

Review Article

Amplifiers of Systemic Inflammation – The Role Advanced Glycation and Lipoxidation End Products in Foods

Stig Bengmark

Lund University, Lund, Sweden

Departments of Hepatology and Surgery, University College London (UCL), London University, London, UK
Institute of Hepatology, University College, London Medical School, London, UK

Kuwait Medical Journal 2008, 40 (1): 3-17

ABSTRACT

Chronic diseases are repeatedly associated to accumulation in the body of glycated and lipoxidated proteins and peptides. PubMed reports in excess of 5000 papers plus about 14,000 articles about the related HbA_{1c}, RAGE, a member of the immunoglobulin super-family of cell surface molecules and receptor for advanced glycation end products, functions as a master switch, induces sustained activation of NF- κ B, suppresses a series of endogenous auto-regulatory functions and converts long-lasting pro-inflammatory signals into sustained cellular dysfunction and disease. RAGE is activated by high levels of dys-functioning proteins in body fluids and

tissues and is strongly associated with chronic diseases from allergy and Alzheimer to rheumatoid arthritis and urogenital disorders. Heat-treatment, irradiation and ionization of foods increase the content in foods of advanced glycated end-products (AGE) and advances lipoxidated end-products (ALE). Some processed foods, much like tobacco smoking are major contributors to accumulation of glycated and lipoxidated molecules in the tissues. Change of life style: avoidance of foods rich in deranged proteins and peptides and increased consumption of antioxidants, especially polyphenols counteracts such a development.

KEY WORDS: antioxidants, acute diseases, chronic diseases, foods, glycation, inflammation, lipoxidation, Maillard products

INTRODUCTION**Epidemic of Chronic Diseases**

Chronic diseases (ChD) constitute today the leading cause of morbidity and mortality. World Health Organization (WHO) estimates that 46 % of global disease burden and 59 % of global mortality is due to ChD; 35 million individuals die each year from chronic diseases, and it increases steadily^[1]. The fastest increase in ChD is in recent years was seen in the Third World – there are today more cases of type 2 diabetes in India (44 million) and China (22 million) than in the US (17 million) and this increase continues in these countries as in the rest of the world. The picture is similar for most ChDs. It appears as if we in the Western world export the ChDs together with our lifestyle with our enormous surplus of cheap agricultural products: dairy products, especially milk powder and butter, and grains, especially wheat. Little consideration seems to be given to the fact that a large proportion of individuals in these parts of the world are gluten or lactose intolerant and are deficient in the local production of health-promoting fresh fruits and vegetables, rich in nutrients, antioxidants and

health-promoting lactic acid bacteria (LAB).

The increase seems to have begun at the time of the industrial revolution, *e.g.* mainly in the early and middle 19th century. Circumstantial evidence supports an association of ChDs to change in lifestyle with less physical activity, increased mental and physical, stress and transition from natural unprocessed foods to processed, calorie-condensed and chemically modified foods. The food consumption during the last 150-200 years is characterized by significant reduction in intake of plant fibers, plant antioxidants and n-3 polyunsaturated fatty acids (PUFAs), a more than doubled intake of saturated and trans fatty acids (from app 20% to > 40% of daily energy intake) and a > 100-fold increase in high glycemic index (GI) foods: sugary and starchy products - the annual consumption of refined sugars has increased from about one lb per person per year in 1850 to about 100 lbs/person/year in the year 2000.

IMPAIRED INNATE IMMUNE FUNCTIONS

Common to most of the food ingredients mentioned above is that they affect the function

Address Correspondence to:

Stig Bengmark, MD, PhD, FRACS (Hon), FRCPS (Hon), 185 Barrier Point Road, Pontoon Docks, London E16 2SE, United Kingdom. Tel & Fax: +44 20 7511 6842, E-mail: s.bengmark@ucl.ac.uk

of the innate immune system, the inflammatory response and the individual's resistance to disease. While plant fibers, antioxidants and to some extent PUFAs enforce resistance to disease, saturated and trans- fatty acids, sugar and starch, peptides such as gluten, and many chemicals and pharmaceuticals, including antibiotics, suppress resistance to disease. Consequently, most ChD patients suffer increased acute (APR) and chronic (CPR) phase response, increased inflammation/super-inflammation and metabolic syndrome (MS) – (see further Bengmark)^[2]. Important observations are that saturated fat, as well as trans fatty acids, induce significant alterations in the immune response^[3], inhibit the macrophage functions^[4], stimulate Th2 response relative to the Th1 response and increase the risk of getting chronic diseases such as diabetes, certain cancers and rheumatoid arthritis^[4]. It has not been given the attention it deserves that exposure to some chemicals including supply of pharmaceutical drugs such as antibiotics will suppress macrophage functions demonstrated for antibiotics by studies of chemiluminescence response, chemotactic motility, bactericidal and cytostatic ability and of lymphocyte proliferation^[5,6].

ADVANCED GLYCATION AND LIPOXIDATION

It is almost 100 years since Malliard described the non-enzymatic pathway for glycation of proteins and suggested that such chemically modified proteins could play a role in the pathogenesis of ChDs, particularly diabetes^[7]. However, it is only in the last two decades, particularly the last five years, that this concept has received a wider attention. Contributory to the increased interest in recent years is the observation of glycated hemoglobin, HbA_{1c}^[8,9] and its role in diabetes and in various aging-associated diseases, and particularly the identification of several receptors in the body, of which RAGEs are the most well-known and studied^[10,11]. Presently in excess of 5000 papers about the biology of advanced glycation products are to be found on PubMed in addition to the > 13,500 about HbA_{1c}.

RAGE – A MASTER SWITCH

Metabolic syndrome with all its clinical manifestations is strongly associated with development of ChDs. Recent studies suggest that a chronic low-grade inflammation foregoes and plays an important role in the development of and maintenance of metabolic syndrome^[12] and in pathogenesis of ChDs. Common to different ChDs are, in addition to a subinflammatory state, a significantly elevated oxidant stress (OS) and OS-induced gene expression^[12-15]. Much support that receptor for advanced glycation end-products

(RAGE) and various other receptors for advanced glycation (AGEs) and also lipoxidation (ALEs) end products play a central role in the genesis of these changes. RAGE, a member of the immunoglobulin superfamily of cell surface molecules, is known to convert long-lasting cellular activation into sustained cellular dysfunction/disease^[16]. RAGE seems to function as a master switch, converting proinflammatory signals into long-lasting, often permanent cellular dysfunction^[17]. This is done as RAGE induces a sustained activation of proinflammatory transcription factor NF- κ B and suppresses a series of endogenous autoregulatory functions^[18]. Reducing the inflammatory environment though reduction in accumulation in the tissues of AGE and ALE ligands has also been shown to reduce or eliminate sustained exaggerated inflammation and cellular dysfunction and to improve outcome of disease – see further^[16,19].

LIFE-LONG ACCUMULATION OF AGEs AND ALEs

As pointed out by Vlassara^[19], industrial processes aimed to make food safer, flavorful and colorful, such as heating, irradiation and ionization, do all, in combination with gross over-nutrition, significantly contribute to production of, exposure to and accumulation in the body of AGEs / ALEs. Vlassara and her group has also in human studies demonstrated significant correlation between ingested AGEs, circulation AGEs and induction of several markers of inflammation^[20,21]. Furthermore, they demonstrated in animal studies that dietary restriction of AGEs has “protective” effects against impaired immune function in various ChDs and complications to ChDs, particularly diabetes-induced vasculopathy^[22], nephropathy^[23] and impaired wound healing^[24]. And most interestingly, these animals remained close to ‘free from pathology’ state despite the presence of the underlying disease^[19]. Furthermore, dietary AGE restriction seemed in animals to be as effective to extend life span as caloric restriction^[25]. These observations are partially confirmed in humans with diseases such as diabetes, vascular disease and kidney disease, who responded with a considerable reduction in markers of inflammation and vascular dysfunction when supplied a low-AGE diet^[20,26].

AGE's constitute a complex, heterogenous and increasing group of compounds formed mainly by nonenzymatic reactions of reducing sugars with amino acids, nucleic acids, peptides and proteins, which produce early compounds called Amadori products, which later through a so called Maillard reaction undergo complex changes such as cyclization, dehydration, oxidation, condensation, cross-linking and polymerization to form irreversible

chemical products referred to as Maillard products or AGEs/ALEs. In particular, 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 guanidino 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 these processes. High intracellular and extracellular concentrations of reactive carbohydrates such as glucose, but even more the highly reactive fructose, are important triggers for increased glycation and formation of glyoxal, methylglyoxal and 3-deoxyglucosan, which glycate protein and sooner or later form intracellular and extracellular accumulation of AGEs/ALEs. Significantly elevated visceral AGE formation, serum AGE levels, caspase-3 activation and cytoplasmic DNA fragmentation in organs such as heart, liver and kidneys are regularly observed in animals with dyslipidemia due to high-fat diet (32 - 42% fat)^[27], all in line with 50 year old observations that high-fat diet-induced increased rate of diseases such as myocardial infarction, renal infarcts and thrombus formation^[28].

Glyoxal and methylglyoxal formation constitutes an intermediate stage in the Maillard reaction, while pentoside, an often studied glyco-oxidation product and fluorescent cross-link, is formed in the late stage of the reaction, where it becomes stable and irreversible. Many AGEs in tissues have been identified, but most studies are performed in only a few of them: in addition to HbA_{1c} mainly AGEs such as pentoside and/or N^ε-carboxymethyl lysine (CML) and N^ε-(carboxyethyl)lysine (CEL). However, new, previously unknown AGEs are identified at a rate of 2-3 per year^[29]. Furthermore, there is increasing evidence that accumulation of chemically modified lipids in the tissues are as important contributors as carbohydrates to development of diseases^[30]. It is especially the lipids in milk products and meat that, when these foods are heated up, contribute substrate for production and accumulation of ALEs in the tissues. A typical AGE such as CML, seems to be formed from both carbohydrate and lipid sources^[31]. Examples of specific AGEs are pentoside, crosslines, vesperlysines and 3DG-imidazolones while malondialdehyde (MDA) acrolein adducts of lysine, histidine and cysteine are specific examples of ALEs – see further^[31].

