

# Advanced Glycation End Products in Clinical Nephrology

M. Kalousová<sup>a,b</sup> T. Zima<sup>b</sup> V. Tesař<sup>c</sup> S. Štípek<sup>a</sup> S. Sulková<sup>d</sup>

<sup>a</sup>Institute of Medical Biochemistry, <sup>b</sup>Institute of Clinical Chemistry, <sup>c</sup>1st Department of Medicine, and

<sup>d</sup>Department of Medicine Strahov, 1st Faculty of Medicine and University Hospital, Charles University, Prague, Czech Republic

## Key Words

Advanced glycation end products · Hemodialysis · Diabetes mellitus · Oxidative stress · Carbonyl stress · Inflammation · Receptor for advanced glycation end products · Angiotensin-converting enzyme inhibitors

## Abstract

As a result of oxidative and carbonyl stress, advanced glycation end products (AGEs) are involved in the pathogenesis of severe and frequent diseases and their fatal vascular/cardiovascular complications, i.e. diabetes mellitus and its complications (nephropathy, angiopathy, neuropathy and retinopathy, renal failure and uremic and dialysis-associated complications), atherosclerosis and dialysis-related amyloidosis, neurodegenerative diseases, and rheumatoid arthritis. They are formed via non-enzymatic glycation which is specifically enhanced through the presence of oxidative and carbonyl stress, and their ability to form glycoxidation products in peptide and protein structures finally modulating or inducing biological reactivity. Food can be another source of AGEs; however, high serum AGEs in hemodialysis patients might reflect nutritional status better. Several methods of renal replacement therapy have been studied in connection with the AGE removal, but unfortunately the possibilities are still unsatisfactory even if high flux dialysis, hemofiltration, or hemodiafiltration give better

results than conventional low flux dialysis. AGEs are currently being studied in the patients on peritoneal dialysis as their precursors can be formed in the dialysis fluid. AGEs can cause damage to the peritoneum and so a loss of ultrafiltration capacity. Many compounds give promising results in AGE inhibition (inhibition of formation of AGEs, inhibition of their action or degradation of AGEs), are tested for these properties, and eventually undergo clinical studies (e.g. aminoguanidine, OPB-9195, pyridoxamine, antioxidants, N-phenacylthiazolium bromide, antihypertensive drugs, angiotensin-converting enzyme inhibitors and angiotensin II receptor-1 antagonists).

Copyright © 2004 S. Karger AG, Basel

In 1912, advanced glycation end products (AGEs) were described for the first time by the French chemist Maillard [1] who observed the formation of brown matter when heating mixtures of sugars and amino acids. These compounds were first studied by food chemists, but later on they were shown to be at least partly responsible for the development of diabetic complications [2, 3]. In addition, their plasma levels were found to be markedly elevated in uremic patients [4] and were described as new uremic toxins [5]. Moreover they accumulate in the nervous tissue in neurodegenerative diseases [6], and their significance is also being discussed in other ailments and pathological states, e.g. rheumatoid arthritis [7] or chronic pulmonary

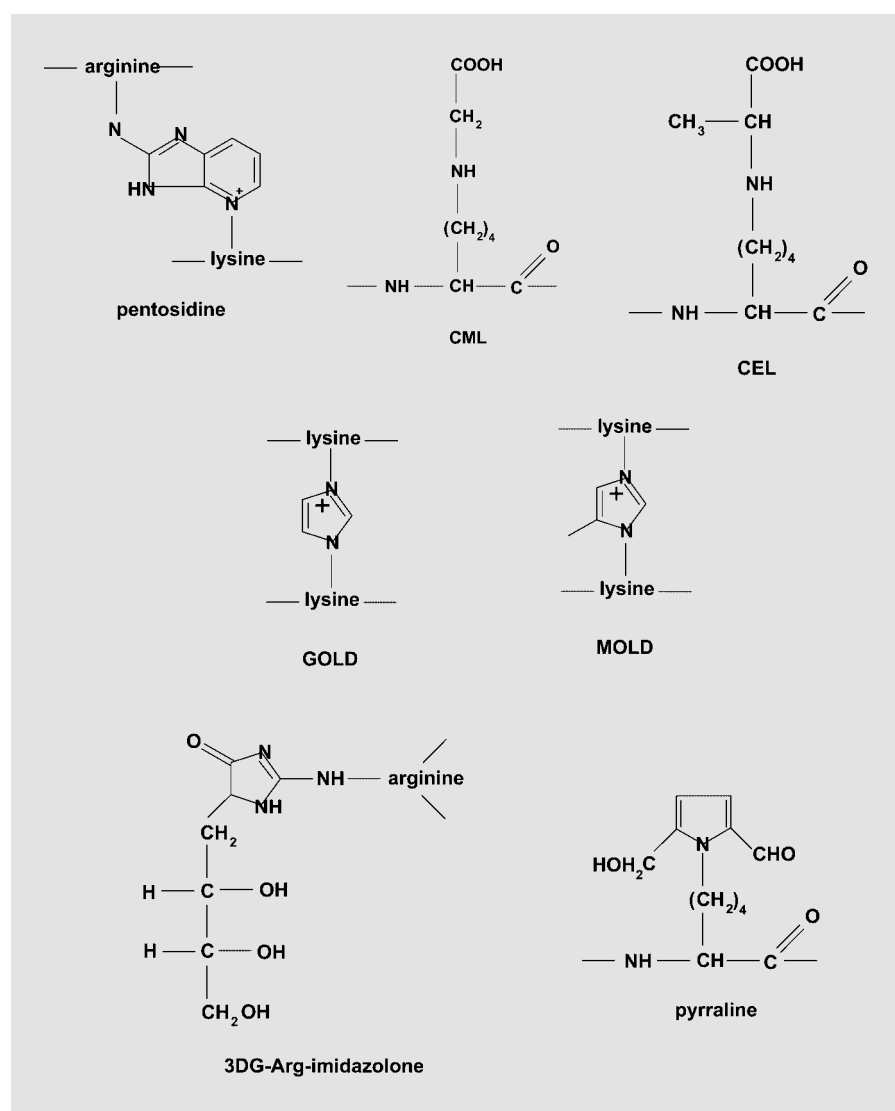
## KARGER

Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

© 2004 S. Karger AG, Basel  
1420–4096/04/0271–0018\$21.00/0

Accessible online at:  
[www.karger.com/kbr](http://www.karger.com/kbr)

M. Kalousová, MD, PhD  
Institute of Medical Biochemistry  
1st Faculty of Medicine, Charles University  
Kateřinská 32, CZ–121 08 Prague 2 (Czech Republic)  
Tel. +420 224964285, Fax +420 224964280, E-Mail [mkalousova@hotmail.com](mailto:mkalousova@hotmail.com)



**Fig. 1.** Structure of AGEs.

diseases [8]. Nevertheless, AGEs are formed in the body under physiological conditions and their formation increases with the age [9].

