BBA - Molecular Basis of Disease 1865 (2019) 611–619

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

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

Impact of advanced glycation end products (AGEs) signaling in coronary artery disease

Marinos Kosmopoulos, Dimitrios Drekolias, Phaedon D. Zavras, Christina Piperi*, Athanasios G. Papavassiliou*

Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 11527 Athens, Greece

ARTICLE INFO

Keywords:
Advanced glycation end products (AGEs)
Coronary artery disease
Endothelium
Platelets
RAGE
Stent restenosis

ABSTRACT

Coronary artery disease remains the leading cause of mortality in adult diabetic population with however, a high predominance also in non-diabetic subjects. In search of common molecular mechanisms and metabolic by-products with potential pathogenic role, increased advanced glycation end products (AGEs) present a critical biomarker for CAD development in both cases. Interaction of AGEs with their transmembrane cell receptor, RAGE in endothelial and smooth muscle cells as well as in platelets, activates intracellular signaling that leads to endothelial injury, modulation of vascular smooth muscle cell function and altered platelet activity. Furthermore, tissue accumulation of AGEs affects current treatment approaches being involved in stent restenosis. The present review provides an update of AGE-induced molecular mechanisms involved in CAD pathophysiology while it discusses emerging therapeutic interventions targeting AGE reduction and AGE-RAGE signaling with beneficial clinical outcome.

1. Introduction

Coronary artery disease (CAD) or ischemic heart disease is the most common form of cardiovascular disease, presenting a prominent cause of mortality globally despite the immense improvements in disease diagnosis and treatment. Atherosclerosis is the underlying cause of CAD, a chronic inflammatory disease of the arteries, caused by the passive deposition of lipids in the coronary arterial wall which in concert with immune cells function, progresses to atherosclerotic plaque formation [1]. The interplay between inflammation and risk factors including hypertension, hypercholesterolemia and smoking in addition to metabolic syndrome, obesity and modern diet plays a decisive role in the progression rate of atherosclerotic plaque which further leads to arterial lumen stenosis, limiting blood flow and affecting cardiovascular function [1,2].

Long-term hyperglycemia has been associated with cardiovascular complications, including CAD development and progression in diabetic population. However, recent studies demonstrate the critical role of

Abbreviations: AGEs, advanced glycation end products; CAD, coronary artery disease; RAGE, receptor for AGEs; MG, methylglyoxal; GL, glyoxal; CML, Nε-carboxymethyl-lysine; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt/PKB, protein kinase B; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor NF-κB; NFAT, nuclear factor of activated T-cells; sRAGE, soluble RAGE; esRAGE, endogenous secretory RAGE; hRAGEsec, human RAGE secreted; HMGB, high mobility group box-1; PAI-1, plasminogen activator inhibitor-1; LOX-1, low density lipoprotein-receptor 1; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; P2YR, G protein-coupled P2Y purinergic receptor; ADMA, asymmetric dimethylarginine; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor beta; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intracellular cell adhesion molecule-1; LOX, lysyl oxidase; ET-1, endothelin-1; ER, endoplasmic reticulum; UPR, unfolded protein response; Trx, thioredoxin; HUVECs, human umbilical vein endothelial cells; VSMCs, vascular smooth muscle cells; KCa 3.1, Ca^{2+}-activated K^+ channel; ROS, reactive oxygen species; MMP2/MMP9, matrix metalloproteinases 2/9; RANKL, receptor activator of nuclear factor kappa-B ligand; BMP, bone morphogenetic protein; Msx2, homeobox protein Msx2; PECAM-1, platelet endothelial cell adhesion molecule 1; CRP, C-reactive protein; PCI, primary coronary intervention; STAT3, signal transducer and activator of transcription 3; LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; ADAM10, ADAM metallopeptidase domain 10; PPAR-γ, peroxisome proliferator-activated receptor gamma; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; AMI, acute myocardial infarct; HSF-1, heat shock factor 1; CKD, chronic kidney disease; PGE2, prostaglandin E2; ARBs, angiotensin II receptor blockers; AP-1, activator protein-1; hNSCs, human neural stem cells; GSH, glutathione; HO-1, heme oxygenase-1; CD86, cluster of differentiation 86

* Corresponding authors at: Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 75 M. Asias Street - Bldg 16, 11527 Athens, Greece.

E-mail addresses: cpiperi@med.uoa.gr (C. Piperi), papavas@med.uoa.gr (A.G. Papavassiliou).

https://doi.org/10.1016/j.bbadis.2019.01.006
Received 19 October 2018; Received in revised form 10 December 2018; Accepted 2 January 2019
Available online 03 January 2019

metabolic memory in the pathogenesis of atherosclerosis and cardiovascular disease despite correction of hyperglycemia [2]. Advanced glycation end products (AGEs) generated from endogenous or exogenous sources present the main mediators of metabolic memory exhibiting a critical cardiometabolic impact in both diabetic and non-diabetic populations [1–3]. In this review, we discuss the pathogenic role of AGEs in CAD development, focusing on the underlying molecular mechanisms and their therapeutic potential.

1.1. AGEs formation and classification

Endogenous formation of AGEs occurs during physiological metabolism and normal aging mainly through the non-enzymatic glycation of proteins, known as the Maillard reaction but also through the Polyol pathway and at prolonged oxidative stress [2]. During all three processes, AGEs synthesis leads to the formation of α-dicarbonyls such as methylglyoxal (MG) and glyoxal (GL), glyceraldehyde and 3-deoxyglucosone which further react with proteins in circulation to form additional AGE molecules [2,3].

The Maillard reaction presents the main source of AGEs formation during which the carbonyl part of a reducing sugar reacts with amino groups of proteins, lipids or nucleic acids, to produce an unstable Schiff base that is further rearranged into a more stable ketosamine, the Amadori product [2]. Amadori products can either be transformed into α-dicarbonyls to form AGE forms such as glucosepane or oxidized to generate other AGE compounds such as *N*-carboxymethyl-lysine (CML) and pentosidine. Additional dehydration and oxidation reactions with extensive crosslinking take place to generate more complex structures, the crosslinked AGEs [4].

Based on their chemical structure, AGEs can be classified to non-fluorescent crosslinking forms (e.g. glucosepane, imidazolium dilysine), fluorescent croslinking molecules (e.g. GL, crossline, pentosidine) and non-crosslinking compounds (e.g. pyralline, CML; Table 1). The most abundant AGE type in vivo is CML, commonly used as a glycation marker and/or a 'representative AGE' in most studies. However, CML is not always associated with disease severity and other AGE forms have been detected that are protein-bound and extensively crosslinked. On top, Western diet presents a major contributor of complex AGE structures other than CML, which are generated during thermal processing or cooking of high fat and meat protein food regimens, enriching the total AGE pool in circulation [5–7].

Recently, a further classification of AGEs has been proposed based on their molecular weight that distinguishes low molecular weight AGEs, such as CML (< 12 kDa) as free or peptide-bound proteins and high molecular weight AGEs as protein-bound proteins [8]. The former are easier absorbed by simple diffusion or peptide transport, readily distributed across the body and removed through renal clearance. The later are more slowly distributed across the body and exhibit a slow, inefficient absorption rate and excretion. High molecular weight AGEs are suggested to exhibit more deleterious effects in tissues than low molecular weight compounds, mainly due to extensive protein crosslinking and resistance to proteolytic degradation [8].

1.2. AGE functions

Accumulation of AGEs in tissues occurs naturally during senescence due to decreased protein turnover. However, hyperglycaemia, oxidative stress and increased free radical formation enhance the generation and accumulation of AGEs in human body [2].

AGEs elicit their cellular effects by two main mechanisms: extracellular and intracellular protein crosslinking and cell surface receptor-mediated signaling. They can alter the physiological properties of extracellular matrix (ECM) proteins such as elastin, collagen, laminin through formation of intermolecular bonds or crosslinking, affecting the mechanical properties of the target tissue and reducing its elasticity [2]. Intracellular accumulation of AGEs in endoplasmic reticulum (ER) impairs normal protein folding and induces stress responses, often leading to inflammation or cell apoptosis [2]. Moreover, AGEs crosslink mitochondrial proteins of respiratory chain, further reducing ATP synthesis and enhancing free radical generation [1,2].

In addition, AGEs presence induces downstream cellular responses by activation of the transmembrane cell Receptor for AGEs, RAGE. Upon AGE binding, RAGE recruits Src kinases, triggers the intracellular cascade and activates the extracellular signal–regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, ultimately leading to activation of the pro-inflammatory nuclear factor NF-κB (NF-κB) [9]. Moreover, RAGE modifies the rate of cell autophagy and apoptosis through activation of other signaling cascades including Phosphatidylinositol-4,5-bisphosphate 3-kinase/Protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) and Nuclear factor of activated T-cells (NFAT) transcription factor [2,9].

Apart from its transmembrane form, RAGE exists in other isoforms including soluble RAGE (sRAGE) that lacks the signal transduction peptide chain, endogenous secretory RAGE (esRAGE) and human RAGE secreted (hRAGEsec). These RAGE variants are present in circulation, acting as scavengers for AGE molecules, being mainly involved in AGE clearance [9,10]. Additionally, other protein ligands such as S100, high mobility group box-1 family members (HMGB-1), amyloid and fibrillar protein aggregates bind to RAGE, eliciting multiple responses with pathogenic potential [11].

At the same time, the pleiotropic effects of AGEs can also be elicited by other cell receptors including CD36 in platelets [12], low density lipoprotein-receptor 1 (LOX-1) in human endothelial cells and macrophage scavenger receptors [13].

The well-established contribution of AGEs in the complications of diabetes has lead to their extensive investigation in many cell types and

Table 1
Structural and fluorescent properties of representative AGEs.