A great variety of different AGEs/ALEs are observed in the tissues and in the circulation of patients with ChDs, and common to most, if not all ChDs is that the levels are significantly increased compared to healthy individuals. Irrespective of source, both AGEs and ALEs, when accumulated in tissues do significantly induce increased

Table 2. 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 |

eNOS, endothelial nitric oxide synthase; TGF-β, transforming growth factor-β; MCP-1, monocyte chemoattractant protein-1; CTGF, connective tissue growth factor; PAI-1, plasminogen activator inhibitor-1.

Fig. 1: Documented cellular events and changes in cytokines associated with AGE and RAGE activation (after Bohlender *et al*)^[128]

inflammation and infection^[32,33], reduce antioxidant defense^[34], weaken immune system^[35], impair DNA repair mechanisms^[36] and accumulation of toxins in the the tissues^[32]. Most importantly, they accelerate the rate of development of various ChDs. And the differences are great - glycated proteins are suggested to produce almost 50 times more free radicals than nonglycated proteins^[37]. The plasma concentrations of free CML and CEL are for example increased about 8-fold and 22-fold, respectively, in hemodialysis patients^[38].

LONG-LIVED MOLECULES / TISSUES ARE SPECIAL TARGETS

Cumulative AGEs/ALEs modification of tissues occurs predominately on long-lived molecules such as collagen, neural myelin and lens crystallins resulting in insoluble, indigestible and dysfunctional compounds that accumulate with time. The crosslinking of glycated collagen leads to decreased elasticity of collagen-rich tissues, which explains the age- and ChD-dependent increase in stiffness of joints and skeletal muscles and lenses, but also of cardiovascular system with increased blood pressure^[39]. AGEs/ALEs exert strong effects on endothelial cells and pericytes: stimulate growth, interact with cell-surface receptor RAGE and activate the NF-κB pathway, induce vascular endothelium growth factor (VGEF), inhibit prostacycline production and stimulate plasminogen activator inhibitor-1 (PAI-1) synthesis by endothelial and other cells. Fig. 1 summarizes documented cellular events and changes associated with AGE and RAGE activation.

Of special interest is that these processes seem all to be sensitive not only to oxidants/antioxidants but also to a large extent to hormones, especially growth and sex hormones. 17 β -estradiol has been shown to significantly upregulate RAGE mRNA and protein level in human microvascular endothelial cells^[40]. This could explain the common observation that diabetic vasculopathy and retinopathy are often exacerbated in pregnancy. 17 β -estradiol in concentrations observed during pregnancy (~ 10 nM) stimulates significant up-regulation of VEGF-dependent angiogenesis^[41]. It is also observed that effects induced on endothelial cells by 7 β -estradiol and RAGE mRNA are totally abolished by supply of antiestrogens such as 4-OH tamoxifen^[41]. This knowledge might explain why commercial bovine milk, known to be rich not only in AGEs/ALEs but also in estrogens including 17 β -estradiol, is often associated with different ChDs such as allergy^[42], coronary heart disease^[43,44], diabetes^[45-47], Parkinson's disease^[48] and various cancers such as breast^[49,50], prostatic^[51,52], testicular^[51] and to some extent ovarian^[53,54] malignancies. Secondary hyperparathyroidism, due to poor supply of vitamin D, especially at higher altitudes (where incidence of ChDs and rate of complications to ChDs are significantly higher during winter), seem also to play a significant role^[55,56]. Parathyroid hormone is known to induce IL-6 and levels of serum IL-6 have been shown to significantly increase in hyperthyroid patients (16-fold) and in overweight patients – see further^[55].

THE ROLE OF AGE/ALE TISSUE DEPOSITION IN COMMON CHDs

Deposition in sensitive tissues of abnormal proteins, often as amyloid is a common feature of various ChDs. These deposits are AGEs/ALEs and are known to produce fluorescence. The degree of ALE/AGE deposition can be relatively easily and reliably measured, especially in organs such as the skin, blood and lenses, through estimation of the degree of fluorescence^[57]. The content of AGEs/ALEs seems to always increase with aging, also in healthy individuals. However, this increase is considerably more pronounced in individuals who will or have acquired various ChDs. It is increasingly recognized that activation of RAGE plays a key role in pathogenesis of various ChDs. Increased deposition of AGEs/ALEs in tissues is also strongly associated to metabolic syndrome and also to downregulated leptin expression in adipocytes^[58-60].

Here follows a short summary of some common ChDs and their association to AGE/ALE-induced changes:

Allergy and autoimmune diseases: Thermal processing, curing and roasting of foods introduce

major changes in allergenicity of foods, and is likely to introduce neoantigens and increase allegenicity. However, further studied are needed, especially as sometimes reduced allergenicity has also been reported^[61-62]. Heated foods such as milk, peanuts and soy are, however, reported to significantly influence levels of AGEs and the IgE-binding capacity^[63,64]. Significantly elevated levels of urinary AGEs such as pentosine have been observed in children in connection with exacerbation of atopic dermatitis^[65].

Alzheimer disease (AD) and other neurodegenerative diseases: Similarities between Alzheimer and type 2 diabetes (T2DM) exist to the extent that Alzheimer has been called “the diabetes of the brain”. The incidence of AD is also reported to be 2 to 5-fold increased in T2DM – see further^[66]. A common feature of both diseases is accumulation of amyloid deposits, a process, which progresses during the whole course of disease. AGEs/ALEs in AD are identified immunohistochemically both in senile plaques, in tau proteins, amyloid β proteins and in neurofibrillary tangles^[67,68]. A threefold increase in content of AGE is also reported in AD brains compared to age-matched controls^[69] supporting a role of AGEs in the pathogenesis of AD. The olfactory bulbs, early targets of AD, also show significant increase in AGE and markers of oxidative damage^[69]. Furthermore, increases in RAGE protein and in percentage of RAGE-expressing microglia are reported to parallel the severity of disease^[70]. Among the changes observed are, in addition to amyloidosis, perturbation of neuronal properties and functions, amplification of glial inflammatory response, increased oxidative stress, increased vascular dysfunction, increased A β in the blood brain barrier and induction of autoantibodies - see further^[70]. Early indications suggest, although this is less studied, that AGEs/ALEs are also involved in the pathogenesis of other neurodegenerative diseases such as Parkinson's disease (PD)^[71,72], amyotrophic lateral sclerosis (ALS)^[73-75], Huntington's disease^[76], stroke^[77], familial amyloidotic polyneuropathy^[78] and, most interestingly, in Creutzfeldt-Jakob disease^[79]. Early accumulation of AGEs is also observed in Down's syndrome and early antiglycation treatment suggested to reduce cognitive impairments^[80]. It was recently suggested that bovine spongiform encephalopathy, a disease with its significant similarities to Alzheimer, is also associated with increased glycation and lipoxidation^[81]. AGEs, amyloid fibrils and prions all seem to have the same target: RAGE and they all do activate the NF- κ B pathway^[81]. Frey suggests, but no studies are yet performed, that glycation will have the capacity

to activate prion proteins. What is clear is that the feeds of dairy cows has in recent decades changed significantly, as has Western foods, from mainly forage-based feeds to that containing more of starch-rich and fast-absorbed carbohydrates: corn, maize grains, barley, molasses and dextrose. Such feeds will most likely induce resistance to insulin (in cows if the cows were allowed to live long enough) and development of diabetes. Insulin resistance has also been observed in intensively milk- and lactose-fed calves^[82].

Arteriosclerosis 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 (carboxymethyllysine) and fluorescent AGEs (spectrofluorimetry) in 42 patients with atherosclerosis when compared to 21 healthy controls ($p < 0.001$)^[83]. Increased levels of malondialdehyde, lipid peroxides and pentosidine were found recently in a study of 225 hemodialysis patients shown to be significantly and positively correlated to coronary artery calcification score (CACS)^[84]. Increased development of arteriosclerosis and deposition of AGE/ALES in the arterial walls, in parallel to a significant increase in lipid oxidation, was 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^[85]. High density lipoproteins (HDL) will, when subject to structural modifications by lipoxidation, glycation, homocysteinylolation or enzymatic degradation, lose their anti-inflammatory and cytoprotective properties^[86]. This has been suggested to be of importance in the pathogenesis of not only arteriosclerosis, but also in neurodegenerative diseases, diabetes and other autoimmune diseases^[87]. Dendritic cells (DCs) are known to play an important role in the pathogenesis of arteriosclerosis. A recent experimental study demonstrates that supplementation of AGE-modified serum albumin increased levels of cytokine secretions, increased maturation of DCs and augmented capacity to stimulate T-cell proliferation^[88].

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 downregulated in lung carcinomas^[89] and the RAGE expression is reported to be elevated in human pancreatic cells with high metastatic ability and low in tumour cells

with low metastatic ability^[90]. High RAGE expression is also reported in colonic^[91] and prostatic^[92] cancers. Little information is, however, 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^[90-92].

Cataract and other eye disorders: AGE/ALEs accumulate with age in all ocular tissues including lacrimal glands and trigger pathogenic events, especially in diabetics, in all parts of the eye^[93,94].

Diabetes (DM): Over-consumption of fat and carbohydrates and not only of glucose but also other carbohydrates such as lactose and fructose, will significantly contribute to the accumulation of AGEs/ALEs in the tissues of diabetics. The consumption of high-fructose corn syrup in the US is today exceeding that of sucrose, and suggested to be the major contributor, not only to obesity and hepatic steatosis, but also to type 2 diabetes and to severe complications of both type 1 and 2 diabetes^[95]. Almost half of the publications about AGEs/ALEs or >2000 deal with their role in DM. Several excellent reviews are recently published^[96-98].