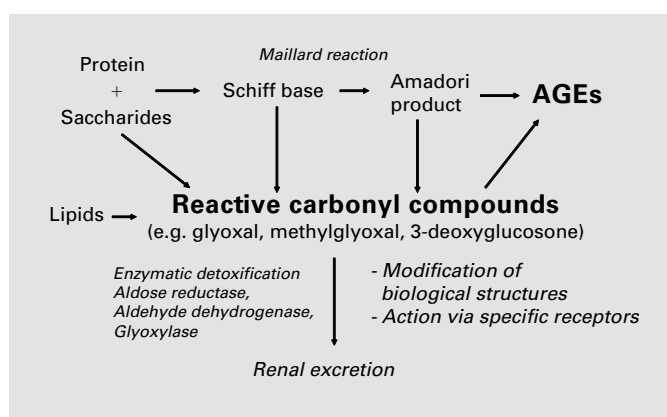
### General Characteristics

AGEs are a group of heterogeneous substances that can modify proteins both in plasma and tissues. The structure of many AGEs is unknown, but some of them were described as model AGEs and new AGE structures are presently being characterized (fig. 1). However, only some of them have pathophysiological function in the organism. The best known AGEs are: pentosidine, N<sup>ε</sup>-carboxy-

methyllsine (CML), N<sup>ε</sup>-carboxyethyllysine (CEL), glyoxal-lysine dimer (GOLD), methylglyoxal lysine dimer (MOLD), imidazolone (3-deoxyglucosone-arginine-imidazolone), and pyrraline [10–12]. The yellow-brown pigmentation, fluorescence, and cross-linking ability are the main characteristic properties of AGEs [13]. However, some AGEs are non-fluorescent and are devoid of cross-linking ability (e.g. CML) [12].

### Formation of AGEs and Their Metabolism

Formation of AGEs as well as their degradation are complex processes. AGEs are sometimes described as Maillard products, as they are products of the classical Maillard reaction (non-enzymatic glycation) [1]. Their



**Fig. 2.** Formation of AGEs and reactive carbonyl compounds.

formation is enhanced in the presence of oxidative and carbonyl stress [14, 15]. In addition, food [16] and tobacco smoke [17] can represent exogenous sources of AGE precursors. AGEs and their precursors can be detoxified by specific enzymes, e.g. reductases [18, 19], degraded by macrophages, excreted by the kidney [20] or may accumulate in tissues. Decreased renal function [4] as well as altered liver function [21] may contribute to their increased levels. The mechanisms mentioned above are interconnected and determine the amount of AGEs in the organism. In the following, we would like to briefly characterize each of them.

**Non-Enzymatic Glycation (Maillard Reaction).** This starts with the bonding of an aldehyde group of a reducing sugar to an amino group of a protein. In this way, a reversible Schiff base is formed. This phase depends on the blood glucose concentration. The Schiff base can be rearranged into an Amadori product (partially reversible) which can be determined as fructosamine (mainly glycated albumin) and glycated hemoglobin (fig. 2). Both are routinely measured in patients with diabetes mellitus in order to monitor long-term treatment. In the late phase, during weeks or months, independent of the sugar concentration, via condensation, dehydration, fragmentation and cyclization, AGEs arise [22]. AGEs can be formed from various sugars, both intra- and extracellular (e.g. glucose, fructose, threose, glucose-6-phosphate, glyceraldehyde-3-phosphate) [23, 24]. This classical pathway is sometimes also called the Hodge pathway [25] and is highly important mainly in diabetes mellitus.

**Oxidative Stress.** This is characterized as an imbalance between reactive oxygen and nitrogen species or free radicals and antioxidants in favor of free radicals. Oxidative

stress is enhanced both in hyperglycemia and uremia and contributes to increased AGE formation [15, 18]. Auto-oxidation of sugars as well as that of the Schiff base and Amadori product can give reactive carbonyl compounds which can form AGEs (so-called Wolf and Namiki pathways) [25]. Via reactive carbonyl compounds, lipoperoxidation of polyunsaturated fatty acids can also result in AGE formation. This pathway can even be enhanced by metal-catalyzed reactions [26]. Due to these two formation possibilities, glycation and oxidation, the products arising are sometimes called glycoxidation products [27].

**Carbonyl Stress.** In the last years, in addition to oxidative stress, attention has also been given to carbonyl stress, which is enhanced in uremia. Miyata et al. [18] characterize carbonyl stress as a reactive carbonyl compound overload, which can be caused by increased formation and/or decreased clearance or detoxification of reactive carbonyl compounds [28]. These compounds are highly reactive aldehydes ( $-CHO$ ) or contain an  $\alpha$ -dicarbonyl group ( $-CO-CHO$ ) [29]. Reactive carbonyl compounds can be derived from carbohydrates, lipids, and amino acids both by oxidative and non-oxidative pathways, can be detoxified by several enzymes and excreted by the kidneys in relation to their function. Through auto-oxidation of sugars and ascorbate, glyoxal, glycolaldehyde and dehydroascorbate can be formed. Degradation of fructose-3-phosphate and triosophosphates gives 3-deoxyglucosone and methylglyoxal (non-oxidative pathway). Amino acids can be a source of glyoxal, methylglyoxal, acrolein and glycolaldehyde [14]. These carbonyl compounds react non-enzymatically with the amino group of proteins, give rise to reversible Schiff base and, during rearrangement, Amadori products and AGEs are formed, e.g. CML, pentosidine, pyrraline, imidazolone, GOLD and MOLD [18]. Polyunsaturated fatty acids as arachidonate can be a source of malondialdehyde, hydroxynonenal, acrolein and glyoxal, which have been known for several years as lipoperoxidation products. Miyata et al. [14] describe these compounds as reactive carbonyl compounds as well. They can bind to proteins and so form advanced lipoperoxidation end products (ALEs), e.g. malondialdehyde lysine, hydroxynonenal and acrolein-protein adducts, as well as AGEs (e.g. CML) [14]. Removal of reactive carbonyl compounds might rely on renal function as they have a rather low molecular weight [30]. In addition, reactive carbonyl compounds can be detoxified by a number of enzymes, e.g. aldose reductase, aldehyde dehydrogenase and glyoxylase which require redox coenzymes (GSH or NAD(P)H) [19, 31]. Pentosidine and CML levels in hemodialysis patients, in contrast to diabetic patients,

do not correlate with the levels of fructosamine. This finding seems to be related to the elevated AGE levels in uremic patients, both diabetic and non-diabetic, which are severalfold higher than in diabetic patients with normal renal function. The elevation is supposed to be the consequence of raised levels of reactive carbonyl compounds apart from other above-mentioned mechanisms [14].

**Food.** Food can be another source of AGEs and their precursors (that is why the term 'glycotoxins' was used for AGEs). It was demonstrated in animal models that AGE modified the diet for up to 12 months and chronic infusion of AGEs resulted in accumulation of pigments in the kidney and liver and in accelerated diabetes-like vascular and renal lesions [16]. It is now accepted that only a minor part (10%) of ingested AGEs, mainly low molecular weight food-derived AGEs, is absorbed into the circulation and from this about 30% is excreted via the kidney and feces [32]. The drawback of most human and animal studies is that artificial model AGE mixtures were administered. Moreover, food chemists claim that certain food-derived AGEs even possess antioxidant properties, i.e. free radical scavenging capacity in vitro [33]. The fate of the majority of orally absorbed AGEs remains unclear. It is questionable whether the absorbed AGEs exert their antioxidant activities even after absorption into the circulation and how the food-derived AGEs contribute to the toxicity of endogenously formed AGEs. However, the healthy kidney should remove part of the food-derived AGEs efficiently, but the renal excretion of orally absorbed AGEs is markedly suppressed in decreased renal function, e.g. diabetic nephropathy patients. Dietary restriction of AGE food intake may greatly reduce the burden of AGEs in diabetic and renal failure patients and possibly improve prognosis [16, 34, 35]. However, recent clinical data surprisingly show that high AGE levels in renal failure patients might better reflect the nutritional status and indicate a better prognosis [36].

AGEs can bind to specific receptors on various cells. After binding of AGE-modified proteins to macrophage receptors, they are engulfed and degraded to small AGE peptides which are released into the circulation and excreted by the kidney [20, 37]. Urinary AGE clearance correlates directly with creatinine clearance. In altered renal function, their excretion is slowed down and these fragments can react with various proteins, modify them and so form the so-called second generation of AGEs. This process is known as recycling [20].