AGE compound	Precursor	Fluorescence	Crosslinking
Nε-carboxymethyl-lysine (CML)	Lysine, glyoxal	No	No
Nε-carboxyethyl-lysine (CEL)	Lysine, methylglyoxal	No	No
N-fructosyl-lysine	Lysine	No	No
Pyrraline	Lysine, 3-deoxyglucosone	No	No
Glucosepane	Lysine	No	Yes
Imidazolium dilysine (IDL)	Lysine	No	Yes
Alkyl formyl glycosyl pyrroles (AFGP)	Lysine	No	Yes
Arginine-lysine imidazole (ALI)	Lysine, arginine	No	Yes
Glyoxal lysine dimer (GOLD)	Lysine, glyoxal	No	Yes
Methylglyoal lysine dimer (MOLD)	Lysine, methylglyoxal	No	Yes
Crossline	Lysine	Yes	Yes
Pentosidine	Lysine, arginine	Yes	Yes
Argpyrimidine	Arginine, methylglyoxal	Yes	Yes
Vesperlysine	Lysine	Yes	Yes

organs revealing their clinical impact in a wide spectrum of diseases including neurodegenerative [14], metabolic, reproductive [15] and cardiovascular diseases [1,2].

2. AGE effects in CAD pathophysiology

Recent studies demonstrate an association between increased AGE levels and the incident of cardiovascular events in diabetic patients being implicated in increased arterial wall stiffness, arrhythmias, systolic and diastolic dysfunction, congestive heart failure, coronary artery diseases and in-stent restenosis risk [2].

In EPIC-NL cohort study with a large number of type 2 diabetic patients, high plasma protein-bound CML, CEL and pentosidine levels were found to significantly correlate with high risk incident of cardiovascular disease after adjustment for confounding factors [16]. In accordance, recent studies demonstrate that elevated plasma levels of methylglyoxal hydroimidazolone, MGH1, CML, CEL, 3-deoxyglucosone hydroimidazolone, and glyoxal hydroimidazolone) and low levels of two oxidation products (2-aminoadipic acid and methionine sulfoxide) were associated with the severity of coronary atherosclerosis and incident of cardiovascular events in patients with T2D [17,18].

Importantly, previous studies on patients undergoing coronary angiography have shown a correlation of elevated serum AGEs in patients with normal glucose and 3-vessel disease compared to no-obstructive disease [19]. Additionally, elevated pentosidine levels were correlated with CAD severity in patients with obstructive CAD, independent of diabetic status [20].

Taken together, these studies support the idea of metabolic memory mediated by AGEs as an important contributor of cardiovascular complications, either independently or synergistically with hyperglycaemia. In the following sections, we review the molecular mechanisms by which AGEs may contribute to CAD pathogenesis.

2.1. Role of AGEs in arterial stiffness, vasodilation and atherogenesis

Cardiovascular dysfunction has been associated with modifications in extracellular and intracellular proteins, affecting vessel function. AGE-induced crosslinking of vascular and myocardial collagen has been demonstrated to reduce vascular elasticity and myocardial flexibility. These effects further contribute to decreased flexibility of vascular walls as well as vascular and myocardial stiffness subsequently leading to diastolic dysfunction observed during aging and in DM patients [21]. Elastin and laminin present in the basement membrane can also be glycated and crosslinked by AGEs, altering cell-matrix interactions and impairing cell adhesion of endothelial cells. They can further reduce NO production and impair vasodilation [2].

Additionally, AGE-induced crosslinking has been detected in intracellular proteins that are involved in Ca^{2+} homeostasis, such as sarcoendoplasmic reticulum Ca^{2+}-ATPase pump and ryanodine receptor (RyR). Crosslinking of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) impairs Ca^{2+} content and affects cardiomyocyte relaxation, resulting in diastolic dysfunction. RyR domains crosslinking by AGEs also affects Ca^{2+} release and disrupts cardiomyocyte contraction [22].

Furthermore, circulating factors can be modified by AGE crosslinking and affect their receptor recognition and processing. Glycated apolipoprotein B100 has been shown to reduce LDL uptake by its receptor and induce its accumulation in the circulation, promoting foam cell generation and atherosclerosis [1,2]. Additionally, glycated fibrinogen is rendered dysfunctional and more resistant to proteolysis with a negative impact in the fibrinolytic process [2].

2.2. Role of AGEs in endothelial dysfunction and inflammation

The aggravating role of AGEs in endothelial dysfunction, a hallmark of CAD has been demonstrated in several studies. AGEs have been shown to impair endothelial cell nitric oxide (NO) production by inhibiting endothelial NO synthase expression [23]. NO is important in mediating vasodilatation but also in the regulation of platelet aggregation and inhibition of inflammatory reactions. Furthermore, AGE-RAGE signaling elevates oxidative stress that can inactivate NO and increase the formation of toxic peroxynitrite. AGEs can also induce the production of asymmetric dimethylarginine (ADMA) which is an inhibitor of NO synthase in endothelial cells and has been associated with endothelial dysfunction in high risk CAD patients [1,24].

In addition to oxidative stress, AGE-RAGE signaling activates many intracellular pathways that result in generation of pro-inflammatory cytokines (IL-6; tumor necrosis factor alpha, TNF-α; Transforming growth factor beta, TGF-β), vascular adhesion molecules (vascular cell adhesion molecule-1, VCAM-1; intracellular cell adhesion molecule-1, ICAM-1; endothelin-1, ET-1) and reactive oxygen species (ROS), further establishing vascular inflammation [1]. More specifically, culture of human aortic endothelial cells (HAECs) in hyperglycemic conditions induces oxidative stress through activation of AGE-RAGE signaling leading to upregulation of MAPK pathways and triggering NF-κB and AP-1 activation [25]. These transcription factors have been found to further upregulate gene expression of the ECM enzyme, lysyl oxidase (LOX) and the vasoconstrictor protein, ET-1, resulting in impaired endothelial homeostasis and cell damage (Fig. 1). In accordance, a positive association between increased ET-1 levels and AGEs was observed in serum of PCOS women and controls, indicating that the detrimental effect of AGEs on endothelial cells may potentially involve elevated ET-1 production [26].

Additionally, AGEs may directly induce endoplasmic reticulum (ER) stress in HAECs, through activation of the unfolded protein response (UPR) leading to endothelial cell apoptosis and dysfunction [27]. This observation was further confirmed in vivo by the systemic effects of AGEs in ER stress induction in major metabolic tissues of normal mice fed with a high-AGEs content diet for 4 weeks [28].

The AGE precursor, MG has been found to exhibit a negative effect over thioredoxin (Trx), an anti-oxidative, anti-apoptotic molecule. Specifically, MG suppressed the activity of the Trx-dependent peroxidase, peroxiredoxin, and reduced Trx protein levels in HAECs via transcriptional regulation, indicating a positive contribution of MG to apoptosis and ROS formation [29].

Methylglyoxal-derived hydroimidazolone 1 (MGH1), the most abundant AGE in human plasma has been shown to increase ROS generation and upregulate ICAM-1 expression in HUVECs through interaction with RAGE. It further enhanced THP-1 macrophage adhesion to HUVECs being implicated in endothelial inflammatory reactions and presenting a potential early phase marker of atherosclerosis [30].

Another study showed the effect of AGEs in endothelial hyperpermeability through induction of profilin-1, an important regulator of cytoskeleton morphological rearrangements (Fig. 1). Endothelial cells exposed to an AGE-rich environment, upregulated the mRNA levels of profilin-1, leading to formation of actin stress fibers, and ultimately to the rearrangement and redistribution of the cell cytoskeleton [31].

The multifactorial role of AGEs in endothelial cell injury is also demonstrated by the AGE-induced upregulation of vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1) leading to pathological neoangiogenesis as well as to a general prothrombotic condition. Higashimoto et al. investigated the potential effect of phosphothioate-modified aptamers in suppressing toxic AGE function in human umbilical vein endothelial cells (HUVECs), showing a significant blockade of AGE-RAGE axis, and a novel therapeutic approach to AGE-induced endothelial damage [32].

In addition, RAGE-induced activation of ERK1/2 phosphorylation on endothelial cells in response to a plethora of ligands is a result of heparan sulfate-induced hexamerization of RAGE extracellular domain. RAGE-heparan sulfate oligomeric complexes play a pivotal role in signaling and interaction with RAGE oligomerization [33].