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, a condition 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, with hormone deficiencies^[99]. Increased glycation and cross-linking of proteins are significant signs of aging, products known to especially accumulate in parenchymal organs, as shown in diabetes and chronic renal disease. Upregulation of putative pathological pathways; accumulation of AGEs, activation of the renin-angiotensin system, oxidative stress and increased expression of growth factors and cytokines are frequently observed in the settings of ChDs, but little information is available about the content of AGEs/ALEs in endocrine organs such as the pituitary gland, thyroids, parathyroids, adrenals, ovaries and testes in health and disease. However, increased AGE serum levels and activation of RAGE is reported in women with polycystic ovary syndrome^[100]. Activation of the renin-angiotensin system, known to have a pivotal role in ChDs such as diabetes and chronic renal

disease, potentiates the pathogenic mechanisms: increase advanced glycation, glycototoxicity and lipotoxicity and contribute to enhanced oxidative stress and inflammation and to increased levels of free fatty acids^[101-103].

Gastrointestinal disorders: It is likely that GI 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 14-16-fold increase of glyoxal-derived adducts in portal and hepatic venous plasma of cirrhotic patients compared to healthy controls^[104]. Plasma AGE levels were also measured in 51 patients with liver cirrhosis, five patients after liver transplantation and 19 healthy controls^[105]. 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 the levels seen in healthy controls and the preoperative decrease in renal function also persisted. One hundred and ten patients with chronic liver disease (CLD) were recently studied and compared to 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 (reported to positively correlate with levels of hyaluronic acid (HA) ($r = 0.639$, $p < 0.0001$)^[106]. A recent animal study suggests that blockage of RAGE is highly protective against hepatocellular death and necrosis on ischemia and reperfusion (I/R) and increases significantly the rate of survival^[107]. Similar observations are also made in acetaminophen-induced hepatotoxicity in mice^[108]. In addition to increased survival, decreased hepatic necrosis and significant increase in glutathione and pro-regenerative cytokines TNF- α and IL-6 was observed.

Pulmonary disorder: 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, if not a dominating, at least a large role in the pathogenesis of these pulmonary diseases, and depletion of antioxidants, particularly GSH, in lung epithelial lining is thought to play a key role in these disorders^[109-111].

Rheumatoid arthritis and other skeletomuscular disorders: A very strong expression of RAGE and among the highest levels of AGE in the body are found in tissues with slow turnover, such as tendons, bone,

cartilage, skin and amyloid plaques. These changes are associated with change in color from white to yellow-brown, increased fluorescence, increased expression of proinflammatory cytokines, matrix metalloproteinases (MMP), especially MMP-1 and -9. These manifestations are likely to be 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^[112,113], rupture of intervertebral discs^[114], Achilles tendons^[115], eventually also of menisci, and rheumatoid diseases^[116-118] such as rheumatoid arthritis and fibromyalgia. A significant increase in glycation of myosin occurs with age^[119] which most likely contributes to age-associated muscular disorders. Observations in subjects with osteoporosis of significantly elevated levels of pentosidine and CML in serum^[120] and significantly increased pentosidine in cortical bone^[121] 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^[122]. The role of bovine milk in prevention of osteoporosis can well be found to be opposite to what has been believed and 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 RAGE receptors. AGEs/ALEs are known to accumulate in dermal elastine and in collagens and to interact with dermal fibroblasts, inhibiting their proliferation capacity. A ten time reduction in proliferation rate is described as normal in humans between the second and seventh decade^[123]. This might well explain the reduced healing capacity of age-related wounds, and especially chronic wounds such as those on the diabetic foot. 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 advanced glycation end products in the body^[124]. Skin autofluorescence is suggested to be so exact that it is able to predict progression of retinopathy and nephropathy in diabetes^[124] as well as mortality in hemodialysis patients^[115]. RAGE and AGE/ALE-induced apoptosis and enhanced loss of fibroblasts and osteoblasts is also regarded as a major pathogenic factor in periodontal pathology, especially in chronic periodontitis^[126]. A 50% increase in RAGE mRNA is observed in gingiva of diabetic patients compared with controls ($p < 0.05$)^[126].

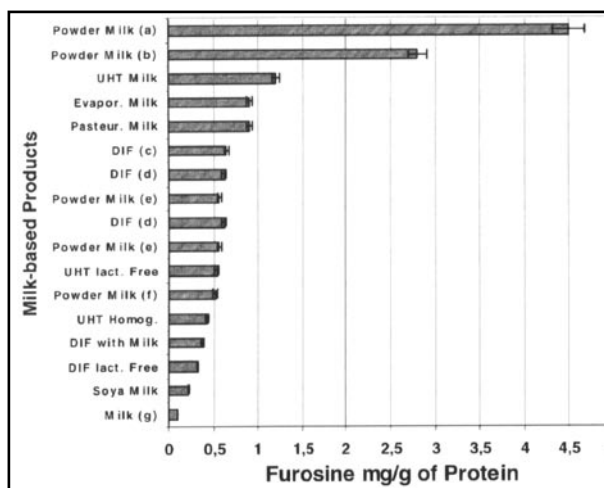


Fig. 2: Relative furosine content in various milk-based products. (a). Milk powder kept for two years at room temperature. (b). Milk powder kept for one year at room temperature. (c). DIF with whey plus casein. (d). DIF with hydrolyzed whey. (e). Milk powder kept for one year at 4 °C. (f). Fresh milk powder. (g). Raw (whole) bovine milk. DIF= dietetic infant formulas, UHT= ultra heat treatment (after Baptista JAB, Carvalho

Urogenital disorders: Nephropathy is common in the modern world and its incidence is fast increasing, much in parallel to the increase in diabetes. Diabetic nephropathy alone today affects 15-25% of patients with type 1 diabetes and as much as 30-40% of patients with type 2 diabetes. Furthermore, it is the single-most important cause of end-stage renal failure in the Western world^[127]. The kidney appears as both culprit and target of AGEs/ALEs, and it is well documented that RAGE is significantly activated and advanced AGEs/ALEs markedly elevated in renal failure patients. There are more than 500 papers on PubMed that deal with RAGE and AGEs/ALEs in renal diseases. A decrease in renal function and reduced clearance is 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^[128] – for detailed information, see recent excellent reviews^[128-133]. Patients with mild chronic uremic renal failure are reported to have plasma glycation free adduct concentrations increased up to five-fold and patients with end stage renal disease as much as 18-fold when on peritoneal dialysis and up to 40-fold on hemodialysis^[134]. Kidney transplantation is reported to improve but does not fully correct the increased AGE/ALE levels in previously dialysed patients^[135].

DIET-INDUCED INCREASE IN AGES/ALEs

By far the greatest of contributors of AGEs/ALEs seem to be dairy products, bread and meat, not only because they are all rich in these chemicals, but also as they constitute the bulk of modern food, especially in the Western world. Also plants

contribute to accumulation in the body of AGEs/ALEs, especially fruits, containing larger amounts of fructose, which is highly reactive with proteins and a large contributor to the development of AGEs.

Important AGE/ALE contributing foods are:

Diary products: Consumption of drinking milk is, although it has decreased during the last 50 years, still high in the Western world (USA 1950: 144 and 2000: 92 quarts per person and year). Instead it is, although at lower levels, increasing in other parts of the world, particularly in Asia (Japan 1950: 11 and 2000: 72 quarts/person/year). However, the consumption of cheese has quadrupled during the same period (USA 1950: 8 and 2000: 30 pounds/person/year; EU 2000: 38 pounds), to a large extent because of the increasing use in fast foods such as pizza, tacos, nachos, salads, fast-food sandwiches, and sauces for potatoes and vegetables. Also the global production of whole milk powder (WMP), which unfortunately contains much more of AGEs/ALEs than plain milk, has increased dramatically and continuous to do so (annual increase 2.7%) and is expected to reach 9.5 billion pounds in the year 2010.

It is unfortunate that it is AGEs/ALEs that to a large extent provide palatability to foods. This, in combination with the low price, might explain why milk powders increasingly are used as ingredient in food products such as bread, baby formulas, clinical nutrition formulas, chocolate, ice-cream, reconstituted milk and hundreds of other common foods. A milk product, which is reported to be especially rich in AGEs/ALEs, is custard. Ten to 20 %, sometimes up to 70 %, of the amino acid lysine is reported to be modified during common technological treatment (sterilization, pasteurization, irradiation etc.) of milk^[136]. Fructoselysine is the dominating modified molecule, but also CML, and pyrraline are produced during processing of milk^[136]. Content of sugars, level and time of elevated temperature and heat-exposure^[137], time and storage time contribute most to the production of AGEs/ALEs^[138]. Certain heavily processed cheeses such as Scandinavian “Mesost” and Norwegian “Brunost” contain especially large amounts of AGEs/ALEs (Brunost: 1691 mg CML/kg protein)^[139]. Microwaving of milk also increases dramatically the content of Maillard products^[140]. Fig. 2 illustrates the content of one Maillard product - furosine - in various dairy products, when fresh and stored for 1-2 years. It is important to observe that the already high amount in fresh milk powder increases four to nine times when the milk powder is stored for longer periods in room temperature (which is the standard today for baby formulas and often also for clinical nutrition solutions) in comparison to storage at 4 °C^[138].

Significant increase in numbers of both limited ($p < 0.001$) and extensive ($p < 0.001$) DNA-damaged cells has also been demonstrated on peripheral blood lymphocytes of infants fed cow's milk^[141].

Grains, cereals, bakery products: Consumption of bread is often associated with increased inflammation and ChDs, and is suggested to be associated with the content of proinflammatory molecules such as gluten in breads and grain products (especially those made of wheat, rye and barley)^[142]. Bread crusts and toasts and crisp breads such as rye crisps (Knäckebröd) are reported to be rich in AGEs/ALEs. Bread crusts are often used in animal experiments to increase the content in the body of AGEs/ALEs when the aim is to study the effects of these compounds on bodily functions. Fresh whole bread contains about 0.5 kU/g of AGEs/ALEs and toasted bread is reported to provide about 30 kU/serving^[143]. Pancakes (10 kU/g) and cereals such as Rice Krispies (Kellogg Co. Battle Creek MI – 600 kU/serving) and particularly toasted waffles and biscotti (1000 kU/serving) are other sources of large amounts of AGEs/ALEs^[143]. Pretzels (500 kU/serving) in contrast to popcorn (40 kU/serving) are also rich in AGEs/ALEs^[142].

