal tubules, intertubular area and predentin surface, and

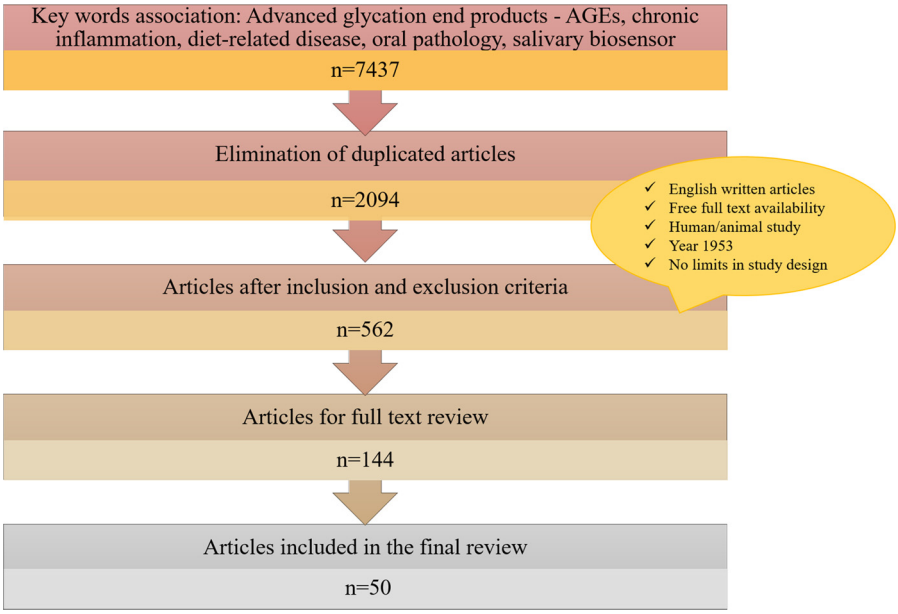

Fig. 1. Review extraction data methodology chart.

cross-link collagen fibers. In the periodontal ligament, AGEs disintegrate collagen fibers, leading to loss of attachment. They also activate osteoclast activity and inhibit osteoblast differentiation, promoting the resorption of supporting alveolar bone.

Additionally, AGEs pathogenic mechanisms involve removal of Ca^{2+} ions from dentin and their precipitation in the dentinal tubules. Thus, collagen fibers are reinforced and dentinal tubules are obliterated, with subsequent increase in tissue hardness. The lack of nutrients and fluids due to loss of tubular permeability leads to increased fracture risk. Color changes, from yellow to brown, are time and dose-dependent. Age-related discoloration might be associated with high accumulation of AGEs in dentin and loss of enamel in physiological or pathological dento-maxillary functions (Fig. 2).

2.4. AGEs in implantology

Few studies investigated the role of AGEs in implant osseointegration. Pietropaoli et al. (2013) examined the differences in salivary oxidative stress markers (Thiobarbituric Acid Reactive Substances–TBARS), and AGEs in three groups of healthy, periimplantitis and periodontitis subjects. They found that AGEs accumulation in periimplant tissues was higher compared with healthy tissues, but lower compared with periodontopathic tissues. The authors suggested that higher AGEs concentration in periodontitis is due to the chronic inflammation; moreover, AGEs overexpression could be linked to the early onset and progression of the disease. Another study reported higher salivary AGEs levels in the periimplantitis group, while TBARS were overexpressed in the periodontopathic group (Ramzan & Malik, 2013). Koutouzis, Catania, Neiva, and Wallet, 2013 investigated the consequences of implant therapy in a group of patients susceptible to periodontal disease compared with unaffected subjects and demonstrated higher expression of RAGE and toll-like receptor 2 (TLR2) in gingival biopsies in the diseased group and before therapy.

2.5. AGEs in periodontal tissues

Chronic periodontitis is a site-specific infectious and inflammatory disease that affects the supportive tissues of teeth, with progressive attachment and bone loss. Its etiology is represented by bacterial plaque accumulated on dental surfaces, especially in subjects non-compliant with oral hygiene (Gurrav, 2016). A study that simulated human periodontal ligament cells with *Porphyromonas gingivalis* and matrix glycation reported the upregulation of RAGE and TLRs, and thus, a clear connection between the level of glycemia and oxidative stress, resulting in damage of collagen fibers (Chang, Chien, Chong, Kuo, & Hsiao, 2013). Another study on experimental periodontal disease a murine model showed a strong relationship between *P. gingivalis*, diabetes mellitus and AGE-RAGE interaction in accelerating bone loss and collagen fiber dissolution (Lalla, Lamster, Feit, Huang, & Schmidt, 1998).

