MDPI

Review

Accelerated AGEing: The Impact of Advanced Glycation End Products on the Prognosis of Chronic Kidney Disease

Elena Dozio [1], Lara Caldiroli [2,*,†], Paolo Molinari [2,†], Giuseppe Castellano [2,3], Nicholas Walter Delfrate [2], Massimiliano Marco Corsi Romanelli [1,4] and Simone Vettoretti [2]

[1] Department of Biomedical Science for Health, Università degli Studi di Milano, 20133 Milan, Italy
[2] Unit of Nephrology, Dialysis and Kidney Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, 20122 Milan, Italy
[3] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, 20122 Milan, Italy
[4] Service of Laboratory Medicine1-Clinical Pathology, IRCCS Policlinico San Donato, San Donato Milanese, 20097 Milan, Italy
* Correspondence: lara.caldiroli@policlinico.mi.it; Tel.: +39-025-5034-552; Fax: +39-025-5034-550
† These authors contributed equally to this work.

Abstract: Advanced glycation end products (AGEs) are aging products. In chronic kidney disease (CKD), AGEs accumulate due to the increased production, reduced excretion, and the imbalance between oxidant/antioxidant capacities. CKD is therefore a model of aging. The aim of this review is to summarize the present knowledge of AGEs in CKD onset and progression, also focusing on CKD-related disorders (cardiovascular diseases, sarcopenia, and nutritional imbalance) and CKD mortality. The role of AGEs as etiopathogenetic molecules, as well as potential markers of disease progression and/or therapeutic targets, will be discussed.

Keywords: advanced glycation end products (AGEs); aging; cardiovascular diseases; chronic kidney disease (CKD); inflammation; mortality; pro-oxidant milieu; sarcopenia

1. Introduction

Advanced glycation end products (AGEs) are known as aging products. In chronic kidney disease (CKD), AGEs build up due to increased production, reduced excretion, and imbalance between oxidizing/antioxidant abilities. CKD is therefore a model of aging. AGEs can, in turn, promote CKD progression and CKD-related complications. AGEs are studied not only for their etiopathogenetic role but also as new potential markers of disease progression and/or therapeutic targets. The aim of this review is to summarize the present knowledge of AGEs in CKD and CKD-related disorders.

2. Advanced Glycation End Products (AGEs) in Chronic Kidney Disease (CKD): Synthesis and Endogenous Defensive Strategies

AGEs are a class of compounds derived from the non-enzymatic reaction of glucose and its metabolites with protein, lipids, and nucleic acids. Since hyperglycemia is the main promoter of AGE synthesis, the highest concentrations of AGEs can be observed in diabetes mellitus (DM). Aging and other pathological conditions characterized by increased oxidative stress and inflammation may promote AGE accumulation through the synthesis of highly reactive carbonyl intermediates and their interaction with other bioactive molecules [1,2].

The Maillard reaction is one of the main pathways leading to AGE synthesis. This is a series of non-enzymatic reactions in which the carbonyl groups of reducing sugars, such as glucose, react with amino groups to produce Schiff bases, which then undergo Amadori rearrangements and further oxidative modifications (glycoxidation). These reactions are promoted by reactive oxygen species (ROS) and reactive nitrogen species (RNS) and give

rise to dicarbonyl compounds such as glyoxal. Auto-oxidation of glucose and Schiff bases are other sources of dicarbonyl compounds, such as methylglyoxal, which can further react with amino groups and undergo further glycoxidation. The result is a variety of protein cross links and protein modifications known as AGEs. Lysine and arginine residues are the main target amino acids involved in the synthesis of AGEs. From a chemical point of view, the AGE family is very heterogeneous and includes fluorescent cross-linking AGEs (i.e., vesperlysine, pentosidine, and crossline), non-fluorescent cross-linking AGEs (i.e., imidazolium dilysine cross links, alkyl formyl glycosyl pyrroles, and arginine–lysine imidazole cross links), and non-cross-linking AGEs (i.e., N-fructosyl-lysine, N carboxyethyl-lysine, and N-carboxymethyl-lysine) [1–4]. AGE production is a relatively slow mechanism under physiological conditions, but once formed, the process is nearly irreversible. Different defensive strategies to prevent their synthesis and accumulation exist, but aging and the pro-oxidant and proinflammatory milieu that characterizes many chronic disorders such as CKD induces an imbalance between AGE synthesis and detoxification. The main AGE compounds of biologic importance are represented in Figure 1.

Oxidative stress promotes the accumulation of reactive carbonyl compounds, which are AGE precursors. Different enzymes, such as aldose reductase, aldehyde dehydrogenase, and glyoxalase-1 and -2 (GLO-1 and GLO-2), can work as first-line defensive strategies, preventing AGE synthesis. GLO-1 and GLO-2 block AGE synthesis by promoting the degradation of dicarbonyl compounds [5]. GLO-1, which catalyzes the first step of detoxification, is the rate-limiting enzyme, and its activity strongly depends on glutathione concentration. Its function is affected both by gene expression and post-translational modifications.

Other membrane receptors are involved in AGE metabolism. These receptors include RAGE (receptor for AGEs), AGE-R1 (OST-48, p60), AGE-R2 (80K-H phosphoprotein), AGE-R3 (galectin-3), and the macrophage scavenger receptors ScR-II and CD-36 [6]. Except for RAGE, the other molecules are clearance receptors; they remove AGEs from the circulation and promote their degradation. AGE-R1, AGE-R2, and AGE-R3 are components of the AGE–receptor complex. This receptor is mainly localized in the caveolin-rich membrane domain and, by taking up AGEs, promotes their degradation and prevents AGE-damaging effects [7]. AGE-R1 was the first discovered and the most expressed of these components. Its level increases in parallel with AGEs, but it is downregulated by persistently high levels of AGEs [8]. AGE-R1 promotes AGE turnover by mesangial cells and contributes to counter regulation of AGE-induced inflammation [9]. AGE-R2 is a membrane protein without binding activities. It is involved in stabilization of the receptor complex in combination with AGE-R3, a carbohydrate-binding protein that shows strong affinity for a wide variety of AGEs and regulates different functions, from the cell cycle to inflammation [10,11]. Of interest, prolonged exposure to AGEs increases AGE-R3 expression [12].

RAGE is a surface molecule that belongs to the immunoglobulin superfamily. It is a multiligand receptor that can recognize, bind, and transduce the signal of various molecules involved in the activation of the inflammatory response, both in homeostasis and in the presence of chronic diseases. The transduction of the RAGE-mediated signal leads to the formation of ROS, activation of the transcription factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), and the upregulation of inflammatory mediators and adhesion molecules. AGEs, S100 calgranulins, β-amyloid peptides, and amphoterins are among the main RAGE ligands. The RAGE gene extends for 3080 bp in humans and is located on chromosome 6 within the HLA class III near the junction area with class II. RAGE is transcribed at low levels in numerous cells. RAGE activation increases the expression of the receptor itself, with the consequent amplification of the response [13]. Along with the form of the membrane receptor, RAGE also exists as a soluble receptor (sRAGE). sRAGE includes the extracellular portion of the membrane form; it can bind the ligands, but it cannot transduce the signal. sRAGE is not a single form but a pool composed of two different isoforms: cRAGE (cleaved RAGE) and esRAGE (endogenous secretory RAGE). cRAGE is the result of the proteolytic cleavage of the membrane receptor promoted by different proteases, such as ADAM10 (a disintegrin and metalloproteinase 10)

and MMP (metalloproteinase)-9, MMP-13, and MMP-3 [14,15]. In contrast, esRAGE derives from alternative gene splicing. Different splicing variants of RAGE exist, but, except for esRAGE, all are degraded at the mRNA level by the NMD (nonsense-mediated mRNA decay) pathway. esRAGE retains part of intron 9, with partial removal of exon 10. The result is a change in the reading sequence of the protein at amino acid 332 and the consequent loss of both the cytoplasmic and transmembrane domains. The resulting protein resolves at 48 kDa in size compared to 55 kDa for the membrane form [16]. sRAGE is a decoy receptor. By binding AGEs in the circulation, both cRAGE and esRAGE can prevent membrane RAGE activation and RAGE-induced proinflammatory and detrimental effects. Although the role is the same, the mechanisms promoting cRAGE and esRAGE synthesis are different. Therefore, we can suppose a different role as biomarkers for these two receptor forms. Because the expression and activity of the MMP enzymes that are involved in cRAGE synthesis are increased in inflammatory disorders, cRAGE can be considered a surrogate marker of inflammation. In contrast, esRAGE is considered the real decoy receptor that is produced as an endogenous defensive strategy against AGEs, i.e., sRAGE and esRAGE decrease in patients with hypertension [17] and metabolic syndrome (MS) [18]. All these biological processes are summarized in Figure 2.

Lower total sRAGE levels are also associated with increased body mass index (BMI), waist circumference (WC), and fat mass [19,20]. In contrast, in DM and CKD. sRAGE levels increase [21,22] have been independently associated with cardiovascular outcome [21,23]. This means that changes in sRAGE levels depend on the clinical setting. Simultaneous measurement of esRAGE and cRAGE could help to identify the contribution of each form to total sRAGE and their relationship with the disorder.

The kidney plays a major role in AGE metabolism and excretion. In healthy subjects, AGEs are filtered by the glomeruli and taken up in the proximal tubules or directly collected from the blood in the peritubular capillaries. AGE metabolism mainly occurs in the proximal tubule cells (PTCs). AGEs are then metabolized to non-reactive compounds that can be excreted into urine. PTCs express specific endocytotic receptors on their apical membrane, which take up and metabolize low-molecular-weight proteins (LMWPs) filtered by the glomeruli in the lysosomes. Megalin is a large glycoprotein (~600 kDa) of the low-density lipoprotein receptor family [24] known to serve as a major receptor for endocytosis of multiple LMWPs, including transcobalamin-B12, vitamin D-binding protein, retinol-binding protein, parathyroid hormone, insulin, β2-microglobulin, epidermal growth factor, prolactin, lysozyme, cytochrome c, α1-microglobulin, and transthyretin [25]. Megalin is also one of the receptors involved in AGE uptake and metabolism [26]. By using a rat yolk-sac-derived L2 cell line system and antimegalin IgG antibodies, it has been found that megalin is involved in AGE endocytosis through co-operation with other membrane and intracellular proteins and is then recycled to the cell membrane after endocytosis has occurred [25,27]. Cubilin and Na+−H+ exchanger 3 (NHE3) are two membrane proteins that interact with megalin and comodulate its endocytic function [28,29]. ANKRA (ankyrin-repeat family A protein), ARH (autosomal-recessive hypercholesterolemia), Dab2 (disabled protein 2), GIPC (Gα-interacting protein (GAIP) interacting protein C terminus), MAGI-1 (membrane-associated guanylate kinase with inverted orientation-1), and MegBP (megalin-binding protein) bind the cytoplasmic domain of megalin and are supposed to have signaling functions, leading to AGE metabolism and further excretion into the urine [30].

