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Advanced Glycosylation End Products and Nutrition—A Possible Relation with Diabetic Atherosclerosis and How to Prevent It

A. XANTHIS, A. HATZITOLIOS, G. KOLIAKOS, AND V. TATOLA

ABSTRACT: Advanced glycosylation end product (AGE) levels are elevated in diabetic patients and may contribute to the excessive cardiovascular disease in this population, promoting oxidant stress and chronic vascular inflammation. AGEs in people with diabetes mellitus are formed mainly by protein and lipid glucosylation in an environment of chronic hyperglycemia and also by prolonged thermal food processing (diet derived AGEs). This brief review summarizes current literature about food derived AGEs and their relationship with diabetic vascular disease and supports the importance of low AGE diet as an essential preventive or therapeutic intervention against atheromatosis progress.

Keywords: advanced glycosylation end products, diet, atheromatosis, diabetes

Introduction

Type II diabetes mellitus (DM II) has reached pandemic proportions involving 11% of the population in the United States, and it is estimated to increase to 20% by the year 2020. A number of studies have confirmed the relation between DM II and the risk of cardiovascular disease and since 2002, DM II is assumed to involve coronary artery disease (National Cholesterol Education Program, ATP III Guidelines 2002) (NCEP 2002). Diabetes macroangiopathy has multiple pathophysiological explanations, one of the most important being the formation of advanced glycosylation end products—AGEs. AGEs constitute a heterogeneous group of substances that is formed by the nonenzymatic glycosylation, that is, reaction of glucose reduction with free amino acids of proteins, lipids, and nucleic acids. (Vlassara and Palace 2002).

AGE formation occurs *via* several pathways (Figure 1). Chemically reversible glycated derivatives—Schiff bases—are initially produced. These products are converted to more stable compounds—called Amadori derivatives—in the following weeks. Amadori derivatives are formed by reversible reactions highly dependent on plasma glucose level. Low plasma glucose causes amino acids to release the hydrocarbons to which they were bound. On the other hand, persistent hyperglycemia causes formation of irreversible bonds between H/C and amino groups, which undergo a series of oxidations, reductions, and hydrations leading to the formation of AGEs. An alternative route of AGE formation is by increased and persistent oxidative stress that transforms glucose to bicarbonyl derivatives (Figure 1). These compounds bind to monoacids to form AGEs. Furthermore, glucose can directly form AGEs through polyoles pathway via the aldose reductase enzyme (Brownlee and others 1988; Baynes and Thorpe 2000). The presence of multiple production mechanisms implies that AGEs constitute a heterogeneous group of substances with different physicochemical properties (Fig-

ure 2), (that is, certain AGEs are fluorescent when exposed in ultraviolet light), but with a common glucose origin (Sato and others system 2006). According to the Szwergold theory an enzymatic deglycation catalyzed by fructosamine-6-kinase inhibits AGE formation, offering protection (Szwergold and others 2002).

In the diabetic patient persistent hyperglycemia inhibits deglycation systems and enhances glycation leading to increased and continuous AGE production (Thornalley and others 1999). AGEs are generally divided in 2 main categories:

1. Those that crosslink with plasma and tissue lipoproteins and plasma lipids, (that is, pentosidine, croslin, vesperlysine, and glycosepene) and
2. Those that do not crosslink (that is, carboxymethyllysine, argopyrimidine, and imidazolones).

The most well studied *in vivo* AGEs responsible for diabetic vascular atheromatosis are carboxymethyllysine and pentosidine due to their increased concentration in plasma and tissues (Van Nguyen and others 2006). AGEs crosslink with endothelium, basic membrane, and matrix proteins leading to differentiation of their structure and function. Crosslink refers to the irreversible binding of AGEs with substances like collagen, intracellular proteins, phospholipids, cellular membranes, DNA, and lipoproteins (for example, LDL), which render them part of an atherogenetic procedure (Schmidt and others 1995; Vlassara and others 1995, 1998; Esposito and others 1998). AGEs exert their action via linking with a specific cell surface receptor named RAGE (receptor of AGEs), which activates a cascade of intracellular reactions leading to increased oxidative stress and production of proinflammatory cytokines. Induction of nuclear factor NF- κ B via the MAP-kinase enzyme route induces the preceding chain of reactions.

These chemical interactions result in increased production of molecules promoting vasoconstriction (endothelium), prothrombotic state (PAI-I), monocytes, and platelets accumulation and adherence in endothelium (VCAM-vascular cellular adhesion molecules) and inflammation (IL-6, TNF) (Figure 3). It has been proved that chronic AGE accumulation in endothelium accelerates

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atheromatosis and causes microangiopathy in kidney and ocular small vessels, as well as macroangiopathy due to diffuse coronary atheromatosis (Yamagishi and others 2007). AGE crosslinking in retina, endothelial, and mesenchymal renal cells leads to:

1. Endothelial dysfunction (impairing vasodilation, due to decreased production of nitrogen monoxide—NO),
2. Accelerated macrophage activation to foam cells,
3. Decreased flexibility of smooth muscle cells, thus compromising arterial compliance, and
4. Making LDL more sensitive to oxidation.

