

You Are What You Eat, So Don't Eat Crust: Will Strategies to Suppress Advanced Glycation End Products (AGEs) Prove to be "Our Fountain of Youth"?

Joseph Debé, DC, DACBN

THERE ARE MANY BIOLOGICAL CO-CONSPIRATORS INVOLVED IN THE AGING PROCESS and the development and perpetuation of degenerative diseases. Advanced glycation end products (AGEs) are prime culprits that have not received the attention they deserve. AGEs act in multiple ways to impair human function and damage tissues. There are also multiple ways we can intervene to minimize the damage produced by AGEs.

AGEs are a group of some 20 heterogeneous destructive substances continually formed in the human body, as reducing sugars non-enzymatically react with proteins, lipids, and nucleic acids. Fructose participates in glycation reactions ten times more rapidly than glucose.¹

Levels of AGEs in the body increase under certain conditions that accelerate their formation (such as hyperglycemia, oxidative stress, and inflammation) or impair their excretion (such as renal failure).

The level of AGEs in the human body is the result of several factors. These include: endogenous formation, exogenous intake (diet and tobacco smoke),² biotransformation, and renal clearance.

There is an accumulation of AGEs in the body with age. Kidney function is an important determinant of AGE levels. As renal function declines with aging, AGEs are not excreted as efficiently. AGEs in turn damage the kidneys. Serum levels of AGEs were found to predict declines in glomerular filtration rate.³ This is one of the self-perpetuating cycles involving tissue AGEs. Although this process occurs in normal aging, it is accelerated by renal disease.

Another vicious cycle involving AGEs is that involving oxidative stress. AGEs result in oxidative stress and deplete glutathione,⁴ which in turn leads to more AGE formation.

Tissue AGEs contribute to inflammation and insulin resistance, as well. These aberrant states of physiology, in turn, result in increased endogenous AGE production and exaggerated effects.

It would seem that one would want to break all of these cycles where possible.

A significant contributor to body burden of AGEs is the diet. AGEs, also referred to as glycotoxins, are found within food. Actually, diet contributes more to tissue AGE levels than does endogenous formation. A typical diet contains 25-75 mg. of AGEs per day, mostly as carboxymethyl-lysine (CML) and pyrraline.⁵ Approximately 10% of dietary AGEs are absorbed and most of them remain in tissues, producing damage.⁶ AGE content varies tremendously among foods and is influenced by cooking methods. Whether formed in the body or from

dietary sources, AGEs have the same detrimental effect. The modern Western diet is high in AGEs. Could this be a significant factor in the chronic degenerative disease epidemic of 21st century America?

AGEs structurally-damage (cross-link) tissue proteins and impair their function. Collagen, the major connective tissue protein, becomes stiffer and weaker when cross-linked. AGE-induced damage to enzymes results in impaired metabolic function. AGEs can also damage histone proteins and chromatin structure, contributing to genomic instability.

The biological effect of tissue AGEs is influenced by their interaction with different tissue receptors. When AGEs bind to the receptor for advanced glycation end products (RAGE), nuclear factor-kappa beta (NFkB) and its target genes are upregulated,⁷ resulting in oxidative stress and inflammation. In a study of older women, high levels of serum AGEs and RAGE were associated with increased mortality from cardiovascular disease.⁸

A six year study of 1013 people aged 65 years or older, examined the association between cardiovascular and all-cause mortality and plasma CML (an AGE). Subjects were divided into tertiles based on plasma CML levels. It was found that individuals in the group with the highest plasma CML levels were more likely to die from cardiovascular and all causes.⁹

As with all biological functions, genotype plays a role in the AGE-RAGE interaction. For example, a study of patients with hypertension and coronary artery disease (CAD) found a correlation between the RAGE G82S polymorphism and serum CRP levels as well as CAD but not hypertension.¹⁰ Testing to identify individuals with the G82S allelic variation could lead to tailored preventive strategies.

When should one consider developing an AGE-prevention strategy? Evidence would suggest before birth.