Among different conditions promoting AGE accumulation, CKD deserves great attention. With decreasing renal function, AGEs increase, regardless of the presence of DM [31]. Of interest, AGE accumulation can be observed not only in patients with already established kidney failure but also in individuals with or without DM, in whom reduced renal function is not yet clinically evident [32–34]. AGE levels are elevated in CKD due both to increased synthesis and reduced kidney filtration and tubular metabolism.
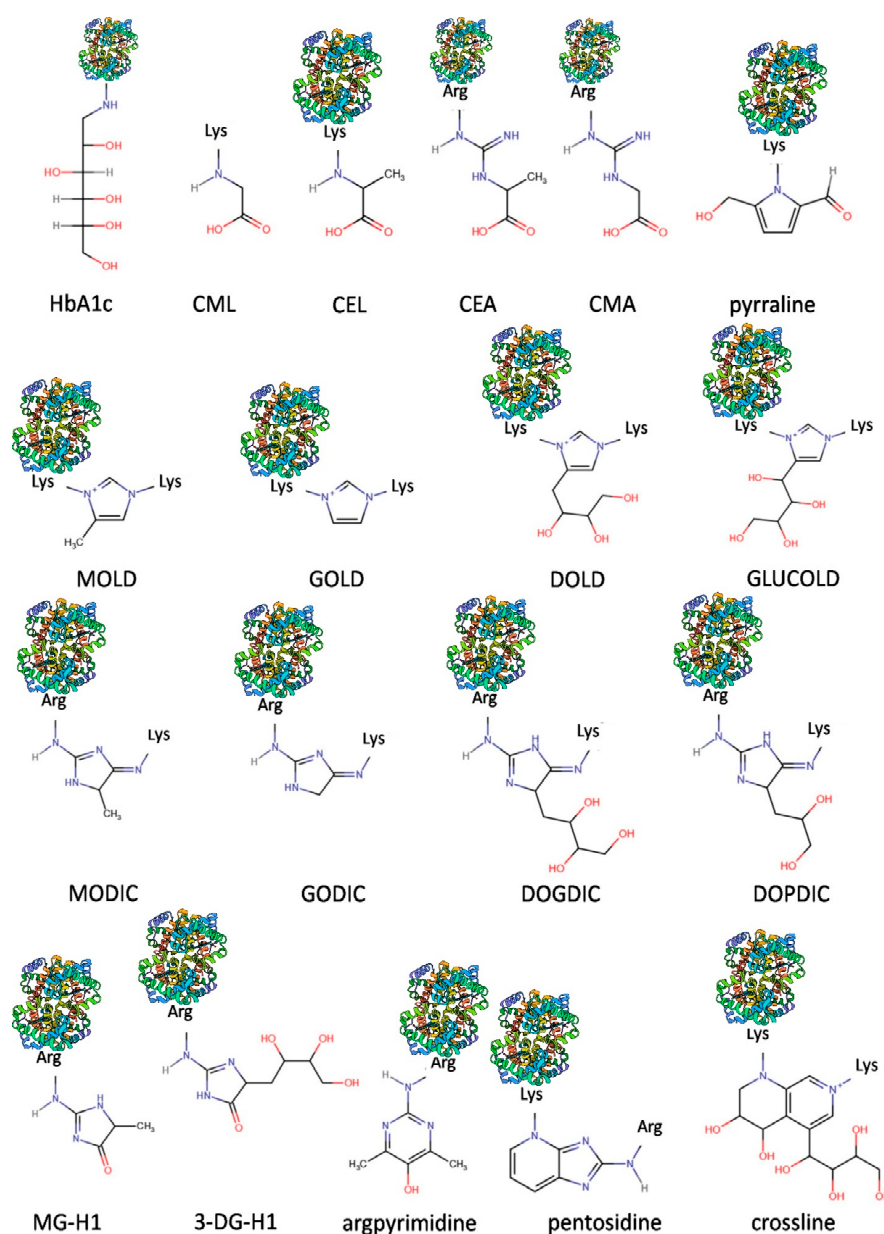
Figure 1. Different types of AGE–protein compounds. **Note:** Glycated hemoglobin (HbA1c), N^ε–(carboxymethyl)lysine (CML), N^ε-(1-carboxyethyl)lysine (CEL), N^7–(1-carboxyethyl)arginine (CEA), N^7–(carboxymethyl)arginine (CMA), 6-(2-formyl-5-hydroxymethyl-1-pyrrolyl)-L-norleucine (pyrraline), 6-{1-[(5S)-5-ammonio-6-oxido-6-oxohexyl]-4-methyl-imidazolium-3-yl}-L-norleucine (MOLD), 6-{1-[(5S)-5-ammonio-6-oxido-6-oxohexyl]imidazolium-3-yl}-L-norleucine (GOLD),1,3-di(N^ε-lysino)-4-(2,3,4-trihydroxybutyl)-imidazolium (DOLD),1,3-bis-(5-amino-5-carboxypentyl)-4-(1,2,3,4-tetrahydroxybutyl)-3H-imidazolium (GLUCOLD), 2-ammonio-6-({2-[4-ammonio-5-oxido-5-oxopently)amino]4-methyl-4,5-dihydro-1H-imidazol-5-ylidene}amino)hexanoate (MODIC), N^6-(2-{4S(-4-ammonio-5-oxido-5-oxopentyl]amino}-3,5-dihydro-4H-imidazol-4-ylidene)-L-lysine (GODIC), N^6-{2-{[(4S)-4-ammonio-5-oxido-5-oxopentyl]amino}-5-[(2S,3R)-2,3,4-trihydroxybutyl]-3,5-dihydro-4H-imidazol-4-ylidene}-L-lysinate (DOGDIC), N^6-{2-{[(4S)-4-ammonio-5-oxido-5-oxopentyl]amino}-5-[(2S)-2,3-dixydroxypropyl]3,5-dihydro-4H-imidazol-4-ylidene}-L-lysinate (DOPDIC), N^δ-(5-methyl-4-imidazolon-2-yl)-L-ornithine (MG-H1), N^δ-(45-hydro-5-(2,3,4-trihydroxybutyl)-4-imidazolon-2-yl]-L-ornithine (3DG-H1), N^δ-(5-hydroxy-4,6-dimethylpyrimidine-2-yl)-L-ornithine (argpyrimidine), and 6-[2-[[(4S)-4-amino-5-hydroxy-5-oxopentyl]amino]-4-imidazo [4,5-b]pyridinyl]-L-norleucine (pentosidine). Modified protein surface models are based on the structure of human hemoglobin (PDB ID 1COH).
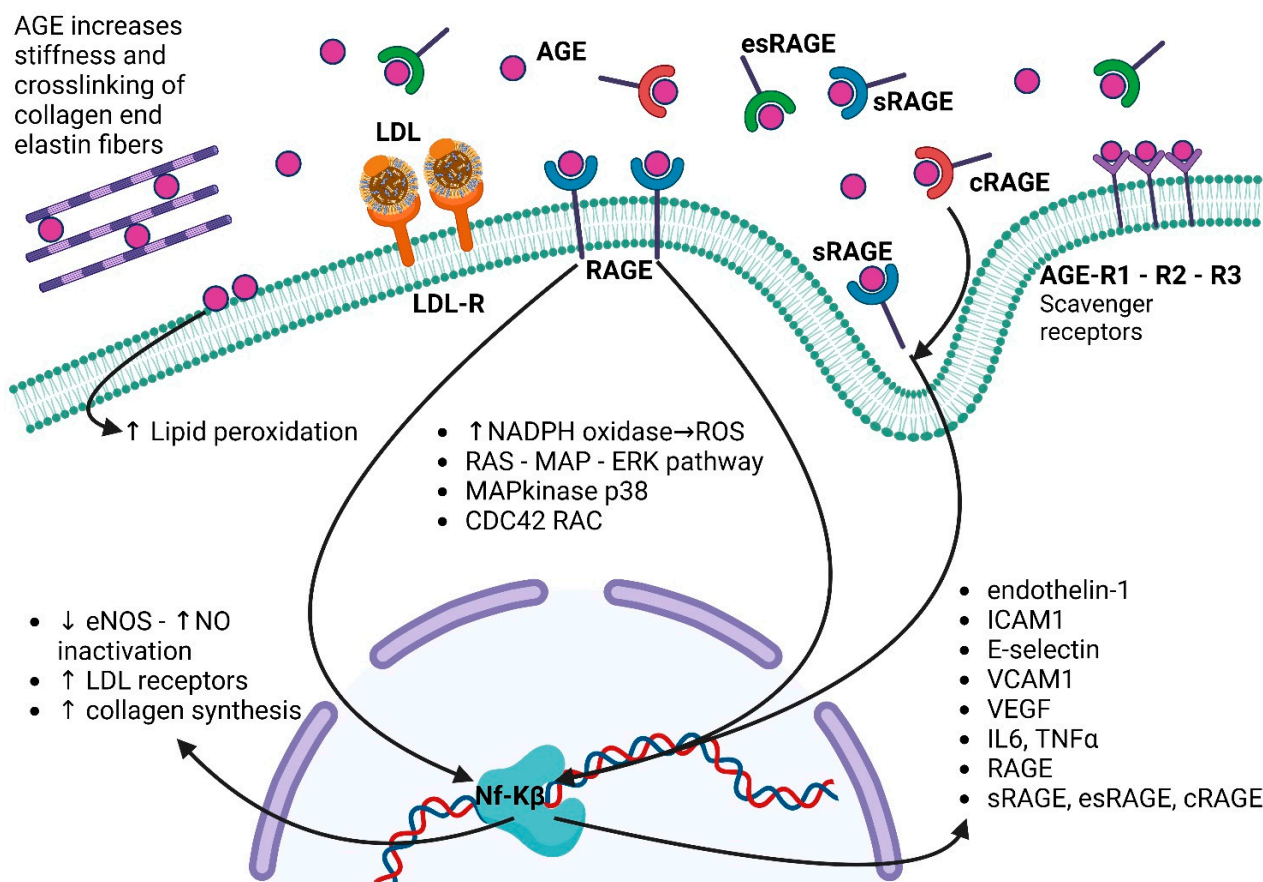
Figure 2. AGE–RAGE interaction at the intracellular level and RAGE activation cascade. **Note:** In the ECM, AGEs form on several different molecules, including lipids, collagen, laminin, elastin, and vitronectin. The formation of AGEs on ECM molecules impairs the constitution of the matrix and increases its stiffness. AGEs that bind to RAGEs on the cell surface begin a signaling cascade, stimulating NAD(P)H oxidase and increasing ROS, p21 RAS, and MAPKs. The ligand–RAGE interaction may also stimulate signaling via p38 MAPK and Rac/Cdc. A key target of RAGE signaling is Nf-κB. Nf-κB is translocated to the nucleus, where it promotes transcription of several proteins, including endothelin-1, ICAM-1, E-selectin, and tissue factor. Moreover AGE–RAGE interaction stimulates the synthesis of sRAGE (soluble receptor for advanced glycation end products), cRAGE (cleaved receptor of advanced glycation end products), and esRAGE (endogenous spliced receptor of advanced glycation end products). AGE and ligands for RAGE, sRAGE, and cRAGE trigger inflammatory response, while esRAGE serves as a scavenger molecule for circulating AGEs. AGEs seem to lower NO availability by decreasing activity of NOS and by quenching NO.

In CKD patients, uremic toxins and inflammatory mediators reduce the availability of detoxifying enzymes and the clearance of these products, thereby increasing carbonyl stress and AGE synthesis [8,26]. As better described in the next section, the increased concentration of AGEs can induce kidney damage at both the glomerular and tubular levels. Excess AGE content can lead to oxidative stress, inflammation, and lipid deposition in renal tubules [35–37]. The urinary level of full-length megalin was positively correlated with kidney damage in patients with DM. In cultured immortalized rat proximal tubule cells, AGE-modified BSA promoted lysosomal dysfunction and megalin excretion via extracellular vesicles [35]. AGE overload therefore leads to the progressive loss of tubular metabolism. With reduced megalin, AGE metabolism is impaired, and RAGE activation by AGEs in proximal tubular cells can further promote kidney damage [38], as well as at glomerular levels [39]. This mechanism, along with direct AGE-induced glomerular damage, contribute to an increase in circulating AGEs.

3. AGEs in CKD Onset and Progression

In CKD, AGEs accumulate because of both the reduced filtration by the kidneys and the increase in production due to an unbalanced oxidative/antioxidant metabolism. The uremic environment, which is characterized by increased oxidative stress and inflammation, supports the production of AGEs [40,41]. AGEs promote a worsening in kidney function [42] and the increase in cardiovascular risk and mortality in end-stage renal disease (ESRD) and in kidney-transplanted patients (RTx-ps) [40,42,43]. With the impairment of renal function, AGEs accumulate, and there is an amplification of the oxidative stress.

Studies based on murine models support the detrimental role of AGEs in kidney damage development, showing a thickening of the basement membrane and expansion of the mesangial matrix in AGE-injected animals [44]. This could be linked to an increase in TGFβ (transforming growth factor β) levels and a reduction in the production of nitric oxide consequent to AGE activities at the renal level [45]. Another cause of the noxious effects of AGEs may also be the activation of RAGE.

Anatomically, proximal renal tubule cells are characterized by a great number of lysosomes for protein absorption/degradation, and lots of mitochondria are needed to supply the energy needed to sustain their metabolism [37,46]. Most of substances filtered at the glomerular level are reabsorbed by proximal renal tubules through endocytosis. As reported above, proximal tubular endosomal–lysosomal activity is mainly controlled by megalin, an endocytic receptor [30,38,47]. The excessive uptake of AGEs causes proximal dysfunction of tubular lysosomes and it has been suggested to be involved in the development of DM nephropathy. AGEs that are reabsorbed by proximal renal tubules lead to increased glucotoxicity on PTCs [38,48,49]. Under severe hyperglycemia, continuous activation of the AGE–RAGE pathway results in a positive feedback loop that increases injury at the proximal tubular level in patients with DM nephropathy [38].

4. AGEs as Biomarkers of Mortality in CKD

In patients with CKD, uremia, chronic inflammation, and oxidative stress can lead to an increase in ED production, which, in turn, promotes CKD-related complications and mortality [50–52]. Kidneys normally filter circulating AGEs, but it has been observed that the levels of these products increase both in DM and non-DM nephropathy [40,41]. Higher serum AGE concentrations may contribute to the worsening of renal function and the increase in cardiovascular risk and mortality both in conservative and replacement therapy patients [41–43].

Skin autofluorescence (SAF), which is a measure of AGE accumulation, has been linked with increased mortality risk in dialysis patients. A landmark study conducted in 109 patients receiving hemodialysis (HD) showed, for the first time, strong evidence that SAF is an independent risk factor for all-cause mortality in CKD [41,53], along with previous cardiovascular disease (CVD), serum albumin, and C-reactive protein (CRP). Numerous successive studies and a meta-analyses [54] of HD patients have confirmed that higher SAF could be an independent risk factor for all-cause mortality [55,56]. Similarly, SAF seems to be an independent risk factor for increased mortality in peritoneal dialysis (PD) patients [57,58]. In a study by McIntyre et al., SAF levels were found to be similar in PD and HD patients, even if years of dialysis were significantly lower in the PD cohort [59]. On the contrary, Oleniuc et al. showed higher SAF in HD patients [60]. Two other studies compared SAF levels in both PD and HD patients after adjustment for the years of dialysis and other potential confounders. They found higher SAF in PD patients [61,62]. The glucose present in peritoneal dialysis fluid may be a key factor that contributes to AGE accumulation during PD [53]. This has been confirmed by several studies that showed an association between the magnitude of glucose exposure and SAF [59,62,63]. A study performed in a mixed population of patients with stage 5 CKD not yet on dialysis (n = 130), PD (n = 93) and HD (n = 38) explored the association of SAF and the augmentation index (AIx), a measure of arterial stiffness, with all-cause and CV mortality in comparison to traditional risk factors assessed with the Framingham Risk Score (FRS) [64]. Both SAF and

AIx independently predicted these outcomes. SAF remained significant after adjustment for the FRS but not after additional adjustment for the presence of CVD, CRP, and serum albumin [64]. For this reason, SAF was confirmed to be a risk factor for mortality, but traditional risk factors still accounted for most of the observed risk.

SAF levels have also been investigated in patients with earlier stages of CKD. In a large study conducted by Fraser et al., SAF was observed to be elevated in 1707 persons with stage 3CKD (mean estimated glomerular filtration (eGFR), -52.5 ± 10.4 mL/min/1.73 m^2). After 3.6 years of follow-up, SAF was associated with increased all-cause mortality even after adjustment for age and sex, although after adjustment for multiple risk factors, the association was no longer statistically significant [65].