Meat, poultry and fish: The content of AGEs/ALEs in beef, chicken and tuna fish is reported to be about similar (50 – 60 kU/g) although the content depends much on the method of preparation. The AGE/ALE content in for example, chicken breast is reported to increase 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)^[143]. Other compounds produced when beef, poultry and fish are heated above 100 °C are carcinogenic compounds called heterocyclic amines, and its amount produced increases with increasing temperature, and increasing presence of sugars and fats^[144].

Vegetables: Only few studies exist and most of them focus on effects of processes such as maturation, curing, and roasting and heat-treatment of plant products, mostly nuts and beans. Thermal processing alters significantly both biophysical and immunological properties of vegetable proteins such as peanut proteins: their structure, function, solubility, digestibility, immunoglobulin E (IgE) binding, and T-cell response^[145]. Curing at higher temperatures (> 77 °C) increases significantly both the levels of AGEs and the IgE binding capacity^[146].

Coffee, tea, alcohol and beer: The coffee bean, like the untreated tobacco leaf, when fresh and

unprocessed is extraordinary rich in powerful antioxidants, but when roasted at high temperature, it becomes a rich source of AGEs/ALEs. This is much in contrast to various teas, and particularly green tea and yerbamate tea, which to a large extent maintain their richness in strong antioxidants and ability to inhibit both protein nitration, second phase glycation reactions, and prevent the free-radical mediated conversion of the early so called Amadori products to irreversible AGEs^[147,148]. Consumption of an AGE-rich food such as coffee (200 ml/day) is also reported to increase serum levels of CRP by 30%, TNF α by 28% and IL6 by 50%^[149]. Alcohol is cytotoxic mainly due to its main metabolite acetaldehyde (AA), a main contributor of AGEs/ALEs. AGE fluorescence is observed to be significantly higher in alcohol abusers than in healthy subjects with a more modest alcohol consumption^[150]. Barley undergoes significant glycation during the malting process^[151], which is said to provide the foaming properties to beer^[152]. Beer is also a rich source of AGEs/ALEs. It is likely, although no studies are available, that dark beer contains more AGEs/ALEs than light beer. Similarly sugar-rich liquors might contain considerably more of AGEs/ALEs than pure and plain aquavit.

DIETARY MEASURES TO REDUCE AGEs/ALEs

Vegan diet seems to induce statistically significant lower systolic and diastolic blood pressure, lower serum total cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood sugar, less weight problems and less incidence of ChDs, especially diabetes and complications of diabetes. However, there are also problems with vegetarian (lacto-vegetarian and vegan) lifestyle, which need to be corrected, among them risk of shortage in vitamin B12, higher serum levels of homocystein and poor taurine status^[153]. It is of special interest that AGEs/ALEs are reported to be higher in longtime healthy lacto-vegetarians than in vegans and healthy omnivorous^[154]. One explanation could be, as suggested by these authors, a higher intake of fructose, especially since 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, to compensate for the lack of meat and fish in the diet.

Several measures have been shown to significantly decrease serum and tissue concentrations of AGEs/ALEs, among them:

Caloric restriction (CL): Evidence from animal studies shows that restriction in intake of AGE/ALE-rich food is an effective means of extending median life span, and preventing ChDs, much in the

same way as is observed with caloric restriction^[15]. However, there are only a few studies available in primates and almost no studies in humans. Significant benefits of long-term (2-11 years) CL in comparison to Western diet were recently reported from a study in healthy humans: blood pressure $102 \pm 10 / 61 \pm 7$ Vs. $131 \pm 11 / 83 \pm 6$ mmHg, CRP 0.3 ± 0.3 Vs. 1.9 ± 2.8 mg/l, TNF- α 0.8 ± 0.5 Vs. 1.5 ± 1.0 pg/ml, TGF- β 29.4 ± 6.9 ng/ml Vs. 35.4 ± 7.1 ng/ml respectively^[155]. Patients with rheumatoid arthritis (RA) on a low energy diet for 54 days demonstrated a significant reduction in RA disease activity paralleled by a significant reduction of urinary pentosidine^[156]. However, studies in other groups of ChD patients are generally lacking.

Vitamins and antioxidants: Glutathione (gamma-glutamylcysteinyl glycine [GSH]) is thought to be an important factor in cellular function and a strong defense against oxidative stress. Dietary GSH suppresses oxidative stress, reduces glycation and prevents diabetic complications such as diabetic nephropathy and neuropathy^[157]. Rich supply of vitamins A, C, E, and particularly B6, B12 and folic acid (Fig. 3) is emphasized^[158]. Vitamin D should most likely be supplemented, especially at higher latitudes^[50]. Several thousands of plant-derived chemo-preventive agents, polyphenols and many other, most often unexplored, substances seem to have potential to reduce the speed of aging and prevent degenerative malfunction 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^[159] the main yellow pigments in turmeric curry foods, and daidzein and genistein from the soy bean. These compounds have all slightly different functions and seem to complement each other well. Several, most likely the majority, of these substances are able to inhibit the second phase of the glycation process, *e.g.* the conversion of the Amadori products to AGEs. A significant number of animal studies support the health benefits of these antioxidants and AGE/ALE scavengers^[160,161] but human studies are still largely lacking.

Taurine, carnitine, carnosine, histidine: Taurine, a small sulphonic acid, is found in high intracellular concentrations in most cellular animal tissues, and

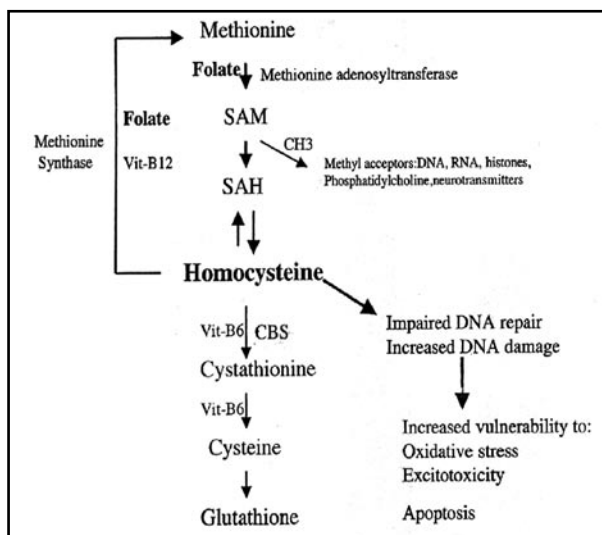
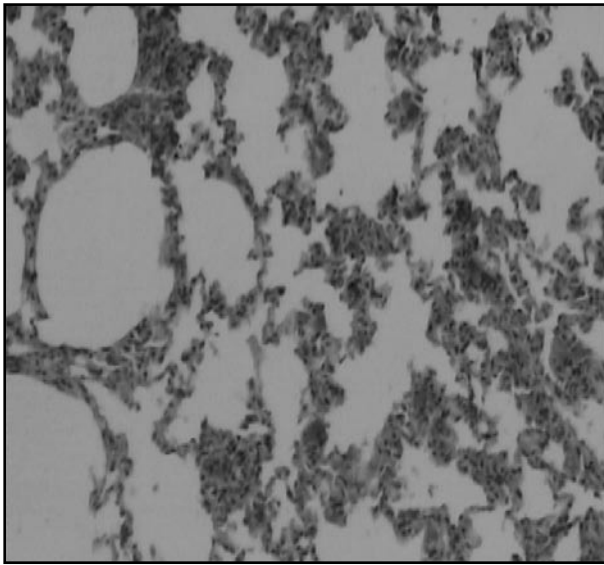


Fig. 3: Involvement of homocysteine folic acid and vitamin B6 and B12 influences metabolism and possible mechanisms whereby elevated homocysteine contributes to increased risks of chronic diseases (after Mattsson MP)^[158].

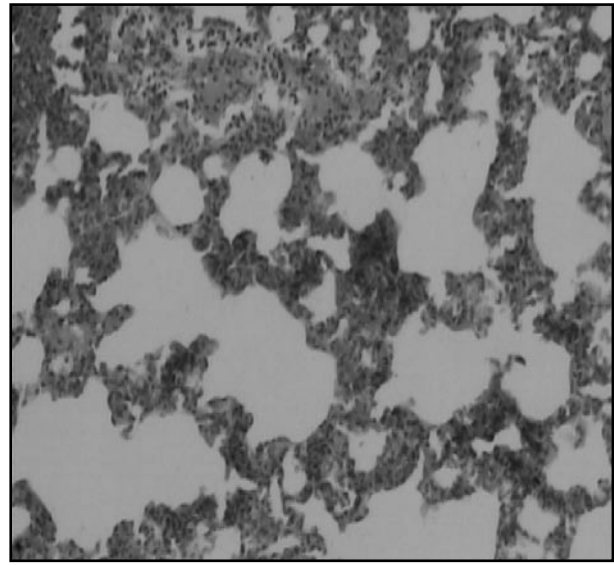
especially in blood cells, retina and nervous tissues. The highest concentration is found in neutrophils, where it is suggested to reduce inflammation^[162]. The richest sources of taurine is seafood, fish and poultry. Moderate amounts are also found in meat, while plants with the only known exception of some algae, and consequently vegan diets, are totally devoid of this amino acid^[163]. Taurine has also a well known strong hypoglycemic effect, known already since the 1930s^[164]. It reduces production of AGEs/ALEs, and prevents collagen abnormalities in high fructose-fed animals^[156,157]. *In vitro* as well as animal studies suggest that similar effects are obtained by supplementing amino acids or peptides such as histidine, carnitine and carnosine. However, again no human studies seem yet to have been performed.