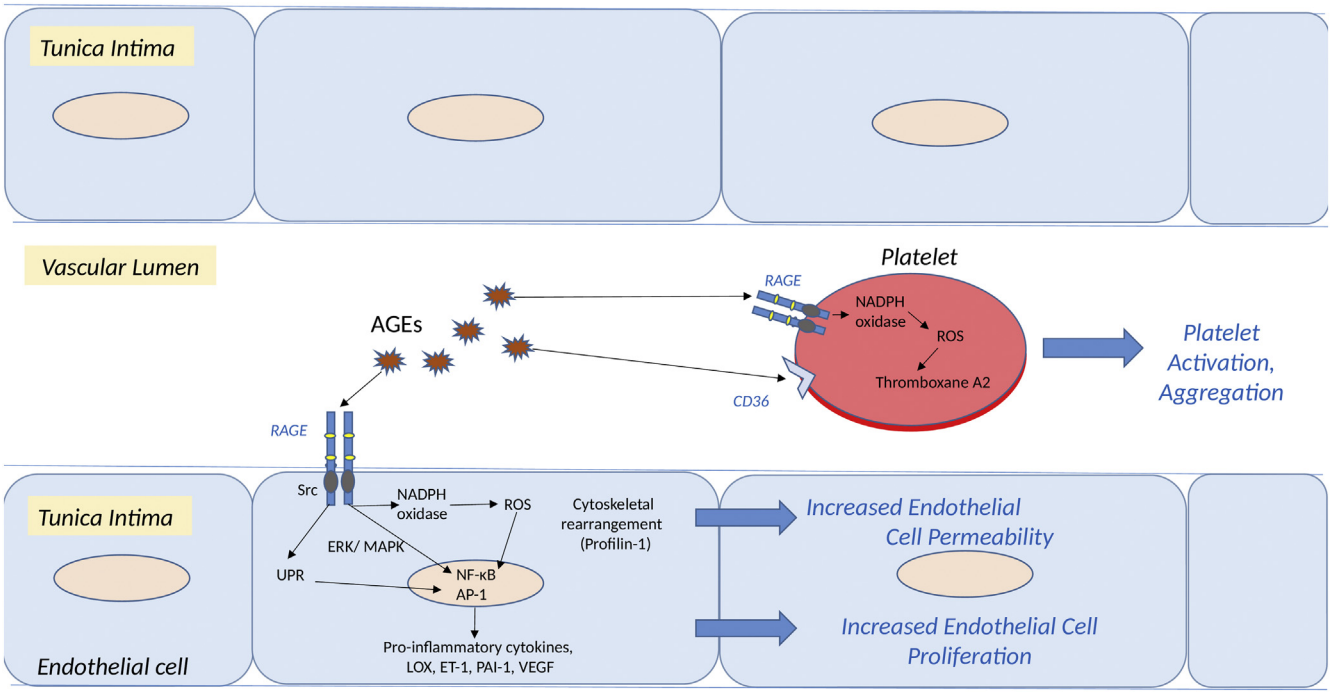

Fig. 1. Effects of AGE-RAGE signaling in platelets and endothelial cell function.
Accumulation of AGEs in vascular lumen affects platelets activity and aggregation through binding to RAGE and/or CD36 scavenger receptor. In tunica intima, AGEs bind to transmembrane receptor RAGE in endothelial cells and can either activate UPR or ERK/MAPK pathway leading to AP-1 and NF-κB induction. These signaling pathways increase the transcription of pro-inflammatory cytokines, LOX, ET-1, PAI-1, VEGF and enhance endothelial proliferation and inflammation. Furthermore, AGEs may activate NADPH oxidase and induce ROS generation followed by NF-κB activation and inflammatory response. Finally, AGEs may directly induce cytoskeletal rearrangements in endothelial cells enhancing their permeability.
AGEs, advanced glycation end products; RAGE, receptor for AGEs; UPR, unfolded protein response; ROS, reactive oxygen species; ERK, extracellular signal-regulated kinase; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-κB; AP-1, activator protein-1; LOX, lysyl oxidase; ET-1, endothelin-1; PAI-1, plasminogen activator inhibitor-1.

Recently, HMGB1/RAGE signaling pathway was revealed as the underlying molecular mechanism of hyperuricemia's contribution to endothelial injury. Elevated uric acid was found to potentiate the expression of HMGB1 and its subsequent extracellular release [34].

Besides RAGE, AGEs can also bind to several other receptors on endothelial cells, which mainly exhibit a scavenger role including LOX-1 and galectin-3 [13,35]. AGEs can upregulate LOX-1 expression which has a prominent role in the pathogenesis of atherosclerosis and microvascular pathology. The combination of oxidative stress, inflammatory cytokines secretion (especially IL-6), and AGE-induced NADPH oxidase activation seems to play a central role in the atherosclerotic process and may serve as a potential therapeutic target [13].

2.3. Role of AGEs in vascular smooth muscle cells function and atherosclerosis

Vascular smooth muscle cells (VSMCs) constitute the major cell type in blood vessel walls. The migration and proliferation of VSMCs is very important for the development of atherosclerosis. VSMCs express RAGE and the AGE-RAGE signaling axis has been shown to modulate their function in response to damage signals while inducing phenotypic changes that contribute to atherosclerosis [36].

Furthermore, accumulation of AGEs in VSMCs affects cell cycle progression being implicated in their proliferation, apoptosis and autophagy through activation of ERK/MAPK and Akt/mTOR molecular pathways (Fig. 2). Zhao et al. also showed that upon RAGE binding, the expression of Ca^{2+}-activated K^+ channel (KCa 3.1) is upregulated in rat VSMCs followed by activation of ERK1/2, p38 MAPK kinases and PI3K, thus affecting cell proliferation. However, RAGE inhibition attenuated growth signals [37].

Moreover, RAGE activates NADPH oxidase and induces the generation of reactive oxygen species (ROS) in VSMCs. ROS were shown to independently lead to p38 MAPK activation, further augmenting mitotic signals [38].

The effect of AGEs in autophagy is controversial, with ERK activation been implicated in induction of autophagy and Akt/mTOR involved in its repression. In primary rat VSMCs, RAGE-induced ERK activation was shown to positively correlate with the translocalization of microtubule-associated protein 1 light chain 3 (LC3-II) from the cytoplasm to lysosomal membrane, an initiating step of autophagy. However, Akt/mTOR activation abolished this effect [36].

Further studies demonstrate that AGEs downregulate Cathepsin D, a lysosomal degradative enzyme suggesting that the increased autophagolysosomes observed, derive possible from impaired degradation rather than increased formation [39]. RAGE activation in human carotid smooth muscle cells leads to enhanced cell survival mediated by activation of the NFAT signaling pathway. NFAT induction was shown to upregulate anti-apoptotic proteins such as Bcl-2 and stabilize mitochondrial membrane potential [9]. However, RAGE activation in aortic rat VSMCs was reported to increase caspase 3/7 activity and increase cells' susceptibility to apoptosis [40]. This contradicting evidence indicates the complexity of AGE/RAGE signaling in VSMCs that needs further elucidation.

In addition to proliferation, AGEs modulate the interaction of VSMCs with extracellular matrix. RAGE activation is responsible for upregulation of matrix metalloproteinases 2 and 9 (MMP2/MMP9) and thus augmentation of their migratory capacity. Moreover, protein expression of lipocalin-2 is also increased. As a result, MMP2 is stabilized and its autodegradation is prevented [41,42]. The above effects are exaggerated when VSMCs are viewed in perspective to their surrounding tissue. Glycotoxins may interact directly with fibronectin. Glycated fibronectin binds to RAGE exhibiting enhanced adhesion to

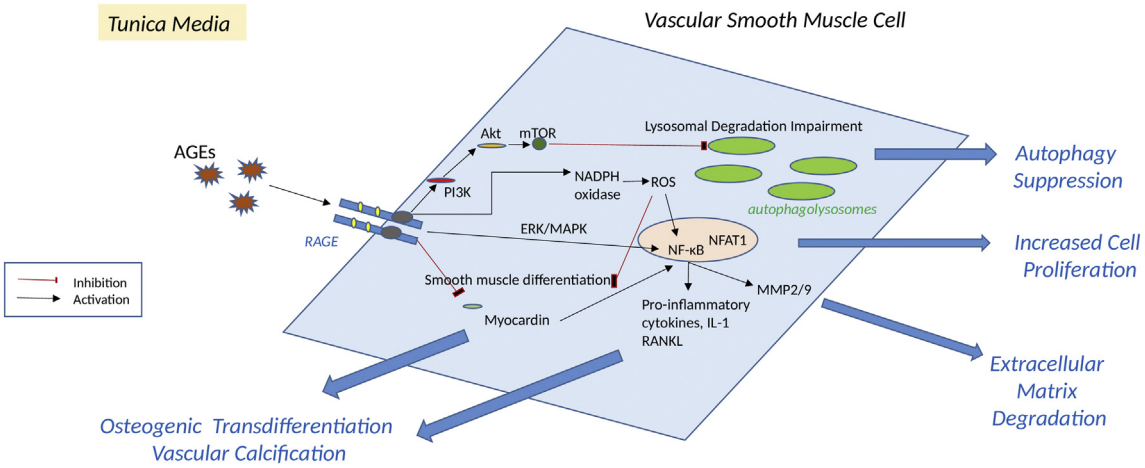

Fig. 2. Effects of AGE-RAGE signaling in VSMCs. In tunica media, AGEs bind to RAGE in VSMCs and activate ERK/MAPK pathway resulting to NF-κB induction, inflammatory cytokine formation and MMP2/9 activation being ultimately implicated in enhanced proliferation, inflammation and extracellular matrix degradation. Upon RAGE binding, AGEs also activate PI3k/Akt/mTOR pathways inducing impaired lysosomal degradation and suppressing autophagy. Moreover, AGE-RAGE signaling in VSMCs reduces the activity of myocardin, a protein responsible for smooth muscle differentiation. Furthermore, ROS production via NADPH oxidase activation favors the enhanced transcription of RANK Ligand which induces osteogenic differentiation leading to vascular calcification. Finally, AGEs may directly glycate fibronectin that binds to RAGE in VSMCs and activates intracellular signaling.
AGEs, advanced glycation end products; RAGE, receptor for AGEs; VSMCs, vascular smooth muscle cells; PI3K, phosphoinositide 3-kinase; Akt, AKT serine/threonine kinase; mTOR, mammalian target of rapamycin; ERK, extracellular signal-regulated kinase; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor-κB; NFAT1, nuclear factor of activated T cells 1; MMP2/MMP9, matrix metalloproteinases 2/9; RANKL, receptor activator of nuclear factor-κB ligand.

VSMCs compared to normal substrate [42]. Moreover, endothelial damage leads to increased production of inflammatory cytokines such as IL-1. IL-1 binding to VSMCs increases sensitivity to purinergic signals like UTP through upregulation of G protein-coupled P2Y purinergic receptor (P2YR). UTP was shown to induce expression of RAGE and its downstream molecules while enhancing proliferation and migration of IL-1β-pretreated VSMCs, thus accelerating the atherosclerotic process [43].