It is thought that free AGEs and AGE peptides are filtered by renal glomeruli, reabsorbed in proximal tubuli where they are degraded or modified and finally excreted

into the urine. Their clearance is 0.7 ml/min [38]. Unfortunately, more than 90% of AGEs are protein-bound and cannot undergo this process [39]. So they remain in the body and modify tissue proteins.

#### *Effects of AGEs and AGE-RAGE Interaction in the Organism*

Tissue accumulation of AGEs in the organism has several toxic effects. Some effects are also ascribed to Amadori adducts on proteins [40, 41]. AGEs can either directly damage the structure of the extracellular matrix, change its physical and chemical properties and metabolism and cause cross-linking [20], quench the action of nitric oxide [23], induce lipoperoxidation [3, 42], or act via AGE-specific receptors. Several receptors for AGEs have been described: RAGE (specific receptor for AGEs), P60/OST-48 protein (AGE-R1), 80 K-H phosphoprotein (AGE-R2), galectin (AGE-R3) and other AGE-binding proteins, such as the scavenger receptor [43]. RAGE, the best known and characterized, has been isolated and cloned from bovine lung and has been classified as a member of the immunoglobulin superfamily. RAGE can be expressed on the surface of various cells (e.g. monocytes, macrophages, mesangial cells, neurons, endothelial cells, smooth muscle cells and fibroblasts), sometimes after stimulation of growth factors, e.g. TNF- $\alpha$  [43–48]. After interaction of AGEs with their receptor, signaling involving P21<sup>ras</sup>, MAP-kinase and nuclear factor- $\kappa$ B is activated [44, 49]. This is connected with oxidative stress [50]. Subsequently, the AGE-RAGE interaction results in the stimulation of transcription of genes for cytokines and growth factors (TNF, IL-1, PDGF, IGF-1, interferon- $\gamma$ ), and adhesion molecules (ICAM-1, VCAM-1), stimulation of cell proliferation, increase in vascular permeability, induction of migration of macrophages, stimulation of endothelin-1 formation, downregulation of thrombomodulin, increased synthesis of collagen IV, fibronectin and proteoglycans, increased synthesis of pro-coagulant tissue factor, etc. [42, 44, 51].

RAGE also has other ligands (e.g. S100 protein, amyloid- $\beta$  peptide) and other functions, it is important for the development of the central nervous system. During maturation, its presence decreases. In adults, it is involved in the regulation of anti-inflammatory processes [52]. Its increased expression is connected with pathological states, e.g. diabetic vasculopathy, nephropathy, retinopathy and neuropathy, Alzheimer's disease and immune inflammation of the vessel wall [48, 50, 53].

## Specific Features of AGEs in Nephrology

In patients with decreased renal function, serum AGEs are elevated severalfold more than in patients with diabetes mellitus and normal renal function. AGE fluorescence is increased 3- to 4-fold [54], CML 3-fold [55] and pentosidine even 10-fold in comparison to healthy subjects [4, 56]. The serum levels of AGEs correlate with the accumulation of AGEs in the organs [57].

The AGE increase in renal insufficiency cannot only be explained by their formation through the classical glycation pathway or their decreased renal excretion. Both oxidative and carbonyl stresses seem to play an important role in their formation [14]. Many experiments have shown increased oxidative stress in renal failure, e.g. increased serum levels of lipoperoxidation products [18] as well as advanced oxidation protein products [58]. Moreover, the patients with end-stage renal disease often have decreased antioxidant defense, enzymes and their cofactors Zn, Se, and vitamins [59]. There is also evidence for carbonyl stress in uremia, which is characterized by reactive carbonyl compounds overload. Carbonyl compounds derived from carbohydrates and lipids are thought to be a source of both AGEs and ALEs. AGEs are elevated both in patients with renal failure and in patients on renal replacement therapy, both hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) [4, 60, 61]. In addition to the classical mechanisms of formation, the AGE increase in the patients on maintenance hemodialysis is probably due to the interaction of blood with the dialysis membrane, and in CAPD patients possibly due to exposition to glucose and its degradation products in the peritoneal dialysis fluid [62].

Similar to Miyata et al. [19], we observed enormous levels of pentosidine in the serum of one hemodialyzed patient (5-fold elevation in comparison to other hemodialyzed patients and 50-fold elevation in comparison to healthy subjects; unpubl. data). However, the characteristic AGE fluorescence was similar to other hemodialyzed patients. This rarity could be explained by glyoxylase deficiency [19].

### *AGEs in Patients with Renal Insufficiency and Diabetes mellitus*

Glycoxidation in patients with renal insufficiency and diabetes mellitus is enhanced due to hyperglycemia as well as oxidative and carbonyl stress. The AGE increase can be found both in the serum and tissues, and the serum AGE level correlates with the severity of organ injury (glomerular lesions) [57]. They contribute to the development

of diabetic complications, nephropathy, micro- and macroangiopathy, neuropathy, retinopathy, modification of coagulation factors, etc. [20, 23, 45]. Diabetic nephropathy is a typical late complication of poorly compensated diabetes mellitus and its development depends on blood glucose concentration. It is characterized by enlargement of the mesangial matrix, deposits in the basement membrane, increased vascular permeability, changing proteins of the basement membrane with a subsequent change of the charge and permeability, etc. [20, 23, 63].

Nevertheless, the view on their serum levels is still controversial, as some authors report no difference in the serum AGE level in the patients with and without diabetes mellitus on chronic dialysis treatment [9, 64, 65]. On the other hand, Makita et al. [38] and Vlassara [66] described higher AGE levels in dialyzed patients with diabetes mellitus, which is in line with our finding in a large cohort of patients [67]. We described the same magnitude in difference of the serum fluorescent AGE levels between hemodialyzed patients with and without diabetes mellitus (22.7%) and patients with diabetes mellitus and normal renal function and healthy subjects (22.6%). Our finding indicates the same contribution of the presence of diabetes mellitus on the AGE level independent of renal function [67]. However, unlike patients with type-1 diabetes with normal renal function [68], AGEs do not correlate with the parameters of compensation of the carbohydrate metabolism in diabetes mellitus, i.e. glucose and glycated hemoglobin HbA1c. However, the composition of AGEs in diabetic patients is different – Henle et al. [61] described a significantly higher fluorescence of the low molecular weight fraction (below 2 kD) and higher pre-dialysis plasma concentrations of the Amadori product fructose lysine (a major precursor of CML) in hemodialyzed diabetics. Similarly, Stein et al. [69] observed higher pre-dialysis AGE peptide concentrations in the diabetic group (contrary to pentosidine). The increased AGE level in hemodialyzed patients with diabetes mellitus might contribute to more pronounced complications and higher morbidity and mortality.

### *AGEs and Long-Term Uremic Complications*

Irreversible non-enzymatic modification of proteins contributes to the development of complications associated with chronic renal failure and dialysis, mainly accelerated atherosclerosis and dialysis-related amyloidosis [70, 71].

