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Review

Advanced Glycation and Lipoxidation End Products–Amplifiers of Inflammation: The Role of Food

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ABSTRACT. *Background:* High levels of glycated and lipoxidated proteins and peptides in the body are repeatedly associated with chronic diseases. These molecules are strongly associated with activation of a specific receptor called RAGE and a long-lasting exaggerated level of inflammation in the body. *Methods:* PubMed reports over 5000 papers plus >13,500 articles about the related HbA_{1c}, most of them published in the past 5 years. Most of the available abstracts have been read and approximately 800 full papers have been studied. *Results:* RAGE, a member of the immunoglobulin superfamily of cell surface molecules and receptor for advanced glycation end products, known since 1992, functions as a master switch, induces sustained activation of nuclear factor κB (NFκB), suppresses a series of endogenous autoregulatory functions, and converts long-lasting proinflammatory signals into sustained cellular dysfunction and disease. Its activation is associated with high levels of dysfunctioning proteins in body fluids and tissues, and is strongly associated with a series of diseases from allergy and Alzheimers to rheumatoid arthritis and urogenital disorders. Heat treatment, irradiation, and ionization of foods increase the content of dysfunctioning molecules. *Conclusions:* More than half of the studies are performed in diabetes and chronic renal diseases; there are few studies in other diseases. Most of our knowledge is based on animal studies and *in vitro* studies. These effects are worth further exploration both experimentally and clinically. An avoidance of foods rich in deranged proteins and peptides, and the consumption of antioxidants, especially polyphenols, seem to counteract such a development. (*Journal of Parenteral and Enteral Nutrition* **31:**430–440, 2007)

It has been almost 100 years since Malliard[1] described the nonenzymatic pathway for glycation of proteins and suggested that such chemically modified proteins could play a role in the pathogenesis of chronic diseases (ChDs), particularly diabetes (DM). However, it is only during the last 2 decades, and especially the last 5 years, that this concept has received wider attention among scientists. Still, most practicing physicians and nutrition experts are still unaware of the concept and its eventual implications on health. Contributory to the recent increase in interest is the observation that glycated hemoglobin, HbA_{1c},[2,3] is deeply involved in DM and in various age-associated diseases and, probably more important, the identification of several receptors in the body, which are involved in these processes, of which RAGEs are the most well known and studied.[4,5] More than 5000 papers about the biology of advanced glycation products, plus over 13,500 articles about HbA_{1c}, are presently available on PubMed.

RAGE: A Master Switch

Metabolic syndrome, with all its clinical manifestations, is strongly associated with the development of ChDs. A discrete, often long-lasting, increased inflammation plays an important role in the development of and maintenance of this syndrome,[6] and in the pathogenesis of ChDs. Common to ChDs are, in addition to the increased inflammatory state, a significant elevated oxidant stress (OS) and OS-induced gene expression.[6–9] RAGE, a member of the immunoglobulin superfamily of cell surface molecules and receptor for advanced glycation end products (AGEs), functions as a master switch, converting long-lasting proinflammatory signals into sustained cellular dysfunction and disease (Table I).[10,11] This receptor and various other receptors for AGEs and lipoxidation end products (ALEs) play important roles in both oxidative stress and inflammation. RAGE induces a sustained activation of proinflammatory transcription factor NFκB and suppresses a series of endogenous autoregulatory functions.[12] Experimental studies suggest that increased deposition of AGEs/ALEs in tissues is strongly associated with down-regulation of leptin expression in adipocytes and metabolic syndrome.[13] Reducing the inflammatory environment through reduction of tissue accumulation of AGE and ALE ligands has also been shown to reduce sustained exaggerated inflammation and cellular dysfunction, and to improve outcome of disease.[10,14]

Tissue Accumulation of AGEs and ALEs

As described by Vlassara,[14] industrial processes aimed to make food safer, flavorful, and colorful, such

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TABLE I
Cytokines and cellular events associated with AGE or RAGE activation

VCAM-1 ↑	Endothelial cells
ICAM-1 ↑	Endothelial cells
E-selectin ↑	Endothelial cells
PDGF ↑	Pancreatic cancer cells
eNOS ↓	Endothelial cells
Tissue factor ↑	Endothelial cells
TGF-β ↑	Mesangial cells, proximal tubular cells, vascular smooth muscle cells, macrophages
TNF-α ↑	Endothelial cells, mesangial cells, mononuclear macrophages
IGF-1 ↑	Mesangial cells
MCP-1 ↑	Mesangial cells, endothelial cells
CTGF ↑	Fibroblasts, mesangial cells
IL-6 ↑	Endothelial cells
PAI-1 ↑	Endothelial cells
RAGE ↑	Mesangial cells, endothelial cells, podocytes
VEGF ↑	Podocytes, endothelial cells, mesangial cells
ANG II-dependent cell activation ↑	Vascular smooth muscle cells
Type IV collagen expression ↑	Mesangial cells
Fibronectin ↑	Mesangial cells
Cell cycle progression ↓	Fibroblasts, mesangial cells

