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Review

Advanced glycoxidation end products in chronic diseases—clinical chemistry and genetic background

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Abstract

Several diseases (atherosclerosis, diabetes mellitus, chronic renal failure) are associated with oxidative and carbonyl stress, microinflammation and eventually autoimmune reaction. Both oxidative and carbonyl stress cause damage to important biological structures—proteins, carbohydrates, lipids and nucleic acids and may enhance inflammatory response. New compounds and modified structures are formed, among them advanced oxidation protein products (AOPP), advanced glycation end products (AGEs—e.g. pentosidine, carboxymethyllysine) and advanced lipoperoxidation end products (ALEs).

Accumulation of glycoxidation products, upregulation of protective mechanisms like glyoxalase I as well as enhanced transcription of genes coding for cytokines, growth factors and adhesive molecules via AGE–RAGE (receptor for AGEs) interaction and subsequent increase of classical acute phase reactants (e.g. CRP—C-reactive protein or orosomucoid) can be observed in a variety of chronic diseases. Additionally, several RAGE gene polymorphisms have shown association with some pathological states—diabetic complications, vascular damage, inflammatory response or antioxidant status.

Recent advances in understanding the pathogenesis of chronic diseases provide new possibilities for diagnostics and monitoring of severely ill patients, however, further studies are still required to establish efficient therapeutical strategies.

Keywords: Oxidative stress; Inflammation; Diabetes mellitus; Dialysis; Atherosclerosis; Advanced glycation end products; AGEs; RAGE

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Contents

Chronic diseases such as diabetes mellitus, atherosclerosis, chronic renal failure are associated with oxidative and carbonyl stress, microinflammation and eventually autoimmune reaction. Oxidative stress is known as dysbalance between reactive oxygen species and antioxidants in favour of free radicals while carbonyl stress is characterized as reactive carbonyl compounds overload, which can be caused by their increased formation both via oxidative stress and via non-oxidative pathway from glycolysis intermediates and/or decreased clearance or detoxification via several enzymes, e.g. glyoxalase. These compounds are highly reactive aldehydes (–CHO) or contain α-dicarbonyl group (–CO–CHO) [1]. Both oxidative and carbonyl stress cause damage to important biological structures—proteins, carbohydrates, lipids and nucleic acids and may enhance inflammatory response. New compounds and modified structures, which can serve as markers of these mechanisms are formed, among them advanced oxidation protein products (AOPP), advanced glycation end products (AGEs) and advanced lipoperoxidation end products (ALEs). Structural changes and disclosure of new epitopes might trigger autoimmune response. Nucleotide glycation can result in mutations.

1. Advanced glycation end products (AGEs)

Advanced glycation end products are represented by a heterogeneous group of compounds (e.g. pentosidine, carboxymethyllysine (CML), imidazolone, etc.), some of them with characteristic fluorescence, ability of crosslinking of proteins and reaction with AGE-specific receptor RAGE (receptor for AGEs) [2,3]. AGEs formation as well as AGE action is linked both to oxidative stress and inflammation. Apart from non-enzymatic glycation, AGEs can rise via autooxidation of sugars as well as other glycation intermediates—Schiff base and Amadori product and via lipoperoxidation of polyunsaturated fatty acids, both giving reactive carbonyl compounds known as precursors of AGE. AGEs derived from lipids are also designed as advanced lipoperoxidation end products (ALEs) [4]. Additionally, some AGEs (e.g. CML) can be formed in inflammed foci both via NADPH oxidase [5] as well as via myeloperoxidase action [6]. AGE–RAGE interaction induces oxidative stress and activates nuclear factor NF-κB which is followed by overexpression of genes for cytokines, growth factors and adhesive molecules, increased vascular permeability and further toxic effects [7–9]. AGEs take part in the pathogenesis of diabetic as well as uremic and dialysis related complications, atherosclerosis (Table 1) and neurodegenerative diseases (Alzheimer disease).