As for atherogenesis, AGEs accumulate in the vessel wall and lead, e.g., to protein cross-linking. Increased production of extracellular matrix in the intima causes thick-

ening of the vessel wall and thinning of the lumen. Moreover, quenching of the vasodilatation effect of nitric oxide as well as NO<sup>•</sup>/O<sub>2</sub><sup>-</sup> dysbalance lead to vasoconstriction. Damage to endothelial cells and pro-coagulation activity may lead to thrombosis. Macrophages are stimulated to production of cytokines and growth factors, which are responsible for vascular proliferation [20, 23]. In addition, AGE accumulation is hypothesized to be linked to C-reactive protein (CRP) production which has been shown to be a risk factor for cardiovascular mortality and overall mortality in hemodialysis patients, but it is still unknown whether CRP is involved in atherosclerosis [72]. The complement system also seems to play a role in the genesis of the microinflammatory state and atherogenesis [73]. The action of complement is even potentiated by glycation of its inhibitor protein CD 59 [74]. Moreover, pentosidine is associated with the monocyte activation, which could contribute to accelerated rates of complications and death [75]. Despite the relationship between glycoxidation and inflammation shown in in vitro studies, clinical studies give controversial results as some investigators observed an association between AGEs and cytokines or classical inflammatory markers [58], while others did not [36, 76; for review see, 77]. We also failed to demonstrate any relationship between pentosidine and other fluorescent AGEs to inflammatory markers (C3 and C4 factors of complement, CRP, serum amyloid A protein,  $\alpha_2$ -macroglobulin, fibrinogen and pregnancy-associated protein A), probably due to a complex reaction of the whole organism [78]. Pregnancy-associated protein A was recently described as an exquisite marker of acute coronary syndrome [79], which is why we suppose that AGEs could better describe chronic long-lasting damage than an acute one.

Additionally, low-density lipoprotein (LDL) particles can undergo glycation as well. Glycated LDL is easily oxidized and vice versa. AGE-modified LDL is engulfed by macrophages slower than normal LDL and its lysosomal degradation is slower than that of normal LDL [20, 80]. Accelerated atherosclerosis plays an important role both in renal failure and diabetes mellitus as it increases the cardiovascular risk.

Dialysis-related amyloidosis is another long-term uremic complication.  $\beta_2$ -Microglobulin was proven histologically in amyloid deposits and can be modified by carbonyl stress compounds, e.g. CML [81]. AGE modification of  $\beta_2$ -microglobulin is responsible for monocyte/macrophage attraction which is followed by cytokine release and can result in inflammatory bone and joint destruction which is characteristic for dialysis-related amyloidosis [70].

#### *AGEs: A Prognostic or a Confounding Factor?*

Although it is generally accepted that AGEs take part in the pathogenesis of diabetic as well as uremic and dialysis-related complications (AGEs have shown several toxic effects in in vitro studies and were found in atherosclerotic plaques), high serum levels of AGEs in hemodialysis patients were not linked to increased mortality [36]. It still remains to be elucidated whether high serum AGEs represent only an epiphenomenon or whether they reflect a better nutritional status [36]. Similarly, Stein et al. [82] did not show AGEs as an independent risk factor for cardiovascular events and left ventricular hypertrophy in chronic renal failure patients.

Similarly, in patients after successful renal transplantation, AGE levels remain substantially elevated, not corresponding to the improvement in renal function, although this group of patients generally has a better prognosis if compared with those on dialysis [83–86]. Even heart transplantation is associated with a substantial rise in circulation AGE levels if compared with both healthy controls and patients with chronic heart disease [87].

#### *AGEs and Renal Replacement Therapy*

##### *Hemodialysis and Other Extracorporeal Techniques.*

Conventional methods are not efficient enough in AGE clearance [54]. Short daily dialysis seems to be better in AGE clearance than 4-hour dialysis three times a week [88]. Moreover, dialysis membranes contribute to oxidative stress according to their biocompatibility [89] and so can potentiate formation of AGEs. High-flux dialysis (biocompatible membranes) can bring better results in the reduction of AGEs than low-flux dialysis [56]. They reduce plasma pentosidine but not protein-bound AGEs or Amadori products. So this reduction is most obvious in the low molecular weight fraction [61]. According to Jadoul et al. [30], patients treated with polysulfone membranes have lower plasma levels of both protein-linked and free pentosidine than patients treated with other membranes. Hemofiltration and hemodiafiltration have slightly better results in AGE removal than hemodialysis [90]. Promising results have been obtained by very high-flux dialysis (such as superflux or polyamide), vitamin E-coated low-flux dialyzers and convectional therapies [91]. LDL HELP apheresis (heparin-induced extracorporeal LDL precipitation) may lead to enhanced AGE removal [92].

*CAPD.* Elevation of AGEs can also be observed in peritoneal dialysis patients. In comparison to hemodialysis patients, they have lower serum pentosidine levels, but higher peritoneal pentosidine concentrations and similar

pentosidine concentrations in the skin [60, 93]. The difference in the serum level may be explained by the higher clearance of protein-bound pentosidine in peritoneal dialysis than in hemodialysis [94]. A higher peritoneal concentration of pentosidine in peritoneal dialysis patients is influenced by long-term exposure of the peritoneal membrane to glucose from the dialysis fluids and its glycation [60, 93–96]. AGE accumulation in the mesothelial layer, in the adjacent coarse connective tissue and in the vascular walls of the peritoneum can be observed as early as 3 months after beginning the CAPD therapy [97]. The quality of the peritoneal membrane deteriorates progressively with the duration of peritoneal dialysis and can lead to increased permeability of the peritoneum [98], loss of ultrafiltration capacity [94] and failure of peritoneal dialysis [97, 99]. Heat sterilization of peritoneal dialysis fluids induces the formation of glucose degradation products. Many of these products are highly reactive precursors of AGEs (e.g. 3-deoxyglycosone,  $\alpha$ -dicarbonyl compounds). During dwell time these precursors can enter the body leading to enhanced AGE formation in vivo [29, 62, 100–102]. Keeping glucose separate from the electrolyte buffer solution during heat sterilization, thus avoiding heat exposure (but using sterile filtration), and mixing these different compartments immediately before use, significantly reduces the concentration of highly reactive glucose degradation products, i.e. carbonyl stress compounds [29]. Lower but still significant levels of reactive carbonyl components can also be achieved by using dialysis fluids containing icodextrin and amino acids [99, 103]. In addition, treatment with non-glucose solutions may result in ‘washout’ of glycated protein from the peritoneal membrane [94].

**Kidney Transplantation.** A beneficial effect of successful kidney transplantation on the AGE level has been observed [104]. Low molecular weight AGEs decline rapidly to almost normal levels [83, 84], while a drop in high molecular weight AGEs is only moderate [84–86].

## AGE Inhibitors

Many compounds give promising results in the AGE inhibition (inhibition of formation of AGEs, inhibition of their function or degradation of AGEs) and after having been tested for these properties, eventually undergo clinical studies.

### *Inhibition of AGE Formation*

**Aminoguanidine (Pimagedine).** Aminoguanidine is the drug most discussed. Its nucleophil hydrazine group binds to the carbonyl group and so prevents cross-linking. It inhibits the late phase of glycation and lipoperoxidation. Aminoguanidine reduces albuminuria and prevents the development of glomerulosclerosis, decreases thickening of glomerular basement membrane and mesangial expansion in experimental studies. Its effects are not limited to the kidney, it also prevents cross-linking of proteins in the lens and functional abnormalities in peripheral nerves, prevents accumulation of AGEs in tissues, slows down the onset of vascular complications in retina, etc. [23]. Unfortunately, its use is limited due to serious side effects (induction of autoantibody formation, rapid progressive glomerulonephritis and anemia) [105].

**OPB-9195 ( $\pm$ 2-Isopropylidenehydrazono-4-oxo-thiazolidine-5-ylacetanilide).** OPB-9195 belongs to a group of thiazolidine derivatives. OPB-9195 reacts with the carbonyl groups thereby forming hydrazones. Although this mechanism is similar to aminoguanidine, OPB-9195 is expected to be more potent. In in vitro studies, OPB-9195 lowers pentosidine formation and in in vivo experiments, it inhibits the neointima formation of rat carotid artery [14, 106].

**Amadorins.** These were defined as inhibitors of the conversion of Amadori intermediates to AGEs in the absence of free or reversibly bound (Schiff base) sugar. Pyridoxamine (pyridorine) was identified as the first member of this class and its therapeutic potential is currently being investigated, and is now showing promising results in animal models [25, 107].