Pre- and probiotics: All the various powerful antioxidants and AGE/ALE scavengers need, for the body to benefit from them, to be broken down and made available for absorption. This is almost entirely dependent on microbial enzymes, mainly provided by the flora in the lower gastrointestinal tract. However, the microbial flora is severely impaired in about 75% of omnivorous Americans and one third of vegetarian Americans^[167]. Lactic acid bacteria (LAB) are also in their own capacity strong oxidation scavengers and effective inhibitors of inflammation. LAB will most likely have the capacity to eliminate AGE/ALE protein and peptides from foods before resorption, as they have been shown to eliminate gluten^[168] and carcinogens^[169] from food. Support for such an assumption derives from an *in vitro* study, where fructoselysine, the main modified molecule in heated milk^[138] was

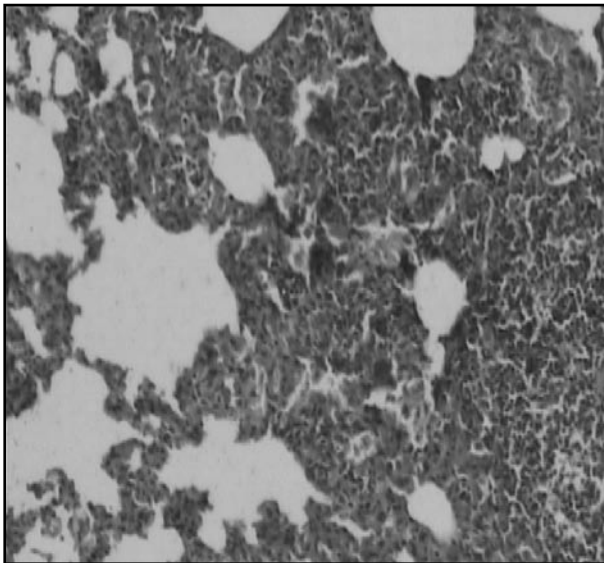
Fig. 4: A. B. C. Histological sections of rat lung 24 hours after cecal ligation and puncture. Mayers' s heamatoxylin staining. Original magnification 100



A. After placebo treatment



B. After treatment with only bioactive fibers



C. After treatment with both bioactive fibers and live lactic acid bacteria (Synbiotic 2000). Photo by Dr Ozer Ilkgul, Izmir, Turkey

eliminated (deaminated) when incubated with live flora^[170]. Pretreatment before cecal ligation and puncture^[171] with oral administration of LAB in combination with prebiotic fibers (Synbiotic 2000 Forte, Medipharm, Kågeröd Sweden & Des Moines, Iowa USA) or subcutaneous injection^[172] with the same LAB prevented effectively increases in lung tissue of myeloperoxidase (MPO), malondialdehyde (MDA) and nitric oxide and most importantly, pulmonary neutrophil accumulation and lung tissue destruction (Fig. 4 A-C). In line with this is the observation that the same combination of LAB and fiber significantly downregulates expression of Toll-like receptors, reduces production of TNF- α ^[173] and significantly improves stage of disease (from Child C to B, or from B to A) in liver cirrhosis^[174].

FUTURE DIRECTIONS

Most studies in the past have focused on coronary heart disease, type 2 diabetes and chronic renal disease. However, increasing evidence suggests that an “unhealthy” life style is negatively associated with all ChDs. Common to most ChDs is a more or less permanent exaggerated inflammation, strongly associated with metabolic syndrome and also increased deposition in tissues of AGEs/ALEs. It is suggested that all ChD patients, including those with inherent genetic disorders such as Down's syndrome^[74,175], and cystic fibrosis^[176,177] but eventually also schizophrenia^[178,179] and mental depression^[180-182], diseases with obscure etiology but seemingly associated with increased oxidation and aberrant inflammation will benefit from measures to control AGEs/ALEs. Studies in the US demonstrate an 83% reduction in rate of coronary heart disease^[183], a 91% reduction in diabetes in women^[184] and a 71% reduction in colon cancer in men^[185] in patients adhering to what today is regarded as an “healthy lifestyle”. It is likely, but yet not proven, that control of intake and cellular production of AGEs/ALEs is an important ingredient in a healthy lifestyle, and might further improve outcome.

An exaggerated inflammation is also observed in patients, who suffer complications to acute diseases: infections, trauma and advanced surgical and medical treatments such as transplantations. Complications and sequelae to these events are significantly more common in elderly and particularly in those with ChDs. Much evidence supports that the lifestyle of the patients and degree of inflammation before trauma significantly affects outcome - see further^[186]. It is clearly documented that presence of metabolic syndrome does also in acute

morbidities negatively affect outcome. Recently accumulated knowledge about the link between metabolic syndrome and increased deposition of AGEs/ALEs in the body support the suggestion that future attempts to minimize accumulation in the body of such substances might significantly reduce both acute and chronic morbidities. However, the research in this field is in its early infancy, and most studies remain to be done.

REFERENCES

- World Health Organization. Process for a global strategy on diet, physical activity and health. WHO Geneva 2003.
- Bengmark S. Acute and "chronic" phase response – a mother of disease. *Clin Nutr* 2004; 23:1256-1266.
- Lin BF, Huang CC, Chiang BL, Jeng SJ. Dietary fat influences Ia antigen expression, cytokines and prostaglandin E2 production in immune cells in autoimmune-prone NZBxNZW F1 mice. *Brit J Nutr* 1996; 75:711-722.
- Watanabe S, Onozaki K, Yamamoto S, Okuyama H. Regulation by dietary essential fatty acid balance of tumor necrosis factor production in mouse macrophages. *J Leukoc Biol* 1993; 53:151-156.
- Roszkowski K, Ko KL, Beuth J, *et al.* Intestinal microflora of BALB/c-mice and function of local immune cells. *Zeitschrift für Bakteriologie und Hygien* 1988; 270:270-279.
- Pulverer G, Beuth J, Roszkowski W, *et al.* Bacteria of human physiological microflora liberate immunomodulating peptides. *Zentralbl Bakteriol* 1990; 272:467-476.
- Maillard LC. Action des acides amine sur des sucres: formation des melanoides per voie methodique. *C R Acad Sci* 1912; 154:66-68.
- Rahbar S. An abnormal hemoglobin in red cells of diabetics. *Clin Chem Acta* 1968; 22:296-298.
- Rahbar S. The discovery of glycated haemoglobin. A major event in the study of nonenzymatic chemistry in biological systems. *Ann N Y Acad Sci* 2005; 1043:9-19.
- Chavakis T, Bierhaus A, Nawroth PP. RAGE (receptor for advanced glycation end products): a central player in the inflammatory response. *Microb Infect* 2004; 6:1219-1225.
- Ramasamy R, Vannucci SJ, Yan SS, *et al.* Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. *Glycobiology* 2005; 15:16R-28R.
- Das UN. Metabolic syndrome X: an inflammatory condition? *Current Hypertension Reports* 2004; 6:66-73.
- Black PH. The inflammatory response is an integral part of stress response: implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. *Brain Behav Immunol* 2003; 17:350-364.
- Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 2004; 27:813-823.
- Libby P. Inflammation in atherosclerosis. *Nature* 2003; 420:868-874.
- Bierhaus A, Humpert PM, Stern DM, *et al.* Advanced glycation end product receptor-mediated cellular dysfunction. *Ann N Y Acad Sci* 2005; 1043:676-680.
- Schmidt AM, Yan SD, Yan SF, Stern DM. The multiligand receptor RAGE is a progression factor amplifying immune and inflammatory responses. *J Clin Invest* 2001; 108:949-955.
- Bierhaus A, Schiekofer S, Schwaninger M, *et al.* Diabetes-associated sustained activation of the transcription factor nuclear factor- κ B. *Diabetes* 2001; 50:2792-2808.
- Vlassara H. Advanced glycation in health and disease. Role of the modern environment. *Ann N Y Acad Sci* 2005; 1043:452-460.
- Vlassara H, Cai J, Crandall J, *et al.* Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc Natl Acad Sci USA* 2002; 99:15596-15601.
- Peppas M, Uribarri J, Cai W, *et al.* Glycoxidation and inflammation in renal failure patients. *Am J Kidney Dis* 2004; 43:690-695.
- Lin RY, Choudhury W, Cai W, *et al.* Dietary glycotoxins promote diabetic atherosclerosis in apolipoprotein E-deficient mice. *Atherosclerosis* 2003; 168:213-220.
- Zheng F, He C, Cai W, *et al.* Prevention of nephropathy in mice by a diet low in glycoxidation products. *Diabetes Metab Res Rev* 2002; 18:224-237.
- Peppas M, Brem P, Ehrlich J, *et al.* Adverse effects of glycotoxins on wound healing in genetically diabetic mice. *Diabetes* 2003; 52:2805-2813.
- Cai W, He JC, Lu M, *et al.* Amelioration of insulin resistance, weight gain and markers of oxidant stressing aging mice by dietary glycotxin restriction: a therapeutic alternative to caloric restriction. *Diabetes* 2004; suppl 2:A343.
- Uribarri J, Peppas M, Cai W, *et al.* Restriction of dietary glycotoxins markedly reduces AGE toxins in renal failure patients. *J Am Soc Nephrol* 2003; 14:728-731.
- Li SY, Sigmin VK, McCort A, Ren J. High fat diet enhances visceral advanced glycation end products, nuclear O-Glc-Nac modification, p38 mitogen-activated protein kinase activation and apoptosis. *Diab Obes Metab* 2005; 7:448-454.
- Hartroft WS, Thomas WA. Pathological lesions related to disturbances of fat and cholesterol metabolism in man. *JAMA* 1957; 164:1899-1905.
- Thorpe SR, Baynes JW. Maillard reaction products in tissue proteins: new products and new perspectives. *Amino Acids* 2003; 25:275-281.
- Baynes JW, Thorpe SR. Glycoxidation and lipoxidation in atherosclerosis. *Free Radic Biol Med* 2000; 28:1708-1716.
- Thorpe SR, Baynes JW. Maillard reaction products in tissue proteins: new products and new perspectives. *Amino Acids* 2003; 25:275-281.
- Vamvakas S, Bahner U, Heidland A. Cancer in end-stage renal disease: potential factors involved. *Am J Nephrol* 1998; 18:89-95.
- Loske C, Neumann A, Cunningham AM, *et al.* Cytotoxicity of advanced glycation endproducts is mediated by oxidative stress. *J Neural Transm* 1998; 105:1005-1015.
- Morena M, Cristol JP, Senecal L, *et al.* Oxidative stress in hemodialysis patients: is NADPH oxidase complex the culprit? *Kidney Int* 2002; 80:S109-114.
- Descamps-Latscha B, Jungers BP, Witko-Sarsat V. Immune system dysregulation in uremia: the role of oxidative stress. *Blood Purif* 2002; 20:481-484.
- Zevin D, Malachi T, Gaftor U, *et al.* Impaired DNA repair in patients with end-stage renal disease and its improvement with hemodialysis. *Miner Electrol Metab* 1991; 17:303-306.
- Mullarkey CJ, Edelstein D, Brownlee M. Free radical generation by early glycation products; a mechanism for accelerated atherosclerosis in diabetes. *Biochem Biophys Res Commun* 1990; 173:932-939.
- Agalou S, Ahmed N, Dawnay A, Thornally PJ. Removal of advanced glycation products in clinical renal failure by peritoneal dialysis and haemodialysis. *Biochem Soc Trans* 2003; 31:1394-1396.
- Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertension* 2003; 21:3-12.
- Yamagishi S, Fujimori H, Yonekura H, *et al.* Advanced glycation end products inhibit prostacyclin production