A rise in sRAGE levels has also been linked with a higher mortality risk in HD and PD patients [66–68]. Recently, our group reported an association between increased sRAGE levels and mortality in HD and PD patients [69]. For these reasons, glycated albumin, an early precursor of AGEs correlated with the overall prognosis of patients on dialysis [70], may affect the prognosis of advanced CKD patients [69].

5. AGE–RAGE Pathway in Cardiovascular System: Role in the Etiopathogenesis of Diseases and as Biomarkers

The risk of CVD is increased in patients with CKD. As CKD progresses, the incidence of CVD events, hospitalization, and death increases [71]. Data from the US Renal Data System (USRDS) (2020) indicate that the risk of CVD in CKD was higher than in non-CKD patients [72]. Among CKD patients, the prevalence of CVD was higher in patients with stages G4–5 (75.3%) compared to stage G3 (66.6%) and stage G1-2 (63.4%). Several CVDs, including left ventricular dysfunctions, cardiomyopathy, atherosclerosis, stroke, heart failure, peripheral artery disease, abdominal aortic aneurysm, and venous thrombosis, are associated with CKD and represent the most common causes of death in CKD patients. Traditional CVD risk factors such as hypertension, advanced age, dyslipidemia, and DM, which are frequent in CKD, can only partially clarify the high risk of diseases in CKD. Malnutrition, anemia, accumulation of uremic toxins, activation of fibroblast growth factor 23 pathway (FGF-23) oxidative stress, and inflammation are other "non-traditional" risk factors in CKD that must be considered in computing the overall likelihood of developing CVD [73]. Therefore, the need for other risk markers is compelling in these patients.

AGEs are known to be involved in the onset and progression of different CVDs, regardless of the presence of CKD [74,75]. As previously discussed, the uremic milieu, along with reduced kidney function, may play a pivotal role in AGE generation and accumulation. Therefore, AGEs must be considered in CKD both for their pathogenetic role and as disease biomarkers and therapeutic targets to prevent and delay CVD complications.

Left ventricular hypertrophy (LVH), which can lead to heart failure (HF), is one of the main cardiac manifestations in CKD [76,77]. AGEs are supposed to activate at least three different pathways that can lead to HF. First, AGEs can directly promote protein cross linking, which undermines matrix protein flexibility, increases rigidity, and may ultimately lead to heart dysfunction. Second, by binding to RAGEs, AGEs activate intracellular signals that upregulate profibrotic mediators such as transforming grow factor β (TGF-β). Third, AGEs induce a delay in calcium uptake, which increases the duration of the repolarization phase of cardiac contraction [78]. AGEs can also promote LVH and increase the risk of HF by inducing the expression of FGF23, a recently discovered hormone that regulates phosphate and vitamin D metabolism by the kidney and has been proposed as an additional causal factor in pathologic LVH [79]. Furthermore, both translational and human studies have indicated a role of AGEs in HF. Diastolic function was shown to correlate with AGEs in diabetic obese rats, and calcium concentration was reduced in the heart of transgenic mice overexpressing RAGE [80,81]. Most studies describing the association of AGEs with systolic and diastolic function in humans were performed in non-CKD patients or in ESRD [82,83]. Plasma AGEs, in particular N(epsilon)-(carboxymethyl)- lysine (CML) levels, were correlated with the severity of HF and predicted patient outcome, even after

correction for known predictors of outcome in HF [83]. High serum levels of pentosidine, another AGE, were suggested as a prognostic element and a marker for risk stratification in HF patients [82]. The association found between skin AGEs and HF among participants in the cross-sectional, population-based Rotterdam study indicated that higher levels of AGEs are associated with the higher odds of HF [84]. Similar results were described for ESRD patients, in whom pentosidine levels correlated with alterations in heart geometry [85]. Instead of AGEs, other studies explored the role of sRAGE as a diagnostic and prognostic marker of HF, but results are conflicting, as in CKD. Lower circulating levels of sRAGE were independently associated with the development of HF in the Atherosclerosis Risk in Communities Study [86]. In some other studies, high sRAGE levels predicted poorer prognosis in patients with HF [87,88]. However as previously mentioned, this evidence is not unanimous [89]. Previous research from our group suggested a potential role for high sRAGE levels as a prognostic factor for mortality in ESRD patients displaying an active process of cardiac remodeling [67]. In contrast, a significant inverse relationship was found between sRAGE and left ventricular mass index and mean wall thickness in CKD patients [90]. Considering that sRAGE levels increase with worsening of kidney function and in DM, their role as a marker of cardiac remodeling may be hampered by the clinical setting of the patients. For this reason, additional studies performed on selected patient subgroups could help to explain the discrepancies observed so far.

CKD patients—even those with a very mild reduction in renal function—display arterial stiffness, a vascular biomarker associated with an independent risk of CVD [91,92]. The stiffening process and its consequences are the result of uremic toxin accumulation, which promotes vascular inflammation, endothelial dysfunction, and calcification. AGEs are contributors, among different toxins, of the development of uremic vasculopathy. AGEs induce arterial stiffness by reducing the expression and phosphorylation of endothelial nitric oxide synthases, which leads to endothelial dysfunction and activation of the proinflammatory response, which further leads to cross linking of the media collagen molecules and osteogenic differentiation of vascular smooth muscle cells [93]. Furthermore, AGEs have been correlated with markers of coronary artery calcifications in both CKD and ESRD patients [94,95].

As a direct consequence of what has been stated above, CKD patients also experience a high incidence of atherosclerotic disease. Low-density lipoprotein (LDL) oxidation may begin atherosclerotic lesion formation or speed up its development. One potential mechanism linking CKD and the development of atherosclerosis is the modification of LDL by AGEs. Exposure of LDL to human, serum-derived AGEs leads to the synthesis of AGE–LDL, which mimics classic LDL oxidation [96,97]. Accumulation of AGEs in coronary atheroma in diabetic ESRD patients was also demonstrated using an anti-AGE-specific antibody [98]. Little information is available about the relationship between AGEs and subclinical atherosclerosis during the early stages of CKD. A close relationship was found between skin autofluorescence (AF) and asymptomatic atheromatous disease. Furthermore, skin AF was negatively correlated with eGFR, suggesting that AGE-related vascular disease could be one of the factors by which AGEs hamper renal function [99].

6. AGEs, Sarcopenia, and Nutritional Status: Pathogenic Role and Biomarker of Muscle Wasting

Currently, most studies regarding how AGEs can influence muscle function and their role in the onset and progression of sarcopenia are conducted in DM, cancer, and aging [100,101]. In muscle, myoblasts differentiate into myocytes. Anything that can promote myoblast loss and myocytes dysfunction affects skeletal muscle mass and promotes sarcopenia. In a murine study, C57Bl/6j mice fed a high-fat and high-sugar diet and ob/ob mice fed a standard diet showed inflammation, oxidative stress, and accumulated AGEs in muscle fibers. This increase in AGE levels can cause myosteatosis, a reduction in muscle mass, and a decrease in mitochondrial efficiency and induce the transition of fast-to-low-speed muscle fibers [101–103]. At the same time, increased RAGE expression on the cellular membrane

and the consequent activation of the SCAP (SREBP cleavage-activating protein)/SREBP (sterol regulatory element binding protein) lipogenic pathway could be a link between intracellular AGE accumulation and muscle wasting [104]. Moreover, as observed in in C2C12 myoblasts, AGEs can also inhibit myoblast differentiation and promote cellular death [105]. Both in murine and human cell lines, it has been observed that AGE concentration is also associated with a decrease in myofiber diameter and increased expression of MAFbx (muscle atrophy F-box), a protein of the ubiquitin proteasome pathway, which can induce the degradation of intracellular protein in skeletal muscle [105]. Interestingly, it has been shown that chronic activation/overexpression of RAGE affects muscle fiber atrophy and inflammation, while its absence seems to delay the loss of muscle mass and strength [101]. Moreover, in a murine model, it was demonstrated that pharmacologic RAGE inhibition can revert skeletal muscle alteration induced by aging, [106] suggesting that the negative effects of AGEs on myotube and myogenesis can be prevented by an AGE inhibitor [105] and that the AGE–RAGE pathway may have a crucial role in inducing myopathy.

Mitochondria are involved in many fundamental cellular processes of skeletal muscle, such as energy supply, calcium homeostasis, and regulation of apoptosis [106]. Many studies have already proven the role of mitochondria in the onset of sarcopenia. In CKD, there is an imbalance between ROS generation and detoxification. Reduced kidney filtration promotes AGE accumulation and the activation of an inflammaging circle that may exacerbate mitochondrial dysfunctions. Although modulation of the AGE/RAGE axis has been proposed as a valid strategy to enhance mitochondrial damage, the link between RAGE, mitochondria, and inflammation and their role in the onset of sarcopenia are poorly described, although they seem to play a major role in CKD [107].

Studies conducted in elderly people, as well as in patients with diabetes, have suggested that AGEs are inversely associated with muscle strength and mass [100,108]. A reduction in appendicular lean mass was correlated with levels of an AGE subtype, pentosidine, which was indicated as a possible biomarker for sarcopenia [100]. In older women urinary excretion of CML, another AGE subtype, was negatively associated with grip strength and suggested as a possible screening tool for sarcopenia [108]. In a recent study, Yabuuchi et al. showed an association between increased AGE levels in the gastrocnemius muscle of nephrectomized mice and muscle morphological anomalies, capillary rarefaction, and mitochondrial dysfunctions [102]. Moreover, they demonstrated that in frail patients, serum AGE levels were significantly increased, while in dialysis patients, AGEs were inversely associated with physical performance and physical activity. In these patients, AGE–aptamer treatment improved the pathological derangement of muscle structure and function. AGEs were found to be associated with slowness and weight loss, two components of the Fried frailty phenotype. In older community-dwelling adults, a similar association has been observed, confirming that AGEs can affect muscle function [109]. In PD patients, Fonseca et al. observed an association between AGE accumulation and lower muscle stiffness/density [109].

Several mechanisms have been suggested as mediators of the negative effects of AGEs. Among these possible mechanisms, RAGE activation and subsequent inflammation, malnutrition, endothelial dysfunction, and connective tissue protein stiffness might explain how AGEs can worsen muscle function. CKD is characterized, among other complications, by insulin resistance and loss of muscle mass. Defects in insulin signaling can contribute to the development of sarcopenia. Insulin is an anabolic hormone. Insulin resistance and reduced insulin levels are known to correlate with protein breakdown, while increased insulin levels stimulate protein synthesis [110]. AGEs could be a link between insulin resistance and loss of muscle mass. Mice fed a high-fat and AGE-rich diet showed a reduction in insulin sensitivity [111]. It is also important to remember that in both healthy individuals and CKD patients, the dietary content of AGEs may influence the systemic levels of AGEs.

Since AGEs were found to be inversely correlated with average metabolic equivalent of task (MET) [102], exercise was suggested as a potential strategy to reduce AGE burden and improve AGE-related dysfunctions in CKD patients. However, more studies are needed to clarify this hypothesis.

Chronic inflammation and oxidative stress lead to muscle proteolysis and hyporexia, two mechanisms that lead to the development of malnutrition and hypoproteinemia [112,113]. Malnutrition may, in turn, promote AGE formation because it sustains an inflammatory and oxidative milieu.

In ESRD patients, since AGEs can cause weight loss and protein catabolism and enhance energy expenditure [102,114], AGE levels have been associated with the prevalence of malnutrition [102,115]. In a recent study conducted in patients with end-stage kidney disease, Suliman et al. found that plasma pentosidine levels were associated with inflammation and the development of malnutrition [102,115]. Inflammatory status can influence nutritional status in several ways; TNFα lead to a catabolic state through the induction of anorexia, stimulating both protein degradation and inhibition of protein synthesis [116–118]. Thus, advanced CKD patients with a higher inflammatory status develop a negative protein balance due to an inhibition of anabolic protein synthesis and the production of acute-phase proteins [118,119]. In a study by our group, we did not find any significant difference in serum AGE concentrations between well-nourished patients and patients at risk of malnutrition or malnourished patients. Instead, we observed an association between malnutrition and increased levels of sRAGEs and esRAGEs. The absence of a direct correlation between AGEs and malnutrition may depend on the fact that our study assessed patients with advanced CKD not yet on dialysis who did not have such high AGE levels as those described in dialyzed patients. Moreover, the three groups of patients classified according to their nutritional status showed the same value of eGFR. This may have weakened the possible effect of renal dysfunction degree on AGE levels [120].

The main possible detrimental effects of AGEs on patient health are summarized in Figure 3.
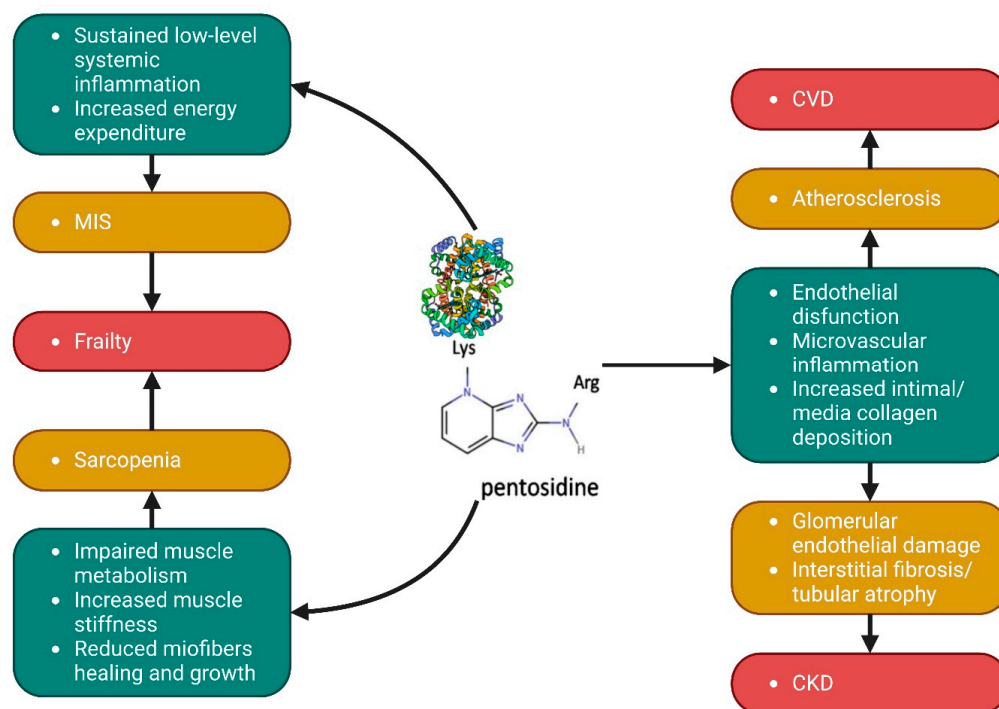

Figure 3. The influence of AGEs on nutrition, as well as muscle, cardiovascular, and kidney health. **Note:** MIS: malnutrition–inflammation syndrome; CVD: cardiovascular disease; CKD: chronic kidney disease. Modified protein surface models are based on the structure of human hemoglobin (PDB ID 1COH).