**Antioxidants.** Antioxidants (e.g. GSH, lipoic acid, vitamin E, etc.) are also being discussed for their possible role in AGE inhibition as oxidative stress is involved in AGE formation as well as in AGE–RAGE interaction and its consequences. Many antioxidants were tried in experiments and might eventually have some effect [14, 23, 106].

**Benfotiamine.** Benfotiamine, a liposoluble thiamine derivative, inhibited formation of AGEs in diabetic rats. It may offer protective effects on peripheral nervous tissue against diabetic damage especially when administered early in the course of the disease [108].

**Antihypertensive Drugs.** Angiotensin-converting enzyme inhibitors and angiotensin II receptor-1 antagonists lower formation of AGEs in vitro as shown recently [109]. They do not trap reactive carbonyl precursors for AGE, but impact on the production of reactive carbonyl precursors for AGEs by chelating transition metals and inhib-

iting various oxidative steps, at both the pre- and post-Amadori steps. These data are in accordance with the experimental studies on diabetic [110] and subtotaly nephrectomized rats [111] in which administration of ramipril and losartan, respectively, attenuated the accumulation of AGEs. Similar results were obtained after the administration of ramipril to patients with non-diabetic nephropathies [112].

An unsuspected AGE-lowering effect was also shown by another antihypertensive drug, hydralazine. It is due to both reactive carbonyl compound trapping and modification of the oxidative metabolism [113]. Nifedipine, a calcium channel blocker, does not exert an AGE-lowering effect [109].

*Drugs Cleaving AGE-Modified Proteins – Cross-Links.* N-phenacylthiazoliumbromide [23] or ALT-711 [114] have also been tested. They might be effective in patients with a massive tissue AGE accumulation, but further studies are required to verify this ability.

The effects of AGEs caused by their interaction with RAGE could be prevented by blockage of this receptor or

by binding of AGEs to the soluble receptor sRAGE [46, 115].

AGEs seem to be important in both clinical and experimental medicine (diabetology, nephrology, neurology, rheumatology, hepatology, and probably further specializations) as they take part in the pathogenesis of severe and frequent diseases and their complications. Although a lot has already been done in this area, further experimental and clinical studies could bring more information about their formation and mechanisms of action and clarify the possibilities for the treatment of severe and frequent pathological states.

## Acknowledgements

We would like to thank to Dr. R. Deppisch and Dr. W. Beck from Gambro Corporate Research, Hechingen, Germany, for valuable comments. The studies on advanced glycation end products in nephrology were supported by grant IGA MH CZ No NB/7035-3.

## References

- Maillard LC: Action des acides amines sur les sucres; formation des melanioidines par voie methodique. *CR Acad Sci* 1912;154:66–68.
- Bucala R, Cerami A: Advanced glycosylation: Chemistry, biology and implications for diabetes and aging. *Adv Pharmacol* 1992;23:1–34.
- Brownlee M: Advanced protein glycosylation in diabetes and aging. *Annu Rev Med* 1995;46:223–234.
- Miyata T, Ueda Y, Schinzato T, Yoshiyasu I, Tanaka S, Kurokawa K, Ypersele de Strihou C, Maeda K: Accumulation of albumin-linked and free-form pentosidine in the circulation of uremic patients with end-stage renal failure: Renal implications in the pathophysiology of pentosidine. *J Am Soc Nephrol* 1996;7:1198–1206.
- Ritz E, Deppisch R, Nawroth P: Toxicity of uremia – Does it come from AGE? *Nephrol Dial Transplant* 1994;9:1–2.
- Munch G, Gerlach M, Sian J, Wong A, Riederer P: Advanced glycation end products in neurodegeneration: More than early markers of oxidative stress? *Ann Neurol* 1998;44:S85–S88.
- Miyata T, Ishiguro N, Yasuda Y, Ito T, Nangaku M, Iwata H, Kurokawa K: Increased pentosidine, an advanced glycation end product, in plasma and synovial fluid from patients with rheumatoid arthritis and its relationship with inflammatory markers. *Biochem Biophys Res Commun* 1998;244:45–49.
- Thorpe SR, Baynes JW: Role of the Maillard reaction in diabetes mellitus and diseases of aging. *Drugs Aging* 1996;9:69–77.
- Dolhofer-Bliesener R, Lechner B, Deppisch R, Ritz E, Gerbitz KD: Immunological determination of advanced glycosylation end-products in human blood and urine. *Nephrol Dial Transplant* 1995;10:657–664.
- Ahmed MU, Thorpe SR, Baynes JW: Identification of Nε-carboxymethyllysine as a degradation product of fructoselysine in glycated protein. *J Biol Chem* 1986;261:4889–4994.
- Sell DR, Monnier VM: Structure elucidation of a senescence cross-link from human extracellular matrix: Implication of pentoses in the aging process. *J Biol Chem* 1989;264:21597–21602.
- Wells Knecht KJ, Brinkhamann E, Wells Knecht MC, Litchfield JE, Ahmed MU, Reddy S, Zyzak DV, Thorpe SR, Baynes JW: New biomarkers of Maillard reaction damage to proteins. *Nephrol Dial Transplant* 1996;11:S41–S47.
- Makita Z, Vlassara H, Cerami A, Bucala R: Immunochemical detection of advanced glycosylation end products in vivo. *J Biol Chem* 1992;267:5133–5138.
- Miyata T, Kurokawa K, van Ypersele de Strihou C: Relevance of oxidative and carbonyl stress to long-term uremic complications. *Kidney Int* 2000;58:S120–S125.
- Miyata T, Maeda K, Kurokawa K, van Ypersele de Strihou C: Oxidation conspires with glycation to generate noxious advanced glycation end products in renal failure. *Nephrol Dial Transplant* 1997;12:255–258.
- Koschinski T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H: Orally absorbed reactive glycation products (glycotoxins): An environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci USA* 1997;94:6474–6479.
- Cerami C, Founds H, Nicoll I, Mitsuhashi T, Giordano D, Vanpatten S, Lee A, Al Abed Y, Vlassara H, Bucala R, Cerami A: Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci USA* 1997;94:13915–13920.
- Miyata T, van Ypersele de Strihou C, Kurokawa K, Baynes JW: Alterations in nonenzymatic biochemistry in uremia: Origin and significance of 'carbonyl stress' in long-term uremic complications. *Kidney Int* 1999;55:389–399.
- Miyata T, van Ypersele de Strihou C, Imasawa T, Yoshino A, Ueda Y, Hiroyuki O, Kominami K, Onogi H, Inagi R, Nangaku M, Kurokawa K: Glyoxylase I deficiency is associated with an unusual level of advanced glycation end products in a hemodialyzed patient. *Kidney Int* 2001;60:2351–2359.
- Vlassara H: Recent progress in advanced glycation end products and diabetic complications. *Diabetes* 1997;46:S19–S25.