2. Advanced oxidation protein products (AOPP)

Advanced oxidation protein products are proteins, predominantly albumin and its aggregates damaged by oxidative stress [10]. They contain abundantly dityrosines which allow crosslinking, disulfide bridges and carbonyl groups [11] and are formed mainly by chlorinated oxidants—hypochloric acid and

Table 1
Role of AGEs in the pathogenesis of vascular damage, relationship to classical risk factors and non-traditional mechanisms of atherosclerosis

Risk factor/possible mechanism of atherosclerosis progression	Relationship to AGEs
Age	Formation of AGEs increases with the age
Hyperlipidemia	Modification of LDL particles (formation of glycated and glycoxidated LDL), induction of lipoperoxidation
Smoking	Tobacco smoke contains precursors of AGEs
Hypertension	Role of oxidative stress and probably also AGEs in the pathogenesis of hypertension
Diabetes mellitus	Enhanced formation of AGEs via non-enzymatic glycation and oxidative stress
Inflammation	Proinflammatory effects of AGEs via interaction with RAGE followed by increased transcription of genes for cytokines (IL-1, TNF-α), growth factors (VEGF) and adhesion molecules (ICAM-1, VCAM-1)
Others	Quenching of vasodilatatory activity of nitric oxide, induction of prothrombotic state—modification of coagulation factors and changes in their function, modification of extracellular matrix-crosslinking

chloramines resulting from myeloperoxidase activity [10,11]. AOPP have several similar characteristics as AGE-modified proteins. Apart from a common formation mechanism (oxidative stress) leading to protein damage, they share some biological effects as well, including interaction with RAGE. Induction of proinflammatory activities, adhesive molecules and cytokines is even more intensive than that caused by AGEs [12]. They are referred to as markers of oxidative stress as well as markers of neutrophil activation [13]. Protein oxidation products mediated by chlorinated species generated by an enzyme myeloperoxidase were found in the extracellular matrix of human atherosclerotic plaques [14] and increased levels of advanced oxidation protein products were described as an independent risk factor for coronary artery disease [15].

3. Receptor for advanced glycation end products (RAGE)

Advanced glycation end products as well as advanced oxidation protein products, advanced lipoperoxidation end products and reactive carbonyl compounds, apart from direct effect on the extracellular matrix, can exert biological activities via specific receptors, among them the best known and characterized is RAGE (receptor for AGEs). Other AGE-binding receptor include P60/OST-48 protein (AGE-Rl), 80 K-H phosphoprotein (AGE-R2), galectin (AGE-R3) and for example the scavanger receptor [16]. RAGE, a 35 kDa protein, has been isolated and cloned from the bovine lung and has been classified as a member of the immunoglobulin superfamily. RAGE can be expressed on the surface of various cell (e.g. monocytes, macrophages, mesangial cells, neurons, endothelial cells, smooth muscle cells and fibroblasts), sometimes after stimulation with growth factors, e.g. TNF-α [8,17]. RAGE is responsible for the activation of intracellular signal transduction pathways, such as the ERK kinase, the $p38^{MAPK}$, the JNK kinases, and the NF-κB (nuclear factor κB) pathway [18]. Subsequently, the AGE–RAGE interaction results in the stimulation of transcription of genes for cytokines and growth factors (TNF-α, IL-1, PDGF, IGF1, interferon γ), and adhesion molecules (ICAM-1, VCAM-1), stimulation of cell proliferation, increase of vascular permeability, induction of migration of macrophages, stimulation of formation of endothelin-1, down regulation of trombomodulin, increased synthesis of collagen IV, fibronectin and proteoglycans, increased synthesis of procoagulant tissue factor, etc. [8,9].

RAGE is a multiligand receptor (Table 2) and recognizes also β-amyloid, a component of neurodegenerative plaques in Alzheimer disease, amphoterins which play a role in the ontogenesis of the central nervous system and also in carcinogenesis and metastasing [19,20] and S100 proteins/calgranulins which are involved in inflammatory processes—rheumatic diseases and multiple sclerosis [21].