Zizzi A et al. investigated *in vivo* the accumulation of AGEs in gingival tissues in both healthy subjects and patients with periodontitis (with or without associated diabetes), and the influence of external factors (Zizzi et al., 2013). Their results evidenced a high percentage of AGEs in gingival fibroblasts, vessels and epithelium, and a direct correlation between the amount of AGEs deposited and the time passed from the installation of diabetes. The authors noticed no correlation between AGEs accumulation and factors such as glycated hemoglobin, age and body mass index. They also suggested that a prolonged hyperglycemia could modify the proteins, by increasing their resistance to proteolytic enzymes.

AGEs influence the progression and severity of periodontitis that clinically manifests by slow loss of soft and hard supporting tissues. Inflammatory cells express RAGE proteins linked to AGEs, thus inducing the overexpression of superoxides and dissolution of collagen fibers and morphophysiological changes in periodontal cells (Gurav, 2013; Lalla, Lamster, Stern, & Schmidt, 2001). A study on human dermal microvascular endothelial cells (HMVEC) exposed to TNF-α, E2 (17b-estradiol) and AGE-BSA (AGE-modified bovine serum albumin) reported increased RAGE gene expression by activation of NF-κB and Sp-1, stress proteins, leading to increased AGEs production (Tanaka et al., 2000). These observations suggested that AGEs-RAGE interaction is self-supporting and self-stimulating, maintaining the inflammatory state (Schmidt, Yan, Yan, & Stern, 2000).

In gingival fibroblasts, AGEs activate metalloproteinase-1 (MMP-1), by the RAGE-NF-κB pathway and mediate the production of proinflammatory chemokines with increased apoptosis (Xu, Xiong, Huang, & Chen, 2015; Yu, Li, Ma, & Fu, 2012). Moreover, NF-κB promote *de novo* AGEs synthesis (Lin, Park, & Lakatta, 2009). Periodontal ligament (PDL) fibroblasts of the middle third of the root treated with AGE-BSA showed high levels of RAGE and caspase-3 (a proinflammatory shock protein) (Li, Deng, Lv, & Ke, 2014). These molecules diminish cell