- 21 Šebeková K, Kupčová V, Schinzel R, Heidland A: Markedly elevated levels of plasma advanced glycation end products in patients with liver cirrhosis – Amelioration by liver transplantation. *J Hepatol* 2002;36:66–71.
- 22 Njorge FG, Monnier VM: The chemistry of the Maillard reaction under physiological conditions: A review. *Prog Clin Biol Res* 1989;304:85–107.
- 23 Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP: AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. *Cardiovasc Res* 1998;37:586–600.
- 24 King GL, Brownlee M: The cellular and molecular mechanisms of diabetic complications. *Endocrinol Metab Clin North Am* 1996;25:255–270.
- 25 Khalifah RG, Baynes JW, Hudson BG: Amadorins: Novel post-Amadori inhibitors of advanced glycation reactions. *Biochem Biophys Res Commun* 1999;257:251–258.
- 26 Weiss MF, Erhard P, Kader-Attia FA, Wu YC, Deoreo PB, Araki A, Glomb MA, Monnier VM: Mechanism for the formation of glycoxidation products in end-stage renal disease. *Kidney Int* 2000;57:2571–2585.
- 27 Fu MX, Requena JR, Jenkins AJ, Lyons TJ, Baynes JW, Thorpe SR: The advanced glycation end product, N<sup>ε</sup>-(carboxymethyl)lysine, is a product of both lipid peroxidation and glycation reactions. *J Biol Chem* 1996;271:9982–9986.
- 28 Baynes JW, Thorpe SR: Role of oxidative stress in diabetic complications. *Diabetes* 1999;48:1–9.
- 29 Wieslander A, Linden T, Musí B, Jarkelid L, Speidel R, Beck W, Henle T, Deppisch R: Exogenous uptake of carbonyl stress compounds promoting AGE formation from peritoneal dialysis fluids; in D'Angelo A, Favaro S, Gambaro G (eds): *Advanced Glycation End Products in Nephrology*. Contrib Nephrol. Basel, Karger, 2001, vol 131, pp 82–89.
- 30 Jadoul M, Ueda Y, Yasuda Y, Saito A, Robert A, Ishida N, Kurokawa K, van Ypersele de Strihou C, Miyata T: Influence of hemodialysis membrane type on pentosidine plasma level, a marker of carbonyl stress. *Kidney Int* 1999;55:2487–2492.
- 31 Thornalley PJ: Advanced glycation and development of diabetic complications: Unifying the involvement of glucose, methylglyoxal and oxidative stress. *Endocrinol Metab* 1996;3:149–166.
- 32 Faist V, Ebersdobler HF: Metabolic transit and in vivo effects of melanoidins and precursor compounds deriving from the Maillard reaction. *Ann Nutr Metab* 2001;45:1–12.
- 33 Alaiz M, Hidalgo FJ, Zamora R: Comparative antioxidant activity of Maillard- and oxidized lipid-damaged bovine serum albumin. *J Agric Food Chem* 1997;45:3250–3254.
- 34 Vlassara H, Cai W, Cranall J, Goldberg T, Oberstein R, Dardaine V, Peppas M, Rayfield EJ: Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc Natl Acad Sci USA* 2002;99:15596–15601.
- 35 Uribarri J, Peppas M, Cai W, Goldberg T, Lu M, He C, Vlassara H: Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. *J Am Soc Nephrol* 2003;14:728–731.
- 36 Schwedler S, Metzger T, Schinzel R, Wanner C: Advanced glycation end products and mortality in hemodialysis patients. *Kidney Int* 2002;62:301–310.
- 37 Wu JT: Advanced glycosylation end products: A new disease marker for diabetes and aging. *J Clin Lab Anal* 1993;7:252–255.
- 38 Makita Z, Bucala R, Rayfield EJ, Friedman EA, Kaufman AM, Korbet SM, Barth RH, Winston JW, Fuh H, Manogue KR, Cerami A, Vlassara H: Reactive glycosylation end products in diabetic uraemia and treatment of renal failure. *Lancet* 1994;343:1519–1522.
- 39 Miyata T, Ueda Y, Horie K, Nankagu M, Tanaka S, van Ypersele de Strihou C, Kurokawa K: Renal catabolism of advanced glycation end products: The fate of pentosidine. *Kidney Int* 1998;53:416–422.
- 40 Amore A, Cirina P, Mitola S, Peruzzi L, Gianoglio B, Rabbone I, Sacchetti C, Cerutti F, Grillo C, Coppo R: Nonenzymatically glycated albumin (Amadori adducts) enhances nitric oxide synthase activity and gene expression in endothelial cells. *Kidney Int* 1997;51:27–35.
- 41 Raj DSC, Choudhury D, Welbourn TC, Levi M: Advanced glycation end products: A nephrologist's perspective. *Am J Kidney Dis* 2000;35:365–380.
- 42 Makita Z, Vlassara H, Rayfield E, Cartwright K, Friedman E, Rodby R, Cerami A, Bucala R: Hemoglobin-AGE: Circulating marker of advanced glycosylation. *Science* 1992;258:651–653.
- 43 Thornalley PJ: Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. *Cell Mol Biol* 1998;44:1013–1023.
- 44 Bierhaus A, Ritz E, Nawroth PP: Expression of receptor for advanced glycation end-products in occlusive vascular and renal disease. *Nephrol Dial Transplant* 1996;11(suppl):87–90.
- 45 Chappey O, Dosquet C, Wautier M-P, Wautier J-L: Advanced glycation end products, oxidant stress and vascular lesions. *Eur J Clin Invest* 1997;27:97–108.
- 46 Schmidt AM, Hori O, Cao R, Yan SD, Brett J, Wautier JL, Ogawa S, Kuwabara K, Matsumoto M, Stern D: RAGE: A novel cellular receptor for advanced glycation end products. *Diabetes* 1996;45:S77–S80.
- 47 Yan SD, Stern D, Schmidt AM: What's the RAGE? The receptor for advanced glycation end products (RAGE) and the dark side of glucose. *Eur J Clin Invest* 1997;27:179–181.
- 48 Abel M, Ritthaler U, Zhang Y, Deng Y, Schmidt AM, Greten J, Sernau T, Wahl P, Andrassy K, Ritz E: Expression of receptors for advanced glycosylated end-products in renal disease. *Nephrol Dial Transplant* 1995;10:1662–1667.
- 49 Heidland A, Sebekova K, Schinzel R: Advanced glycation end products and the progressive course of renal disease. *Am J Kidney Dis* 2001;38(suppl):S100–S106.
- 50 Yan SD, Schmidt AM, Anderson GM, Zhang J, Brett J, Zou YS, Pinky D, Stern D: Enhanced cellular oxidant stress by the interaction of advanced glycation and products with their receptors/binding proteins. *J Biol Chem* 1994;269:9889–9897.
- 51 Kislinger T, Fu C, Huber B, Qu W, Taguchi A, Yan SD, Hofmann M, Yan SF, Pischensrieder M, Stern D, Schmidt AM: N<sup>ε</sup>-(carboxymethyl) lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression. *J Biol Chem* 1999;274:31740–31749.
- 52 Bierhaus A: Physiological function of RAGE (abstract). *AGEs Symp*, Jena, 2003, p 6.
- 53 Li J, Schmidt AM: Characterization and functional analysis of the promoter of RAGE, the receptor for advanced glycation end products. *J Biol Chem* 1997;272:16498–16506.
- 54 Kalousova M, Zima T, Tesar V, Lachmanova J: Advanced glycation end products and advanced oxidation protein products in hemodialyzed patients. *Blood Purif* 2002;20:531–536.
- 55 Degenhardt TP, Grass L, Reddy S, Thorpe SR, Diamanti EP, Baynes JW: Technical note. The serum concentration of the advanced glycation end-product N epsilon-(carboxymethyl) lysine is increased in uremia. *Kidney Int* 1997;52:1064–1067.
- 56 Schinzel R, Munch G, Heidland A, Sebekova K: Advanced glycation end products in end-stage renal disease and their removal. *Nephron* 2001;87:295–303.
- 57 Kaunuchi M, Nishioka H, Dohi K: Serum levels of advanced glycosylation end products in diabetic nephropathy. *Nephron* 2001;89:228–230.
- 58 Witko-Sarsat V, Friedlander M, Capeillere-Blandin C, Nguyen-Khoa T, Nguyen AT, Zingraff J, Jungers P, Deschamps-Latscha B: Advanced oxidation protein products as a novel marker of oxidative stress in uraemia. *Kidney Int* 1996;49:1304–1313.
- 59 Loughrey CM, Young IS, Lightbody JH, McMaster D, McNamee PT, Trimble ER: Oxidative stress in haemodialysis. *Q J Med* 1994;87:679–683.
- 60 Friedlander MA, Wu YC, Schullak JA, Monnier VM, Hricik DE: Influence of dialysis modality on plasma and tissue concentration of pentosidine in patients with end-stage renal disease. *Am J Kidney Dis* 1995;25:445–451.
- 61 Henle T, Deppisch R, Beck W, Hergesell O, Hansch GM, Ritz E: Advanced glycation end-products (AGE) during haemodialysis treatment: Discrepant results with different methodologies reflecting the heterogeneity of AGE compounds. *Nephrol Dial Transplant* 1999;14:1968–1975.
- 62 Zeier M, Deppisch R, Haug U, Schwenger V, Henle T, Bahner U, Wanner C, Schneider H, Ritz E: Resorption of AGE-promoting glucose degradation products (GDP) from peritoneal dialysis (PD) fluids leads to increased levels of AGE in plasma. *J Am Soc Nephrol* 2000;11:223A.