7. Potential Future Therapeutic Solutions

Considering the role of the AGE–RAGE axis in CKD progression and involvement in CKD-related complications, this pathway could represent a potential treatment target. Therapeutic solutions could be aimed at reducing AGE intake, AGE formation and RAGE expression, blocking RAGE, and degrading AGEs and/or ROS.

1. AGE intake reduction: AGE levels can be lowered by reducing intake of food containing a high number of AGEs and encouraging consumption those containing the lowest amount of AGEs. AGE-rich foods include red meat, animal fat, cheese, sweetened food, and foods cooked at high temperatures in dry heat (frying, broiling, grilling, and roasting) [121]. This nutritional approach could be useful during the early stages of CKD, when patients are suggested which foods to consume and limit. In the advanced stage of CKD, patients are recommended to adhere more strictly to nutritional prescription. The reduced consumption of meat and animal-derived products is an ongoing practice in CKD patients that already limits AGE intake. Other AGE-lowering procedures include stopping cigarette smoking and exercise promotion [122,123].

    Amelia K. Fotheringham et al. recently discussed the potential involvement of the gut microbiota in the modulation of plasma AGE concentration in CKD [124]. On one hand, it has been demonstrated that in dialysis patients, AGE restriction can modulate the microbiota [125]; however, we do not know how these changes can affect plasma concentration. Since the modulation of gut permeability and bacterial species results in a reduction in circulating inflammatory markers [126], we cannot exclude an effect on AGE synthesis and absorption, and further investigations are required.

2. Reduction of AGE synthesis: Several AGE-lowering compounds and AGE formation inhibitors have been developed and progressed to clinical trials; however, due to side effects or because companies have discontinued activities, these studies had to be retracted. AGE-lowering therapy can be classified into direct and indirect therapies. Names and mechanisms of action of molecules belonging to this group are presented in Table 1. Clinical trials of these anti-AGE drugs have been gradually developed. Despite some studies confirming some beneficial effects on AGE levels, nephropathy progression, endothelial function, inflammation, ventricular mass, and parameters of heart function, other reports produced conflicting results. A more detailed description of these studies and studies on other compounds can be found in the works by Sarmah S. at al. [127–130];

3. Suppression of RAGE expression: statins, candesartan, nifedipine, and rosiglitazone have been shown to reduce RAGE expression [131,132];

4. Blockade of RAGE activation.: Azeliragon has been used as a RAGE blocker in patients with Alzheimer's disease, but it has not been applied to other clinal diseases [133]. Increasing sRAGE levels have also been proposed as an additional therapy. sRAGE levels can be increased by exogenous administration or by upregulating sRAGE expression with drugs such as statins, ACE inhibitors, and rosiglitazone [134–136]. sRAGE administration has been studied in preclinical models of atherosclerosis but not in humans [137]. sRAGE levels are already high in CKD, but since the AGE/sRAGE ratio still favors AGEs, this approach must not be excluded;

5. AGE degradation in vivo: GLO-1, the endogenous enzyme that blocks AGE synthesis by promoting the degradation of dicarbonyl compounds, is not available for clinical use, but its activity was upregulated in a placebo–control crossover clinical trial by the combined use of trans-resveratrol found in grapes and hesperidin found in orange [138];

6. Antioxidants: Transition metal ions are associated with the formation of AGEs and ROS generation. As a result, metal ion chelation can also prevent the formation of these products. In addition, antioxidants my reduce AGE–RAGE-induced oxidative stress [131,135].

Table 1. Direct and indirect AGE-lowering compounds.

Direct AGE-Lowering Compounds		
Name	**Actions**	**Clinical Use/Development Stage**
Algebrium chloride [139–141]	A carbonyl scavenger that can also reduce cross links and ROS.	Clinical trials demonstrated beneficial effects in treating cardiovascular disorders, but the company seems to have discontinued operations.
Aminoguanidine [142,143]	A scavenger of carbonyl and dicarbonyl compounds and an ROS inhibitor.	Investigated for the treatment of diabetic nephropathy. Clinical trials were started, but commercial efforts to develop aminoguanidine as a drug were stopped by the company.
Benfotiamine [144]	A synthetic, fat-soluble S-acyl derivative of thiamine (vitamin B1) that reduces glycolysis and the polyol pathway, ROS generation, and activation of transketolase.	Approved in some countries as a medication/dietary supplement to treat diabetic sensorimotor polyneuropathy.
Carnosine [145]	Scavenger of ROS and alpha-beta unsaturated aldehydes created by peroxidation of fatty acid cell membranes during oxidative stress. Carnosine can oppose glycation, and it can chelate divalent metal ions.	Available as a dietary supplement. Clinical trials suggested a renoprotective effect in diabetic nephropathy.
OPB-9195 [146]	A carbonyl scavenger that can also reduce ROS levels.	Used in preclinical studies; however, no human data on this agent have been published.
Piridoxamine [147]	It reacts with carbonyl groups in Amadori products, thereby preventing AGE synthesis from these intermediates. It can also scavenge and reduce ROS production by chelating transition metals.	In experimental models, reduced AGE accumulation by pyridoxamine improved renal function. Beneficial reduction from baseline in serum creatinine was demonstrated by clinical trials in diabetes.
Thiamine [148]	It reduces glycolysis and the polyol pathway, ROS generation, and activation of transketolase.	Beneficial reduction in urinary albumin excretion was demonstrated by clinical trials in diabetes.
Direct AGE-Lowering Compounds		
Name	**Actions**	**Clinical Use/Development Stage**
ACE inhibitors [149]	They inhibit ROS and, by reducing angiotensin II, exert anti-inflammatory effects.	Already used in clinical practice for hypertension. Ramipril reduced fluorescent AGEs, blood pressure, and proteinuria in diabetes.
Statins [150,151]	They stimulate RAGE shedding.	Already used in clinical practice for hypercholesterolemia. Simvastin reduced carotid plaque RAGE expression by decreasing AGE generation in diabetes. Atorvastatin reduced proteinuria and AGE levels in CKD.
AT1R antagonists [152,153]	They inhibit ROS and exert anti-inflammatory effects by reducing angiotensin II signaling.	Already used in clinical practice for hypertension. In diabetes and hypertension, a significant decrease in AGE levels was demonstrated with valsartan and candesartan, which also reduced albumin excretion.

Table 1. *Cont.*

Direct AGE-Lowering Compounds		
Name	**Actions**	**Clinical Use/Development Stage**
Metformin [154,155]	It controls glucose homeostasis, reduces gluconeogenesis, and traps reactive carbonyl groups.	Already used in clinical practice for diabetes. Research on the anti-AGE effects of metformin mainly focuses on cellular experiments.
SGLT-2 inhibitors [156]	They control glucose homeostasis.	Already used in clinical practice for diabetes. Inhibition of oxidative, inflammatory, and fibrotic reactions in the kidney of diabetic rats, partly via suppression of the AGE–RAGE axis, was described.
sRAGE [157–159]	It blocks AGE from binding to RAGE, thereby working as a decoy receptor.	No human data on this agent have been published. Research on sRAGE effects mainly focuses on preclinical models.
Thiazolidinediones [160,161]	They control glucose homeostasis.	An increase in sRAGE levels was observed in clinical trials with pioglitazone and rosiglitazione in diabetes.

ACE, angiotensin-converting enzyme; AGEs, advanced glycation end products; AT1R, angiotensin II receptor type 1; CKD, chronic kidney disease; RAGE, receptor for advanced glycation end products; ROS: reactive oxygen species; SGLT-2, sodium/glucose cotransporter-2; sRAGE, soluble receptor for advanced glycation end products.

Most of clinical data available on the use of anti-AGE compounds have been obtained in DM cohorts. Some of these studies looked at kidney damage as a DM complication. Only a few of studies have been performed in CKD patients; however, these studies only focused on CKD progression and not on other CKD-related complications such as vascular remodeling and heart failure. The need for studies in this field is therefore compelling.

8. Methods for AGE Quantification

As previously discussed, AGEs have been suggested as potential biomarkers in many diseases, but their use in clinical practice has not been implemented to date. Analytical approaches that are currently used in the research field range from global AGE quantification to evaluation of specific compounds. The real challenge associated with introducing their use in clinical practice is the development of robust and standardized analytical methods. The main methods described in the literature include enzyme-linked immunosorbent assays (ELISAs), measurement of skin autofluorescence (SAF) or fluorescent AGEs on other biological samples such plasma and serum, and more sophisticated techniques such as mass spectrometry (MS)-based analyses. SAF and quantification of fluorescent AGEs by measuring the fluorescence properties shared by different compounds allow for the quantification of a specific class of AGEs, including pentosidine. ELISAs and MS offer the possibility of measuring single targets, such as CML or methylglyoxal-hydroimidazolone-1 (MG-H1), or more AGEs simultaneously [162,163].

In their review on analytical methods for assessing AGEs, Jaisson S. et al. indicated ELISA and SAF as the most widely used methods for total AGE quantification (60% of the 70 articles evaluated for their manuscript). The most frequently measured individual AGE was CML (in 20% of articles). Less than 10% of studies focused on other targets, such as pentosidine, carboxyethyl lysine (CEL), MG-H1, argpyrimidine, and glucosepane. ELISA was the most used method for individual AGE quantification. The main differences between methods deal concern the possibility of measuring individual or multiple compounds, equipment availability, and costs. MS analysis is highly promising for AGE detection, but it is time-intensive and costly. In recent years, novel in vivo and non-invasive spectroscopic methods that measure the autofluorescence of AGEs have been developed,

and the quantification of skin autofluorescence as a marker of AGE accumulation has become a non-invasive method for use in clinical practice [163]. However, detection of the autofluorescence of AGEs is limited because it can exclusively measure the total fluorescent glycation. The same detection method can be used on plasma. On one hand, this method cannot quantify total AGEs or identify the contribution of individual compounds as pathogenetic molecules and/or biomarkers; on the other hand, it easily allows for the quantification of multiple compounds that can provide more information about AGE production. From a technical point of view, autofluorescence detection is limited by expression in arbitrary units and a lack of standardization. To date, the lack of standardization represents the main limitation of clinical application of AGE assays. Moreover, since the characterization of new AGEs is still ongoing, new appropriate assays need to be developed. With respect to SAF assessment, it would be also necessary to transform arbitrary units into AGE concentration equivalents.

9. Conclusions

AGE accumulation is a naturally occurring aging process that is further promoted in conditions that promote AGE synthesis and reduced detoxification, such as CKD. AGEs have a pathogenetic role since they can activate responses leading to the progression of CKD and CKD-related disorders. AGEs, along with different forms of sRAGE, can work as circulating biomarkers for CKD risk stratification. Collectively, the studies discussed in the present review seem to suggest that targeting the AGE–RAGE pathways could be useful in preventing the damaging effects of these molecules on different organs.

References

1. Nowotny, K.; Jung, T.; Höhn, A.; Weber, D.; Grune, T. Advanced Glycation End Products and Oxidative Stress in Type 2 Diabetes Mellitus. *Biomolecules* **2015**, *5*, 194–222. [CrossRef] [PubMed]
2. Cho, S.-J.; Roman, G.; Yeboah, F.; Konishi, Y. The Road to Advanced Glycation End Products: A Mechanistic Perspective. *Curr. Med. Chem.* **2007**, *14*, 1653–1671. [CrossRef] [PubMed]
3. Thornalley, P.J. Dietary AGEs and ALEs and Risk to Human Health by Their Interaction with the Receptor for Advanced Glycation Endproducts (RAGE)–an Introduction. *Mol. Nutr. Food Res.* **2007**, *51*, 1107–1110. [CrossRef] [PubMed]
4. Reddy, V.P.; Beyaz, A. Inhibitors of the Maillard Reaction and AGE Breakers as Therapeutics for Multiple Diseases. *Drug. Discov. Today* **2006**, *11*, 646–654. [CrossRef]
5. Rabbani, N.; Thornalley, P.J. Methylglyoxal, Glyoxalase 1 and the Dicarbonyl Proteome. *Amino Acids* **2012**, *42*, 1133–1142. [CrossRef]
6. Busch, M.; Franke, S.; Rüster, C.; Wolf, G. Advanced Glycation End-Products and the Kidney. *Eur. J. Clin. Investig.* **2010**, *40*, 742–755. [CrossRef]
7. Stitt, A.W.; Burke, G.A.; Chen, F.; McMullen, C.B.T.; Vlassara, H. Advanced Glycation End-Product Receptor Interactions on Microvascular Cells Occur within Caveolin-Rich Membrane Domains. *FASEB J.* **2000**, *14*, 2390–2392. [CrossRef]
8. Thornalley, P.J. Glyoxalase I–Structure, Function and a Critical Role in the Enzymatic Defence against Glycation. *Biochem. Soc. Trans.* **2003**, *31*, 1343–1348. [CrossRef]
9. Lu, C.; He, J.C.; Cai, W.; Liu, H.I.; Zhu, L.; Vlassara, H. Advanced Glycation Endproduct (AGE) Receptor 1 Is a Negative Regulator of the Inflammatory Response to AGE in Mesangial Cells. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11767–11772. [CrossRef]
10. Ribau, J.C.O.; Hadcock, S.J.; Teoh, K.; DeReske, M.; Richardson, M. Endothelial Adhesion Molecule Expression Is Enhanced in the Aorta and Internal Mammary Artery of Diabetic Patients. *J. Res.* **1999**, *85*, 225–233. [CrossRef]
11. Identification of Galectin-3 as a High-Affinity Binding Protein for Advanced Glycation End Products (AGE): A New Member of the AGE-Receptor Complex. Available online: https://pubmed.ncbi.nlm.nih.gov/8529130/ (accessed on 23 January 2023).