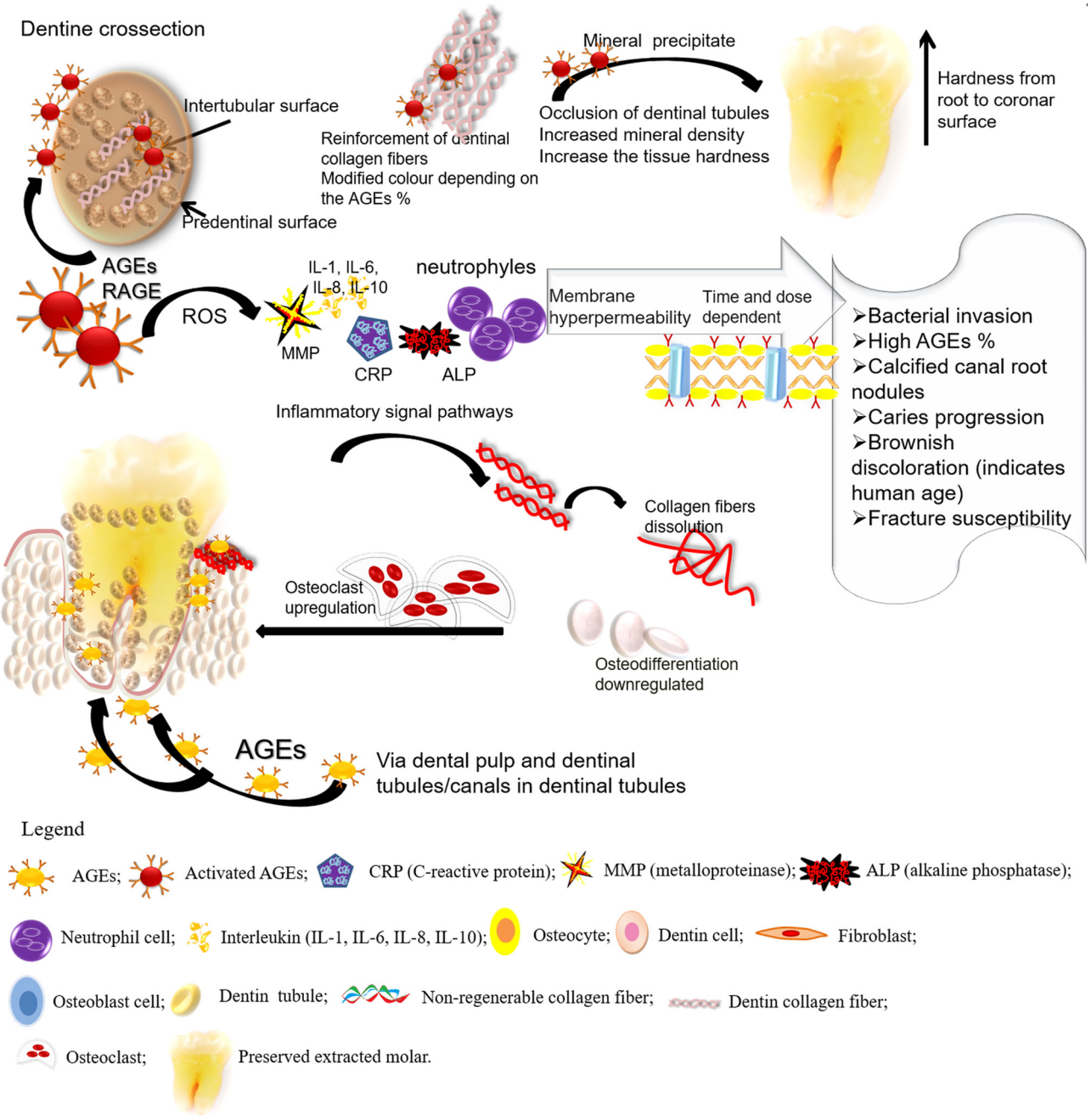

Fig. 2. AGEs negative influence on dental and periodontal tissues.

viability and perpetuate high AGEs levels *via* ROS production. AGEs accumulation in the tissues induces the formation of ROS and the subsequent activation of the proinflammatory NF-κB transduction factor; AGEs bonds to RAGE, upregulates the vascular cell adhesion molecules (VCAM-1) and the intercellular adhesion molecules (ICAM-1), thus easing their pathway to the periodontal site (Abbass, Korany, Salama, Dmytryk, & Safiejko-Mroczka, 2012).

A study that evaluated RAGE and ROS in gingival tissue of diabetic and non-diabetic periodontic patients showed that RAGE had a higher expression in the inflammatory cells compared with epithelial cells, and in periodontal gingiva. However, there was no correlation with the glycemic status. (Schmidt et al., 1996).

Osteodifferentiation potential of diabetic or healthy periodontal-derived stem cells (D-PDLSC/H-PDLSC) is downregulated by the AGE-RAGE interaction, by the Wnt (wingless-related integration site) signaling pathway. This leads to underexpression of stemness markers and osteogenic promoters such as ALP (Liu et al., 2015). The Wnt signaling is formed by canonical (including β-catenin protein) and non-canonical pathways, and is shown to be involved in cell differentiation and wound healing (Daskalopoulus, Janssen, & Blankesteijn, 2013; Fathke et al., 2006). In contrast, in periodontal tissues, AGEs disintegrate collagen fibers (Fig. 3).

2.6. AGEs in the saliva

Among other biological fluids used in diagnosis and monitoring the oral and general pathology, saliva represents an accessible and friendly source, and it prevents the inconvenient of blood and urine/feces collection. Salivary TBARS, peroxidation membrane biomarkers, and Advanced Oxidation Protein Products (AOPP) were studied because they show the severity or efficacy of periodontal therapy (Behuliak et al., 2009; Guentsch et al., 2008; Sculley & Langley-Evans, 2003; Wei,