RAGE has also a physiological function as it is important for the development of the central nervous system. During maturation, its presence decreases. In adults, it is involved in the inflammatory response

Table 2
RAGE (receptor for AGEs)—a multiligand receptor

Ligand	Clinical significance
AGEs (advanced glycation end products)	Diabetic and uremic complications, atherosclerosis
β-Amyloid	Alzheimer's disease
Amphoterin	Ontogenesis of the central nervous system (neurite outgrowth), carcinogenesis and metastasing
S100 proteins/ calgranulins	Inflammatory processes—rheumatic diseases, multiple sclerosis

[22] and under physiological conditions, its expression is only minimal. Its increased expression is connected with pathological states—e.g. diabetes mellitus, immune–inflammatory processes [7,8], Alzheimer disease [23], preeclampsia [24] and cancer where it also plays a role in metastasing [19,20].

4. Advanced glycation and oxidation products in clinical chemistry

In clinical chemistry examinations, glycoxidation products as well as some acute phase reactants produced by the liver upon cytokine stimulation (mainly IL-6) are elevated to various extent in patients with a variety of chronic ailments—slightly in atherosclerosis, diabetes mellitus, and rheumatic diseases and even several fold in renal impairment, especially hemodialysis patients. Elevation of some autoantibodies (anticardiolipin antibodies (ACA), anti-β_2-glycoprotein I antibodies (anti-β_2-GPI)) which might contribute to vascular damage—atherosclerosis and trombosis can also be present. Generally, we usually observe similar trend, i.e. simultaneous elevation of these markers, although regulation of each process is multifactorial and the reaction of the organisms is more complex than only AGE–RAGE interaction. Even closer relationship between oxidative stress parameters and acute phase reactants is visible in states with more pronounced inflammation, e.g. in patients with rheumatoid arthritis, where multiple stepwise regression revealed an independent influence of CRP on plasma pentosidine levels and pentosidine was proposed as a useful biomarker of chronic inflammation [25]. In another chronic inflammatory diseases, ankylosing spondylitis, where various functions of neutrophil are increased, AOPP were positively correlated both with CRP and erythrocyte sedimentation rate [26]. Similar results were found in patients with Behcet's disease [27].

4.1. Oxidative/carbonyl stress and inflammation in patients with diabetes mellitus

Oxidative stress and microinflammation are typical also for diabetes mellitus (DM) and elevation of typical markers (CRP, cytokines, AGEs, malondialdehyde) was observed by several groups. Significant elevation of AGEs, AOPP, CRP and anti-β_2-GPI are common in patients with type 2 diabetes when compared with healthy subjects ($p < 0.001$, $p < 0.01$, $p < 0.0001$, $p < 0.0001$, respectively). In patients with type 1 diabetes, anti-β_2-GPI were elevated ($p < 0.0001$) as well but there was only slight increase of AOPP and no difference in CRP levels. Occurrence of various autoantibodies can be given by autoimmune nature of the disease (DM1) but can also represent a response of the organism to modified biological structures through oxidative and carbonyl stress (more in DM2). In patients with type 1 diabetes, AOPP correlate significantly with anti-β_2-GPI ($r = 0.68$, $p < 0.05$) and in DM2, there is a significant correlation between anti-β_2-GPI and PAPP-A (pregnancy-associated plasma protein A, a new marker of vascular damage) ($r = 0.45$, $p < 0.05$) [28,29]. Additionally, a weak correlation of AGEs with CRP and of AGEs with IL-6 was found in DM2 and AGEs were shown as an independent determinant of plasma CRP levels, suggesting that subclinical inflammation in these patients may therefore be partly due to activation of inflammatory response by AGEs [30]. In summary, both oxidative stress which is of multifactorial etiology (mitochondrial respiration, cytochrom P450, xantinoxidase, protein kinase C dependent activation of NADH/NADPH oxidase and superoxide formation, oxidation of glucose and AGE–RAGE induced oxidative stress) and inflammation are more pronounced in DM2 and are partially related. In DM1, oxidative stress seems to be in closer link to autoimmune reaction. All these mechanisms may contribute to acceleration of atherosclerosis, mainly in DM2 which is a more complex metabolic disorder with more pronounced reaction of the whole organism-dysregulation of lipid metabolism, oxidative stress, and microinflammation.