- and induce plasminogen activator inhibitor-1 in human microvascular endothelial cells. *Diabetologica* 1998; 41:1435-1441.
41. Suzuma K, Otani A, Oh H, *et al.* 17- Beta-estradiol increases VEGF receptor-2 and promotes DNA synthesis in retinal microvascular endothelial cells. *Invest Ophthalmol Vis Sci* 1999; 40:2122-2129.
 42. Rautava S, Isolauri E. Cow's milk allergy in infants with atopic eczema is associated with aberrant production of interleukin-4 during oral cow's milk challenge. *J Pediatr Gastroenterol Nutr* 2004; 39:529-535.
 43. Artaud-Wild SM, Connor SL, Sexton G, Connor WE. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. A paradox. *Circulation* 1993; 88:2771-2779.
 44. Moss M, Freed DL. Survival trends, coronary event rates, and the MONICA project. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; 354:862-865.
 45. Dahl-Jorgensen K, Joner G, Hanssen KF. Relationship between cows' milk consumption and incidence of IDDM in childhood. *Diabetes Care* 1991; 14:1081-1083.
 46. Gimeno SG, de Souza JM. IDDM and milk consumption. A case-control study in Sao Paulo, Brazil. *Diabetes Care* 1997; 20:1256-1260.
 47. Virtanen SM, Hypponen E, Laara E, *et al.* Cow's milk consumption, disease-associated autoantibodies and type 1 diabetes mellitus: a follow-up study in siblings of diabetic children. *Childhood Diabetes in Finland Study Group. Diabet Med* 1998; 15:730-738.
 48. Park M, Ross GW, Petrovitch H, *et al.* Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurology* 2005; 64:1047-1051.
 49. Outwater JL, Nicholson A, Barnard N. Dairy products and breast cancer: the IGF-I, estrogen, and bGH hypothesis. *Med Hypotheses* 1997; 48:453-461.
 50. Hjartaker A, Laake P, Lund E. Childhood and adult milk consumption and risk of premenopausal breast cancer in a cohort of 48,844 women - the Norwegian women and cancer study. *Int J Cancer* 2001; 93:888-893.
 51. Ganmaa D, Li XM, Wang J, *et al.* Incidence and mortality of testicular and prostatic cancers in relation to world dietary practices. *Int J Cancer* 2002; 98:262-267.
 52. Ganmaa D, Li XM, Qin LQ, *et al.* The experience of Japan as a clue to the etiology of testicular and prostatic cancers. *Med Hypotheses* 2003; 60:724-730.
 53. Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr* 2004; 80:1353-1357.
 54. Genkinger JM, Hunter DJ, Spiegelman D, *et al.* Dairy products and ovarian cancer: a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev* 2006; 15:364-372.
 55. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. *Br J Nutr* 2005; 94:483-492.
 56. McCarty MF. Secondary hyperparathyroidism promotes the acute phase response – a rationale for supplementing vitamin D in prevention of vascular events in elderly. *Medical Hypotheses* 2005; 64:1022-1026.
 57. Meerwaldt R, Links Th, Graaff R, *et al.* Simple non-invasive measurement of skin autofluorescence. *Ann N Y Acad Sci* 2005; 1043:290-298.
 58. Unno Y, Sakai M, Sakamoto Y, *et al.* Advanced glycation end products-modified proteins and oxidized LDL mediate down-regulation of leptin in mouse adipocytes via CD36. *Biochem Biophys Res Commun* 2004; 325:151-156.
 59. Soldatos G, Cooper ME, Jandeleit-Dahm KA. Advanced-glycation end products in insulin-resistant states. *Curr Hypertens Rep* 2005; 7:96-102.
 60. Koyama H, Shoji T, Yokoyama H, *et al.* Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol* 2005; 25:2587-2593.
 61. Davis PJ, Smales CM, James DC. How can thermal processing modify the antigenicity of proteins? *Allergy* 2001; 56:556-60.
 62. Sancho AI, Rigby NM, Zuidmeer L, *et al.* The effect of thermal processing on the IgE reactivity of the non-specific lipid transfer protein from apple, Mal d 3. *Allergy* 2005; 60:1262-1268.
 63. Chung SY, Champagne ET. Association of end-product adducts with increased IgE binding of roasted peanuts. *J Agric Food Chem* 2001; 49:3911-3916.
 64. Franck P, Moneret Vautrin DA, Dousset B, *et al.* The allergenicity of soybean-based products is modified by food technologies. *Int Arch Allergy Immunol* 2002; 128:212-219.
 65. Tsukahara H, Shibata R, Ohta P, *et al.* High levels of urinary pentosidine, an advanced glycation end product, in children with acute exacerbation of atopic dermatitis: relationship with oxidative stress. *Metabolism* 2003; 52:1601-1605.
 66. Nicolls MR. The clinical and biological relationship between type II diabetes mellitus and Alzheimer's disease. *Current Alzheimer Research* 2004; 1:47-54.
 67. Smith MA, Taneda S, Rickey PL, *et al.* Advanced Maillard reaction end products are associated with Alzheimer pathology. *Proc Soc Natl Acad Sci USA* 1994; 91:5710-5714.
 68. Vitek MP, Bhattacharya K, Gendening JM, *et al.* Advanced glycation end products contribute to amyloidosis in Alzheimer disease. *Proc Soc Natl Acad Sci USA* 1994; 91:4766-4770.
 69. Moreira PI, Smith MA, Zhu X, *et al.* Oxidative stress and neurodegeneration. *Ann N Y Acad Sci* 2005; 1043:543-552.
 70. Lue LF, Yan SD, Stern DM, Walker DG. Preventing activation of receptor for advanced glycation end products in Alzheimer's disease. *Current Drug Targets – CNS & Neurological Disorders* 2005; 4:249-266.
 71. Castellani R, Smith MA, Richey PJ, Petty G. Glycoxidation and oxidative stress in Parkinson disease and diffuse Lewy body disease. *Brain Res* 1996; 737:195-200.
 72. Dalfo E, Portero-Otin M, Ayala V, *et al.* Evidence of oxidative stress in the neocortex in incidental Lewy body disease. *J Neuropathol Exp Neurol* 2005; 64:816-830.
 73. Kikuchi S, Shinpo K, Ogata A, *et al.* Detection of N-(carboxymethyl) lysine (CML) and non-CML advanced glycation end products in the anterior horn of amyotrophic lateral sclerosis spinal cord. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2002; 3:63-68.
 74. Chou SM, Wang HS, Taniguchi A, Bacula R. Advanced glycation end products in neurofilament conglomeration of motorneurons in familial and sporadic amyotrophic lateral sclerosis. *Mol Med* 1998; 4:324-332.
 75. Kaufmann E, Boehm BO, Sussmuth SD, *et al.* The advanced glycation end-product N epsilon-(carboxymethyl) lysine level is elevated in cerebrospinal fluid of patients with amyotrophic lateral sclerosis. *Neurosci Lett* 2004; 371:226-229.
 76. Ma L, Nicholson LF. Expression of the receptor for advanced glycation end products in Huntington's disease caudate nucleus. *Brain Res* 2004; 1018:10-17.
 77. Zimmerman GA, Meistrell M, Bloom O, *et al.* Neurotoxicity of advanced glycation endproducts during focal stroke and neuroprotective effects of aminoguanidine. *Proc Natl Acad Sci U S A* 1995; 92:3744-3748.
 78. Gomes R, Sousa Silva M, Quintas A, *et al.* Argpyrimidine, a methylglyoxal-derived advanced glycation end-product