A study entitled "Maternally transmitted and food-derived glycotoxins: a factor preconditioning the young to diabetes?" examined the relationship between maternal serum AGE levels and those of their newborns. Sixty

healthy women were tested during labor and a correlation was found between the mother's AGE and 8-isoprostane levels and that of her newborn. The babies had additional blood tests at one year of age. A positive correlation was found between levels of maternal AGEs during labor and the one-year old's levels of insulin or homeostasis model assessment. The infant's adiponectin levels were found to correlate negatively with mother's serum AGE levels.

This study also found an increase in infant serum AGEs with the introduction of processed infant food. The authors concluded, "Maternal blood and food-derived AGEs prematurely raise AGEs in children to adult norms, preconditioning them to abnormally high oxidant stress and inflammation and thus possibly to early onset of disease, such as diabetes."¹¹

Of additional concern related to infant nutrition, infant formulas have been found to contain from 28 to 389 times as much AGEs as breast milk.¹²

Whereas the AGE-RAGE interaction causes cellular damage, the AGER1, AGER3, and CD36 receptors bind and degrade AGEs. AGER1 receptor has anti-inflammatory and other AGE-opposing effects. AGER1 is suppressed in high-oxidative stress states such as occurs in diabetes. The body also has AGE-inactivating and "decoy" proteins, such as lysozyme, defensins, and lactoferrin.¹³

The detrimental cardiovascular effects of AGEs include increased glycation and oxidization of Apolipoprotein A1, LDL cholesterol and Apolipoprotein B; inhibition of LDL cholesterol clearance, impairment of HDL cholesterol function, inactivation of nitric oxide, and increased collagen crosslinking. AGEs have been demonstrated to induce premature senescence and apoptosis of endothelial cells despite intact telomeres and telomerase activity. Additionally, dietary AGEs have been found to lower leptin and adiponectin, increase oxidative stress (8-isoprostanes), inflammation (tumor necrosis factor alpha and C-reactive protein), and plasminogen activator inhibitor 1, vascular cell adhesion molecule-1 and intercellular adhesion molecule. AGE-RAGE interaction has been demonstrated to induce calcification of vascular smooth muscle cells.¹⁴ Elevated serum AGEs have been found to correlate with increased arterial stiffness.¹⁵

A partial list of conditions in which AGEs have been implicated include: skin aging, delayed healing, osteoarthritis, osteoporosis, autoimmune disease, hypertension, insulin resistance, diabetes, polycystic ovary syndrome, male and female infertility, reduced success with assisted reproductive technology, stroke, atherosclerosis, heart failure, periodontal disease, asthma, anemia, renal disease, nonalcoholic steatohepatitis, cirrhosis, cancer and metastasis, neurodegenerative conditions, Alzheimer's dis-

ease, glaucoma, cataracts, and diabetic complications, including neuropathy, nephropathy, and retinopathy. Elevated serum AGEs are associated with increased fracture risk in diabetics despite normal bone density. Synovial fluid AGE levels correlate with disease activity in rheumatoid arthritis.

AGEs contribute to deterioration of function at the "whole-body" level. AGEs accumulate in skeletal muscle with aging. Japanese adult men were assessed for the relation between AGE levels by skin autofluorescence and muscle strength. There was an inverse relationship between levels of tissue AGEs and grip strength as well as leg extension power.¹⁶

Another study of older adults found higher plasma carboxymethyl-lysine (CML) was associated with slow walking speed.¹⁷

Tissue levels of AGEs in cerebral cortex and cerebral vessels have been shown to correlate with degree of cognitive impairment. "These findings support the possibility that cerebral accumulation of AGEs may contribute to dementia in people with cerebrovascular disease."¹⁸

The ways in which we can protect ourselves from the adverse effects of AGEs may include strategies to: 1. Reduce endogenous AGE formation; 2. Reduce intake of exogenous AGEs; 3. Neutralize adverse physiological effects of AGE-RAGE; 4. Increase AGE excretion; and, 5. Degrade established tissue AGEs.