12. Iacobini, C.; Amadio, L.; Oddi, G.; Ricci, C.; Barsotti, P.; Missori, S.; Sorcini, M.; di Mario, U.; Pricci, F.; Pugliese, G. Role of Galectin-3 in Diabetic Nephropathy. *J. Am. Soc. Nephrol.* **2003**, *14*, S264–S270. [CrossRef]

13. Schmidt, A.M.; du Yan, S.; Yan, S.F.; Stern, D.M. The Multiligand Receptor RAGE as a Progression Factor Amplifying Immune and Inflammatory Responses. *J. Clin. Investig.* **2001**, *108*, 949–955. [CrossRef]

14. Raucci, A.; Cugusi, S.; Antonelli, A.; Barabino, S.M.; Monti, L.; Bierhaus, A.; Reiss, K.; Saftig, P.; Bianchi, M.E. A Soluble Form of the Receptor for Advanced Glycation Endproducts (RAGE) Is Produced by Proteolytic Cleavage of the Membrane-Bound Form by the Sheddase a Disintegrin and Metalloprotease 10 (ADAM10). *FASEB J.* **2008**, *22*, 3716–3727. [CrossRef]

15. Lee, A.C.H.; Lam, J.K.Y.; Shiu, S.W.M.; Wong, Y.; Betteridge, D.J.; Tan, K.C.B. Serum Level of Soluble Receptor for Advanced Glycation End Products Is Associated with A Disintegrin And Metalloproteinase 10 in Type 1 Diabetes. *PLoS ONE* **2015**, *10*, e0137330. [CrossRef]

16. Jules, J.; Maiguel, D.; Hudson, B.I. Alternative Splicing of the RAGE Cytoplasmic Domain Regulates Cell Signaling and Function. *PLoS ONE* **2013**, *8*, e78267. [CrossRef]

17. Liu, Q.; Chen, H.B.; Luo, M.; Zheng, H. Serum Soluble RAGE Level Inversely Correlates with Left Ventricular Hypertrophy in Essential Hypertension Patients. *Genet. Mol. Res.* **2016**, *15*, gmr.15028414. [CrossRef]

18. Momma, H.; Niu, K.; Kobayashi, Y.; Huang, C.; Chujo, M.; Otomo, A.; Tadaura, H.; Miyata, T.; Nagatomi, R. Lower Serum Endogenous Secretory Receptor for Advanced Glycation End Product Level as a Risk Factor of Metabolic Syndrome among Japanese Adult Men: A 2-Year Longitudinal Study. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 587–593. [CrossRef]

19. Norata, G.D.; Garlaschelli, K.; Grigore, L.; Tibolla, G.; Raselli, S.; Redaelli, L.; Buccianti, G.; Catapano, A.L. Circulating Soluble Receptor for Advanced Glycation End Products Is Inversely Associated with Body Mass Index and Waist/Hip Ratio in the General Population. *Nutr. Metab. Cardiovasc. Dis.* **2009**, *19*, 129–134. [CrossRef]

20. Dozio, E.; Briganti, S.; Delnevo, A.; Vianello, E.; Ermetici, F.; Secchi, F.; Sardanelli, F.; Morricone, L.; Malavazos, A.E.; Corsi Romanelli, M.M. Relationship between Soluble Receptor for Advanced Glycation End Products (SRAGE), Body Composition and Fat Distribution in Healthy Women. *Eur. J. Nutr.* **2017**, *56*, 2557–2564. [CrossRef]

21. Dozio, E.; Corradi, V.; Vianello, E.; Scalzotto, E.; de Cal, M.; Corsi Romanelli, M.M.; Ronco, C. Increased Levels of SRAGE in Diabetic CKD-G5D Patients: A Potential Protective Mechanism against AGE-Related Upregulation of Fibroblast Growth Factor 23 and Inflammation. *Mediat. Inflamm.* **2017**, *2017*, 9845175. [CrossRef]

22. Sabbatinelli, J.; Castiglione, S.; Macrì, F.; Giuliani, A.; Ramini, D.; Vinci, M.C.; Tortato, E.; Bonfigli, A.R.; Olivieri, F.; Raucci, A. Circulating Levels of AGEs and Soluble RAGE Isoforms Are Associated with All-Cause Mortality and Development of Cardiovascular Complications in Type 2 Diabetes: A Retrospective Cohort Study. *Cardiovasc. Diabetol.* **2022**, *21*, 95. [CrossRef] [PubMed]

23. Leurs, P.; Lindholm, B. The AGE-RAGE Pathway and Its Relation to Cardiovascular Disease in Patients with Chronic Kidney Disease. *Arch. Med. Res.* **2013**, *44*, 601–610. [CrossRef] [PubMed]

24. Saito, A.; Pietromonaco, S.; Loo, A.K.C.; Farquhar, M.G. Complete Cloning and Sequencing of Rat Gp330/"megalin", a Distinctive Member of the Low Density Lipoprotein Receptor Gene Family. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 9725–9729. [CrossRef] [PubMed]

25. Saito, A.; Nagai, R.; Tanuma, A.; Hama, H.; Cho, K.; Takeda, T.; Yoshida, Y.; Toda, T.; Shimizu, F.; Horiuchi, S.; et al. Role of Megalin in Endocytosis of Advanced Glycation End Products: Implications for a Novel Protein Binding to Both Megalin and Advanced Glycation End Products. *J. Am. Soc. Nephrol.* **2003**, *14*, 1123–1131. [CrossRef]

26. Gugliucci, A.; Bendayan, M. Renal Fate of Circulating Advanced Glycated End Products (AGE): Evidence for Reabsorption and Catabolism of AGE-Peptides by Renal Proximal Tubular Cells. *Diabetologia* **1996**, *39*, 149–160. [CrossRef]

27. Christensen, E.I.; Birn, H. Megalin and Cubilin: Multifunctional Endocytic Receptors. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 258–268. [CrossRef]

28. Biemesderfer, D.; Nagy, T.; DeGray, B.; Aronson, P.S. Specific Association of Megalin and the Na+/H+ Exchanger Isoform NHE3 in the Proximal Tubule. *J. Biol. Chem.* **1999**, *274*, 17518–17524. [CrossRef]

29. Hryciw, D.H.; Lee, E.M.; Pollock, C.A.; Poronnik, P. Molecular Changes in Proximal Tubule Function in Diabetes Mellitus. *Clin. Exp. Pharmacol. Physiol.* **2004**, *31*, 372–379. [CrossRef]

30. De, S.; Kuwahara, S.; Saito, A. The Endocytic Receptor Megalin and Its Associated Proteins in Proximal Tubule Epithelial Cells. *Membranes* **2014**, *4*, 333–335. [CrossRef]

31. Oberg, B.P.; McMenamin, E.; Lucas, F.L.; McMonagle, E.; Morrow, J.; Ikizler, T.A.; Himmelfarb, J. Increased Prevalence of Oxidant Stress and Inflammation in Patients with Moderate to Severe Chronic Kidney Disease. *Kidney Int.* **2004**, *65*, 1009–1016. [CrossRef]

32. Uribarri, J.; Cai, W.; Peppa, M.; Goodman, S.; Ferrucci, L.; Striker, G.; Vlassara, H. Circulating Glycotoxins and Dietary Advanced Glycation Endproducts: Two Links to Inflammatory Response, Oxidative Stress, and Aging. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2007**, *62*, 427–433. [CrossRef]

33. Genuth, S.; Sun, W.; Cleary, P.; Sell, D.R.; Dahms, W.; Malone, J.; Sivitz, W.; Monnier, V.M. Glycation and Carboxymethyllysine Levels in Skin Collagen Predict the Risk of Future 10-Year Progression of Diabetic Retinopathy and Nephropathy in the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications Participants with Type 1 Diabetes. *Diabetes* **2005**, *54*, 3103–3111. [CrossRef]

34. Miyata, T.; van Ypersele De Strihou, C.; Kurokawa, K.; Baynes, J.W. Alterations in Nonenzymatic Biochemistry in Uremia: Origin and Significance of "Carbonyl Stress" in Long-Term Uremic Complications. *Kidney Int.* **1999**, *55*, 389–399. [CrossRef]

35. Sun, H.; Chen, J.; Hua, Y.; Zhang, Y.; Liu, Z. New Insights into the Role of Empagliflozin on Diabetic Renal Tubular Lipid Accumulation. *Diabetol. Metab. Syndr.* **2022**, *14*, 121. [CrossRef]

36. Kaifu, K.; Ueda, S.; Nakamura, N.; Matsui, T.; Yamada-Obara, N.; Ando, R.; Kaida, Y.; Nakata, M.; Matsukuma-Toyonaga, M.; Higashimoto, Y.; et al. Advanced Glycation End Products Evoke Inflammatory Reactions in Proximal Tubular Cells via Autocrine Production of Dipeptidyl Peptidase-4. *Microvasc. Res.* **2018**, *120*, 90–93. [CrossRef]

37. Haraguchi, R.; Kohara, Y.; Matsubayashi, K.; Kitazawa, R.; Kitazawa, S. New Insights into the Pathogenesis of Diabetic Nephropathy: Proximal Renal Tubules Are Primary Target of Oxidative Stress in Diabetic Kidney. *Acta Histochem. Cytochem.* **2020**, *53*, 21–31. [CrossRef]

38. Liu, B.; Sun, T.; Li, H.; Qiu, S.; Li, Y.; Zhang, D. Proximal Tubular RAGE Mediated the Renal Fibrosis in UUO Model Mice via Upregulation of Autophagy. *Cell Death Dis.* **2022**, *13*. [CrossRef]

39. Tan, R.J.; Li, Y.; Rush, B.M.; Cerqueira, D.M.; Zhou, D.; Fu, H.; Ho, J.; Stolz, D.B.; Liu, Y. Tubular Injury Triggers Podocyte Dysfunction by β-Catenin-Driven Release of MMP-7. *JCI Insight* **2019**, *4*, e122399. [CrossRef]

40. Bucala, R.; Vlassara, H. Advanced Glycosylation End Products in Diabetic Renal and Vascular Disease. *Am. J. Kidney Dis.* **1995**, *26*, 875–888. [CrossRef]

41. Shimoike, T.; Inoguchi, T.; Umeda, F.; Nawata, H.; Kawano, K.; Ochi, H. The Meaning of Serum Levels of Advanced Glycosylation End Products in Diabetic Nephropathy. *Metabolism* **2000**, *49*, 1030–1035. [CrossRef]

42. Tezuka, Y.; Nakaya, I.; Nakayama, K.; Nakayama, M.; Yahata, M.; Soma, J. Methylglyoxal as a Prognostic Factor in Patients with Chronic Kidney Disease. *Nephrology* **2019**, *24*, 943–950. [CrossRef] [PubMed]

43. Calviño, J.; Cigarran, S.; Gonzalez-Tabares, L.; Menendez, N.; Latorre, J.; Cillero, S.; Millan, B.; Cobelo, C.; Sanjurjo-Amado, A.; Quispe, J.; et al. Advanced Glycation End Products (AGEs) Estimated by Skin Autofluorescence Are Related with Cardiovascular Risk in Renal Transplant. *PLoS ONE* **2018**, *13*, e0201118. [CrossRef] [PubMed]

44. Nogueira, A.; Pires, M.J.; Oliveira, P.A. Pathophysiological Mechanisms of Renal Fibrosis: A Review of Animal Models and Therapeutic Strategies. *In Vivo* **2017**, *31*, 1–22. [CrossRef] [PubMed]

45. Vlassara, H.; Striker, L.J.; Teichberg, S.; Fuh, H.; Li, Y.M.; Steffes, M. Advanced Glycation End Products Induce Glomerular Sclerosis and Albuminuria in Normal Rats. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11704–11708. [CrossRef]

46. Zhuo, J.L.; Li, X.C. Proximal Nephron. *Compr. Physiol* **2013**, *3*, 1079–1123. [CrossRef]

47. Saito, A.; Sato, H.; Iino, N.; Takeda, T. Molecular Mechanisms of Receptor-Mediated Endocytosis in the Renal Proximal Tubular Epithelium. *J. Biomed. Biotechnol.* **2010**, *2010*, 403272. [CrossRef]

48. Kuwahara, S.; Hosojima, M.; Kaneko, R.; Aoki, H.; Nakano, D.; Sasagawa, T.; Kabasawa, H.; Kaseda, R.; Yasukawa, R.; Ishikawa, T.; et al. Megalin-Mediated Tubuloglomerular Alterations in High-Fat Diet-Induced Kidney Disease. *J. Am. Soc. Nephrol.* **2016**, *27*, 1996–2008. [CrossRef]

49. Saito, A.; Takeda, T.; Sato, K.; Hama, H.; Tanuma, A.; Kaseda, R.; Suzuki, Y.; Gejyo, F. Significance of Proximal Tubular Metabolism of Advanced Glycation End Products in Kidney Diseases. *Ann. N. Y. Acad. Sci* **2005**, *1043*, 637–643. [CrossRef]