Vascular calcification constitutes a hallmark of atherosclerosis and the pattern of calcium deposition determines plaque stability while increasing the risk of thromboembolic events. VSMCs orchestrate this process as they undergo a phenotypic shift towards bone differentiation (Fig. 2). AGE-RAGE signaling has been shown to reduce the activity and expression of myocardin, a protein responsible for smooth muscle differentiation [44]. Furthermore, RAGE ligands function in synergy to bone morphogenetic protein (BMP) to activate Notch/Homeobox protein Msx2 (Msx2) signaling pathways that lead to elevated expression of alkaline phosphatase, an essential enzyme for vascular calcification [45]. Moreover, ROS production via NADPH oxidase activation favors the enhanced transcription of receptor activator of nuclear factor-κB ligand (RANKL) which induces osteogenic differentiation [46]. From a qualitative perspective, RAGE upregulation has been associated with granular instead of diffuse calcification, exposing the lipid core of atheromatous plaques, leading to instability and rupture predisposition [47].

2.4. Role of AGEs in platelets activation and aggregation

AGEs play a critical regulatory role over platelet activity [48]. MG, glycated albumin and S100 calcium binding proteins have been shown to bind and activate RAGE in platelets as well as the scavenger receptor, CD36 and modulate platelet function through intracellular signaling [9].

Several studies demonstrate that AGEs increase both platelet activation and aggregation. Incubation of platelets with AGEs has been shown to upregulate adhesion molecules such as P-Selectin and platelet endothelial cell adhesion molecule 1 (PECAM-1), thus stabilizing platelet-endothelium interaction [49,50]. Regarding cell aggregation, AGEs modify the phospholipids transmembrane ratio through externalization of phosphatidylserine, a marker of platelet activity [49]. Upregulation of platelet glycoproteins including glycoprotein GPIIb, the main effector of platelet aggregation has also been observed [50]. Upon AGE binding to RAGE, NADPH hyperactivity is observed, leading to ROS generation which is associated with increased cyclooxygenase activity and thromboxane A2 (TXB) generation in platelets, further contributing to microthrombus formation (Fig. 1) [51]. Moreover, Vazzana et al. showed an inverse relationship between the AGE scavenger receptor, endogenous soluble RAGE (esRAGE) and urinary 11-dehydro TXB2 levels, a thromboxane metabolite [52]. In a cohort of patients with non-alcoholic fatty liver disease, esRAGE was found inversely correlated with platelet-independent hypercoaguability of patients' serum as expressed by the elevated endogenous thrombin potential [53].

Recently, RAGE has been implicated in another pathway of the platelet aggregation cascade. Neutrophil migration is considered essential for the stabilization of platelet thrombi. The most potent messenger for neutrophils is the RAGE ligand, HMGB1. In patients with acute myocardial infarction treated with thrombus ablation, HMGB1 was shown to bind to neutrophil RAGE and upregulate the formation of autophagolysosomes through the MAPK pathway [11]. Moreover, upon HMGB1 binding to TLR4, it acts as a pro-survival agent by stabilizing the mitochondrial potential [54]. However, further studies are needed to elucidate the specific intracellular mechanisms responsible for these effects.

2.5. Role of AGE-RAGE signaling axis in stent restenosis

Primary coronary intervention (PCI) is considered as the class I treatment recommendation for CAD in both American and European clinical practice guidelines [55]. However, despite optimal stent placement, a significant amount of patients will express restenosis in the position of angioplasty and require further interventions with a prevalence approximating 26% [56]. Therefore, the identification of potential prognostic risk factors is crucial to ameliorate patient outcome. AGEs and their receptor isoforms seem to have an important contribution in both pathogenesis and clinical outcome of stent restenosis.

The study of Falcone et al. was the first to associate the -374AT/TT polymorphism in RAGE gene promoter with increased risk for both CAD

and stent restenosis after PCI [57]. In the same study, the -374AA RAGE polymorphism was inversely correlated with stent restenosis and associated with upregulated RAGE expression [58]. This is in accordance with a cross-sectional study of non-diabetic patients where prePCI sRAGE levels and prePCI AGE/sRAGE ratio, were predictive of restenosis risk with a positive predictive value of 85% and 84%, respectively. Interestingly, biomarkers of inflammation such as TNF-α and C-reactive protein (CRP) were inversely correlated with sRAGE levels pointing to a reduced vascular injury due to the scavenger effect of sRAGE [59].

Diabetic patients undergoing PCI, however, present the opposite findings with sRAGE levels being positively correlated with increased risk of stent restenosis [60]. This may be attributed to the established vascular inflammation present in diabetic patients where increased circulating AGEs and sRAGE levels are indicative of the upregulated tissue RAGE expression, mediating further oxidative stress and endothelial damage [61].

In accordance, reduced serum levels of the endogenous secretory RAGE (esRAGE) which represents the soluble isoform of RAGE, were assessed in diabetic and non-diabetic patients in relation to their risk for restenosis and were associated with poor patients' prognosis and clinical outcome [62].

Concerning sRAGE ligands, both total circulating AGEs and specifically CML has been correlated with increased risk of stenosis and increased vascular injury post PCI, respectively [60,63]. In addition, HMGB2, another RAGE ligand has been suggested as a significant modulator of in-stent restenosis risk in CAD patients due to its effects on smooth muscle cell migration and intimal hyperplasia in response to vascular injury. This effect was further attenuated by RAGE inhibition, confirming its critical role in restenosis risk [64].

Regarding RAGE ligand-induced signaling cascades that lead to arterial restenosis, both activation of signal transducer and activator of transcription 3 (STAT3) transcription factor and of the anti-apoptotic molecule NFAT1 have been found upregulated leading to stabilization of mitochondrial membrane potential and depolarization of smooth muscle cell membrane, along with increased cell proliferation. [38]. Ligand binding to RAGE has been demonstrated to promote arterial intima formation in response to arterial injury in murine models by decreasing the activity of the two metabolic kinases, liver kinase B1 (LKB1) and AMP-activated protein kinase (AMPK) in smooth muscle cells while increasing STAT3 phosphorylation [65].

Furthermore, HMGB protein family has been involved in RAGE-dependent neointimal hyperplasia through upregulation of the NADPH oxidase generating ROS and increasing the expression of ECM proteins including collagen and matrix metalloproteinases [56]. HMGB1 has also been demonstrated to dedifferentiate VSMCs leading to a more aggressive phenotype and increased activity of mitotic pathways such as p38-MAPK/NF-κB. Interestingly, it downregulates superoxide dismutase and decreases the cell decoying capacity of ROS [66]. In accordance to clinical observations, the aforementioned cellular events can be modified by the scavenger receptor sRAGE which prevents binding to membrane RAGE, thus inhibiting neointima formation, further highlighting its prognostic and therapeutic value [67].

3. Therapeutic targeting of ages for CAD

3.1. Effects of dicarbonyl scavengers in AGE levels

The 2-aminomethyphenol pyridoxamine, a vitamin B6 analog has the ability to scavenge 1,2-dicarbonyls and was demonstrated to reduce CML and CEL along with plasma triglycerides and total cholesterol in STZ-treated rats [68]. It also reduced vascular calcification in rats fed with a high fat diet and warfarin [69]. Interestingly, treatment with pyridoxamine inhibited the development of atherosclerotic lesions in atherosclerosis-prone STZ-treated apoE−/− mice and improved cardiac ejection fraction in STZ-induced diabetic mice with experimental myocardial infarction [70]. In a study of 212 diabetic patients with nephropathy, pyridoxamine supplementation for six months improved creatinine levels and reduced CML, CEL levels and urinary TGFβ excretion, with minimal adverse effects [71].

Treatment with another 2-aminomethylphenol, 2-hydroxybenzylamine (2-HOBA) has shown protective effects in vascular function in vivo. Supplementation of HOBA for five months of transgenic mice that overexpress the p22 subunit of NADPH oxidase resulting in elevated superoxide generation, markedly reduced aortic stiffness and hypertension [72].

3.2. Effects of metformin in AGE levels

The impact of metformin's action in AGE levels has been a subject of extensive research during recent years. The study of Dziubak et al. reported that among its plethora of functions, metformin suppresses the biogenesis as well as the aggregation of AGEs [73]. In agreement, Lin et al. showed that in human neural stem cells (hNSCs), metformin potentiates AMPK effects and specifically AMPK-dependent suppression of RAGE levels. Moreover, it protected AGE-induced damaged hNSCs from direct oxidation stress and downregulation of oxidation defense enzymes including glutathione (GSH), catalase, and heme oxygenase-1 (HO-1). These protective effects were hindered by the addition of an AMPK inhibitor, highlighting the AMPK-dependence of metformin action [74,75].

In patients with metabolic syndrome, Haddad et al. investigated the effects of metformin upon plasma pentosidine, CML and sRAGE levels. A significant reduction of plasma pentosidine was observed along with a statistically significant increase in sRAGE levels [76]. Zhou et al. demonstrated that metformin-pretreated cells inhibited the inflammatory effects of AGEs in murine bone marrow-derived macrophages. It reduced the expression of AGEs-induced cluster of differentiation 86 (CD86) M1 pro-inflammatory macrophage marker, and at the same time, metformin induced CD206 (M2 anti-inflammatory macrophage marker) surface expression as well as the production of the anti-inflammatory IL-10. These protective effects were also attenuated by the AMPK antagonist, Compound C, indicating that metformin's action is partly mediated by AMPK activation and suppression of the RAGE/NF-κB pathway [77].