Factors accelerating endogenous formation of AGEs that can be assessed by laboratory testing and modulated by nutrition and lifestyle interventions include hyperglycemia, inflammation, and oxidative stress.

Reduction of AGE intake is accomplished by dietary modification and smoking cessation. Foods high in protein and fat tend to have higher AGE levels. As a rule, animal products such as meats and cheese are high in AGEs. For most Americans, reduction in animal products is a good strategy to lower intake of dietary AGEs (dAGEs). For more precise tailoring of dAGE consumption, tables have been published on AGE content of hundreds of foods.¹⁹ One can, for example, choose pistachios (with an AGE content of 380 kU/100 g) over pine nuts (with an AGE content of 11,210 kU/100 g) to significantly reduced AGE intake.

There have been many human studies examining the effects of dietary AGEs. One such study fed a high-AGE beverage to diabetic and non-diabetic subjects. Ninety minutes after consuming the high-AGE beverage, both groups of subjects had increases in serum levels of AGEs and plasminogen activator inhibitor 1, and a decrease in flow-mediated dilation. The authors conclude: "Significant

increases in serum AGEs can occur together with altered clinical measures of endothelial function in diabetic and nondiabetic subjects after a single modest AGE-rich beverage. Thus, repeated or chronic exposure to high AGE diets could over time lead to and/or accelerate vascular disease.”²⁰

The importance of dietary AGEs in cardiovascular disease was further demonstrated in a study in which diabetics were randomly assigned to a standard diet (High-AGE) or a low (20 % of the standard diet) AGE diet for six weeks to examine the impact on LDL cholesterol. The LDL cholesterol from the diabetics on the low-AGE diet had much less structural damage from glycation and oxidation than LDL cholesterol from diabetics on the High-AGE diet. Whereas High-AGE LDL cholesterol caused significant activation of inflammatory and cell adhesion molecules when added to endothelial cells, the LDL cholesterol from the low-AGE group was found to activate inflammatory and cell adhesion factors to only a slightly greater degree than seen with LDL from non-diabetic subjects. This suggests that dietary AGEs may be a more important factor than blood glucose levels and that “limiting AGE-apolipoprotein B-LDL formation by way of reducing dietary AGE intake could prevent atherogenic events attributed to the LDL particle.”²¹

The Maillard reaction, in which reducing sugars react with amino acids in heated foods, not only improves flavor and gives a brown color to food but results in the formation of AGEs. Cooking methods are another modifiable factor related to dAGE levels. Raw food has substantially less AGEs than cooked food. Cooking with dry heat (frying, grilling, roasting, and broiling) causes the formation of more dAGEs than cooking with moisture (boiling, poaching, stewing, and steaming). Microwaving for times required to cook food, produces less AGEs than other dry cooking methods.

Cooking temperature is an important modifiable factor, as well. The higher the cooking temperature, the more AGEs are formed. In fact, AGE researchers often take advantage of this effect and use a study design whereby two groups of subjects are fed the same diet with the only variable being how much the food is cooked. Cooking time also influences dAGE levels. Reduce cooking time in order to minimize AGE formation.

There are several lines of evidence that AGEs, including dAGEs, contribute to insulin resistance. One study of healthy men and women examined the association between circulating AGEs and insulin resistance. The authors conclude: “We have demonstrated that circulating level of AGEs is associated with insulin resistance even in nonobese, non-diabetic subjects independent of adiponectin.”²²

In a study of healthy human subjects, two different diets were followed for one month each. The diets differed in cooking methods and content of AGEs. The high-AGE diet was found to result in lower insulin sensitivity, elevated plasma cholesterol and triglycerides, and reduced levels of vitamins C and E and long-chain omega 3 fatty acids.²³