ANG II, angiotensin II; ICAM, intercellular adhesion molecule; IGF, insulin-like growth factor; IL, interleukin; PDGF, platelet-derived growth factor; RAGE, advanced glycation end products receptor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; TGF-β, transforming growth factor-β; MCP-1, monocyte chemotactic protein-1; CTGF, connective tissue growth factor; PAI-1, plasminogen activator inhibitor-1. Reprinted from Bohlender et al.,[122] used with permission from the American Physiological Society.

as heating, irradiation, and ionization, do this but in combination with gross overnutrition, and also contribute significantly to production of, exposure to, and accumulation of AGEs/ALEs in the body. Vlassara and her group[15,16] have demonstrated in human studies significant correlation between ingested AGEs, circulating AGEs, and induction of markers of inflammation. In animal studies, dietary restriction of AGEs has shown "protective" effects against impaired immune function in induced ChDs and in complications to ChDs: DM-induced vasculopathy,[17] nephropathy,[18] and impaired wound healing.[19] Furthermore, it was concluded that the animals remained nearly free of pathology despite the remaining presence of the underlying disease.[14] Dietary AGE restriction in animals seemed to be as effective in extending lifespan as caloric restriction (CR).[20] Similar observations have been made in human studies, in DM, vascular disease, and kidney disease: patients who were supplied a low-AGE diet responded with a considerable reduction in inflammatory markers and vascular dysfunction.[15,21]

AGEs constitute a complex and heterogenous group of compounds formed by nonenzymatic reactions of reducing sugars with amino acids, nucleic acids, peptides, and proteins. The first compounds produced, generally called Amadori products, will slowly undergo complex changes, cyclization, dehydration, oxidation, condensation, cross-linking, and polymerization, to finally form more irreversible chemical products, referred to as AGEs/ALEs. These processes are also called Maillard reactions and the products, Maillard products. Some highly reactive carbonyls such as glyoxal and methylglyoxal have been found to rapidly modify reactive side chains of proteins. The ε-amino group of lysine and the guanido group of arginine are identified as the most preferential targets for the highly reactive dicarbonyls, which makes lysine- and arginine-rich tissues and foods special targets for such processes. High intracellular and extracellular concentrations of reactive carbohydrates such as glucose, and especially the highly reactive fructose, are important triggers for increased glycation and formation of glyoxal, methylglyoxal, and 3-deoxyglucosan, which glycate proteins, which accumulate both intra- and extracellularly. Significantly elevated visceral AGE formation, serum AGE levels, caspase-3 activation, and cytoplasmic DNA fragmentation are observed in organs such as heart, liver, and kidneys in animals with dyslipidemia due to high-fat diet (32–42% fat),[22] findings well in line with >50-year-old observations that a high-fat diet contributes to manifestations of diseases: thrombus formation, renal infarcts, and myocardial infarctions.[23]

Glyoxal and methylglyoxal formation constitutes an intermediate stage in the Maillard reaction, whereas pentoside, an often-studied glyco-oxidation product and fluorescent cross-link, is formed in the late stage of the reaction, where it becomes more stable and irreversible. Many AGE/ALE compounds have been identified in tissues, and new previously unknown substances are identified at a rate of 2–3 per year. Most studies thus far have focused only on a handful of these substances, apart from HbA_{1c}, mainly pentoside, N^{ε}-(carboxymethyl)lysine (CML) and N^{ε}-(carboxyethyl) lysine (CEL). Recent and increasing evidence suggests that lipids are as important contributors as carbohydrates to chemical modification of proteins, accumulation in tissues of Maillard products, and pathogenesis of diseases.[24] As diary products and meat are the dominating sources of fats and are usually exposed to higher temperature, it is these foods that are the largest contributor of ALEs to the body. Some Maillard products are formed from both carbohydrate and lipid sources; one such example is CML.[25] Products derived only from carbohydrate sources, AGEs, are pentoside, crosslines, vesperlysines, and 3DG-imidozolones. Malondialdehyde (MDA), acrolein adducts of lysine, histidine, and cysteine are specific AGEs.[24]

AGEs/ALEs and Disease

The levels of AGEs/ALEs in individuals with incipient or manifest ChDs are, when compared with healthy individuals, dramatically and significantly increased. There is, however, great variation in pattern of AGEs/ALEs in the tissues and in the circulation between various patients and groups of patients with ChDs. Both AGEs and ALEs will, when accumulated in tissues, significantly increase the level of inflammation in the body,[26,27] reduce antioxidant defense,[28] weaken the immune system,[29] impair DNA repair mechanisms,[30] and increase accumulation of toxins within

the tissues[26] and increase the rate of infection.[26,27] The differences are great; glycated proteins are suggested to produce almost 50 times more free radicals than nonglycated proteins,[31] and the plasma concentrations of free CML are reported to be increased about 8-fold with CEL reported at 22-fold in hemodialysis patients.[32]

Accumulation of modified insoluble, indigestible, and dysfunctional proteins (AGEs/ALEs) occurs predominantly in long-lived tissues such as collagen, neural myelins, and lenses. It leads to decreased elasticity of collagen-rich tissues, which seems to explain the age-dependent (and ChD-dependent) increase in stiffness of lenses, joints, skeletal muscles, vascular walls, and an increase in systolic and decrease in diastolic pressure.[33] AGEs/ALEs exert strong effects also on short-lived cells such as endothelial cells and pericytes, stimulate growth, interact with cell-surface receptor RAGE, and activate the NFκB pathway, induce vascular endothelium growth factor (VEGF), inhibit prostacycline production, and stimulate plasminogen activator inhibitor-1 (PAI-1) synthesis by endothelial and other cells. Table 1 summarizes documented cellular events and changes associated with AGE and RAGE activation.