50. Vettoretti, S.; Caldiroli, L.; Armelloni, S.; Ferrari, C.; Cesari, M.; Messa, P. Sarcopenia Is Associated with Malnutrition but Not with Systemic Inflammation in Older Persons with Advanced CKD. *Nutrients* **2019**, *11*, 1378. [CrossRef]

51. Kooman, J.P.; Dekker, M.J.; Usvyat, L.A.; Kotanko, P.; van der Sande, F.M.; Schalkwijk, C.G.; Shiels, P.G.; Stenvinkel, P. Inflammation and Premature Aging in Advanced Chronic Kidney Disease. *Am. J. Physiol. Ren. Physiol.* **2017**, *313*, F938–F950. [CrossRef]

52. Paoletti, E.; de Nicola, L.; Gabbai, F.B.; Chiodini, P.; Ravera, M.; Pieracci, L.; Marre, S.; Cassottana, P.; Lucà, S.; Vettoretti, S.; et al. Associations of Left Ventricular Hypertrophy and Geometry with Adverse Outcomes in Patients with CKD and Hypertension. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 271–279. [CrossRef]

53. Hörner, D.V.; Taal, M.W. Skin Autofluorescence: An Emerging Biomarker in Persons with Kidney Disease. *Curr. Opin. Nephrol. Hypertens.* **2019**, *28*, 507–512. [CrossRef]

54. Cavero-Redondo, I.; Soriano-Cano, A.; Álvarez-Bueno, C.; Cunha, P.G.; Martínez-Hortelano, J.A.; Garrido-Miguel, M.; Berlanga-Macías, C.; Martínez-Vizcaíno, V. Skin Autofluorescence-Indicated Advanced Glycation End Products as Predictors of Cardio-vascular and All-Cause Mortality in High-Risk Subjects: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **2018**, *7*, e009833. [CrossRef]

55. Gerrits, E.G.; Lutgers, H.L.; Smeets, G.H.W.; Groenier, K.H.; Smit, A.J.; Gans, R.O.B.; Bilo, H.J.G. Skin Autofluorescence: A Pronounced Marker of Mortality in Hemodialysis Patients. *Nephron Extra* **2012**, *2*, 184–191. [CrossRef]

56. Nongnuch, A.; Davenport, A. Skin Autofluorescence Advanced Glycosylation End Products as an Independent Predictor of Mortality in High Flux Haemodialysis and Haemodialysis Patients. *Nephrology* **2015**, *20*, 862–867. [CrossRef]

57. Mácsai, E.; Benke, A.; Kiss, I. Skin Autofluorescence and Mortality in Patients on Peritoneal Dialysis. *Medicine* **2015**, *94*, e1933. [CrossRef]

58. Siriopol, D.; Hogas, S.; Veisa, G.; Mititiuc, I.; Volovat, C.; Apetrii, M.; Onofriescu, M.; Busila, I.; Oleniuc, M.; Covic, A. Tissue Advanced Glycation End Products (AGEs), Measured by Skin Autofluorescence, Predict Mortality in Peritoneal Dialysis. *Int. Urol. Nephrol.* **2015**, *47*, 563–569. [CrossRef]

59. McIntyre, N.J.; Chesterton, L.J.; John, S.G.; Jefferies, H.J.; Burton, J.O.; Taal, M.W.; Fluck, R.J.; McIntyre, C.W. Tissue-Advanced Glycation End Product Concentration in Dialysis Patients. *Clin. J. Am. Soc. Nephrol.* **2010**, *5*, 51–55. [CrossRef]

60. Oleniuc, M.; Schiller, A.; Secara, I.; Onofriescu, M.; Hogas, S.; Apetrii, M.; Siriopol, D.; Covic, A. Evaluation of Advanced Glycation End Products Accumulation, Using Skin Autofluorescence, in CKD and Dialysis Patients. *Int. Urol. Nephrol.* **2012**, *44*, 1441–1449. [CrossRef]

61. Mac-Way, F.; Couture, V.; Utescu, M.S.; Ignace, S.; de Serres, S.A.; Loignon, R.C.; Marquis, K.; Larivière, R.; Agharazii, M. Advanced Glycation End Products, Aortic Stiffness, and Wave Reflection in Peritoneal Dialysis as Compared to Hemodialysis. *Int. Urol. Nephrol.* **2014**, *46*, 817–824. [CrossRef]

62. Jiang, J.; Chen, P.; Chen, J.; Yu, X.; Xie, D.; Mei, C.; Xiong, F.; Shi, W.; Zhou, W.; Liu, X.; et al. Accumulation of Tissue Advanced Glycation End Products Correlated with Glucose Exposure Dose and Associated with Cardiovascular Morbidity in Patients on Peritoneal Dialysis. *Atherosclerosis* **2012**, *224*, 187–194. [CrossRef]

63. Uflacker, R.; Paolini, R.M.; Nobrega, M. Ablation of Tumor and Inflammatory Tissue with Absolute Ethanol. *Acta Radiol. Diagn.* **1986**, *27*, 131–138. [CrossRef] [PubMed]

64. Mukai, H.; Svedberg, O.; Lindholm, B.; Dai, L.; Heimbürger, O.; Barany, P.; Anderstam, B.; Stenvinkel, P.; Qureshi, A.R. Skin Autofluorescence, Arterial Stiffness and Framingham Risk Score as Predictors of Clinical Outcome in Chronic Kidney Disease Patients: A Cohort Study. *Nephrol. Dial. Transplant.* **2019**, *34*, 442–448. [CrossRef] [PubMed]

65. Fraser, S.D.S.; Roderick, P.J.; McIntyre, N.J.; Harris, S.; McIntyre, C.W.; Fluck, R.J.; Taal, M.W. Skin Autofluorescence and All-Cause Mortality in Stage 3 CKD. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 1361–1368. [CrossRef] [PubMed]

66. Steenbeke, M.; Speeckaert, R.; Desmedt, S.; Glorieux, G.; Delanghe, J.R.; Speeckaert, M.M. The Role of Advanced Glycation End Products and Its Soluble Receptor in Kidney Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 3439. [CrossRef]

67. Dozio, E.; Ambrogi, F.; de Cal, M.; Vianello, E.; Ronco, C.; Corsi Romanelli, M.M. Role of the Soluble Receptor for Advanced Glycation End Products (SRAGE) as a Prognostic Factor for Mortality in Hemodialysis and Peritoneal Dialysis Patients. *Mediat. Inflamm.* **2018**, *2018*, 1347432. [CrossRef]

68. Jung, E.S.; Chung, W.; Kim, A.J.; Ro, H.; Chang, J.H.; Lee, H.H.; Jung, J.Y. Associations between Soluble Receptor for Advanced Glycation End Products (SRAGE) and S100A12 (EN-RAGE) with Mortality in Long-Term Hemodialysis Patients. *J. Korean Med. Sci.* **2017**, *32*, 54–59. [CrossRef]

69. Dozio, E.; Vettoretti, S.; Caldiroli, L.; Nerini-Molteni, S.; Tacchini, L.; Ambrogi, F.; Messa, P.; Corsi Romanelli, M.M. Advanced Glycation End Products (AGE) and Soluble Forms of AGE Receptor: Emerging Role as Mortality Risk Factors in CKD. *Biomedicines* **2020**, *8*, 638. [CrossRef]

70. Dozio, E.; Corradi, V.; Proglio, M.; Vianello, E.; Menicanti, L.; Rigolini, R.; Caprara, C.; de Cal, M.; Corsi Romanelli, M.M.; Ronco, C. Usefulness of Glycated Albumin as a Biomarker for Glucose Control and Prognostic Factor in Chronic Kidney Disease Patients on Dialysis (CKD-G5D). *Diabetes Res. Clin. Pract.* **2018**, *140*, 9–17. [CrossRef]

71. Go, A.S.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Hsu, C. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N. Engl. J. Med.* **2004**, *351*, 1296–1305. [CrossRef]

72. Johansen, K.L.; Chertow, G.M.; Foley, R.N.; Gilbertson, D.T.; Herzog, C.A.; Ishani, A.; Israni, A.K.; Ku, E.; Kurella Tamura, M.; Li, S.; et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am. J. Kidney Dis.* **2021**, *77*, A7–A8. [CrossRef]

73. Sarnak, M.J.; Levey, A.S.; Schoolwerth, A.C.; Coresh, J.; Culleton, B.; Hamm, L.L.; McCullough, P.A.; Kasiske, B.L.; Kelepouris, E.; Klag, M.J.; et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* **2003**, *108*, 2154–2169. [CrossRef]

74. Yamagishi, S.; Sotokawauchi, A.; Matsui, T. Pathological Role of Advanced Glycation End Products (AGEs) and Their Receptor Axis in Atrial Fibrillation. *Mini Rev. Med. Chem.* **2019**, *19*, 1040–1048. [CrossRef]

75. Baumann, M. Role of Advanced Glycation End Products in Hypertension and Cardiovascular Risk: Human Studies. *J. Am. Soc. Hypertens.* **2012**, *6*, 427–435. [CrossRef]

76. Matsushita, K.; Kwak, L.; Sang, Y.; Ballew, S.H.; Skali, H.; Shah, A.M.; Coresh, J.; Solomon, S. Kidney Disease Measures and Left Ventricular Structure and Function: The Atherosclerosis Risk in Communities Study. *J. Am. Heart Assoc.* **2017**, *6*, e006259. [CrossRef]

77. Park, M.; Hsu, C.Y.; Li, Y.; Mishra, R.K.; Keane, M.; Rosas, S.E.; Dries, D.; Xie, D.; Chen, J.; He, J.; et al. Associations between Kidney Function and Subclinical Cardiac Abnormalities in CKD. *J. Am. Soc. Nephrol.* **2012**, *23*, 1725–1734. [CrossRef]

78. Willemsen, S.; Hartog Jasper, W.L.; Heiner-Fokkema, M.R.; van Veldhuisen, D.J.; Voors, A.A. Advanced Glycation End-Products, a Pathophysiological Pathway in the Cardiorenal Syndrome. *Heart Fail. Rev.* **2012**, *17*, 221–228. [CrossRef]

79. Faul, C.; Amaral, A.P.; Oskouei, B.; Hu, M.C.; Sloan, A.; Isakova, T.; Gutiérrez, O.M.; Aguillon-Prada, R.; Lincoln, J.; Hare, J.M.; et al. FGF23 Induces Left Ventricular Hypertrophy. *J. Clin. Investig.* **2011**, *121*, 4393–4408. [CrossRef]

80. Schäfer, S.; Huber, J.; Wihler, C.; Rütten, H.; Busch, A.E.; Linz, W. Impaired Left Ventricular Relaxation in Type 2 Diabetic Rats Is Related to Myocardial Accumulation of N(Epsilon)-(Carboxymethyl) Lysine. *Eur. J. Heart Fail.* **2006**, *8*, 2–6. [CrossRef]

81. Petrova, R.; Yamamoto, Y.; Muraki, K.; Yonekura, H.; Sakurai, S.; Watanabe, T.; Li, H.; Takeuchi, M.; Makita, Z.; Kato, I.; et al. Advanced Glycation Endproduct-Induced Calcium Handling Impairment in Mouse Cardiac Myocytes. *J. Mol. Cell. Cardiol.* **2002**, *34*, 1425–1431. [CrossRef]

82. Koyama, Y.; Takeishi, Y.; Arimoto, T.; Niizeki, T.; Shishido, T.; Takahashi, H.; Nozaki, N.; Hirono, O.; Tsunoda, Y.; Nitobe, J.; et al. High Serum Level of Pentosidine, an Advanced Glycation End Product (AGE), Is a Risk Factor of Patients with Heart Failure. *J. Card. Fail.* **2007**, *13*, 199–206. [CrossRef] [PubMed]

83. Hartog, J.W.L.; Voors, A.A.; Schalkwijk, C.G.; Scheijen, J.; Smilde, T.D.J.; Damman, K.; Bakker, S.J.L.; Smit, A.J.; van Veldhuisen, D.J. Clinical and Prognostic Value of Advanced Glycation End-Products in Chronic Heart Failure. *Eur. Heart J.* **2007**, *28*, 2879–2885. [CrossRef] [PubMed]

84. Arshi, B.; Chen, J.; Ikram, M.A.; Zillikens, M.C.; Kavousi, M. Advanced Glycation End-Products, Cardiac Function and Heart Failure in the General Population: The Rotterdam Study. *Diabetologia* **2022**, *66*, 472–481. [CrossRef] [PubMed]

85. Pentosidine, Carotid Atherosclerosis and Alterations in Left Ventricular Geometry in Hemodialysis. Available online: https://pubmed.ncbi.nlm.nih.gov/11506253/ (accessed on 23 January 2023).