- in familial amyloidotic polyneuropathy. *Biochem J* 2005; 385:339-345.
79. Sasaki N, Takeuchi M, Choei H, *et al.* Advanced glycation end products (AGE) and their receptor (RAGE) in the brain of patients with Creutzfeldt-Jacob disease with prion plaques. *Neurosci Lett* 2002; 326:117-120.
80. Thiel R, Fowkes SW. Can cognitive deterioration associated with Down syndrome be reduced? *Med Hypotheses* 2005; 64:524-532.
81. Frey J. Bovine spongiform encephalopathy: are the cows mad or full of carbohydrate. *Clin Chem Lab Med* 2002; 40:101-103.
82. Vlassara H, Palace MR. Diabetes and advanced glycation end products. *J Int Med* 2002; 251:87-101.
83. Hostettler-Allen RL, Tappy L, Blum JW. Insulin resistance, hyperglycemia, and glucosuria in intensively milk-fed calves. *J Anim Sci* 1994; 72:160-173.
84. Kalousova M, Zak A, Soukupova J. Advanced glycation and oxidation products in patients with atherosclerosis. *Cas Lek Cesk* 2005; 144:385-390 [Article in Czech].
85. Taki K, Takayama F, Tsuruta Y, Niwa T. Oxidative stress, advanced glycation end product, and coronary artery calcification in hemodialysis patients. *Kidney Int.* 2006; 70:218-224 (Epub before print).
86. Tokita Y, Hirayama Y, Sekikawa A, *et al.* Fructose ingestion enhances atherosclerosis and deposition of advanced glycated end-products in cholesterol-fed rabbits. *J Atheroscler Thromb* 2005; 12:260-267.
87. Ferretti G, Bacchetti T, Negre-Salvayre A. Structural modifications of HDL and functional consequences. *Atherosclerosis* 2006; 184:1-7.
88. de Leeuw K, Kallenberg C, Bijl M. Accelerated atherosclerosis in patients with systemic autoimmune diseases. *Ann N Y Acad Sci* 2005; 1051:362-371.
89. Ge J, Jia Q, Liang C, *et al.* Advanced glycosylation end products might promote atherosclerosis through inducing the immune maturation of dendritic cells. *Arterioscler Thromb Vasc Biol* 2005; 25:2157-2163.
90. Bartling B, Hofmann HS, Weigle B, *et al.* Down-regulation of the receptor for advanced glycation end-products (RAGE) supports non-small cell lung carcinoma. *Carcinogenesis* 2005; 26:293-301.
91. Takada M, Hirata K, Ajiki T, *et al.* Expression of receptor for advanced glycation end products (RAGE) and MMP-9 in human pancreatic cancer cells. *Hepatogastroenterology* 2004; 51:928-930.
92. Yamagishi S, Nakamura K, Inoue H, *et al.* Possible participation of advanced glycation end products in the pathogenesis of colorectal cancer in diabetic patients. *Med Hypotheses* 2005; 64:1208-1210.
93. Ishiguro H, Nakaigawa N, Miyoshi Y, *et al.* Receptor for advanced glycation end products (RAGE) and its ligand, amphoterin are overexpressed and associated with prostate cancer development. *Prostate* 2005; 64:92-100.
94. Stitt AL. The Maillard reaction in eye disease. *Ann N Y Acad Sci* 2005; 1043:582-597.
95. Gaby AR. Adverse effects of dietary fructose. *Altern Med Rev* 2005; 10:294-306.
96. Wada R, Yagihashi S. Role of advanced glycation end products and their receptors in development of diabetic neuropathy. *Ann N Y Acad Sci* 2005; 1043:598-604.
97. Monnier VM, Sell DR, Genuth S. Glycation products as markers and predictors of the progression of diabetic complications. *Ann N Y Acad Sci* 2005; 1043:567-581.
98. Yamagishi S, Imaizumi T. Diabetic vascular complications: pathophysiology, biochemical basis and potential therapeutic strategy. *Curr Pharm Des* 2005; 11:2279-2299.
99. Hertoghe T. The "multiple hormone deficiency" theory of aging: is human senescence caused mainly by multiple hormone deficiencies? *Ann N Y Acad Sci* 2005; 1057:448-465.
100. Diamanti-Kandarakis E, Piperi C, Kalofoutis A, Creatsas G. Increased levels of serum advanced glycation end-products in women with polycystic ovary syndrome. *Clin Endocrinol* 2005; 62:37-43.
101. Flyvbjerg A, Khatir DS, Jensen LJ, *et al.* The involvement of growth hormone (GH), insulin-like growth factors (IGFs) and vascular endothelial growth factor (VEGF) in diabetic kidney disease. *Curr Pharm Des* 2004; 10:3385-3394.
102. Allen TJ, Jandeleit-Dahm KA. Preventing atherosclerosis with angiotensin-converting enzyme inhibitors: emphasis on diabetic atherosclerosis. *Curr Drug Targets Cardiovasc Haematol Disord* 2005; 5:503-512.
103. Tikellis C, Cooper ME, Thomas MC. Role of the renin-angiotensin system in the endocrine pancreas: Implications for the development of diabetes. *Int J Biochem Cell Biol* 2005; 38:737-751.
104. Ahmed N, Lüthen R, Häussinger D, *et al.* Increased protein glycation in cirrhosis and therapeutic strategies to prevent it. *Ann N Y Acad Sci* 2005; 1043:718-724.
105. Sebekova K, Kupcova 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.
106. Yagmur E, Tacke F, Weiss C, *et al.* Elevation of Nepsilon-(carboxymethyl)lysine-modified advanced glycation end products in chronic liver disease is an indicator of liver cirrhosis. *Clin Biochem* 2006; 39:39-45.
107. Zeng S, Feirt N, Goldstein M, *et al.* Blockade of receptor for advanced glycation end product (RAGE) attenuates ischemia and reperfusion injury to the liver in mice. *Hepatology* 2004; 39:422-432.
108. Ekong U, Zeng S, Dun H, *et al.* Blockade of the receptor for advanced glycation end products attenuates acetaminophen-induced hepatotoxicity in mice. *J Gastroenterol Hepatol* 2006; 21:682-688.
109. Nadeem A, Raj HG, Chhabra SK. Increased oxidative stress and altered levels of antioxidants in chronic obstructive pulmonary disease. *Inflammation* 2005; 29:23-32.
110. Hartl D, Starosta V, Maier K, *et al.* Inhaled glutathione decreases PGE2 and increases lymphocytes in cystic fibrosis lungs. *Free Radic Biol Med* 2005; 39:463-472.
111. Rahman I, Biswas SK, Kode A. Oxidant and antioxidant balance in the airways and airway diseases. *Eur J Pharmacol* 2006; 533:222-239.
112. DeGroot J. The AGE of the matrix: chemistry, consequence and cure. *Curr Opin Pharmacol* 2004; 4:301-305.
113. Steenvoorden MM, Huizinga TW, Verzijl N, *et al.* Activation of receptor for advanced glycation end products in osteoarthritis leads to increased stimulation of chondrocytes and synoviocytes. *Arthritis Rheum* 2006; 54:253-263.
114. Hormel SE, Eyre DR. Collagen in the ageing human intervertebral disc: an increase in covalently bound fluorophores and chromophores. *Biochem Biophys Acta* 1991; 1078:243-250.
115. Reddy GK. Cross-linking in collagen by nonenzymatic glycation increases the matrix stiffness in rabbit achilles tendon. *Exp Diabetes Res* 2004; 5:143-153.
116. Hofmann MA, Drury S, Hudson BI, *et al.* RAGE and arthritis: the G82S polymorphism amplifies the inflammatory response. *Genes Immun* 2002; 3:117-118.
117. Hein GE, Kohler M, Oelzner P, *et al.* The advanced glycation end product pentosidine correlates to IL-6 and other relevant inflammatory markers in rheumatoid arthritis. *Rheumatol Int* 2005; 26:137-141.
118. Sunahori K, Yamamura M, Yamana J, *et al.* Increased