Hormones Potentiate AGE/ALE-Induced Inflammation

The process of inflammation is, in addition to being dependent on the status of oxidation/antioxidation, also enhanced by hormones, especially growth and sex hormones, and low levels of vitamins, particularly vitamin D. 17β-Estradiol, for example, has been shown to significantly up-regulate RAGE mRNA in human microvascular endothelial cells[34] and VEGF-dependent angiogenesis.[35] This could explain a common observation, exacerbation of diabetic vasculopathy and retinopathy during pregnancy. This assumption is further supported by the finding that RAGE mRNA activation on endothelial cells induced by 7β-estradiol is abolished when an antiestrogen such as 4-OH tamoxifen is supplemented.[35] These observations might also explain why commercial bovine milk, rich in not only AGEs/ALEs but also in estrogens (eg, 17β-estradiol) have been associated with ChDs such as allergy,[36] coronary heart disease,[37,38] DM,[39–41] Parkinson disease (PD),[42] and various cancers such as breast,[43,44] prostatic,[45,46] testicular,[46] and to some extent ovarian[47,48] malignancies. It might not be a coincidence that ChDs and rate of complications to ChDs are significantly higher, especially during the winter, at higher altitudes (northern Europe, northern North America), where also secondary hyperparathyroidism, due to poor supply of vitamin D, is more often found.[49,50] Parathyroid hormone is known to induce IL-6 and is claimed to significantly increase IL-6 both in hyperthyroid patients (16-fold) and in overweight patients.[49]

The Role of AGE/ALE Tissue Deposition in Common ChDs

The deposition of dysfunctioning proteins in tissues will, when pronounced, result in accumulation of histologic changes referred to as amyloid, a common feature in various ChDs. These deposits of AGEs/ALEs produce a significant fluorescence, and the degree of ALE/AGE in tissues and body fluids can easy and reliably be measured in organs such as the skin, blood, and lenses through estimation of their fluorescence.[51] There is with aging a continuous but slow increase in content of AGEs/ALEs also in healthy individuals, but the increase is significantly more pronounced in individuals who are developing or have acquired ChDs. Pronounced increase in levels of AGEs/ALEs in tissues is reported to be strongly associated to metabolic syndrome[4,52] and to down-regulation of leptin expression in adipocytes.[53]

Clinical Relevance of AGEs/ALEs in Specific Groups of Diseases

Accumulation of AGEs/ALEs in tissues and changes suggested to be induced by AGEs/ALEs have been reported in the following ChDs.

Allergy and autoimmune diseases. Thermal processing, curing, and roasting of foods introduce major changes in allergenicity of foods and will often introduce neoantigens and increase allergenicity. Further studies are needed, however, as reduced allergenicity has sometimes been reported.[54,55] Heated foods like milk, roasted peanuts and soy are reported to induce significant increases in AGE levels and affect the IgE-binding capacity.[56,57] Significantly elevated urinary levels of the AGE pentosine are observed in allergic children with clinical signs of exacerbation of atopic dermatitis.[58]

Alzheimers disease (AD) and other neurodegenerative diseases. Similarities between AD and type 2 diabetes (T2DM) exist to the extent that AD has been called "the diabetes of the brain." The incidence of AD is also reported to be 2- to 5-fold increased in T2DM.[59] A common feature of both diseases is accumulation of amyloid deposits, a process that progresses during the course of disease. Increased levels of AGEs/ALEs have repeatedly been demonstrated with immunohistochemical methods in senile plaques, tau proteins, amyloid β proteins, and in neurofibrillary tangles.[60,61] A 3-fold increase in content of AGE is also reported in the brains of AD patients compared with age-matched controls.[62] Increased levels of AGEs and signs of oxidative damage are also observed in olfactory bulbs, known to be early targets of AD.[62] A strong association between severity of disease, RAGE-expression in microglia, and increases in RAGE protein has been reported.[63] Signs of amyloidosis, pertubation of neuronal properties and functions, amplification of glial inflammatory response, increased oxidative stress, increased vascular dysfunction, increased Aβ in the blood-brain barrier, and induction of autoantibodies were also reported.[63] Involvement of AGEs/ALEs in the pathogenesis of other neurodegenerative diseases is also reported: PD,[64,65] amyotrophic lateral sclerosis (ALS),[65–68] Huntington disease,[69] stroke,[70] familial amyloidotic polyneuropathy,[71] and Creutzfeldt-Jakob disease.[72] Early accumulation of AGEs is also observed in Down syndrome and early antiglycation treatment suggested to reduce cognitive impairments.[73] It was recently sug-

gested that bovine spongiform encephalopathy (BSE), a disease with its significant similarities to AD, might also be associated with increased glycation and lipoxidation.[74] AGEs, amyloid fibrils, and prions seem all to have the same target, RAGE, and all activate the NFκB pathway. Involvement in BSE of glycation products and activation of prion proteins are also suggested by other authors.[75,76]