- 63 Salahudeen AK, Kanji V, Reckelhoff JF, Schmidt AM: Pathogenesis of diabetic nephropathy: A radical approach. *Nephrol Dial Transplant* 1997;12:664–668.
- 64 Munch G, Kies R, Wessel A, Riederer P, Bahner U, Heidland A, Niwa T, Lemke HD, Schinzel R: Determination of advanced glycation and products in serum by fluorescence spectroscopy and competitive ELISA. *Eur J Clin Chem Clin Biochem* 1997;35:669–677.
- 65 Papanastasiou P, Grass L, Rodela H, Patrikarea A, Oreopoulos D, Diamandis EP: Immunological quantification of advanced glycosylation end-products in the serum of patients on hemodialysis or CAPD. *Kidney Int* 1994;46:216–222.
- 66 Vlassara H: Serum advanced glycosylation end products: A new class of uremic toxins? *Blood Purif* 1994;12:54–59.
- 67 Kalousova M, Zima T, Tesar V, Sulkova S, Škrha J, Deppisch R, Beck W: Glycooxidation in hemodialyzed patients with diabetes mellitus; in Timio M, Wizemann V, Venanzi S (eds): *Cardionephrology*. Cosenza, Editoriale Bios, 2002, vol 7, pp 297–300.
- 68 Kalousova M, Škrha J, Zima T: Advanced glycation end products and advanced oxidation protein products in patients with diabetes mellitus. *Physiol Res* 2002;51:597–604.
- 69 Stein G, Franke S, Mahiout A, Schneider S, Sperschneider H, Borst S, Vienken J: Influence of dialysis modalities on serum AGE levels in end-stage renal disease patients. *Nephrol Dial Transplant* 2001;16:999–1008.
- 70 Miyata T, Ueda Y, Saito A, Kurokawa K: Carbonyl stress and dialysis-related amyloidosis. *Nephrol Dial Transplant* 2000;15(suppl):25–28.
- 71 Wada T, Miyata T, Kurokawa K: Implication of carbonyl stress in long term uraemic complications. *Nephrol Dial Transplant* 1999;14(suppl):79–81.
- 72 Schwedler S, Schinzel R, Vaith P, Wanner C: Inflammation and advanced glycation end products in uremia: Simple coexistence, potentiation or causal relationship? *Kidney Int* 2001;59:S32–S36.
- 73 Deppisch RM, Beck W, Goehl H, Ritz E: Complement components as uremic toxins and their potential role as mediators of microinflammation. *Kidney Int* 2001;59:S271–S277.
- 74 Acosta J, Hettinga J, Fluckiger R, Krumrei N, Goldfine A, Angarita L, Halperin J: Molecular basis for a link between complement and the vascular complications of diabetes. *Proc Natl Acad Sci USA* 2000;97:5450–5455.
- 75 Friedlander MA, Witko-Sarsat V, Nguyen AT, Wu YC, Labrunte M, Verger C, Jungers P, Descamps-Latscha B: The advanced glycation end product pentosidine and monocyte activation. *Clin Nephrol* 1996;45:379–382.
- 76 Šebeková K, Podracká L, Heidland A, Schinzel R: Enhanced plasma levels of advanced glycation end products (AGE) and pro-inflammatory cytokines in children/adolescents with chronic renal insufficiency and after renal replacement therapy by dialysis and transplantation – Are they inter-related? *Clin Nephrol* 2001;56:S21–S26.
- 77 Kalousova M, Zima T, Tesar V, Sulkova S, Fialová L: Relationship between advanced glycooxidation end products, inflammatory markers/acute phase reactants and some autoantibodies in chronic hemodialysis patients. *Kidney Int Suppl* 2003;84:62–64.
- 78 Kalousova M, Sulkova S, Fialová L, Soukupová J, Malbohan IM, Spacek P, Braun M, Mikulíková L, Fořtová M, Hořejší M, Tesar V, Zima T: Glycooxidation and inflammation in chronic hemodialysis patients. *Nephrol Dial Transplant* 2003, in press.
- 79 Bayes-Genis A, Conover CA, Overgaard MT, Bailey KR, Christiansen M, Holmes DR Jr, Virmani R, Oxvig C, Schwartz RS: Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. *N Engl J Med* 2001;345:1022–1029.
- 80 Menzel E J, Sobal G, Staudinger A: The role of oxidative stress in the long-term glycation of LDL. *Biofactors* 1997;6:111–124.
- 81 Motomiya Y, Oyama N, Iwamoto H, Uchimura T, Maruyama I: N-Epsilon-(carboxymethyl) lysine in blood from maintenance hemodialysis patients may contribute to dialysis-related amyloidosis. *Kidney Int* 1998;54:1357–1366.
- 82 Stein G, Busch M, Muller A, Wendt T, Franke C, Niwa T, Franke S: Are advanced glycation end products cardiovascular risk factors in patients with CRF? *Am J Kidney Dis* 2003;41(suppl 2):S52–S56.
- 83 Hricik DE, Wu YC, Schulak A, Friedlander MA: Disparate changes in plasma and tissue levels after kidney and kidney-pancreas transplantation. *Clin Transplant* 1996;10:568–573.
- 84 Miyata T, Ueda Y, Yoshida A, Sugiyama S, Iida Y, Jadoul M, Maeda K, Kurokawa K, van Ypersele de Strihou C: Clearance of pentosidine, an advanced glycation end product, by different modalities of renal replacement therapy. *Kidney Int* 1997;51:880–887.
- 85 Šebeková K, Podracká L, Blazicek P, Syrova D, Heidland A, Schinzel R: Plasma levels of advanced glycation end products in children with renal disease. *Pediatr Nephrol* 2001;16:1105–1112.
- 86 Franke S, Muller A, Sommer M, Busch M, Kientsch-Engel R, Stein G: Serum levels of total homocysteine, homocysteine metabolites and of advanced glycation end products (AGEs) in patients after renal transplantation. *Clin Nephrol* 2003;59:88–97.
- 87 Heidland A, Frangiosa A, De Santo L, Cirillo M, Rossi, Cotrufo M, Klassen A, Schinzel R, Šebeková K, De Santo N: AGEs in human heart disease: Mild decrease in congestive heart failure and enhanced levels after heart transplantation in the presence of a reduced GFR. *Nephrol Dial Transplant* 2002;S1:330.
- 88 Fagugli RM, Vanholder R, De Smet R, Selvi A, Antolini F, Lameire N, Floridi A, Buoncristiani U: Advanced glycation end products: Specific fluorescence changes of pentosidine-like compounds during short daily hemodialysis. *Int J Artif Organs* 2001;24:256–262.
- 89 Inagi R, Miyata T: Oxidative protein damage with carbohydrates and lipids in uremia. Carbonyl stress. *Blood Purif* 1999;17:95–98.
- 90 Gerdemann A, Wagner Z, Solf A, Bahner U, Heidland A, Vienken J, Schinzel R: Plasma levels of advanced glycation end products during haemodialysis, haemodiafiltration and haemofiltration: Potential importance of dialysate quality. *Nephrol Dial Transplant* 2002;17:1045–1049.
- 91 Tessitore N, Lapolla A, Arico CN, Gammara L, Bernich P, Fedel D: Hemodialysis techniques and advanced glycation end products; in D'Angelo A, Favaro S, Gammara G (eds): *Advanced Glycation End Products in Nephrology*. Contrib Nephrol. Basel, Karger, 2001, vol 131, pp 33–39.
- 92 Krieter DH, Lemke HD, Gerdemann A, Schinzel R, Heidland A, Baumeister U: Effect of LDL apheresis on the removal of advanced glycation end products (AGE) (abstract). 37th ERA-EDTA Congress. Nice, 2000.
- 93 Friedlander MA, Wu YC, Elgawish A, Monnier VM: Early and advanced glycosylation end products. Kinetics of formation and clearance in peritoneal membrane. *J Clin Invest* 1996;97:728–735.
- 94 Ho-dac-Pannekeet MM, Weiss MF, deWaart DR, Erhard P, Hiralall JK, Krediet RT: Analysis of nonenzymatic glycosylation in vivo: Impact of different dialysis solutions. *Perit Dial Int* 1999;19(suppl):S68–S74.
- 95 Lamb E, Cattel WR, Dawney A: Glycated albumin in serum and dialysate of patients on continuous ambulatory peritoneal dialysis. *Clin Sci (Lond)* 1993;84:619–626.
- 96 Ateshkadi A, Johnson CA, Founds HW, Zimmerman SW: Serum advanced glycosylation end products in patients on hemodialysis and CAPD. *Perit Dial Int* 1995;15:129–133.
- 97 Yamada K, Miyahara Y, Hamaguchi K, Nakayama M, Nakano H, Nozaki O, Miura Y, Suzuki S, Tsuchida H, Mimura N: Immunohistochemical study of human advanced glycosylation end-products (AGE) in chronic renal failure. *Clin Nephrol* 1994;42:354–361.
- 98 Nakayama M, Kawaguchi Y, Yamada K, Hasegawa T, Takozoe K, Katoh N, Hayakawa H, Osaka N, Yamamoto H, Ogawa A, Kubo H, Shigematsu T, Sakai O, Horiuchi S: Immunohistochemical detection of advanced glycosylation end-products in the peritoneum and its possible pathophysiological role in CAPD. *Kidney Int* 1997;51:182–186.
- 99 Dawney AB, Millar DJ: Glycation and advanced glycation end product formation with icodextrin and dextrose. *Perit Dial Int* 1997;17:52–58.
- 100 Linden T, Forsback G, Deppisch R, Henle T, Wieslander A: 3-Deoxyglucosone, a promoter of advanced glycation end products in fluids for peritoneal dialysis. *Perit Dial Int* 1998;18:209–213.
- 101 Zeier M, Schwenger V, Deppisch R, Haug U, Weigel K, Bahner U, Wanner C, Schneider H, Henle T, Ritz E: Glucose degradation products in PD fluids: Do they disappear from the peritoneal cavity and enter the systemic circulation? *Kidney Int* 2003;63:298–305.