- expression of receptor for advanced glycation end products by synovial tissue macrophages in rheumatoid arthritis. *Arthritis Rheum* 2006; 54:97-104.
119. Ramamurthy B, Hook P, Jones AD, Larsson L. Changes in myosin structure and function in response to glycation. *FASEB J* 2001; 15:2415-2422.
120. Hein G, Wiegand R, Lehmann G, *et al.* Advanced glycation end-products pentosidine and N epsilon-carboxymethyllysine are elevated in serum of patients with osteoporosis. *Rheumatology* 2003; 42:1242-1246.
121. Odetti P, Rossi S, Monacelli F, *et al.* Advanced glycation end products and bone loss during aging. *Ann N Y Acad Sci* 2005; 1043:710-717.
122. Miyata T, Kawai R, Taketomi S, Sprague SM. Possible involvement of advanced glycation end-products in bone resorption. *Nephrol Dial Transplant* 1996; 11:S54-57.
123. Stamatas GN, Estanislao RB, Suero M, *et al.* Facial skin fluorescence as a marker of the skin's response to chronic environmental insults and its dependence on age. *Br J Dermatol* 2006; 154:125-132.
124. Meerwaldt R, Hartog JW, Graaff R, *et al.* Skin autofluorescence, a measure of cumulative metabolic stress and advanced glycation end products, predicts mortality in hemodialysis patients. *J Am Soc Nephrol* 2005; 16:3687-3693.
125. Holla LI, Kankova K, Fassmann A, *et al.* Distribution of the receptor for advanced glycation end products gene polymorphisms in patients with chronic periodontitis: a preliminary study. *J Periodontol* 2001; 72:1742-1746.
126. Katz J, Bhattacharyya I, Farkhondeh-Kish F, *et al.* Expression of the receptor of advanced glycation end products in gingival tissues of type 2 diabetes patients with chronic periodontal disease: a study utilizing immunohistochemistry and RT-PCR. *J Clin Periodontol* 2005; 32:40-44.
127. Ostergaard J, Hansen TK, Thiel S, Flyvbjerg A. Complement activation and diabetic vascular complications. *Clin Chim Acta* 2005; 361:10-19.
128. Bohlender JM, Franke S, Stein G, Wolf G. Advanced glycation end products and the kidney. *Am J Physiol Renal Physiol* 2005; 289:F645-659.
129. Khan ZA, Farhangkhoe H, Chakrabarti S. Towards newer molecular targets for chronic diabetic complications. *Curr Vasc Pharmacol* 2006; 4:45-57.
130. Thomas MC, Forbes JM, Cooper ME. Advanced glycation end products and diabetic nephropathy. *Am J Ther* 2005; 12:562-572.
131. Kalousova M, Zima T, Tesar V, *et al.* Advanced glycoxidation end products in chronic diseases-clinical chemistry and genetic background. *Mutat Res* 2005; 579:37-46.
132. Saito A, Takeda T, Sato K, *et al.* Significance of proximal tubular metabolism of advanced glycation end products in kidney diseases. *Ann N Y Acad Sci* 2005; 1043:637-643.
133. Jensen LJ, Ostergaard J, Flyvbjerg A. AGE-RAGE and AGE Cross-link interaction: important players in the pathogenesis of diabetic kidney disease. *Horm Metab Res* 2005; 37:S26-34.
134. Agalou S, Ahmed N, Babaei-Jadidi R, *et al.* Profound mishandling of protein glycation degradation products in uremia and dialysis. *J Am Soc Nephrol* 2005; 16:1471-1485.
135. Hartog JW, de Vries AP, Lutgers HL, *et al.* Accumulation of advanced glycation end products, measured as skin autofluorescence, in renal disease. *Ann N Y Acad Sci* 2005; 1043:299-307.
136. Henle TH. AGEs in foods: Do they play a role in uremia? *Kidney International* 2003; 63:S145-S147.
137. Mendoza MR, Olano A, Villamiel M. Chemical indicators of heat treatment in fortified and special milks. *J Agric Food Chem* 2005; 53:2995-2999.
138. Baptista JAB, Carvalho RCB. Indirect determination of Amadori compounds in milk-based products by HPLC/ELSD/UV as an index of protein deterioration. *Food Research International* 2004; 37:739-747.
139. Drusch S, Faist V, Erbersdobler HF. Determination of N-carboxymethyllysine in milk products by a modified reversed-phase HPLC method. *Food Chemistry* 1999; 65:547-553.
140. Meissner K, Erbersdobler HF. Maillard reaction in microwave cooking: Comparison of early Maillard products in conventionally and microwave-heated milk. *J Sci Food Agric* 1996; 70:307-310.
141. Dündaröz R, Ulaçan H, Aydın HI, *et al.* Analysis of DNA damage using the comet assay in infants fed cow's milk. *Biol Neonate* 2003; 84:135-141.
142. Braly J, Hoggan R. *Dangerous grains*. Avery-Penguin Putnam Inc, New York 2002.
143. Goldberg T, Cai W, Peppas M, *et al.* Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc* 2004; 104:1287-1291.
144. Jagerstad M, Skog K. Genotoxicity of heat-processed foods. *Mutat Res* 2005; 574:156-172.
145. Maleki SJ, Hurlburt BK. Structural and functional alterations in major peanut allergens caused by thermal processing. *J AOAC Int* 2004; 87:1475-1479.
146. Chung SY, Butts CL, Maleki SJ, Champagne ET. Linking peanut allergenicity to the processes of maturation, curing, and roasting. *J Agric Food Chem* 2003; 51:4273-4277.
147. Lunceford N, Gugliucci A. *Ilex paraguariensis* extracts inhibit AGE formation more efficiently than green tea. *Fitoterapia* 2005; 76:419-427.
148. Bixby M, Spieler L, Menini T, Gugliucci A. *Ilex paraguariensis* extracts are potent inhibitors of nitrosative stress: a comparative study with green tea and wines using a protein nitration model and mammalian cell cytotoxicity. *Life Sci* 2005; 77:345-358.
149. Kuhlmann MK, Levin NW. Interaction between nutrition and inflammation in hemodialysis patients. *Contrib Nephrol* 2005; 149:200-207.
150. Kalousova M, Zima T, Popov P, *et al.* Advanced glycation end-products in patients with chronic alcohol misuse. *Alcohol* 2004; 39:316-320.
151. Perrocheau L, Rogniaux H, Boivin P, Marion D. Probing heat-stable water-soluble proteins from barley to malt and beer. *Proteomics* 2005; 5:2849-2858.
152. Kuhlmann MK, Levin NW. Interaction between nutrition and inflammation in hemodialysis patients. *Contrib Nephrol* 2005; 149:200-207.
153. McCarty MF. The low-AGE content of low fat vegan diets could benefit diabetics – though concurrent taurine supplementation may be needed to minimize endogenous AGE production. *Medical Hypotheses* 2005; 64:394-398.
154. Sebekova K, Krajcovicova-Kudlackova M, Schinzel R, *et al.* Plasma levels of advanced glycation end products in healthy, long-term vegetarians and subjects on a western mixed diet. *Eur J Nutr* 2001; 40:275-281.
155. Meyer TE, Kovács SJ, Ehsani AA, *et al.* Long-term caloric restriction ameliorates the decline in diastolic function in humans. *J Am Coll Cardiol* 2006; 47:398-402.
156. Iwashige K, Kouda K, Kouda M, *et al.* Calorie restricted diet and urinary pentosidine in patients with rheumatoid arthritis. *J Physiol Anthropol Appl Human Sci* 2004; 23:19-24.
157. Osawa T, Kato Y. Protective role of antioxidative food factors in oxidative stress caused by hyperglycemia. *Ann N Y Acad Sci* 2005; 1043:440-451.
158. Mattsson MP. Will caloric restriction and folate protect against AD and PD? *Neurology* 2003; 60:690-695.
159. Bengmark S. Curcumin: an atoxic antioxidant and natural

- NF- κ B, COX-2, LOX and iNOS inhibitor - a shield against acute and chronic diseases. *J Parenter Enteral Nutr* 2006; 30:45-51.
160. McCarty MF. Nutraceutical resources for diabetes prevention – an update. *Medical Hypotheses* 2005; 64:151-158.
161. McCarty MF. Potential utility of natural polyphenols for reversing fat-induced insulin resistance. *Medical Hypotheses* 2005; 64:628-635.
162. McCarty MF. The reported clinical utility of taurine of ischemic disorders may reflect a down-regulation of neutrophil activation and adhesion. *Medical Hypotheses* 1999; 53:290-299.
163. Laidlaw S, Grosvenor M, Kopple JD. The taurine content of common foodstuffs. *J Parenter Enteral Nutr* 1990; 14:183-188.
164. Hansen SH. The role of taurine in diabetes and the development of diabetic complications. *Diabetes Metabolism Research Reviews* 2001; 17:330-334.
165. Nandhini ATA, Thirunavakkarasu V, Anuradha CV. Stimulation of glucose utilization and inhibition of protein glycation and AGE products by taurine. *Acta Physiol Scand* 2004; 181:297-303.
166. Nandhini ATA, Thirunavakkarasu V, Anuradha CV. Taurine prevent collagen abnormalities in high fructose-fed rats. *Indian J Med Res* 2005; 122:171-177.
167. Finegold SM, Sutter VL, Mathisen GE. Normal indigenous intestinal flora. In: Hentges DJ, editor. *Human intestinal microflora in health and disease*. London: Academic Press; 1983. p 3-31.
168. di Cagno R, de Angelis M, Alfonsi G, *et al.* Pasta made from durum wheat semolina fermented with selected lactobacilli as a tool for a potential decrease of the gluten intolerance. *J Agric Food Chem* 2005; 53:4393-4402.
169. Tavan E, Cayuela C, Antoine JM, Cassand P. Antimutagenic activities of various lactic acid bacteria against food mutagens: heterocyclic amines. *J Dairy Res* 2002; 69:335-341.
170. Erbersdobler H, Gunsser I, Weber G. Abbau von Fructoselysine durch die Darmflora. *Zentralblatt Vet Med* 1970; A17:573-575.
171. Ilkgul O, Bengmark S, Aydede H, Erhan Y, Taneli F, Ulman C. Pretreatment with pro- and synbiotics reduces peritonitis-induced lung injury in rats. *J Trauma* 2007; 62:880-885.
172. Ilkgul O, Aydede H, Erhan Y, *et al.* Subcutaneous administration of live lactobacillus prevents sepsis-induced lung organ failure in rats. *Br J Int Care* 2005; 15:52-57.
173. Riordan SM, Skinner N, Nagree A, *et al.* Peripheral blood mononuclear cell expression of Toll-like receptors and relation to cytokine levels in cirrhosis. *Hepatology* 2003; 37:1154-1164.
174. Liu Q, Duan CP, Ha DK, *et al.* Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with liver cirrhosis. *Hepatology* 2004; 39:1441-1449.
175. Odetti P, Angelini G, Dapino D, *et al.* Early glycoxidation damage in brains from Down's syndrome. *Biochem Biophys Res Commun* 1998; 243:849-851.
176. Hudson VM. New insights into the pathogenesis of cystic fibrosis: pivotal role of glutathione system dysfunction and implications for therapy. *Treat Respir Med* 2004; 3:353-363.
177. Foell D, Seeliger S, Vogl T, *et al.* Expression of S100A12 (EN-RAGE) in cystic fibrosis. *Thorax* 2003; 58:613-617.
178. Altamura AC, Boin F, Maes M. HPA axis and cytokines dysregulation in schizophrenia: potential implications for the antipsychotic treatment. *Eur Neuropsychopharmacol* 1999; 10:1-4.
179. Muller N, Riedel M, Schwarz MJ. Psychotropic effects of COX-2 inhibitors—a possible new approach for the treatment of psychiatric disorders. *Pharmacopsychiatry* 2004; 37:266-269.
180. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006; 27:24-31.
181. Gundersen Y, Opstad PK, Reistad T, *et al.* Seven days' round the clock exhaustive physical exertion combined with energy depletion and sleep deprivation primes circulating leukocytes. *Eur J Appl Physiol* 2006; Feb 28; [Epub ahead of print].
182. Muller N, Schwarz MJ, Dehning S, *et al.* The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry* 2006; Feb 21 [Epub ahead of print].
183. Stampfer MJ, Hu FB, Manson JE, *et al.* Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000; 343:16-22.
184. Hu FB, Manson JE, Stampfer MJ, *et al.* Diet, lifestyle and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001; 345:790-797.
185. Platz EA, Willett WC, Colditz GA, *et al.* Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. *Cancer Causes Control* 2000; 11:579-588.
186. Bengmark S. Bioecological control of inflammation and infection in critical illness. *Anesthesiology Clinics of North America* 2006; 24:299-332.