Metformin also reacts with MG and was shown to reduce MG metabolism in type 2 diabetic patients after 24 weeks of treatment. Furthermore, it induced the activity of glyoxalase 1, the major detoxification enzyme of MG in peripheral blood mononuclear cells of these patients indicating its dual role in inhibiting AGE formation [78].

Treatment with metformin was also demonstrated to decrease total cholesterol, LDL and triglyceride levels in patients with diabetes, conferring cardiovascular protection [79]. In addition, it reduced platelet aggregation, enhanced fibrinolysis and decreased PAI-1, CRP and clotting factor VII levels [80]. In a long term intervention study, metformin was demonstrated to decrease coronary artery calcium scores in prediabetic men [81] compared to placebo group while it significantly reduced cardiovascular risk factors in type 1 diabetic patients [82].

3.3. Effects of statins in AGE levels

Statins exhibit pleiotropic functions in vasculature that are independent of their lipid-lowering actions including anti-inflammatory and anti-oxidative stress properties [83]. Interestingly, they have been used therapeutically to reduce the harmful effects of AGEs. Several studies show that statins, among other drugs, can increase the plasma levels of sRAGE and thus inhibit the interaction between AGEs and RAGE, both directly and indirectly [84,85].

Chen et al. studied the effect of atorvastatin on cardiac fibrosis in mice treated with AGEs [86]. They report significantly reduced collagen deposits in heart tissues and thus attenuation of diastolic dysfunction in vivo. They also mention a decrease in fibroblast

differentiation to myofibroblasts, thereby limiting cardiac fibrosis [86]. Statins were also shown to bind peroxisome proliferator-activated receptor gamma (PPAR-γ) in heart tissue and fibroblasts, downregulate RAGE expression and suppress AGE-induced ERK1/2 phosphorylation [86].

Moreover, statins and specifically atorvastatin exhibit an inhibitory effect on the toxic glyceraldehyde-derived AGEs which interact with RAGE to induce altered intracellular signaling and release of inflammatory mediators that contribute to oxidative stress and atherosclerosis [87]. The underlying mechanism of action relies on the established inhibitory effects of statins on NF-κB and Rho kinase pathway, or their lipid lowering function [88]. Blockade of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase leads to decreased intracellular farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), which limit the activation of Rho kinase, and ultimately NF-κB. This effect may be rather promising in primary percutaneous intervention (PCI) of patients with acute myocardial infarct (AMI). Another study reports a decrease in RAGE expression in diabetic patients by simvastatin via suppression of myeloperoxidase-dependent AGE production [89]. Moreover, a decrease in prostaglandin E2 (PGE_2)-dependent matrix metalloproteinases was observed which is consistent with reduced inflammation and limited plaque instability.

AGEs are also shown to induce apoptosis of HAECs in a dose-dependent manner, via downregulating the PI3K/Akt pathway and by reducing heat shock factor 1 (HSF-1) which leads to decreased heat shock proteins (HSPs), rendering the organism vulnerable to oxidative stress and endothelial damage [90]. Li et al. showed that atorvastatin can decrease AGEs effects by stimulating the PI3K/Akt pathway and by increasing HSF-1 mRNA transcription. At the same time, the cardioprotective effect of atorvastatin can be attenuated by a PI3K inhibitor [90].

Nakamura et al. showed that AGEs may independently contribute to proteinuria in stage I or II chronic kidney disease (CKD) of non-diabetic patients with dyslipidemia. However, atorvastatin treatment significantly ameliorated protein excretion in urine of this population [91]. On the other hand, statins treatment of patients with brain infarctions exhibiting increased AGEs levels, failed to lower AGEs in their blood [92]. Only co-treatment with statins and angiotensin II receptor blockers (ARBs) managed to slightly reduce AGE levels [92].

Furthermore, Okamoto et al. found that AGEs induce angiogenesis through the AGE-RAGE interaction in endothelial cells with a subsequent activation of the *VEGF* gene transcription through activation of NF-κB and activator protein-1 (AP-1). Cerivastatin was further shown to completely diminish the ensuing angiogenesis by blocking the AGE-RAGE interaction [93].

3.4. Effect of vitamin D supplementation in AGE levels

Vitamin D has been extensively studied with regard to cardiovascular disease, both from the aspect of disease prevention as well as regarding attenuation of morbidity and mortality. However, the pathophysiologic connection between AGEs and vitamin D has not been thoroughly investigated. Lee et al. explored the interplay between vitamin D and RAGE/sRAGE in HL-1 myocardial cells. A significant reduction of RAGE expression and increased sRAGE concentration was observed that was associated with enhanced protein expression of ADAM metallopeptidase domain 10 (ADAM10). However, upon addition of ADAM10 inhibitor the calcitriol's suppressive effect on RAGE was eliminated, indicating an important modulatory role of ADAM10 expression in cardiomyocytes, mediating the inhibitory effect of vitamin D on RAGE [94].

Moreover, Iqbal et al. investigated possible interaction of vitamin D with glycation of human serum albumin (HSA) revealing that vitamin D metabolites may lead to a reduction of glycation [95]. Another study assessed the role of vitamin D on AGE-induced osteoblastic transdifferentiation of VSMCs. AGEs were shown to induce an upregulation of L-type Ca^{2+} channel with ROS elevation and enhancement of NF-κB and ERK, leading towards an osteogenic shift of VSMCs that was however, inhibited by vitamin D supplementation [96].

In accordance, the study of Salum et al. reported the impact of vitamin D administration in diabetic rats, indicating a significant protection against oxidation-mediated vascular complications [97].

4. Conclusion

AGEs constitute a critical family of molecules with pivotal role in the pathophysiology of coronary heart disease [1,2]. Being directly implicated in vascular stiffness and atherosclerosis as well as in modulation of intracellular signaling with detrimental effects in endothelial cell response, VSMCs function and platelet activity, AGEs should be considered as major cardiometabolic risk factors [3].

In addition, their interference with the available treatment modalities predisposes individuals to a persistent cardiovascular risk, emphasizing the need to improve their analytical measurement, establish their biomarker potential [16] and integrate them in risk stratification of patients as well as in treatment decisions.

Future studies should also focus on detection of protein bound high molecular weight AGEs commonly present in exogenous sources and characterize their potential toxic effects in vascular tissue [8,21]. The synergistic action of dietary AGEs to endogenous load further indicates the need for lifestyle changes in preventive and therapeutic schemes of myocardial ischemia and its complications [3,15,81,98,99], along with selective AGE/RAGE modulating drugs [100].

Conflict of interest

The authors declare that they have no conflict of interest.

Transparency document

The Transparency document associated with this article can be found, in online version.

References

[1] S.-I. Yamagishi, T. Matsui, Role of hyperglycemia-induced advanced glycation end product (AGE) accumulation in atherosclerosis, Ann. Vasc. Dis. 11 (2018) 253–258.
[2] S.L. Fishman, H. Sonmez, C. Basman, V. Singh, L. Poretsky, The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: a review, Mol. Med. 24 (2018) 59.
[3] C. Luévano-Contreras, A. Gómez-Ojeda, M.H. Macías-Cervantes, M.E. Garay-Sevilla, Dietary advanced glycation end products and cardiometabolic risk, Curr. Diab. Rep. 17 (2017).
[4] P.J. Thornalley, Dicarbonyl intermediates in the Maillard reaction, Ann. N. Y. Acad. Sci. 1043 (2005) 111–117.
[5] M. Aragno, R. Mastrocola, Dietary sugars and endogenous formation of advanced glycation endproducts: emerging mechanisms of disease, Nutrients 9 (2017) 385.
[6] M. Takeuchi, J.-i. Takino, S. Furuno, H. Shirai, M. Kawakami, M. Muramatsu, Y. Kobayashi, S.-i. Yamagishi, Assessment of the concentrations of various advanced glycation end-products in beverages and foods that are commonly consumed in Japan, PLoS One 10 (2015) e0118652.
[7] L.R. DeChristopher, Perspective: the paradox in dietary advanced glycation end products research—the source of the serum and urinary advanced glycation end products is the intestines, not the food, Adv. Nutr. 8 (2017) 679–683.
[8] D. Deluyker, L. Evens, V. Bito, Advanced glycation end products (AGEs) and cardiovascular dysfunction: focus on high molecular weight AGEs, Amino Acids 49 (2017) 1535–1541.
[9] J. Xie, J.D. Méndez, V. Méndez-Valenzuela, M.M. Aguilar-Hernández, Cellular signalling of the receptor for advanced glycation end products (RAGE), Cell. Signal. 25 (2013) 2185–2197.
[10] J.-S. Maltais, E. Simard, U. Froehlich, J.-B. Denault, L. Gendron, M. Grandbois, iRAGE as a novel carboxymethylated peptide that prevents advanced glycation end product-induced apoptosis and endoplasmic reticulum stress in vascular smooth muscle cells, Pharmacol. Res. 104 (2016) 176–185.
[11] N. Maugeri, L. Campana, M. Gavina, C. Covino, M. De Metrio, C. Panciroli, L. Maiuri, A. Maseri, A. D'Angelo, M.E. Bianchi, P. Rovere-Querini, A.A. Manfredi, Activated platelets present high mobility group box 1 to neutrophils, inducing autophagy and promoting the extrusion of neutrophil extracellular traps, J. Thromb. Haemost. 12 (2014) 2074–2088.
[12] I. Soaita, W. Yin, D.A. Rubenstein, Glycated albumin modifies platelet adhesion and