- 102 Tauer A, Zhang X, Schaub TP, Zimmek T, Niwa T, Passlick-Deetjen J, Pitschensrieder M: Formation of advanced glycation end products during CAPD. *Am J Kidney Dis* 2003;41(suppl 1):S57–S60.
- 103 Ueda Y, Miyata T, Goffin E, Yoshino AQ, Inagi R, Ishibashi Y, Izuhara Y, Saito A, Kurokawa K, van Ypersele de Strihou C: Effect of dwell time on carbonyl stress using icodextrin and amino acid peritoneal dialysis fluids. *Kidney Int* 2000;58:2518–2524.
- 104 Lee WK, Akyol M, Shaw S, Dominiczak MH, Briggs JD: Kidney transplantation decreases the tissue level of advanced glycosylation end-products. *Nephrol Dial Transplant* 1995;10:103–107.
- 105 Singh R, Barden A, Mori T, Beilin L: Advanced glycation end-products: A review. *Diabetologia* 2001;44:129–146.
- 106 Miyata T, Kurokawa K, van Ypersele de Strihou C: Advanced glycation and lipooxidation end products: Role of reactive carbonyl compounds generated during carbohydrate and lipid metabolism. *J Am Soc Nephrol* 2000;11:1744–1752.
- 107 Alderson NL, Chachich ME, Youssef NN, Beattie RJ, Nachtigal M, Thorpe SR, Baynes JW: The AGE inhibitor pyridoxamine inhibits lipemia and development of renal and vascular disease in Zucker obese rats. *Kidney Int* 2003;63:2123–2133.
- 108 Netzel M, Geyer J, Strassl G, Bitsch R, Stracke H, Hammes HP, Werkmann D, Mavarakis K, Federlin KF, Bitsch I: Physiological effects of different thiamine derivatives in diabetic rats (abstract). *AGEs Symp*, Jena, 2003, p 32.
- 109 Miyata T, van Ypersele de Strihou C, Ueda Y, Ichimori K, Inagi R, Onogi H, Ishikawa N, Nangaku M, Kurokawa K: Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: Biochemical mechanisms. *J Am Soc Nephrol* 2002;13:2478–2487.
- 110 Forbes JM, Cooper ME, Thallas V, Burns WC, Thomas MC, Brammar GC, Lee F, Grant SL, Burrell LA, Jerums G, Osicka TM: Reduction of the accumulation of advanced glycation end products by ACE inhibition in experimental diabetic nephropathy. *Diabetes* 2002;51:3274–3282.
- 111 Šebeková K, Schinzel R, Munch G, Krivosikova Z, Dzúrik R, Heidland A: Advanced glycation end-product levels in subtotaly nephrectomized rats: Beneficial effects of angiotensin II receptor 1 antagonist losartan. *Mineral Electrolyte Metab* 1999;25:380–383.
- 112 Šebeková K, Gazdíkova K, Blazíček P, Schinzel R, Heidland A, Dzúrik R: ACEI ramipril ameliorated circulating AGEs and oxidative stress in patients with non-diabetic kidney disease. *Nephrol Dial Transplant* 2002;S1:100.
- 113 Nangaku M, Miyata T, Sada T, Makoto M, Inagi R, Ueda Y, Ishikawa N, Yuzawa H, Koike H, van Ypersele de Strihou C, Kurokawa K: Anti-hypertensive agents inhibit in vivo the formation of advanced glycation end products and improve renal damage in a type 2 diabetic nephropathy rat model. *J Am Soc Nephrol* 2003;14:1212–1222.
- 114 Wolfenbutter BH, Boulanger CM, Crijns FR, Huijberts MS, Poitevin P, Swennen GN, Vasan S, Egan JJ, Ulrich P, Cerami A, Lévy BI: Breakers of advanced glycation end products restore large artery properties in experimental diabetes. *Proc Natl Acad Sci USA* 1998;95:4630–4634.
- 115 Hori O, Yan SD, Ogawa S, Kuwabara K, Matsumoto M, Stern D, Schmidt AM: The receptor for advanced glycation end-products has a central role in mediating the effects of advanced glycation end-products on the development of vascular disease in diabetes mellitus. *Nephrol Dial Transplant* 1996;11:S13–S16.