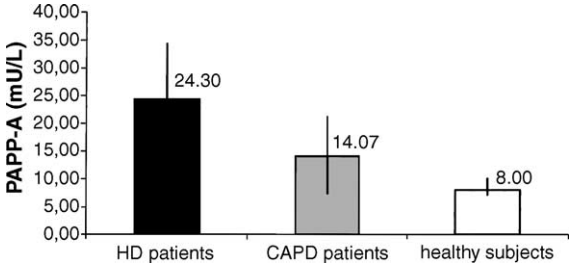

Fig. 1. PAPP-A in dialysis patients and in healthy subjects, HD-patients with renal failure treated with hemodialysis, CAPD-patients with renal failure treated with continuous ambulatory peritoneal dialysis. Results are expressed as median (interquartile range) for HD and controls and as mean ± standard deviation for CAPD patients. $p < 0.001$ HD and CAPD patients vs. healthy subjects. $p < 0.05$ HD patients vs. CAPD patients [32,33].

4.2. Oxidative/carbonyl stress and inflammation in patients with renal failure

Elevation of both glycoxidation products as well as some acute phase reactants (including PAPP-A—a new marker of unstable atherosclerotic plaques, possibly also an acute phase reactant, Fig. 1) and autoantibodies (anticardiolipin antibodies, anti-β_2-glycoprotein I antibodies) in hemodialysis patients in stable clinical state is well known [31–35]. AOPP correlate significantly with cytokines [10,13] and several inflammatory parameters such as orosomucoid (0.39, $p < 0.05$), fibrinogen (0.49, $p < 0.05$) and PAPP-A, a potential acute phase reactant (0.46, $p < 0.05$) [31], which was recently demonstrated as a unique marker of complicated atherosclerotic lesions. Pregnancy-associated plasma protein-A (PAPP-A) belongs to a metzincin superfamily of metalloproteinases. It is responsible for proteolytic cleavage of insulin-like growth factor binding proteins-2, 4 and 5 (IGFBP-2, 4 and 5) and so acts as a positive regulator of IGF bioavailability [36–38]. IGF-I induces the migration of smooth-muscle cells and is important for monocyte chemotaxis and the activation and release of cytokines within the atherosclerotic lesion [39,40]. PAPP-A was demonstrated in eroded and ruptured atherosclerotic plaques, while the expression in stable plaques was only minimal [41]. This protein is significantly elevated in patients with unstable angina pectoris and acute myocardial infarction in comparison with healthy subjects [41], however, the concentration is 100–1000-fold lower than in pregnancy where it is used for prenatal screening (for Down's syndrome during the first trimester). As already mentioned, PAPP-A is elevated in patients with renal impairment, mainly in patients treated with hemodialysis (compared with patients treated with continuous peritoneal dialysis) (Fig. 1) and despite its high molecular weight (400 kDa), it correlates negatively with renal function [33], and might thus reflect the increasing cardiovascular risk.

On the other hand, a correlation between AGEs and inflammatory parameters is usually not found [31,33,42] or is only weak [35]. This is in line with recent results of Hou et al. [43], who refer a significant relationship between pentosidine and RAGE expression in monocytes and acute phase reactants in patients with chronic kidney diseases but not in hemodialysis patients, probably as there are also other sources of inflammation in these patients apart from that mediated via AGEs and their interaction with RAGE, e.g. monocyte stimulation by interaction of blood with bioincompatible dialyzer membranes or exposure of blood to dialysate lipopolysaccharide [43]. However, ultrapure dialysate was shown to reduce plasma pentosidine levels [44]. Nevertheless, oxidative damage shows a closer relationship to inflammation than glycation/glycoxidation and carbonyl stress. Thus, AOPP could represent a more acute biochemical marker of special importance, while AGEs might better describe chronic long-lasting damage. The situation is even more complex as AGEs are significantly linked to nutrition. Recent findings describe that elevation of plasma pentosidine in hemodialysis patients is associated with both inflammation and malnutrition [35]. Additionally, hemodialysis patients with higher levels of AGE-fluorescence and CML had a significantly better survival than patients with AGEs below median, probably due to better nutritional support [33]. Low-AGE diet decreased both serum levels of AGEs and those of inflammatory marker, although they did not correlate with each other suggesting that AGEs have a role in initiation of the inflammatory state of chronic renal failure which eventually leads to increased cardiovascular disease [45].