aggregation responses, Platelets 28 (2017) 682–690.
[13] V. Lubrano, S. Balzan, Roles of LOX-1 in microvascular dysfunction, Microvasc. Res. 105 (2016) 132–140.
[14] S.-Y. Ko, H.-A. Ko, K.-H. Chu, T.-M. Shieh, T.-C. Chi, H.-I. Chen, W.-C. Chang, S.-S. Chang, The possible mechanism of advanced glycation end products (AGEs) for Alzheimer's disease, PLoS One 10 (2015) e0143345.
[15] E. Tantalaki, C. Piperi, S. Livadas, A. Kollias, C. Adamopoulos, A. Koulouri, C. Christakou, E. Diamanti-Kandarakis, Impact of dietary modification of advanced glycation end products (AGEs) on the hormonal and metabolic profile of women with polycystic ovary syndrome (PCOS), Hormones 13 (2014) 65–73.
[16] N.M.J. Hanssen, J.W.J. Beulens, S. van Dieren, J.L.J.M. Scheijen, D.L. van der A, A.M.W. Spijkerman, Y.T. van der Schouw, C.D.A. Stehouwer, C.G. Schalkwijk, Plasma advanced glycation end products are associated with incident cardiovascular events in individuals with type 2 diabetes: a case-cohort study with a median follow-up of 10 years (EPIC-NL), Diabetes 64 (2015) 257–265.
[17] J. Koska, A. Saremi, S. Howell, G. Bahn, B. De Courten, H. Ginsberg, P.J. Beisswenger, P.D. Reaven, VADT Investigators, Advanced glycation end products, oxidation products, and incident cardiovascular events in patients with type 2 diabetes, Diabetes Care 41 (2018) 570–576.
[18] A. Saremi, S. Howell, D.C. Schwenke, G. Bahn, P.J. Beisswenger, P.D. Reaven, VADT Investigators, Advanced glycation end products, oxidation products, and the extent of atherosclerosis during the VA diabetes trial and follow-up study, Diabetes Care 40 (2017) 591–598.
[19] M. Kanauchi, N. Tsujimoto, T. Hashimoto, Advanced glycation end products in nondiabetic patients with coronary artery disease, Diabetes Care 24 (2001) 1620–1623.
[20] M. Kerkeni, I.S. Weiss, S. Jaisson, A. Dandana, F. Addad, P. Gillery, M. Hammami, Increased serum concentrations of pentosidine are related to presence and severity of coronary artery disease, Thromb. Res. 134 (2014) 633–638.
[21] D. Deluyker, V. Ferferieva, J.-P. Noben, Q. Swennen, A. Bronckaers, I. Lambrichts, J.-M. Rigo, V. Bito, Cross-linking versus RAGE: how do high molecular weight advanced glycation products induce cardiac dysfunction? Int. J. Cardiol. 210 (2016) 100–108.
[22] K.R. Bidasee, Y. Zhang, C.H. Shao, M. Wang, K.P. Patel, U.D. Dincer, H.R. Besch, Diabetes increases formation of advanced glycation end products on sarco(endo) plasmic reticulum Ca2 + -ATPase, Diabetes 53 (2004) 463–473.
[23] A. Soro-Paavonen, W.-Z. Zhang, K. Venardos, M.T. Coughlan, E. Harris, D.C.K. Tong, D. Brasacchio, K. Paavonen, J. Chin-Dusting, M.E. Cooper, D. Kaye, M.C. Thomas, J.M. Forbes, Advanced glycation end-products induce vascular dysfunction via resistance to nitric oxide and suppression of endothelial nitric oxide synthase, J. Hypertens. 28 (2010) 780–788.
[24] R. Ando, S. Ueda, S. Yamagishi, H. Miyazaki, Y. Kaida, K. Kaifu, M. Yokoro, Y. Nakayama, N. Obara, K. Fukami, M. Takeuchi, S. Okuda, Involvement of advanced glycation end product-induced asymmetric dimethylarginine generation in endothelial dysfunction, Diab. Vasc. Dis. Res. 10 (2013) 436–441.
[25] C. Adamopoulos, C. Piperi, A.N. Gargalionis, G. Dalagiorgou, E. Spilioti, P. Korkolopoulou, E. Diamanti-Kandarakis, A.G. Papavassiliou, Advanced glycation end products upregulate lysyl oxidase and endothelin-1 in human aortic endothelial cells via parallel activation of ERK1/2–NF-κB and JNK–AP-1 signaling pathways, Cell. Mol. Life Sci. 73 (2015) 1685–1698.
[26] C. Christakou, F. Economou, S. Livadas, C. Piperi, C. Adamopoulos, E. Marinakis, E. Diamanti-Kandarakis, Strong and positive association of Endothelin-1 with AGEs in PCOS: a causal relationship or a bystander? Hormones 10 (2011) 292–297.
[27] C. Adamopoulos, E. Farmaki, E. Spilioti, H. Kiaris, C. Piperi, A.G. Papavassiliou, Advanced glycation end-products induce endoplasmic reticulum stress in human aortic endothelial cells, Clin. Chem. Lab. Med. 52 (2014).
[28] C. Adamopoulos, C. Mihailidou, C. Grivaki, K.A. Papavassiliou, H. Kiaris, C. Piperi, A.G. Papavassiliou, Systemic effects of AGEs in ER stress induction in vivo, Glycoconj. J. 33 (2016) 537–544.
[29] T. Oba, R. Tatsunami, K. Sato, K. Takahashi, Z. Hao, Y. Tampo, Methylglyoxal has deleterious effects on thioredoxin in human aortic endothelial cells, Environ. Toxicol. Pharmacol. 34 (2012) 117–126.
[30] Y. Ishibashi, T. Matsui, N. Nakamura, A. Sotokawauchi, Y. Higashimoto, S.-I. Yamagishi, Methylglyoxal-derived hydroimidazolone-1 evokes inflammatory reactions in endothelial cells via an interaction with receptor for advanced glycation end products, Diab. Vasc. Dis. Res. 14 (2017) 450–453.
[31] Z. Li, Q. Zhong, T. Yang, X. Xie, M. Chen, The role of profilin-1 in endothelial cell injury induced by advanced glycation end products (AGEs), Cardiovasc. Diabetol. 12 (2013) 141.
[32] Y. Higashimoto, T. Matsui, Y. Nishino, J. Taira, H. Inoue, M. Takeuchi, S.-i. Yamagishi, Blockade by phosphorothioate aptamers of advanced glycation end products-induced damage in cultured pericytes and endothelial cells, Microvasc. Res. 90 (2013) 64–70.
[33] D. Xu, J.H. Young, J.M. Krahn, D. Song, K.D. Corbett, W.J. Chazin, L.C. Pedersen, J.D. Esko, Stable RAGE-Heparan sulfate complexes are essential for signal transduction, ACS Chem. Biol. 8 (2013) 1611–1620.
[34] W. Cai, X.-M. Duan, Y. Liu, J. Yu, Y.-L. Tang, Z.-L. Liu, S. Jiang, C.-P. Zhang, J.-Y. Liu, J.-X. Xu, Uric acid induces endothelial dysfunction by activating the HMGB1/RAGE signaling pathway, Biomed. Res. Int. 2017 (2017) 1–11.
[35] D. Pepe, C.G. Elliott, T.L. Forbes, D.W. Hamilton, Detection of galectin-3 and localization of advanced glycation end products (AGE) in human chronic skin wounds, Histol. Histopathol. 29 (2014) 251–258.