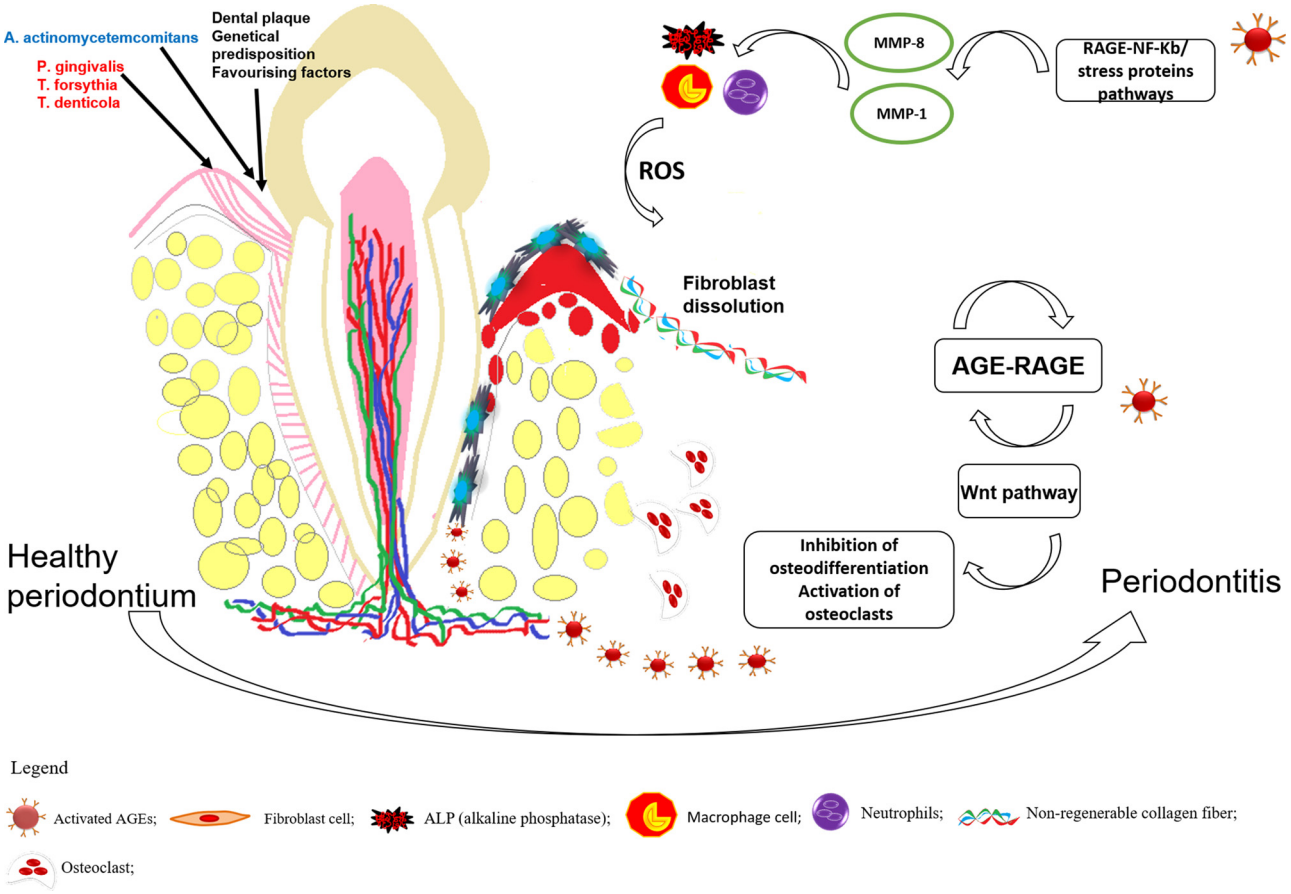

Fig. 3. AGEs implications in periodontal disease.

Zhang, Wanag, Yang, & Chen, 2010). When in pathological conditions the gingival attachment is oxidized, these biomarkers collect in the adjacent saliva, and they show the direct effect of the oxidation process. The Comenius Research Unit in Bratislava used spectrophotometric and spectrofluorometric methods to evaluate AGEs in stimulated versus unstimulated saliva, in a group of 82 children. Their findings showed differences of AGEs in what concerns gender, oral cavity hygiene, dental status and periodontal harm, but the age had no influence in AGEs amount (Tothova', Celecov', & Celeca, 2013). The lack of correlation might be attributed to the healthy condition of the participant patients.

The same RU compared salivary TBARS and AGEs before and after oral hygiene, before and after the administration of 250 mg of ascorbic acid (vitamin C) (Kamodyová, Tóthová, & Celeca, 2013). Spectrophotometric measurements showed a 76% difference of AGEs in the morning and an average 46% decrease after oral hygiene. The single dose of vitamin C administered showed a 64% decrease of AGEs and a strong reduction of carbonyl stress. Therefore, mechanical removal of dental plaque correlated with general administration of antioxidant agents has an immediate effect in decreasing glycation products (saliva was collected 10 min after toothbrushing). Once intravenously injected, vitamin C does not need any conversion. It is an active antioxidant and is correlated with a decrease of inflammatory markers, especially C-reactive protein (Mikirova, Casciari, Riordan, & Hunninghake, 2013). It also acts simultaneously with vitamin E in protecting lipid membrane oxidation, and by regulation of Fe^{2+} of collagen hydroxylases it contributes to collagen fiber synthesis (Du, Cullen, & Buetner, 2012).