86. Lazo, M.; Halushka, M.K.; Shen, L.; Maruthur, N.; Rebholz, C.M.; Rawlings, A.M.; Hoogeveen, R.C.; Brinkley, T.E.; Ballantyne, C.M.; Astor, B.C.; et al. Soluble Receptor for Advanced Glycation End Products and the Risk for Incident Heart Failure: The Atherosclerosis Risk in Communities Study. *Am. Heart J.* **2015**, *170*, 961–967. [CrossRef]

87. Koyama, Y.; Takeishi, Y.; Niizeki, T.; Suzuki, S.; Kitahara, T.; Sasaki, T.; Kubota, I. Soluble Receptor for Advanced Glycation End Products (RAGE) Is a Prognostic Factor for Heart Failure. *J. Card. Fail.* **2008**, *14*, 133–139. [CrossRef]

88. Raposeiras-Roubín, S.; Rodiño-Janeiro, B.K.; Grigorian-Shamagian, L.; Moure-González, M.; Seoane-Blanco, A.; Varela-Román, A.; Almenar-Bonet, L.; Álvarez, E.; González-Juanatey, J.R. Relation of Soluble Receptor for Advanced Glycation End Products to Predict Mortality in Patients with Chronic Heart Failure Independently of Seattle Heart Failure Score. *Am. J. Cardiol.* **2011**, *107*, 938–944. [CrossRef]

89. Willemsen, S.; Hartog, J.W.L.; van Veldhuisen, D.J.; van der Meer, P.; Roze, J.F.; Jaarsma, T.; Schalkwijk, C.; van der Horst, I.C.C.; Hillege, H.L.; Voors, A.A. The Role of Advanced Glycation End-Products and Their Receptor on Outcome in Heart Failure Patients with Preserved and Reduced Ejection Fraction. *Am. Heart J.* **2012**, *164*, 742–749.e3. [CrossRef]

90. Leonardis, D.; Basta, G.; Mallamaci, F.; Cutrupi, S.; Pizzini, P.; Tripepi, R.; Tripepi, G.; de Caterina, R.; Zoccali, C. Circulating Soluble Receptor for Advanced Glycation End Product (SRAGE) and Left Ventricular Hypertrophy in Patients with Chronic Kidney Disease (CKD). *Nutr. Metab. Cardiovasc. Dis.* **2012**, *22*, 748–755. [CrossRef]

91. Zanoli, L.; Empana, J.P.; Perier, M.C.; Alivon, M.; Ketthab, H.; Castellino, P.; Laude, D.; Thomas, F.; Pannier, B.; Laurent, S.; et al. Increased Carotid Stiffness and Remodelling at Early Stages of Chronic Kidney Disease. *J. Hypertens.* **2019**, *37*, 1176–1182. [CrossRef]

92. Briet, M.; Bozec, E.; Laurent, S.; Fassot, C.; London, G.M.; Jacquot, C.; Froissart, M.; Houillier, P.; Boutouyrie, P. Arterial Stiffness and Enlargement in Mild-to-Moderate Chronic Kidney Disease. *Kidney Int.* **2006**, *69*, 350–357. [CrossRef]

93. Townsend, R.R. Arterial Stiffness in CKD: A Review. *Am. J. Kidney Dis.* **2019**, *73*, 240–247. [CrossRef]

94. de Faria Fonseca, L.; Araújo, A.B.; da Silva Quadros, K.R.; Carbonara, C.E.M.; Dertkigil, S.S.J.; Sposito, A.C.; de Oliveira, R.B. AGEs Accumulation Is Related to Muscle Degeneration and Vascular Calcification in Peritoneal Dialysis Patients. *J. Bras. Nefrol.* **2021**, *43*, 191–199. [CrossRef]

95. Wang, A.Y.M.; Wong, C.K.; Yau, Y.Y.; Wong, S.; Chan, I.H.S.; Lam, C.W.K. Skin Autofluorescence Associates with Vascular Calcification in Chronic Kidney Disease. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 1784–1790. [CrossRef]

96. Bucala, R.; Makita, Z.; Vega, G.; Grundy, S.; Koschinsky, T.; Cerami, A.; Vlassara, H. Modification of Low Density Lipoprotein by Advanced Glycation End Products Contributes to the Dyslipidemia of Diabetes and Renal Insufficiency. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 9441–9445. [CrossRef]

97. Makita, Z.; Yanagisawa, K.; Kuwajima, S.; Bucala, R.; Vlassara, H.; Koike, T. The Role of Advanced Glycosylation End-Products in the Pathogenesis of Atherosclerosis. *Nephrol. Dial. Transplant.* **1996**, *11* (Suppl. S5), 31–33. [CrossRef]

98. Immunohistochemical Localization of Advanced Glycosylation End Products in Coronary Atheroma and Cardiac Tissue in Diabetes Mellitus. Available online: https://pubmed.ncbi.nlm.nih.gov/8256853/ (accessed on 23 January 2023).

99. Sánchez, E.; Betriu, À.; Arroyo, D.; López, C.; Hernández, M.; Rius, F.; Fernández, E.; Lecube, A. Skin Autofluorescence and Subclinical Atherosclerosis in Mild to Moderate Chronic Kidney Disease: A Case-Control Study. *PLoS ONE* **2017**, *12*, e0170778. [CrossRef]

100. Eguchi, Y.; Toyoguchi, T.; Inage, K.; Fujimoto, K.; Orita, S.; Suzuki, M.; Kanamoto, H.; Abe, K.; Norimoto, M.; Umimura, T.; et al. Advanced Glycation End Products Are Associated with Sarcopenia in Older Women: Aging Marker Dynamics. *J. Women Aging* **2021**, *33*, 328–340. [CrossRef]

101. Chiappalupi, S.; Sorci, G.; Vukasinovic, A.; Salvadori, L.; Sagheddu, R.; Coletti, D.; Renga, G.; Romani, L.; Donato, R.; Riuzzi, F. Targeting RAGE Prevents Muscle Wasting and Prolongs Survival in Cancer Cachexia. *J. Cachexia Sarcopenia Muscle* **2020**, *11*, 929–946. [CrossRef]

102. Yabuuchi, J.; Ueda, S.; Yamagishi, S.-i.; Nohara, N.; Nagasawa, H.; Wakabayashi, K.; Matsui, T.; Yuichiro, H.; Kadoguchi, T.; Otsuka, T.; et al. Association of Advanced Glycation End Products with Sarcopenia and Frailty in Chronic Kidney Disease. *Sci. Rep.* **2020**, *10*, 17647. [CrossRef]

103. Diesel, W.; Knight, B.K.; Noakes, T.D.; Swanepoel, C.R.; van Zyl Smit, R.; Kaschula, R.O.C.; Sinclair-Smith, C.C. Morphologic Features of the Myopathy Associated with Chronic Renal Failure. *Am. J. Kidney Dis.* **1993**, *22*, 677–684. [CrossRef]

104. Mastrocola, R.; Nigro, D.; Chiazza, F.; Medana, C.; Dal Bello, F.; Boccuzzi, G.; Collino, M.; Aragno, M. Fructose-Derived Advanced Glycation End-Products Drive Lipogenesis and Skeletal Muscle Reprogramming via SREBP-1c Dysregulation in Mice. *Free Radic. Biol. Med.* **2016**, *91*, 224–235. [CrossRef] [PubMed]

105. Chiu, C.Y.; Yang, R.S.; Sheu, M.L.; Chan, D.C.; Yang, T.H.; Tsai, K.S.; Chiang, C.K.; Liu, S.H. Advanced Glycation End-Products Induce Skeletal Muscle Atrophy and Dysfunction in Diabetic Mice via a RAGE-Mediated, AMPK-down-Regulated, Akt Pathway. *J. Pathol.* **2016**, *238*, 470–482. [CrossRef] [PubMed]

106. Davis, H.M.; Essex, A.L.; Valdez, S.; Deosthale, P.J.; Aref, M.W.; Allen, M.R.; Bonetto, A.; Plotkin, L.I. Short-Term Pharmacologic RAGE Inhibition Differentially Affects Bone and Skeletal Muscle in Middle-Aged Mice. *Bone* **2019**, *124*, 89–102. [CrossRef] [PubMed]

107. Dozio, E.; Vettoretti, S.; Lungarella, G.; Messa, P.; Romanelli, M.M.C. Sarcopenia in Chronic Kidney Disease: Focus on Advanced Glycation End Products as Mediators and Markers of Oxidative Stress. *Biomedicines* **2021**, *9*, 405. [CrossRef] [PubMed]

108. Kato, M.; Kubo, A.; Sugioka, Y.; Mitsui, R.; Fukuhara, N.; Nihei, F.; Takeda, Y. Relationship between Advanced Glycation End-Product Accumulation and Low Skeletal Muscle Mass in Japanese Men and Women. *Geriatr. Gerontol. Int.* **2017**, *17*, 785–790. [CrossRef]

109. Semba, R.D.; Bandinelli, S.; Sun, K.; Guralnik, J.M.; Ferrucci, L. Relationship of an Advanced Glycation End Product, Plasma Carboxymethyl-Lysine, with Slow Walking Speed in Older Adults: The InCHIANTI Study. *Eur. J. Appl. Physiol.* **2010**, *108*, 191–195. [CrossRef]

110. Proud, C.G. Regulation of Protein Synthesis by Insulin. *Biochem. Soc. Trans.* **2006**, *34*, 213–216. [CrossRef]

111. Sandu, O.; Song, K.; Cai, W.; Zheng, F.; Uribarri, J.; Vlassara, H. Insulin Resistance and Type 2 Diabetes in High-Fat-Fed Mice Are Linked to High Glycotoxin Intake. *Diabetes* **2005**, *54*, 2314–2319. [CrossRef]

112. Stenvinkel, P.; Heimbürger, O.; Lindholm, B.; Kaysen, G.A.; Bergström, J. Are There Two Types of Malnutrition in Chronic Renal Failure? Evidence for Relationships between Malnutrition, Inflammation and Atherosclerosis (MIA Syndrome). *Nephrol. Dial. Transplant.* **2000**, *15*, 953–960. [CrossRef]

113. Carrero, J.J.; Stenvinkel, P.; Cuppari, L.; Ikizler, T.A.; Kalantar-Zadeh, K.; Kaysen, G.; Mitch, W.E.; Price, S.R.; Wanner, C.; Wang, A.Y.M.; et al. Etiology of the Protein-Energy Wasting Syndrome in Chronic Kidney Disease: A Consensus Statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J. Ren. Nutr.* **2013**, *23*, 77–90. [CrossRef]

114. Semba, R.D.; Arab, L.; Sun, K.; Nicklett, E.J.; Ferrucci, L. Fat Mass Is Inversely Associated with Serum Carboxymethyl-Lysine, an Advanced Glycation End Product, in Adults. *J. Nutr.* **2011**, *141*, 1726–1730. [CrossRef]

115. Suliman, M.E.; Heimbürger, O.; Bárány, P.; Anderstam, B.; Pecoits-Filho, R.; Ayala, E.R.; Qureshi, A.R.; Fehrman-Ekholm, I.; Lindholm, B.; Stenvinkel, P. Plasma Pentosidine Is Associated with Inflammation and Malnutrition in End-Stage Renal Disease Patients Starting on Dialysis Therapy. *J. Am. Soc. Nephrol.* **2003**, *14*, 1614–1622. [CrossRef]

116. Nediani, C.; Dinu, M. Oxidative Stress and Inflammation as Targets for Novel Preventive and Therapeutic Approaches in Non-Communicable Diseases II. *Antioxidants* **2022**, *11*, 824. [CrossRef]

117. Flores, E.A.; Bistrian, B.R.; Pomposelli, J.J.; Dinarello, C.A.; Blackburn, G.L.; Istfan, N.W. Infusion of Tumor Necrosis Factor/Cachectin Promotes Muscle Catabolism in the Rat. A Synergistic Effect with Interleukin 1. *J. Clin. Investig.* **1989**, *83*, 1614–1622. [CrossRef]

118. Kalantar-Zadeh, K.; Ikizler, T.A.; Block, G.; Avram, M.M.; Kopple, J.D. Malnutrition-Inflammation Complex Syndrome in Dialysis Patients: Causes and Consequences. *Am. J. Kidney Dis.* **2003**, *42*, 864–881. [CrossRef]

119. Gabay, C.; Kushner, I. Acute-Phase Proteins and Other Systemic Responses to Inflammation. *N. Engl. J. Med.* **1999**, *340*, 448–454. [CrossRef]

120. Caldiroli, L.; Molinari, P.; Dozio, E.; Rigolini, R.; Giubbilini, P.; Romanelli, M.M.C.; Castellano, G.; Vettoretti, S. In Patients with Chronic Kidney Disease Advanced Glycation End-Products Receptors Isoforms (SRAGE and EsRAGE) Are Associated with Malnutrition. *Antioxidants* **2022**, *11*, 1253. [CrossRef]

121. Uribarri, J.; Woodruff, S.; Goodman, S.; Cai, W.; Chen, X.; Pyzik, R.; Yong, A.; Striker, G.E.; Vlassara, H. Advanced Glycation End Products in Foods and a Practical Guide to Their Reduction in the Diet. *J. Am. Diet. Assoc.* **2010**, *110*, 911–916.e12. [CrossRef]

122. Dual Responses to Increase Validity in Case-Control Studies. Available online: https://pubmed.ncbi.nlm.nih.gov/2181566/ (accessed on 24 January 2023).