Atherosclerosis and cardiovascular diseases. Oxidative stress (lipid peroxidation) and protein glycation have repeatedly been associated with extensive arteriosclerosis. A recent study reports significant increases in both chemical AGEs (carboxymethyl lysine) and fluorescent AGEs (spectrofluorimetry) in 42 patients with atherosclerosis when compared with 21 healthy controls ($p < .001$).[77] Increased levels of MDA, lipid peroxides, and pentosidine in a study of 225 hemodialysis patients were recently shown to be significantly and positively correlated to coronary artery calcification score (CACS).[78] Increased development of atherosclerosis and deposition of AGEs/ALEs in the arterial walls, in parallel to a significant increase in lipid oxidation, were observed when rabbits were fed a diet containing 1% cholesterol or 1% cholesterol +10% fructose in drinking water, and especially so in the fructose-complemented group.[79] High-density lipoproteins (HDL) will, when subject to structural modifications by lipoxidation, glycation, homocysteinylation, or enzymatic degradation, lose their antiinflammatory and cytoprotective properties,[80] suggested as important in the pathogenesis of arteriosclerosis but also in neurodegenerative diseases, DM, and other autoimmune diseases.[81] Dendritic cells (DCs) are known to play an important role in the pathogenesis of arteriosclerosis. A recent experimental study demonstrated that supplementation of AGE-modified serum albumin increased levels of cytokine secretions, increased maturation of DCs, and augmented capacity to stimulate T-cell proliferation.[82]

Cancers. The influence of AGEs/ALEs on the pathogenesis of malignant tumors and their ability to grow is not extensively studied. However, it is reported that the sRAGE receptor, highly expressed in healthy lung tissues and especially at the site of alveolar epithelium, is significantly down-regulated in lung carcinomas,[83] and the RAGE expression is reported to be elevated in human pancreatic cells with high metastatic ability and decreased in tumor cells with low metastatic ability.[84] High RAGE expression is also reported in colonic[85] and prostatic[86] cancers. Little information is available about other types of cancers, including breast cancer, but it has recently been suggested that inhibition of AGE-RAGE interaction might have a potential as a molecular target for both cancer prevention and therapy.[84,86]

Cataract and other eye disorders. AGEs/ALEs accumulate with age in all ocular tissues, including lacrimal glands, and trigger pathogenic events, especially in diabetic patients, in all parts of the eye.[87]

DM. More than 2000 publications listed in PubMed (ie, almost half of all DM papers listed) deal with AGEs/AGEs and their role in DM. Several excellent reviews have recently been published.[88–90] Overconsumption of fat and carbohydrates, not only of glucose but also other carbohydrates such as lactose and fructose, contribute especially in diabetic patients to a significant accumulation of AGEs/ALEs in the tissues. Consumption of high-fructose corn syrup in the United States exceeds that of sucrose and is suggested to be the major contributor not only to obesity and hepatic steatosis but especially to T2DM and to severe complications of both types 1 and 2 DM.[91] The feeding of dairy cows have in recent years, similar to human foods, undergone significant changes from mainly forage-based feeds to significant amounts of starch-rich and fast-absorbed carbohydrates: corn, maize grains, barley, molasses, and dextrose, feeds that induce insulin resistance in cows and, if the cows are allowed to live long enough, will lead to manifest DM. Insulin resistance is also observed in calves when intensively fed milk and lactose.[92]

Endocrine disorders. Many if not most of the signs and symptoms of aging, as well as age-associated diseases, are identical to manifestations seen in hormone deficiencies and in premature aging, which is strongly associated with multiple hormone deficiencies. Most consequences of aging such as excessive free radical formation, imbalanced apoptosis system, tissue accumulation of waste products, failure of repair systems, deficient immune system, poor gene polymorphisms, and premature telomere shortening are also associated, if not caused, by hormone deficiencies.[93] Up-regulation of putative pathologic pathways, accumulation of AGEs, activation of the renin-angiotensin system, oxidative stress, and increased expression of growth factors and cytokines are all associated with aging. However, little information either in health or disease, is available about content of AGEs/ALEs in endocrine organs: the pituitary gland, thyroids, parathyroids, adrenals, ovaries, and testes. Increased serum AGE levels and activation of RAGE are reported in women with polycystic ovary syndrome.[94]

Activation of the renin-angiotensin system, known to have a pivotal role in ChDs such as DM and chronic renal disease, contributes to enhanced pathogenic mechanisms: increased oxidative stress, increased general inflammation, increased serum levels of free fatty acids, increased glycotoxicity and lipotoxicity, and advanced glycation and lipoxidation.[95–97]