2.7. Oral AGEs assessment

In the oral cavity, salivary AGEs might represent the amount of salivary and crevicular fluid accumulation. In periodontal pockets, there is a specific microbiocenosis, differences regarding bacterial support and noxious effect, and as a consequence, different metabolites, including mediators of AGEs production. The separate crevicular evaluation might indicate specific changes or an alteration associated with the progression of periodontal disease and periimplantitis. Crevicular fluid can be collected using a cotton swab, in a routine periodontal diagnostic examination the results of which can offer valuable information.

A salivary biosensor might be developed to provide a real time AGEs alteration. At a future approach, this device might be used as a diagnostic and treatment tool in low-intensity chronic inflammation, and the results transferred to a wireless application. A biosensor represents a mechanism involving a biological component combined with a physiochemical detector (Bănică, 2010). To the best of our knowledge, there is currently no device produced and validated to measure salivary AGEs. This biosensor could be attached to a mouthguard placed in the patients' oral cavity, and repeated non-invasive evaluations would be performed, for a real-time evaluation of AGEs modifications. Non-invasive monitoring of salivary AGEs could be used for the management of healthy subjects and particularly, patients affected by the general disease, and last but not least, for self-management at home.

2.8. AGEs in oral pathology – Quo vadis?

The interrelation between AGEs and oral cavity diseases has a high research potential. It raises multiple questions to answer and subjects to be studied.

Concerning the aging process, it is known that AGEs accumulation has a continuous depositing. It is not known if it can be correlated with AGEs accumulation in the oral mucosa and if the aging process be

evaluated non-invasively, by determination of dental color. There are no studies assessing hard dental tissue accumulation of AGEs in pediatric patients or volunteers. AGEs deposits increase gradually depending on intake and time, but the starting point of AGEs deposition is missing. Consequently, there is a need for prospective monitoring studies in children, with the associated dietary follow-up. These results could be correlated with the known evaluations of healthy or diseased patients. Furthermore, spectroscopic and spectrofluorometric measurements are practical, non-invasive, highly sensitive techniques. Using them, a gradient scale AGEs/dose-time-age axis, or even a dental color map related to AGE expression could be built up. By repeated multiple assessments, a dental color hallmark for each person could be designed, and eventually a storage database could be created.

Dental color changes could show the amount of AGEs from local and general pathological reactions, and their correlation in dental tissues with the deposition in other organs could show a metabolic resonance of chronical disease.

In 1971, a pigment - formed by carbonyl groups - was isolated from the carious dentin in a non-acid non-hydrolysis medium; this pigment was not found in healthy dentine (Kleter, 1998). It was supposed that in carious dentin, due to the oxygen-free environment, small aldehydes reacted with proteins and led to coloration of collagen fibers and incercellular matrix, along with the progression of the carious lesion. AGEs deposits are dose and time-related. After their formation, they deposit wherever they find protein structures. This might partly explain why studies report differences in results concerning AGEs values in biological fluids and organs. Specific nutrients, physiological and negative effect mechanisms contribute to glycation products and ROS outcome, and as a consequence, local aggressiveness of red complex periodontopathic bacteria could increase AGEs values in oral structures, saliva and crevicular fluid. Therefore, AGE-induced dentin color changes might be intensified in local pathologies or the absence of oral hygiene. It is important to consider the other factors that influence dental color, such as intrinsic and extrinsic discoloration, genetic diseases (amelogenesis imperfecta or dentinogenesis imperfecta), tooth vitality, which directly influences the amount of AGEs reaching dental tissues, as well as the patients' specific diet in terms of calories, acidity and pigment content.

Enamel is formed by micrometric prisms of hydroxyapatite, namely crystalline calcium phosphate, and is free of collagen fibers. Since AGEs crosslink collagen fibers and deposit by this mechanism, theoretically, in the enamel they have no structures to bind to. However, there are two proteins, enamelin and amelogenin that AGEs might affect, especially in youngsters, in whom tooth development is not fully complete. DAGEs could even penetrate intraosseous ameloblasts and collagen fibers in deciduous teeth and affect the color and structure of teeth in the process of eruption.