Elevation of both oxidative/carbonyl stress end products (AOPP, AGEs), autoantibodies against modified biological structures and acute phase reactants seems to take part in the development of accelerated atherosclerosis, which contributes to increased cardiovascular morbidity and mortality. These pathogenic

mechanisms are supposed to act synergically, nevertheless, oxidative stress shows a closer relationship to inflammation and acute phase reaction than advanced glycation, and its end product—AOPP could thus better describe acute oxidative stress, while AGEs might serve more as a marker of chronic damage. There are also other sources of acute phase reaction than only that mediated via AGEs and their interaction with RAGE and complex response of the organisms to these stimuli.

5. Advanced glycation end products-genetic background

Molecular mechanisms of glycation, metabolism of AGEs as well as their action are intensively studied in the last years. In this context, following areas of interest should be mentioned: enzymatic detoxification of AGE-precursors, nucleotide glycation, and signal transduction via specific receptors, mainly RAGE, RAGE polymorphisms and soluble RAGE (Fig. 2).

5.1. Role of glyoxalase I

Formation of AGEs as well as their total amount in the organism are influenced genetically. AGE-precursors, reactive carbonyl compounds, can arise from both metal-catalyzed autooxidation of glucose (glyoxal), from decomposition of Amadori product 3-deoxyglucoson), or by non-enzymatic fragmentation of triose phosphate intermediates in the glycolytic pathway (methylglyoxal). Reactive carbonyl compounds can be detoxified via specific enzymatic systems. Methylglyoxal is the major source of intracellular and plasma AGEs and is metabolized predominantly by glutathion-dependent glyoxalase system (glyoxalases I and II). [46]. Indeed, glyoxalase I deficiency was associated with unusually high plasma levels of advanced glycation end products in a hemodialysis patient [47]. In an in vitro study, overexpression of glyoxalase I completely prevented hyperglycemia-induced AGE formation [48]. Additionally, up-regulation of the gene for glyoxalase I was observed in the brain of P301L mutant tau transgenic mice which develop neurofibrillary tangles, a histopathologic hallmark of Alzheimer's disease (due to some similarities with diabetes mellitus, i.e. abnormalities in glucose metabolism and increased AGE-accumulation, this disease is sometimes called "diabetes mellitus of the brain"). Moreover, a single nucleotide E111A polymorphism was studied in humans but was not associated with the risk for Alzheimer's disease in the overall population [49].

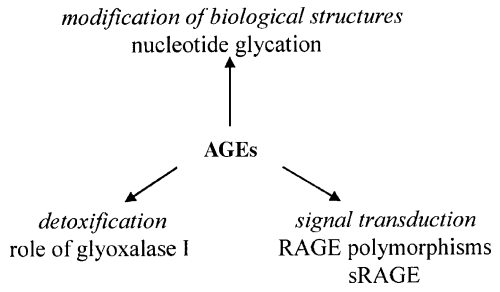

Fig. 2. Genetic background of AGE metabolism and action.

5.2. Nucleotide glycation

DNA can be similarly as other biological structures damaged from oxidation and glycation. The glycation of DNA gives rise to characteristic nucleotide adducts, i.e. AGE-nucleotides derived from carbonyl compounds like glyoxal, methylglyoxal, 3-deoxyglucosone or imidazopurinone derivatives and others. Glycation damage to DNA is associated with mutagenesis and carcinogenesis—glyoxal and methylglyoxal induce multi-base deletions, base-pair substitutions, and transversions. Suppression of nucleotide glycation by glyoxalase I and aldehyde reductases and dehydrogenases, and base excision repair, protects and recovers DNA from damaging glycation.