Gastrointestinal disorders. It is likely that digestive tract disorders such as liver cirrhosis and liver steatosis, as well as inflammatory bowel disorders, are associated with elevated AGEs/ALEs. A recent study reports a 14- to 16-fold increase of glyoxal-derived adducts in portal and hepatic venous plasma of cirrhotic patients compared with healthy controls.[98] Plasma AGE levels were also measured in 51 patients with liver cirrhosis, 5 patients after liver transplantation, and 19 healthy controls.[99] Patients with liver cirrhosis demonstrated significantly increased AGE levels, almost to the same extent as seen in patients with end-stage renal disease. A dramatic improvement was observed in patients after liver transplantation, although the AGE levels did not return to those seen in healthy controls, and the preoperative decrease in renal function did persist. One hundred ten patients

with chronic liver disease (CLD) were recently studied and compared with 124 healthy controls. Serum levels of AGE (CML) were significantly affected by the stage of liver cirrhosis and closely associated with liver function capacity, and AGE (CML) level was reported to positively correlate with levels of hyaluronic acid (HA; $r = 0.639$; $p < .0001$).[100] A recent animal study suggests that blockage of RAGE is highly protective against hepatocellular death and necrosis following ischemia and reperfusion, and increases significantly the rate of survival.[101] Similar observations were also made in acetaminophen-induced hepatotoxicity in mice.[102] In addition to increased survival, decreased hepatic necrosis, and significant increase in glutathione, also significant increases in proregenerative cytokines TNF-α and IL-6 were observed.

Pulmonary disorders. Lack of homeostasis in oxidant/antioxidant balance is obvious in a variety of airway diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and idiopathic pulmonary fibrosis. Interaction of AGEs/ALEs and RAGE plays a large role, if not a dominating one, in the pathogenesis of these pulmonary diseases, and depletion of antioxidants, particularly GSH, in lung epithelial lining is suggested to play a key role in these disorders.[103–105]

Rheumatoid arthritis and other skeletomuscular disorders. A very strong expression of RAGE, and some of the highest levels of AGEs in the body are found in tissues with slow turnover, such as tendons, bone, cartilage, skin, and amyloid plaques. Changes, frequently associated with change in color from white to yellow-brown, include increased fluorescence, increased expression of proinflammatory cytokines, matrix metalloproteinases (MMP), especially MMP-1 and -9. These manifestations are likely responsible for the observed increased tissue stiffness and brittleness in structures such as intervertebral discs, bones tendons, cartilages, synovial membranes, and skeletal muscles and will most likely constitute a major pathogenic factor in diseases such as osteoarthritis,[106,107] rupture of intervertebral discs,[108] Achilles tendons[109] and eventually menisci, and are involved also in rheumatoid diseases[110–112] such as rheumatoid arthritis (RA) and fibromyalgia. A significant increase in glycation of myosin occurs with age,[113] which most likely contributes to age-associated muscular disorders. Observations in subjects with osteoporosis of significantly elevated levels of pentosidine and CML in serum[114] and significantly increased pentosidine in cortical bone[115] are of considerable interest. It has also been observed that the remodeling of senescent bone is impaired by AGEs both through stimulation of bone-resorbing cytokines and enhancement of bone resorption by osteoclasts.[116] The role of bovine milk in prevention of osteoporosis could be found to discredit what has been claimed for decades, should future studies verify that osteoporosis is more due to interactions of RAGE and AGEs/ALEs than to lack of minerals.

Skin and oral cavity. Skin has a high density of AGE receptors. AGEs/ALEs are known to accumulate in dermal elastin and in collagens also, and are known to interact with dermal fibroblasts, inhibiting their proliferation capacity. A 10-times reduction in proliferation rate is described as normal in humans between the second and seventh decade,[117] which might well explain the reduced healing capacity of age-related wounds and especially chronic wounds such as those in the extremities of people with DM. It has also been observed that accumulation of AGEs/ALEs in the skin reflects the AGE/ALE deposition in the rest of the body to such a degree that skin autofluorescence has been suggested as a measure of cumulative metabolic stress and AGEs in the body.[118] Skin autofluorescence is suggested to be so exact that it is able to predict progression of retinopathy and nephropathy in DM, as well as mortality in hemodialysis patients.[118] RAGE and AGE/ALE-induced apoptosis and enhanced loss of fibroblasts and osteoblasts are also regarded as major pathogenic factors in periodontal pathology, especially in chronic periodontitis.[119] A 50% increase in RAGE mRNA is observed in gingiva of diabetic patients compared with controls ($p < .05$).[120]