[36] M. Ma, X. Guo, Y. Chang, C. Li, X. Meng, S. Li, Z.-X. Du, H.-Q. Wang, Y. Sun, Advanced glycation end products promote proliferation and suppress autophagy via reduction of Cathepsin D in rat vascular smooth muscle cells, Mol. Cell. Biochem. 403 (2015) 73–83.
[37] L.-M. Zhao, X.-L. Su, Y. Wang, G.-R. Li, X.-L. Deng, KCa3.1 channels mediate the increase of cell migration and proliferation by advanced glycation endproducts in cultured rat vascular smooth muscle cells, Lab. Investig. 93 (2012) 159–167.
[38] P. Hu, D. Lai, P. Lu, J. Gao, H. He, ERK and Akt signaling pathways are involved in advanced glycation end product-induced autophagy in rat vascular smooth muscle cells, Int. J. Mol. Med. 29 (2012) 613–618.
[39] J. Meloche, R. Paulin, A. Courboulin, C. Lambert, M. Barrier, P. Bonnet, M. Bisserier, M. Roy, M.A. Sussman, M. Agharazii, S. Bonnet, RAGE-dependent activation of the oncoprotein pim1 plays a critical role in systemic vascular remodeling processes, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 2114–2124.
[40] M.-H. Nam, W.-R. Son, Y.S. Lee, K.-W. Lee, Glycolaldehyde-derived advanced glycation end products (glycol-AGEs)-induced vascular smooth muscle cell dysfunction is regulated by the AGES-receptor (RAGE) axis in endothelium, Cell Commun. Adhes. 22 (2015) 67–78.
[41] T.-W. Chung, H.-J. Choi, C.-H. Kim, H.-S. Jeong, K.-T. Ha, Lipocalin-2 elicited by advanced glycation end-products promotes the migration of vascular smooth muscle cells, Biochim. Biophys. Acta (BBA) - Mol. Cell Res. 1833 (2013) 3386–3395.
[42] S. Dhar, Z. Sun, G.A. Meininger, M.A. Hill, Nonenzymatic glycation interferes with fibronectin-integrin interactions in vascular smooth muscle cells, Microcirculation 24 (2017).
[43] S.Y. Eun, Y.S. Ko, S.W. Park, K.C. Chang, H.J. Kim, IL-1β enhances vascular smooth muscle cell proliferation and migration via P2Y2 receptor-mediated RAGE expression and HMGB1 release, Vasc. Pharmacol. 72 (2015) 108–117.
[44] T. Suga, T. Iso, T. Shimizu, T. Tanaka, S.-i. Yamagishi, M. Takeuchi, T. Imaizumi, M. Kurabayashi, Activation of receptor for advanced glycation end products induces osteogenic differentiation of vascular smooth muscle cells, J. Atheroscler. Thromb. 18 (2011) 670–683.
[45] D. Chistiakov, I. Sobenin, A. Orekhov, Y. Bobryshev, Mechanisms of Medial Arterial Calcification in Diabetes, Curr. Pharm. Des. 20 (2014) 5870–5883.
[46] S. Menini, C. Iacobini, C. Ricci, C. Blasetti Fantauzzi, L. Salvi, C.M. Pesce, M. Relucenti, G. Familiari, M. Taurino, G. Pugliese, The galectin-3/RAGE dyad modulates vascular osteogenesis in atherosclerosis, Cardiovasc. Res. 100 (2013) 472–480.
[47] G. Pugliese, C. Iacobini, C.B. Fantauzzi, S. Menini, The dark and bright side of atherosclerotic calcification, Atherosclerosis 238 (2015) 220–230.
[48] R.H. Lee, W. Bergmeier, Sugar makes neutrophils RAGE: linking diabetes-associated hyperglycemia to thrombocytosis and platelet reactivity, J. Clin. Investig. 127 (2017) 2040–2043.
[49] D.A. Rubenstein, Z. Maria, W. Yin, Combined incubation of platelets and endothelial cells with glycated albumin: altered thrombogenic and inflammatory responses, Diab. Vasc. Dis. Res. 11 (2014) 235–242.
[50] D.A. Rubenstein, B.E. Morton, W. Yin, The combined effects of sidestream smoke extracts and glycated serum albumin on endothelial cells and platelets, Cardiovasc. Diabetol. 9 (2010) 28.
[51] S.-I. Yamagishi, T. Matsui, K. Takenaka, K. Nakamura, M. Takeuchi, H. Inoue, Pigment epithelium-derived factor (PEDF) prevents platelet activation and aggregation in diabetic rats by blocking deleterious effects of advanced glycation end products (AGEs), Diabetes Metab. Res. Rev. 25 (2009) 266–271.
[52] N. Vazzana, M.T. Guagnano, C. Cuccurullo, E. Ferrante, S. Lattanzio, R. Liani, M. Romano, G. Davì, Endogenous secretory RAGE in obese women: association with platelet activation and oxidative stress, J. Clin. Endocrinol. Metab. 97 (2012) E1726–E1730.
[53] F. Santilli, P. Blardi, C. Scapellato, M. Bocchia, G. Guazzi, L. Terzuoli, A. Tabucchi, A. Silvietti, B. Lucani, W.R. Gioffrè, F. Scarpini, F. Fazio, G. Davì, L. Puccetti, Decreased plasma endogenous soluble RAGE, and enhanced adipokine secretion, oxidative stress and platelet/coagulative activation identify non-alcoholic fatty liver disease among patients with familial combined hyperlipidemia and/or metabolic syndrome, Vasc. Pharmacol. 72 (2015) 16–24.
[54] L.T. Gan, D.M. Van Rooyen, M.E. Koina, R.S. McCuskey, N.C. Teoh, G.C. Farrell, Hepatocyte free cholesterol lipotoxicity results from JNK1-mediated mitochondrial injury and is HMGB1 and TLR4-dependent, J. Hepatol. 61 (2014) 1376–1384.
[55] G.N. Levine, E.R. Bates, J.C. Blankenship, S.R. Bailey, J.A. Bittl, B. Cercek, C.E. Chambers, S.G. Ellis, R.A. Guyton, S.M. Hollenberg, U.N. Khot, R.A. Lange, L. Mauri, R. Mehran, I.D. Moussa, D. Mukherjee, H.H. Ting, P.T. O'Gara, F.G. Kushner, D.D. Ascheim, R.G. Brindis, D.E. Casey Jr., M.K. Chung, J.A. de Lemos, D.B. Diercks, J.C. Fang, B.A. Franklin, C.B. Granger, H.M. Krumholz, J.A. Linderbaum, D.A. Morrow, L.K. Newby, J.P. Ornato, N. Ou, M.J. Radford, J.E. Tamis-Holland, C.L. Tommaso, C.M. Tracy, Y.J. Woo, D.X. Zhao, 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions, Circulation 133 (2016) 1135–1147.
[56] S. Cassese, R.A. Byrne, T. Tada, S. Pinieck, M. Joner, T. Ibrahim, L.A. King, M. Fusaro, K.-L. Laugwitz, A. Kastrati, Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography, Heart 100 (2013) 153–159.
[57] C. Falcone, E. Emanuele, M.P. Buzzi, L. Ballerini, A. Repetto, U. Canosi, I. Mazzucchelli, S. Schirinzi, I. Sbarsi, C. Boiocchi, M. Cuccia, The-374T/A variant of the rage gene promoter is associated with clinical restenosis after coronary stent placement, Int. J. Immunopathol. Pharmacol. 20 (2007) 771–777.
[58] C.R. Cohen, V.B.N. Diel, V.L. La Porta, L.E. Rohde, A. Biolo, N. Clausell, K.G. dos Santos, Association study of polymorphisms in the receptor for advanced glycation