AGEs' deposition in dentin requires the development of methods for eliminating or decreasing the levels of AGEs from the dental structures. AGEs deposition can be controlled by reducing specific exogenous sources and by enhancing endogenous antioxidant systems. Their reaction before AGEs cross-linking of collagen fibers might prevent color modifications. Studies mentioned earlier showed a clear difference in AGEs concentration between healthy and decayed teeth. AGEs discoloration measurements might represent an innovative approach in prophylactic dentistry, reducing early dentin damage. In dental restorations, dentists create microretentive surfaces by etching the prepared dentin and enamel with acid substances, such as hydrofluoric acid or phosphoric acid, which flatten collagen fibers. High acid concentrations might upregulate the production of ROS and AGEs, which are harmful for both odontoblasts and dentin collagen fibers, since the fibers have been already morpho-functionally altered by the susceptibility to fracture, closed tubules and Ca^{2+} precipitate, and diminished water. A new bonding system which does not dehydrate and affect dentin collagen should be taken into consideration.

In implantology, periodontal AGEs assessment could represent an examination for the diagnosis and prognosis of the future restoration. The evolution of periimplantitis might be evaluated by assessing AGEs deposition in inflamed periodontium or subclinical inflammation. As shown above, few studies have investigated the influence of AGEs in implant osseointegration or local inflammation reaction, such as periimplantitis. The results have evidenced a direct association between AGEs levels and inflammation of periodontal tissues. The differences found in periimplantitis *versus* periodontal disease are based on the chronic condition of the latter. The effects of glycation products are time and dose related, AGEs accumulation being known to be irreversible. Cross-linking, inhibition of osteoregeneration and osteoclast upregulation affect soft and hard tissue support, more severely in pathological conditions such as metabolic syndrome. AGEs screening before implant therapy might represent a direct investigative approach in the prognosis of osseointegration and perimucosal inflammation risk.

Immune response in pulp pathology is possible to be modulated by AGEs molecules and influence the irreversibility of pulpitis. As to root canal sealing materials, they could be modified by adding AGEs blocking agents, and thus, periapical pathological process to be stopped. The main AGEs antagonists are antioxidant agents, which could be associated with general or local targeted drugs such as antidiabetics and metronidazole or Ca^{2+} channel blockers and tetracycline, with the precaution that Ca^{2+} ions downregulate the antibiotic effect. Their efficacy might be transferred to root canal treatment, by developing a sealing agent that includes one of these AGEs inhibitory agents, which can be used as an intermediate process or a final sealing substance, which is an easy and useful approach.

3. Conclusions

The involvement of AGEs in the generation of low-intensity, chronic inflammation demonstrates their implication in the generation and aggravation of general and oral pathologies. Regardless of their origin, these products have a dose and time-related cumulative negative effect on human tissues. The chairside assessment of salivary AGEs could be an innovative approach to the diagnosis of disease showing a low-intensity inflammation, and to the prognosis of future treatment protocols proposed. Interdisciplinarity is necessary for the design of long-lasting, efficient therapies. Both general and dental clinicians can benefit from the information provided by AGE evaluation, and collaborate for a two-sided pathological approach. Salivary AGEs might represent an innovative approach for future diagnostic and prognostic techniques, due to its advantage as an easy, non-invasive collection method, and to the correlation with other biological fluids.

Funding

This study was supported by "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania PhD Grant no 3999/01.10.2016, and partially by the COFUND-ERA-HDHL ERANET Project, European and International Cooperation - Subprogram 3.2 - Horizon 2020, PNCDI III Program - Biomarkers for Nutrition and Health –"Innovative technological approaches for validation of salivary AGEs as novel biomarkers in evaluation of risk factors in diet-related diseases", grant no 25/1.09.2017.

Conflict of interest statement

The author research team declares that this contribution is original. The work has not been published previously and is not currently under evaluation by another journal. The submitted work, including the images, is original. Aranka Ilea and Anida M. Băbţan have equally contributed to the conception and design of the study, acquisition, analysis, interpretation and drafting of the manuscript. Bianca A. Boşca, Maria Crişan and Nausica B. Petrescu were involved in designing the study, drafting anf critically revising of the final paper. Massimo

Collino, Rosa M. Sainz, Jared Q. Gerlach and Radu S. Câmpian provided constructive input for the manuscript. All of the authors agree to be accountable for the work integrity and accuracy. All authors have read and approved the final article. The authors declare no conflicts of interest with respect to the authorship and/or publication of this article. The authors have no conflict of interest to declare.

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