Urogenital disorders. Nephropathy is common in the modern world and its incidence is fast increasing, much in parallel to the increase in DM. Diabetic nephropathy alone affects today 15%–25% of patients with type 1 DM and as many as 30%–40% of patients with T2DM. Furthermore, it is the single most important cause of end-stage renal failure in the western world.[121] The kidney appears as both culprit and target of AGEs/ALEs, and it is well documented that RAGE is significantly activated and levels of AGEs/ALEs are markedly elevated in patients with renal failure. More than 500 papers on PubMed deal with RAGE and AGEs/ALEs in renal diseases. A decrease in renal function and reduced renal clearance are observed much in parallel to increases in circulating AGEs. AGEs are also involved in the structural changes observed in progressing nephropathies such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy[122]; more detailed information has been published in recent excellent reviews.[122–127] Patients with mild chronic uremic renal failure are reported to have plasma glycation free adduct concentrations increased up to 5-fold; patients with end-stage renal disease, as much as 18-fold when receiving peritoneal dialysis and up to 40-fold when receiving hemodialysis.[128] Kidney transplantation is reported to improve but does not fully correct the increased levels of AGE/ALE in patients who have been previously dialyzed.[129]

Dietary Measures to Reduce AGEs/ALEs

The greatest of contributors by far of AGEs/ALEs by food (Table II) seem to be dairy products[130] (Figure 1), bread, and meat, not only because they are rich in these substances but also as these foods constitute the bulk of modern food, especially in the western world. Also, plants contribute to accumulation of AGEs/ALEs in the body, especially fruits, which contain larger amounts of fructose, which is highly reactive with proteins. However, consumption of carbohydrates seem mainly, or only, to be of considerable risk when consumed as industrially concentrated products, refined sugar, and high-fructose corn syrup.[91]

TABLE II
Short list of foods rich in AGEs/ALEs[131]

Dairy products, especially milk powder (present in numerous foods, ice cream, baby formulas, and clinical nutrition solutions) and cheese (used in fast foods: pizza, tacos, nachos, salads, fast-food sandwiches, and sauces for potatoes and vegetables)
Grains, cereals, bakery products: bread, especially toasted bread, bread crusts, and crisp breads
Meat, poultry and fish: content increases as one goes from boiling to oven frying: boiling (1000 kU/serving) < roasting (4300 kU/serving) < broiling (5250 kU/serving) < deep frying (6700 kU/serving) < oven frying (9000 kU/serving)
Egg yolk powder, lecithin powder, Chinese soy products, balsamico products, and other products produced by heating and drying
Coffee, tea, alcohol, and beer

Consuming a vegan diet, known to be low in AGEs/ALEs, seems to result in statistically lower systolic and diastolic blood pressure, lower serum total cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood glucose, fewer weight problems, and less incidence of ChDs, especially DM and its complications. However, there are also problems with a vegetarian (lactovegetarian and vegan) lifestyle which need to be corrected, among them risk of shortage in vitamin B_{12} and poor taurine status,[132] and for lactovegetarians, higher serum levels of homocysteine. The serum levels of AGEs/ALEs are reported as higher in longtime healthy lactovegetarians than in healthy omnivorous people.[133] One explanation could be, as suggested by the authors, a higher intake of fructose, especially because this carbohydrate is significantly more reactive with proteins than sucrose. Another explanation could be a higher consumption of various milk products, especially cheese and milk powder, known to be rich in AGEs/ALEs, meant to substitute meat and fish in the diet.

Several measures have been demonstrated to significantly decrease serum and tissue concentrations of AGEs/ALEs, among which are the following.

Calorie restriction. Evidence from animal studies suggests that restriction in food intake is an effective means to extending median lifespan and preventing ChDs.[15] Few studies are, unfortunately, available in primates and almost no studies in humans. Significant benefits of long-term (2–11 years) CL compared with normal western diet were recently reported in a study in healthy humans: blood pressure 102 ± 10/61 ± 7 *vs* 131 ± 11/83 ± 6 mm Hg, c-reactive protein (CRP) 0.3 ± 0.3 *vs* 1.9 ± 2.8 mg/L, tumor necrosis factor (TNF)-α 0.8 ± 0.5 *vs* 1.5 ± 1.0 pg/mL, transforming growth factor (TGF)-β 29.4 ± 6.9 ng/mL *vs* 35.4 ± 7.1 ng/mL respectively.[134] Patients with RA receiving a low-energy diet for 54 days demonstrated a significant reduction in both urinary pentosidine level and RA disease activity.[135] However, studies on the effects of CL on AGEs/ALEs are thus far lacking in other groups of ChDs.

Vitamins and antioxidants. Glutathione (γ-glutamylcysteinyl glycine [GSH]) is regarded as an important factor for optimal cellular function and defense against oxidative stress. Dietary supply of GSH has been shown to reduce glycation and prevents diabetic complications such as diabetic nephropathy and neuropathy.[136] Rich supply of vitamins A, C, E, and particularly B_6, B_{12}, and folic acid (Figure 2) is often emphasized in the literature.[137] Vitamin D should