end-products (RAGE) gene with susceptibility and prognosis of heart failure, Gene 510 (2012) 7–13.
[59] E.D. McNair, C.R. Wells, A. Mabood Qureshi, R. Basran, C. Pearce, J. Orvold, J. Devilliers, K. Prasad, Soluble Receptors for Advanced Glycation End Products (sRAGE) as a Predictor of Restenosis Following Percutaneous Coronary Intervention, Clin. Cardiol. 33 (2010) 678–685.
[60] C. Spadaccio, G. Patti, F. De Marco, R. Coccia, F. Di Domenico, F. Pollari, R. Zanzonico, M. Pettinari, M. Lusini, G. Di Sciascio, E. Covino, M. Chello, Usefulness of preprocedural levels of advanced glycation end products to predict restenosis in patients with controlled diabetes mellitus undergoing drug-eluting stent implantation for stable angina pectoris (from the prospective ARMYDA-AGEs study), Am. J. Cardiol. 112 (2013) 21–26.
[61] K. Fujisawa, N. Katakami, H. Kaneto, T. Naka, M. Takahara, F. Sakamoto, Y. Irie, K. Miyashita, F. Kubo, T. Yasuda, T.-A. Matsuoka, I. Shimomura, Circulating soluble RAGE as a predictive biomarker of cardiovascular event risk in patients with type 2 diabetes, Atherosclerosis 227 (2013) 425–428.
[62] Z.K. Yang, Y. Shen, W.F. Shen, L.J. Pu, H. Meng, R.Y. Zhang, Q. Zhang, Q.J. Chen, R. De Caterina, L. Lu, Elevated glycated albumin and reduced endogenous secretory receptor for advanced glycation endproducts levels in serum predict major adverse cardio-cerebral events in patients with type 2 diabetes and stable coronary artery disease, Int. J. Cardiol. 197 (2015) 241–247.
[63] G. Basta, S. Berti, F. Cocci, G. Lazzerini, S. Parri, A. Papa, D. Battaglia, V. Lubrano, S. Del Turco, M. Ravani, A. Rizza, R. De Caterina, P. Marraccini, A. Mazzone, Plasma N-epsilon-(carboxymethyl)lysine levels are associated with the extent of vessel injury after coronary arterial stenting, Coron. Artery Dis. 19 (2008) 299–305.
[64] Y.H. He, X.Q. Wang, J. Zhang, Z.H. Liu, W.Q. Pan, Y. Shen, Z.B. Zhu, L.J. Wang, X.X. Yan, K. Yang, R.Y. Zhang, W.F. Shen, F.H. Ding, L. Lu, Association of serum HMGB2 levels with in-stent restenosis, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 717–729.
[65] W. Yu, R. Liu-Bryan, S. Stevens, J.K. Damanahalli, R. Terkeltaub, RAGE signaling mediates post-injury arterial neointima formation by suppression of liver kinase B1 and AMPK activity, Atherosclerosis 222 (2012) 417–425.
[66] J. Chen, J. Zhang, L. Xu, C. Xu, S. Chen, J. Yang, H. Jiang, Inhibition of neointimal hyperplasia in the rat carotid artery injury model by a HMGB1 inhibitor, Atherosclerosis 224 (2012) 332–339.
[67] H.-J. Tae, J.M. Kim, S. Park, N. Tomiya, G. Li, W. Wei, N. Petrashevskaya, I. Ahmet, J. Pang, S. Cruschwitz, R.A. Riebe, Y. Zhang, C.H. Morrell, D. Browe, Y.C. Lee, R.-P. Xiao, M.I. Talan, E.G. Lakatta, L. Lin, The N-glycoform of sRAGE is the key determinant for its therapeutic efficacy to attenuate injury-elicited arterial inflammation and neointimal growth, J. Mol. Med. 91 (2013) 1369–1381.
[68] T.P. Degenhardt, N.L. Alderson, D.D. Arrington, R.J. Beattie, J.M. Basgen, M.W. Steffes, S.R. Thorpe, J.W. Baynes, Pyridoxamine inhibits early renal disease and dyslipidemia in the streptozotocin-diabetic rat, Kidney Int. 61 (2002) 939–950.
[69] M.R. Brodeur, C. Bouvet, S. Bouchard, S. Moreau, J. Leblond, D. deBlois, P. Moreau, Reduction of advanced-glycation end products levels and inhibition of RAGE signaling decreases rat vascular calcification induced by Diabetes, PLoS One 9 (2014) e85922.
[70] A.M.D. Watson, A. Soro-Paavonen, K. Sheehy, J. Li, A.C. Calkin, A. Koitka, S.N. Rajan, D. Brasacchio, T.J. Allen, M.E. Cooper, M.C. Thomas, K.J.A. Jandeleit-Dahm, Delayed intervention with AGE inhibitors attenuates the progression of diabetes-accelerated atherosclerosis in diabetic apolipoprotein E knockout mice, Diabetologia 54 (2011).
[71] M.E. Williams, W.K. Bolton, R.G. Khalifah, T.P. Degenhardt, R.J. Schotzinger, J.B. McGill, Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy, Am. J. Nephrol. 27 (2007) 605–614.
[72] J. Wu, M.A. Saleh, A. Kirabo, H.A. Itani, K.R.C. Montaniel, L. Xiao, W. Chen, R.L. Mernaugh, H. Cai, K.E. Bernstein, J.J. Goronzy, C.M. Weyand, J.A. Curci, N.R. Barbaro, H. Moreno, S.S. Davies, L.J. Roberts, M.S. Madhur, D.G. Harrison, Immune activation caused by vascular oxidation promotes fibrosis and hypertension, J. Clin. Invest. 126 (2016) 1607.
[73] A. Dziubak, G. Wójcicka, The pathophysiological basis of the protective effects of metformin in heart failure, Postepy Hig. Med. Dosw. 71 (2017) 773–787.
[74] C.-H. Lin, Y.-C. Cheng, C.J. Nicol, K.-H. Lin, C.-H. Yen, M.-C. Chiang, Activation of AMPK is neuroprotective in the oxidative stress by advanced glycosylation end products in human neural stem cells, Exp. Cell Res. 359 (2017) 367–373.
[75] M.-M. Chung, C.J. Nicol, Y.-C. Cheng, K.-H. Lin, Y.-L. Chen, D. Pei, C.-H. Lin, Y.-N. Shih, C.-H. Yen, S.-J. Chen, R.-N. Huang, M.-C. Chiang, Metformin activation of AMPK suppresses AGE-induced inflammatory response in hNSCs, Exp. Cell Res. 352 (2017) 75–83.
[76] M. Haddad, I. Knani, H. Bouzidi, O. Berriche, M. Hammami, M. Kerkeni, Plasma levels of pentosidine, carboxymethyl-lysine, soluble receptor for advanced glycation end products, and metabolic syndrome: the metformin effect, Dis. Markers 2016 (2016) 1–8.
[77] Z.E. Zhou, Y. Tang, X. Jin, C. Chen, Y. Lu, L. Liu, C. Shen, Metformin inhibits advanced glycation end products-induced inflammatory response in murine macrophages partly through AMPK activation and RAGE/NFκB pathway suppression, J. Diabetes Res. 2016 (2016) 1–10.
[78] Z. Kender, T. Fleming, S. Kopf, P. Torzsa, V. Grolmusz, S. Herzig, E. Schleicher, K. Rácz, P. Reismann, P.P. Nawroth, Effect of metformin on methylglyoxal metabolism in patients with type 2 diabetes, Exp. Clin. Endocrinol. Diabetes 122 (2014) 316–319.
[79] P. Anagnostis, P. Siolos, K. Christou, N.K. Gkekas, N. Kosmidou, V.G. Athyros, A. Karagiannis, The effect of antidiabetic medications on the cardiovascular system: a critical appraisal of current data, Hormones (Athens) 17 (2018) 83–95.
[80] P.J. Grant, Beneficial effects of metformin on haemostasis and vascular function in man, Diabetes Metab. 29 (2003) 6S44–6S52.
[81] R.B. Goldberg, V.R. Aroda, D.A. Bluemke, E. Barrett-Connor, M. Budoff, J.P. Crandall, D. Dabelea, E.S. Horton, K.J. Mather, T.J. Orchard, D. Schade, K. Watson, M. Temprosa, Diabetes prevention program research group, effect of long-term metformin and lifestyle in the diabetes prevention program and its outcome study on coronary artery calcium, Circulation 136 (2017) 52–64.
[82] J.R. Petrie, N. Chaturvedi, I. Ford, M.C.G.J. Brouwers, N. Greenlaw, T. Tillin, I. Hramiak, A.D. Hughes, A.J. Jenkins, B.E.K. Klein, R. Klein, T.C. Ooi, P. Rossing, C.D.A. Stehouwer, N. Sattar, H.M. Colhoun, REMOVAL Study Group, Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial, The Lancet. Diabetes and, Endocrinology 5 (2017) 597–609.
[83] S.I. McFarlane, Pleiotropic effects of statins: lipid reduction and beyond, J. Clin. Endocrinol. Metab. 87 (2002) 1451–1458.
[84] K. Prasad, S. Tiwari, Therapeutic interventions for advanced glycation-end products and its receptor- mediated cardiovascular disease, Curr. Pharm. Des. 23 (2017) 937–943.
[85] P. Quade-Lyssy, A.M. Kanarek, M. Baiersdörfer, R. Postina, E. Kojro, Statins stimulate the production of a soluble form of the receptor for advanced glycation end products, J. Lipid Res. 54 (2013) 3052–3061.
[86] M. Chen, H. Li, G. Wang, X. Shen, S. Zhao, W. Su, Atorvastatin prevents advanced glycation end products (AGEs)-induced cardiac fibrosis via activating peroxisome proliferator-activated receptor gamma (PPAR-γ), Metabolism 65 (2016) 441–453.
[87] M. Shimomura, J.-i. Oyama, M. Takeuchi, Y. Shibata, Y. Yamamoto, T. Kawasaki, H. Komoda, K. Kodama, M. Sakuma, S. Toyoda, Y. Inoue, D. Mine, M. Natsuaki, A. Komatsu, Y. Hikichi, S.-i. Yamagishi, T. Inoue, K. Node, Acute effects of statin on reduction of angiopoietin-like 2 and glyceraldehyde-derived advanced glycation end-products levels in patients with acute myocardial infarction: a message from SAMIT (Statin for Acute Myocardial Infarction Trial), Heart Vessel. 31 (2015) 1583–1589.
[88] M.K. Jain, P.M. Ridker, Anti-inflammatory effects of statins: clinical evidence and basic mechanisms, Nat. Rev. Drug Discov. 4 (2005) 977–987.
[89] C. Cuccurullo, A. Iezzi, M.L. Fazia, D. De Cesare, A. Di Francesco, R. Muraro, R. Bei, S. Ucchino, F. Spigonardo, F. Chiarelli, A.M. Schmidt, F. Cuccurullo, A. Mezzetti, F. Cipollone, Suppression of Rage as a Basis of Simvastatin-Dependent Plaque Stabilization in Type 2 Diabetes, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2716–2723.
[90] Y. Li, J. Li, L. Cui, Y. Lai, Y. Yao, Y. Zhang, X. Pang, J. Wang, X. Liu, Inhibitory effect of atorvastatin on AGE-induced HCAEC apoptosis by upregulating HSF-1 protein, Int. J. Biol. Macromol. 57 (2013) 259–264.
[91] T. Nakamura, E. Sato, N. Fujiwara, Y. Kawagoe, M. Takeuchi, S. Maeda, S.-i. Yamagishi, Atorvastatin reduces proteinuria in non-diabetic chronic kidney disease patients partly via lowering serum levels of advanced glycation end products (AGEs), Oxidative Med. Cell. Longev. 3 (2010) 304–307.
[92] Y. Ohnuki, R. Nagano, S. Takizawa, S. Takagi, T. Miyata, Advanced glycation end products in patients with cerebral infarction, Intern. Med. 48 (2009) 587–591.
[93] T. Okamoto, S.-I. Yamagishi, Y. Inagaki, S. Amano, K. Koga, R. Abe, M. Takeuchi, S. Ohno, A. Yoshimura, Z. Makita, Angiogenesis induced by advanced glycation end products and its prevention by cerivastatin, FASEB J. 16 (2002) 1928–1930.
[94] T.-W. Lee, Y.-H. Kao, T.-I. Lee, Y.-J. Chen, ADAM10 modulates calcitriol-regulated RAGE in cardiomyocytes, Eur. J. Clin. Investig. 47 (2017) 675–683.
[95] S. Iqbal, M.M. Alam, I. Naseem, Vitamin D prevents glycation of proteins: anin vitrostudy, FEBS Lett. 590 (2016) 2725–2736.
[96] M.S. Molinuevo, J.M. Fernández, A.M. Cortizo, A.D. McCarthy, L. Schurman, C. Sedlinsky, Advanced glycation end products and strontium ranelate promote osteogenic differentiation of vascular smooth muscle cells in vitro: preventive role of vitamin D, Mol. Cell. Endocrinol. 450 (2017) 94–104.
[97] E. Salum, J. Kals, P. Kampus, T. Salum, K. Zilmer, M. Aunapuu, A. Arend, J. Eha, M. Zilmer, Vitamin D reduces deposition of advanced glycation end-products in the aortic wall and systemic oxidative stress in diabetic rats, Diabetes Res. Clin. Pract. 100 (2013) 243–249.
[98] S. Palimeri, E. Palioura, E. Diamanti-Kandarakis, Current perspectives on the health risks associated with the consumption of advanced glycation end products: recommendations for dietary management, Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 8 2015, pp. 415–426.
[99] G. Siasos, D. Tousoulis, C. Vlachopoulos, C. Antoniades, E. Stefanadi, N. Ioakeimidis, K. Zisimos, Z. Siasou, A.G. Papavassiliou, C. Stefanadis, The impact of oral L-arginine supplementation on acute smoking-induced endothelial injury and arterial performance, Am. J. Hypertens. 22 (2009) 586–592.
[100] S. Brings, T. Fleming, M. Freichel, M.U. Muckenthaler, S. Herzig, P.P. Nawroth, Dicarbonyls and advanced glycation end-products in the development of diabetic complications and targets for intervention, Int. J. Mol. Sci. 18 (2017).