The effect of DNA glycation can be particularly observed in uremia, and indeed, patients with renal failure on dialysis have higher incidence of tumours. Glycation of DNA may also contribute to the toxicity of several cytotoxic anti-cancer drugs, and overexpression of the enzymatic anti-glycation defence (mainly glyoxalase I) is associated with multidrug resistance [50].

5.3. RAGE polymorphisms and soluble RAGE

The RAGE gene is located on chromosome 6p21.3 in the major histocompatibility complex locus in the class III region [51]. Several RAGE gene polymor-

phisms have shown association with some pathological states—diabetic complications, vascular damage, inflammatory response or antioxidant status. For example, two intron polymorphisms (1704G/T and 2184A/G) in the RAGE gene were proved to be associated with the antioxidant status in non-insulin-dependent diabetes mellitus subjects (it is known that the extent of diabetic vascular disease is related to the plasma levels of antioxidants) [52]. The functional −374 T/A RAGE gene polymorphism was studied in diabetic as well as non-diabetic populations. In type 1 diabetic patients with AA genotype, less coronary heart disease, acute myocardial infarction and peripheral vascular disease was observed [53]. Similarly, in non-diabetic individuals, the AA genotype was shown to be independently associated with a reduced risk of coronary artery disease [54]. Concerning Gly82Ser polymorphism in exon 3 of the receptor RAGE, this allelic variation within the ligand-binding domain may influence proinflammatory mechanisms, thereby predisposing individuals to heightened inflammatory responses. Cells bearing the RAGE 82S allele displayed enhanced binding and cytokine/matrix metalloproteinases generation following ligation by a prototypic S100/calgranulin compared with cells expressing the RAGE 82G allele. Additionally, increased prevalence of the 82S allele in patients with rheumatoid arthritis compared with healthy subjects was demonstrated. RAGE 82 S may thereby contribute to enhanced proinflammatory mechanisms in immune/inflammatory diseases [55].

Apart from the transmembrane receptor, soluble RAGE (sRAGE) exists which is extracellular domain of RAGE and represents a naturally occurring inhibitor of signalling pathways induced by the membrane-standing RAGE receptor. It was described that pre-mRNA of RAGE in humans must be subject to regulated alternative splicing activated by extracellular cues of yet unknown cellular signalling pathways and it can be hypothesized that there is a complex RAGE regulation network involving isoforms competing for the binding of ligands [56]. In mouse there was no evidence to suggest that alternative splicing of RAGE mRNA contributes to sRAGE biosynthesis, in contrast, carboxyterminal proteolysis of RAGE appeared to be the mechanism of sRAGE formation. These proteolytic pathways may be also important additional mechanisms of regulating sRAGE expression in humans [57].

Table 3
Possible therapeutical influence on formation and action of AGEs

Mechanism	Compounds/drugs
Correction of hyperglycemia and hyperlipidemia—decrease of AGE-procursors	Insulin and other antidiabetics, hypolipidemics
Inhibition of formation	Aminoguanidine, OPB 91-9, amadorins, antioxidants, anti-inflammatory agents, angiotensin converting enzyme inhibitors, angiontensin II receptor 1 antagonists
Degradation of modified proteins (crosslinks)	“Crosslink” breakers, e.g. PTB, ALT-711
Influence of signal transduction via AGE–RAGE interaction	Anti-RAGE antibodies, sRAGE, anti-AGE antibodies

Recent advances in understanding the pathogenesis of chronic diseases provide new possibilities for diagnostics and monitoring of severely ill patients. Different pathways involved in AGE formation and action represent a basis for a great variety of therapeutical strategies (Table 3). However, further studies are still required for efficient intervention.

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