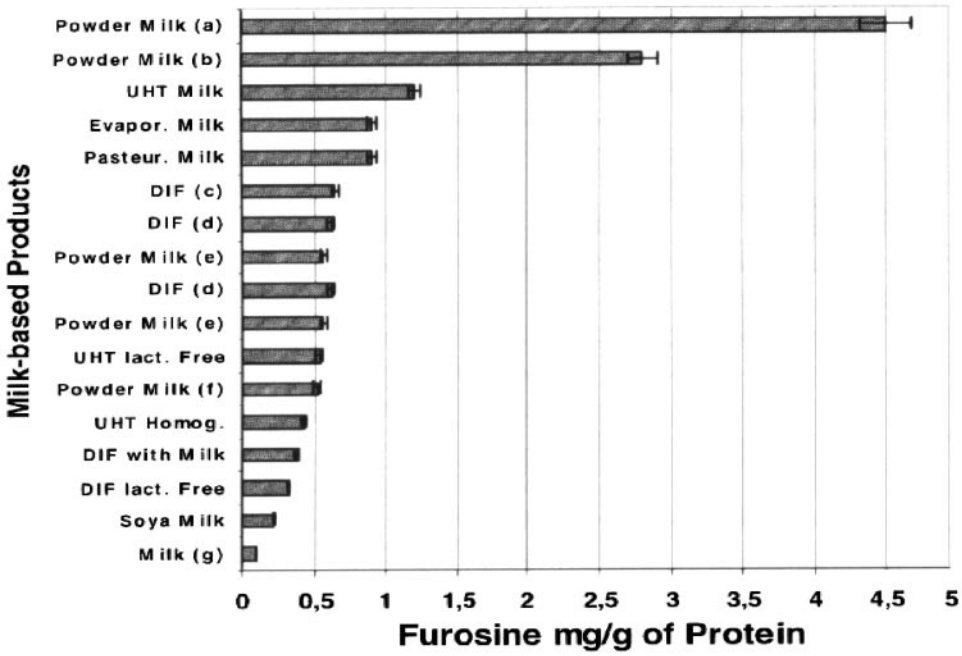

FIGURE 1. Relative furosine content in various milk-based products. A, Milk powder kept for 2 years in room temperature. B, Milk powder kept for 1 year at room temperature. C, DIF with whey plus casein. D, DIF with hydrolyzed whey. E, Milk powder kept for 1 year at 4°C. F, Fresh milk powder. G, Raw (whole) bovine milk. Reprinted from Baptista JAB, Carvalho RCB. Indirect determination of Amadori compounds in milk-based products by HPLC/ELSD/UV as an index of protein deterioration. *Food Res Int.* 2004;37:739–747, with permission from Elsevier.
DIF, dietetic infant formulas; UHT, ultraheat treatment.

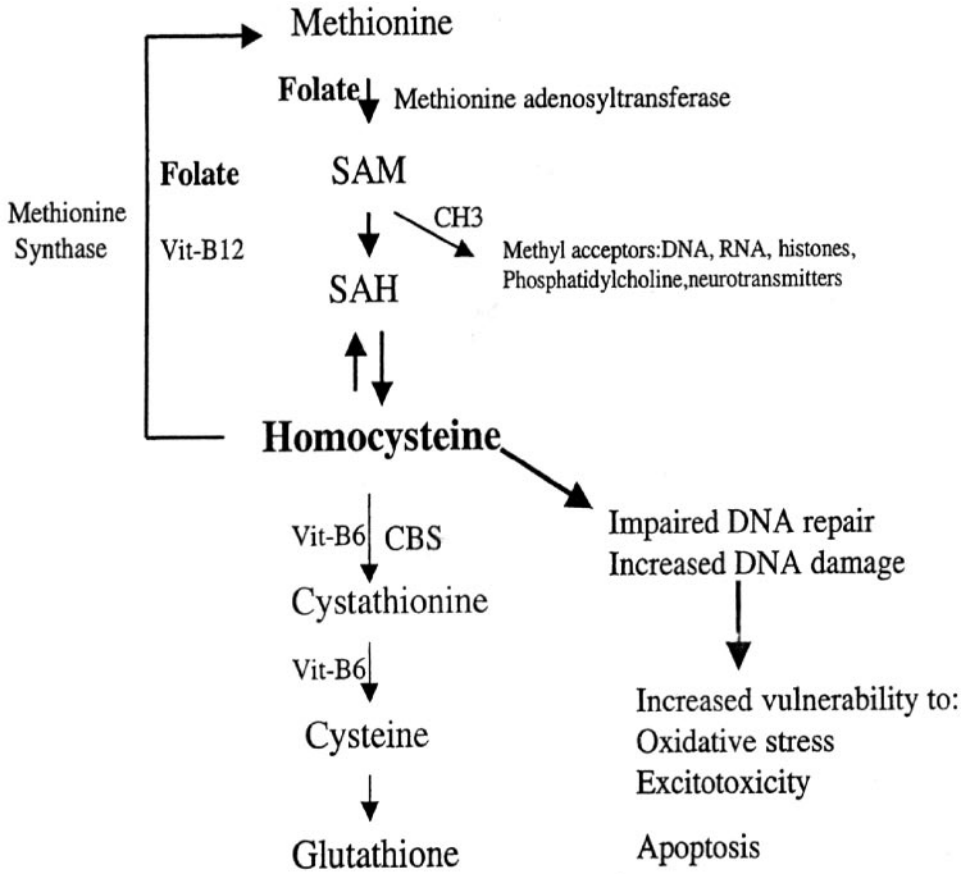

FIGURE 2. Involvement of homocysteine, folic acid, and vitamins B_6 and B_{12} influences metabolism and possible mechanisms whereby elevated homocysteine contributes to increased risks of chronic diseases. Reprinted from Mattson MP. Will caloric restriction and folate protect against AD and PD? *Neurology.* 2003;60:690–695, with permission from Lippincott Williams & Wilkins.[137]