In a remarkable animal study, two groups of mice were fed the same diet from birth, which differed only in AGE content (achieved by altering the cooking time). Mice receiving the low-AGE diet (50% AGE content of the regular-AGE diet) had healthier organs and lived longer. Despite eating the same amount of food, they weighed less. They were found to have improved glutathione status, reduced plasma 8-isoprostanes and tissue RAGE levels. The low-AGE group also had less insulin resistance, albuminuria, and glomerulosclerosis. Importantly, they had an increased expression of AGER1, indicating an enhanced ability to remove and degrade AGEs.²⁴ Thus, it is not necessary (nor desirable) to reduce dietary AGE consumption to “zero”. A small amount of AGE “challenge” causes physiological adaptations and keeps the system primed to process AGEs and boost antioxidant defenses. The key is to not exceed the threshold beyond which the body can adapt. The ideal dietary AGE intake for humans awaits clarification but it is safe to assume it is substantially lower than what is found in the average American diet.

Marinating is another strategy to minimize levels of dAGEs. Marinating beef in lemon juice and vinegar for an hour has been found to cut dAGE levels by more than half.

The use of different spices to reduce formation of AGEs can also help. Cloves, cinnamon, garlic, ginger, Jamaican allspice, apple pie spice [allspice, cinnamon, & nutmeg], oregano, rosemary, cumin, black pepper, and turmeric all have been shown to lower AGEs.

Moderate ethanol consumption may be another strategy to reduce endogenous AGE formation. A study performed on diabetic rats found four weeks of alcohol administration reduced Hb-AGEs by 52%. Perhaps the inhibition of formation of AGEs is at least partly responsible for the “French Paradox” of reduced cardiovascular risk despite a high-fat diet.²⁵

When it comes to choice of alcoholic beverage, perhaps red wine is a good choice, as resveratrol has been found to beneficially modulate AGEs. Other natural substances shown to have positive effects on AGEs include berberine, thiamine, benfotiamine, pyridoxine, pyridoxamine, carnosine, EGCg, taurine, arginine, N-acetyl-L-cysteine, carnitine, acetyl-L-carnitine, alpha lipoic acid, grape seed extract, rutin, quercetin, luteolin, genistein, DHEA, curcumin, sulforaphane, and Ipriflavone. All of these are available as supplements.

In a placebo-controlled study of pyridoxamine supplementation in diabetic nephropathy, pyridoxamine was found to have a beneficial effect on kidney function as measured by serum creatinine levels.²⁶

In an endothelial cell culture model, grapeseed proanthocyanidin extract (GSPE) reduced AGE generated reactive oxygen species and inhibited AGE-induced expression of RAGE.²⁷

One of the natural substances with the most impressive research for ameliorating AGE-inflicted damage is benfotiamine, a lipid-soluble derivative of thiamine.

One study examined the physiological influences of benfotiamine on Type 2 diabetics exposed to a high-AGE meal. Thirteen subjects were fed a high-AGE (HAGE) meal and had measures of macrovascular flow-mediated dilatation (FMD), microvascular reactive hyperemia, and serum measures of endothelial dysfunction (E-selectin, vascular cell adhesion molecule-1, and intracellular adhesion molecule-1), oxidative stress, AGEs, and methylglyoxal. After three days of supplementing 1050 mg. of benfotiamine per day, the above assessment was repeated.

The results, to quote the authors, were the following: "The HAGE induced a maximum reactive hyperemia decrease of -60.0% after 2 h and a maximum FMD impairment of -35.1% after 4 h, without affecting endothelium-independent vasodilatation. The effects of HAGE on both FMD and reactive hyperemia were completely prevented by benfotiamine. Serum markers of endothelial dysfunction and oxidative stress, as well as AGE, increased after HAGE. These effects were significantly reduced by benfotiamine."²⁸

From the health traditions of fasting, to the age-prolongation of caloric restriction seen in animal studies, to the cardiovascular benefits of the French Paradox, healthful changes in levels of AGEs may be part of the explanation. What is certain is that it is time for healthcare professionals to evaluate and treat patients for AGE-related dysfunction in order to stem the tide of chronic degenerative disease and promote optimal function.

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