123. Prasad, K.; Dhar, I.; Caspar-Bell, G. Role of Advanced Glycation End Products and Its Receptors in the Pathogenesis of Cigarette Smoke-Induced Cardiovascular Disease. *Int. J. Angiol.* **2015**, *24*, 75–80. [CrossRef]

124. Fotheringham, A.K.; Gallo, L.A.; Borg, D.J.; Forbes, J.M. Advanced Glycation End Products (AGEs) and Chronic Kidney Disease: Does the Modern Diet AGE the Kidney? *Nutrients* **2022**, *14*, 2675. [CrossRef]

125. Yacoub, R.; Nugent, M.; Cai, W.; Nadkarni, G.N.; Chaves, L.D.; Abyad, S.; Honan, A.M.; Thomas, S.A.; Zheng, W.; Valiyaparambil, S.A.; et al. Advanced Glycation End Products Dietary Restriction Effects on Bacterial Gut Microbiota in Peritoneal Dialysis Patients; a Randomized Open Label Controlled Trial. *PLoS ONE* **2017**, *12*, e0184789. [CrossRef] [PubMed]

126. Margiotta, E.; Caldiroli, L.; Callegari, M.L.; Miragoli, F.; Zanoni, F.; Armelloni, S.; Rizzo, V.; Messa, P.; Vettoretti, S. Association of Sarcopenia and Gut Microbiota Composition in Older Patients with Advanced Chronic Kidney Disease, Investigation of the Interactions with Uremic Toxins, Inflammation and Oxidative Stress. *Toxins* **2021**, *13*, 472. [CrossRef] [PubMed]

127. Nenna, A.; Nappi, F.; Avtaar Singh, S.; Sutherland, F.; di Domenico, F.; Chello, M.; Spadaccio, C. Pharmacologic Approaches Against Advanced Glycation End Products (AGEs) in Diabetic Cardiovascular Disease. *Res. Cardiovasc. Med.* **2015**, *4*, 5. [CrossRef]

128. Sarmah, S.; Roy, A.S. A Review on Prevention of Glycation of Proteins: Potential Therapeutic Substances to Mitigate the Severity of Diabetes Complications. *Int. J. Biol. Macromol.* **2022**, *195*, 565–588. [CrossRef] [PubMed]

129. Sourris, K.C.; Watson, A.; Jandeleit-Dahm, K. Inhibitors of Advanced Glycation End Product (AGE) Formation and Accumulation. *Handb. Exp. Pharmacol.* **2021**, *264*, 395–423. [CrossRef]

130. Ojima, A.; Matsui, T.; Nishino, Y.; Nakamura, N.; Yamagishi, S. Empagliflozin, an Inhibitor of Sodium-Glucose Cotransporter 2 Exerts Anti-Inflammatory and Antifibrotic Effects on Experimental Diabetic Nephropathy Partly by Suppressing AGEs-Receptor Axis. *Horm. Metab. Res.* **2015**, *47*, 686–692. [CrossRef]

131. Prasad, K.; Bhanumathy, K.K. AGE-RAGE Axis in the Pathophysiology of Chronic Lower Limb Ischemia and a Novel Strategy for Its Treatment. *Int. J. Angiol.* **2020**, *29*, 156–167. [CrossRef]

132. Prasad, K. Pathophysiology and Medical Treatment of Carotid Artery Stenosis. *Int. J. Angiol.* **2015**, *24*, 158–172. [CrossRef]

133. Burstein, A.H.; Sabbagh, M.; Andrews, R.; Valcarce, C.; Dunn, I.; Altstiel, L. Development of Azeliragon, an Oral Small Molecule Antagonist of the Receptor for Advanced Glycation Endproducts, for the Potential Slowing of Loss of Cognition in Mild Alzheimer's Disease. *J. Prev. Alzheimer Dis.* **2018**, *5*, 149–154. [CrossRef]

134. Tam, H.L.; Shiu, S.W.M.; Wong, Y.; Chow, W.S.; Betteridge, D.J.; Tan, K.C.B. Effects of Atorvastatin on Serum Soluble Receptors for Advanced Glycation End-Products in Type 2 Diabetes. *Atherosclerosis* **2010**, *209*, 173–177. [CrossRef]

135. Forbes, J.M.; Thorpe, S.R.; Thallas-Bonke, V.; Pete, J.; Thomas, M.C.; Deemer, E.R.; Bassal, S.; El-Osta, A.; Long, D.M.; Panagiotopoulos, S.; et al. Modulation of Soluble Receptor for Advanced Glycation End Products by Angiotensin-Converting Enzyme-1 Inhibition in Diabetic Nephropathy. *J. Am. Soc. Nephrol.* **2005**, *16*, 2363–2372. [CrossRef]

136. Tan, K.C.B.; Chow, W.S.; Tso, A.W.K.; Xu, A.; Tse, H.F.; Hoo, R.L.C.; Betteridge, D.J.; Lam, K.S.L. Thiazolidinedione Increases Serum Soluble Receptor for Advanced Glycation End-Products in Type 2 Diabetes. *Diabetologia* **2007**, *50*, 1819–1825. [CrossRef]

137. Sakaguchi, T.; Yan, S.F.; du Yan, S.; Belov, D.; Rong, L.L.; Sousa, M.; Andrassy, M.; Marso, S.P.; Duda, S.; Arnold, B.; et al. Central Role of RAGE-Dependent Neointimal Expansion in Arterial Restenosis. *J. Clin. Investig.* **2003**, *111*, 959–972. [CrossRef]

138. Xue, M.; Weickert, M.O.; Qureshi, S.; Kandala, N.B.; Anwar, A.; Waldron, M.; Shafie, A.; Messenger, D.; Fowler, M.; Jenkins, G.; et al. Improved Glycemic Control and Vascular Function in Overweight and Obese Subjects by Glyoxalase 1 Inducer Formulation. *Diabetes* **2016**, *65*, 2282–2294. [CrossRef]

139. CERF, O.; METRO, F. Tailing of Survival Curves of Bacillus Licheniformis Spores Treated with Hydrogen Peroxide. *J. Appl. Bacteriol.* **1977**, *42*, 405–415. [CrossRef]

140. Little, W.C.; Zile, M.R.; Kitzman, D.W.; Hundley, W.G.; O'Brien, T.X.; Degroof, R.C. The Effect of Alagebrium Chloride (ALT-711), a Novel Glucose Cross-Link Breaker, in the Treatment of Elderly Patients with Diastolic Heart Failure. *J. Card. Fail.* **2005**, *11*, 191–195. [CrossRef]

141. Fujimoto, N.; Hastings, J.L.; Carrick-Ranson, G.; Shafer, K.M.; Shibata, S.; Bhella, P.S.; Abdullah, S.M.; Barkley, K.W.; Adams-Huet, B.; Boyd, K.N.; et al. Cardiovascular Effects of 1 Year of Alagebrium and Endurance Exercise Training in Healthy Older Individuals. *Circ. Heart Fail.* **2013**, *6*, 1155–1164. [CrossRef]

142. Bolton, W.K.; Cattran, D.C.; Williams, M.E.; Adler, S.G.; Appel, G.B.; Cartwright, K.; Foiles, P.G.; Freedman, B.I.; Raskin, P.; Ratner, R.E.; et al. Randomized Trial of an Inhibitor of Formation of Advanced Glycation End Products in Diabetic Nephropathy. *Am. J. Nephrol.* **2004**, *24*, 32–40. [CrossRef]

143. Freedman, B.I.; Wuerth, J.P.; Cartwright, K.; Bain, R.P.; Dippe, S.; Hershon, K.; Mooradian, A.D.; Spinowitz, B.S. Design and Baseline Characteristics for the Aminoguanidine Clinical Trial in Overt Type 2 Diabetic Nephropathy (ACTION II). *Control. Clin. Trials* **1999**, *20*, 493–510. [CrossRef]

144. Stirban, A.; Negrean, M.; Stratmann, B.; Gawlowski, T.; Horstmann, T.; Götting, C.; Kleesiek, K.; Mueller-Roesel, M.; Koschinsky, T.; Uribarri, J.; et al. Benfotiamine Prevents Macro- and Microvascular Endothelial Dysfunction and Oxidative Stress Following a Meal Rich in Advanced Glycation End Products in Individuals with Type 2 Diabetes. *Diabetes Care* **2006**, *29*, 2064–2071. [CrossRef]

145. Elbarbary, N.S.; Ismail, E.A.R.; El-Naggar, A.R.; Hamouda, M.H.; El-Hamamsy, M. The Effect of 12 Weeks Carnosine Supplementation on Renal Functional Integrity and Oxidative Stress in Pediatric Patients with Diabetic Nephropathy: A Randomized Placebo-Controlled Trial. *Pediatr. Diabetes* **2018**, *19*, 470–477. [CrossRef] [PubMed]

146. Yamagishi, S.I.; Inagaki, Y.; Okamoto, T.; Amano, S.; Koga, K.; Takeuchi, M. Advanced Glycation End Products Inhibit de Novo Protein Synthesis and Induce TGF-Beta Overexpression in Proximal Tubular Cells. *Kidney Int.* **2003**, *63*, 464–473. [CrossRef] [PubMed]

147. Williams, M.E.; Bolton, W.K.; Khalifah, R.G.; Degenhardt, T.P.; Schotzinger, R.J.; McGill, J.B. Effects of Pyridoxamine in Combined Phase 2 Studies of Patients with Type 1 and Type 2 Diabetes and Overt Nephropathy. *Am. J. Nephrol.* **2007**, *27*, 605–614. [CrossRef] [PubMed]

148. Rabbani, N.; Alam, S.S.; Riaz, S.; Larkin, J.R.; Akhtar, M.W.; Shafi, T.; Thornalley, P.J. High-Dose Thiamine Therapy for Patients with Type 2 Diabetes and Microalbuminuria: A Randomised, Double-Blind Placebo-Controlled Pilot Study. *Diabetologia* **2009**, *52*, 208–212. [CrossRef] [PubMed]

149. Šebeková, K.; Gazdíková, K.; Syrová, D.; Blažíček, P.; Schinzel, R.; Heidland, A.; Spustová, V.; Dzúrik, R. Effects of Ramipril in Nondiabetic Nephropathy: Improved Parameters of Oxidatives Stress and Potential Modulation of Advanced Glycation End Products. *J. Hum. Hypertens.* **2003**, *17*, 265–270. [CrossRef]

150. Cuccurullo, C.; Iezzi, A.; Fazia, M.L.; de Cesare, D.; di Francesco, A.; Muraro, R.; Bei, R.; Ucchino, S.; Spigonardo, F.; Chiarelli, F.; et al. Suppression of RAGE as a Basis of Simvastatin-Dependent Plaque Stabilization in Type 2 Diabetes. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 2716–2723. [CrossRef]

151. Nakamura, T.; Sato, E.; Fujiwara, N.; Kawagoe, Y.; Takeuchi, M.; Maeda, S.; Yamagishi, S.I. Atorvastatin Reduces Proteinuria in Non-Diabetic Chronic Kidney Disease Patients Partly via Lowering Serum Levels of Advanced Glycation End Products (AGEs). *Oxid. Med. Cell. Longev.* **2010**, *3*, 304–307. [CrossRef]

152. Komiya, N.; Hirose, H.; Saisho, Y.; Saito, I.; Itoh, H. Effects of 12-Month Valsartan Therapy on Glycation and Oxidative Stress Markers in Type 2 Diabetic Subjects with Hypertension. *Int. Heart J.* **2008**, *49*, 681–689. [CrossRef]

153. Ono, Y.; Mizuno, K.; Takahashi, M.; Miura, Y.; Watanabe, T. Suppression of Advanced Glycation and Lipoxidation End Products by Angiotensin II Type-1 Receptor Blocker Candesartan in Type 2 Diabetic Patients with Essential Hypertension. *Fukushima J. Med. Sci.* **2013**, *59*, 69–75. [CrossRef]

154. Ishibashi, Y.; Matsui, T.; Takeuchi, M.; Yamagishi, S. Metformin Inhibits Advanced Glycation End Products (AGEs)-Induced Renal Tubular Cell Injury by Suppressing Reactive Oxygen Species Generation via Reducing Receptor for AGEs (RAGE) Expression. *Horm. Metab. Res.* **2012**, *44*, 891–895. [CrossRef]

155. Zhou, Z.; Tang, Y.; Jin, X.; Chen, C.; Lu, Y.; Liu, L.; Shen, C. Metformin Inhibits Advanced Glycation End Products-Induced Inflammatory Response in Murine Macrophages Partly through AMPK Activation and RAGE/NF κ B Pathway Suppression. *J. Diabetes Res.* **2016**, *2016*, 4847812. [CrossRef] [PubMed]

156. Afsar, B.; Afsar, R.E. Sodium-Glucose Cotransporter Inhibitors and Kidney Fibrosis: Review of the Current Evidence and Related Mechanisms. *Pharmacol. Rep.* **2023**, *75*, 44–68. [CrossRef] [PubMed]

157. Zhang, J.; Han, X.; Chang, J.; Liu, J.; Liu, Y.; Wang, H.; Du, F.; Zeng, X.; Guo, C. Soluble RAGE Attenuates Myocardial I/R Injuries via FoxO3-Bnip3 Pathway. *Cell. Mol. Life Sci.* **2022**, *79*, 269. [CrossRef] [PubMed]

158. Jeong, J.; Cho, S.; Seo, M.; Lee, B.S.; Jang, Y.; Lim, S.; Park, S. Soluble RAGE Attenuates Ang II-Induced Arterial Calcification via Inhibiting AT1R-HMGB1-RAGE Axis. *Atherosclerosis* **2022**, *346*, 53–62. [CrossRef]

159. Scavello, F.; Zeni, F.; Milano, G.; Macrì, F.; Castiglione, S.; Zuccolo, E.; Scopece, A.; Pezone, G.; Tedesco, C.C.; Nigro, P.; et al. Soluble Receptor for Advanced Glycation End-Products Regulates Age-Associated Cardiac Fibrosis. *Int. J. Biol. Sci.* **2021**, *17*, 2399–2416. [CrossRef]

160. Oz Gul, O.; Tuncel, E.; Yilmaz, Y.; Ulukaya, E.; Gul, C.B.; Kiyici, S.; Oral, A.Y.; Guclu, M.; Ersoy, C.; Imamoglu, S. Comparative Effects of Pioglitazone and Rosiglitazone on Plasma Levels of Soluble Receptor for Advanced Glycation End Products in Type 2 Diabetes Mellitus Patients. *Metabolism* **2010**, *59*, 64–69. [CrossRef]

161. Gada, E.; Owens, A.W.; Gore, M.O.; See, R.; Abdullah, S.M.; Ayers, C.R.; Rohatgi, A.; Khera, A.; de Lemos, J.A.; McGuire, D.K. Discordant Effects of Rosiglitazone on Novel Inflammatory Biomarkers. *Am. Heart J.* **2013**, *165*, 609–614. [CrossRef]

162. Poojary, M.M.; Zhang, W.; Greco, I.; de Gobba, C.; Olsen, K.; Lund, M.N. Liquid Chromatography Quadrupole-Orbitrap Mass Spectrometry for the Simultaneous Analysis of Advanced Glycation End Products and Protein-Derived Cross-Links in Food and Biological Matrices. *J. Chromatogr. A* **2020**, *1615*, 460767. [CrossRef]

163. Perrone, A.; Giovino, A.; Benny, J.; Martinelli, F. Advanced Glycation End Products (AGEs): Biochemistry, Signaling, Analytical Methods, and Epigenetic Effects. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 3818196. [CrossRef]