most likely also be supplemented, especially at higher latitudes.[49] Several thousands of plant-derived chemopreventive agents, polyphenols, and many others, most often yet unexplored, have the potential to reduce the speed of aging and prevent degenerative malfunctions of organs, among them, isothiocyanates in cruciferous vegetables, anthocyanins and hydroxycinnamic acids in cherries, epigallocatechin-3-gallate (EGCG) in green tea, chlorogenic acid and caffeic acid in coffee beans and also tobacco leaves, capsaicin in hot chili peppers, chalcones in apples, eugenol in cloves, gallic acid in rhubarb, hisperitin in citrus fruits, naringenin in citrus fruits, kaempferol in white cabbage, myricetin in berries, rutin and quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine and virgin peanuts, various curcumenoids, the main yellow pigments in turmeric curry foods,[138] and daidzein and genistein from the soybean. These compounds have all slightly different functions and seem to complement each other well. Several, most likely the majority, of these substances have a great capacity to inhibit the second phase of the glycation process, eg, the conversion of the Amadori products to AGEs. A significant number of animal studies support health benefits of these antioxidants and AGE/ALE scavengers.[139,140] Again, human studies are largely lacking.

Taurine, carnitine, carnosine, histidine. Taurine, a sulfonic acid compound, is normally found in high concentrations intracellularly in most animal tissues, and especially in blood cells, retina, and nervous tissues. The highest concentrations are found in neutrophils, where it is suggested to reduce inflammation.[141] The richest sources of taurine are seafood, fish, and poultry. Moderate amounts are also found in meat, whereas plants, with the only known exception of some algae, and consequently also vegan diets, are devoid of this amino acid.[142] Taurine has strong hypoglycemic effects, observed already in the 1930s.[143] It reduces production of AGEs/ALEs and prevents high-fructose-diet-induced collagen abnormalities in animals.[144,145] *In vitro* and animal studies suggest that similar effects are obtained also from supplementing amino acids such as histidine or peptides such as carnitine and carnosine. Again, no human studies have been undertaken.

Pre- and pro-biotics. Plant-derived antioxidants and AGE/ALE scavengers need to be released from the plant fibers during passage through the digestive tract. This process is mainly dependent on microbial enzymes, provided by the flora in the lower gastrointestinal tract. This flora is reported to be severely impaired in about 75% of omnivorous Americans and one-third of vegetarian Americans.[146] Lactic acid bacteria (LAB) are also in their own capacity strong oxidation scavengers and effective inhibitors of inflammation. LAB might also have the capacity, before the food

is absorbed to eliminate AGE/ALE protein and peptides, as was earlier demonstrated for gluten[147] and carcinogens.[148] Support for such an assumption derives from an *in vitro* study, where fructose lysine, the main modified molecule in heated milk,[126] is eliminated (deaminated) when incubated with live flora.[149]

Future Directions

In the past, most studies on lifestyle-associated disease have focused mainly on coronary heart disease, T2DM, and chronic renal disease. Increasing evidence suggests that an "unhealthy" lifestyle is negatively associated with most, if not all, ChDs. Common to the ChDs is a permanent, often silent, exaggerated inflammation, strongly associated with metabolic syndrome and increased deposits in tissues of AGEs/ALEs. ChD patients, including those with obscure etiology and those with inherent genetic disorders (Down syndrome,[73,150] cystic fibrosis,[151,152] schizophrenia,[153,154] and mental depression[155–157]) might well benefit from reduced AGE/ALE intake. However, more studies are needed. Studies performed in the United States have reported that the incidence of a number of chronic diseases would be greatly reduced if people would follow a "healthy lifestyle." These estimates suggest that the incidence of coronary artery disease could be reduced by 83%, diabetes mellitus in women could be reduced by 91%, and colon cancer in men by 71%.[160] It is likely that controlled intake and cellular production of AGEs/ALEs constitute important contributions to such a healthy lifestyle.

Exaggerated inflammation is also observed in patients who have complications to acute diseases: sepsis, trauma, and advanced surgical and medical treatments such as transplantations. Complications and sequelae to these events are significantly more common in elderly people and in those with ChDs. Clearly, lifestyle of the individual and inflammation before the trauma will significantly influence outcome.[161] Presence of metabolic syndrome has been shown to have a strong negative influence on outcome in acute morbidities and in ICU patients. Future attempts to minimize accumulation of such substances in the body might provide significant benefits in both acute and chronic morbidities. It is important to stress that research in this field is in its infancy, and many more studies are needed, particularly in humans. I wish such studies will be given the highest priority.

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