Furthermore, it has been shown that AGEs are increased in non-diabetic individuals with coronary disease, thus proving their crucial role in promoting atheromatosis (Yamagishi and others 2006).

Their levels are also related to vascular disease severity in diabetics; that is to say, individuals with increased AGEs tend to present with more micro and macroangiopathic lesions compared to individuals with lower plasma AGEs (Henle 2005). An increasing number of studies show their relation to peripheral diabetic neuropathy, degenerative diseases, and chronic inflammations, like skin aging, rheumatoid arthritis, Alzheimer dementia, and so on. A recent study showed that in type 2 diabetics, a high-AGE meal induced a more pronounced acute impairment of vascular endothelial function than does an otherwise identical low-AGE meal (Negrean and Stirban 2007).

Food AGE Origin

Two major routes of AGE production are described: endogenous and exogenous. Endogenous includes (1) AGE formation in intracellular and plasma environment due to persistent hyperglycemia, (2) renal failure that causes retention of produced AGEs,

Early and advanced glycation

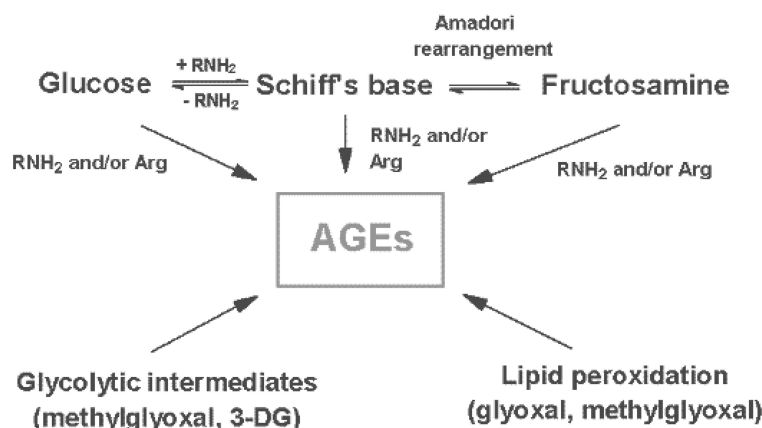


Figure 1 – AGE formation *in vivo*.

Proteins AGEs:

N ϵ -carboxymethyl-lysine (CML), pentosidine, hydroimidazolones and many others

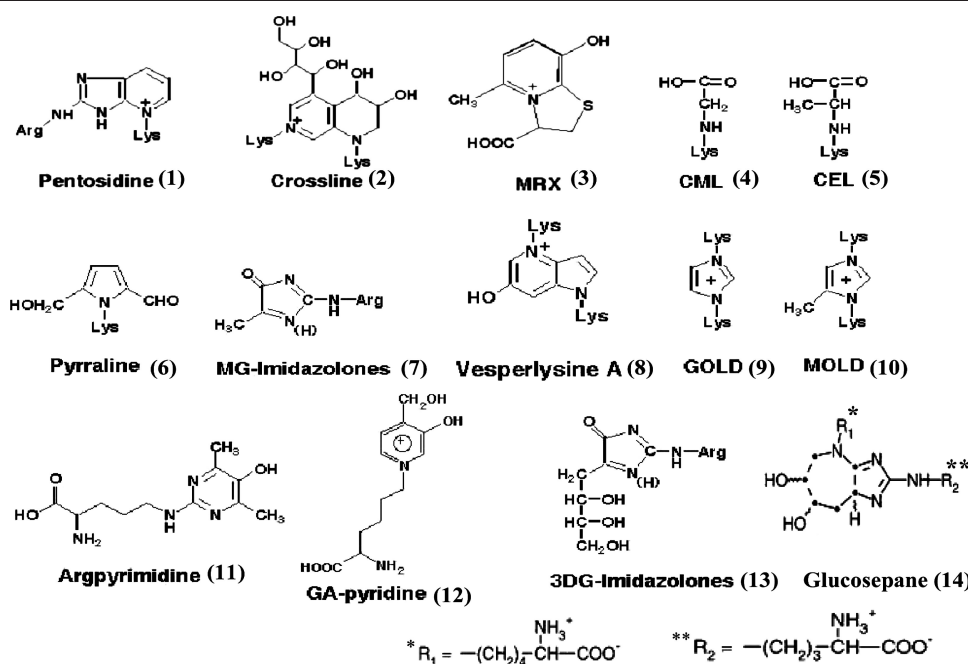


Figure 2 – Chemical structures of some representative AGEs found in foods.

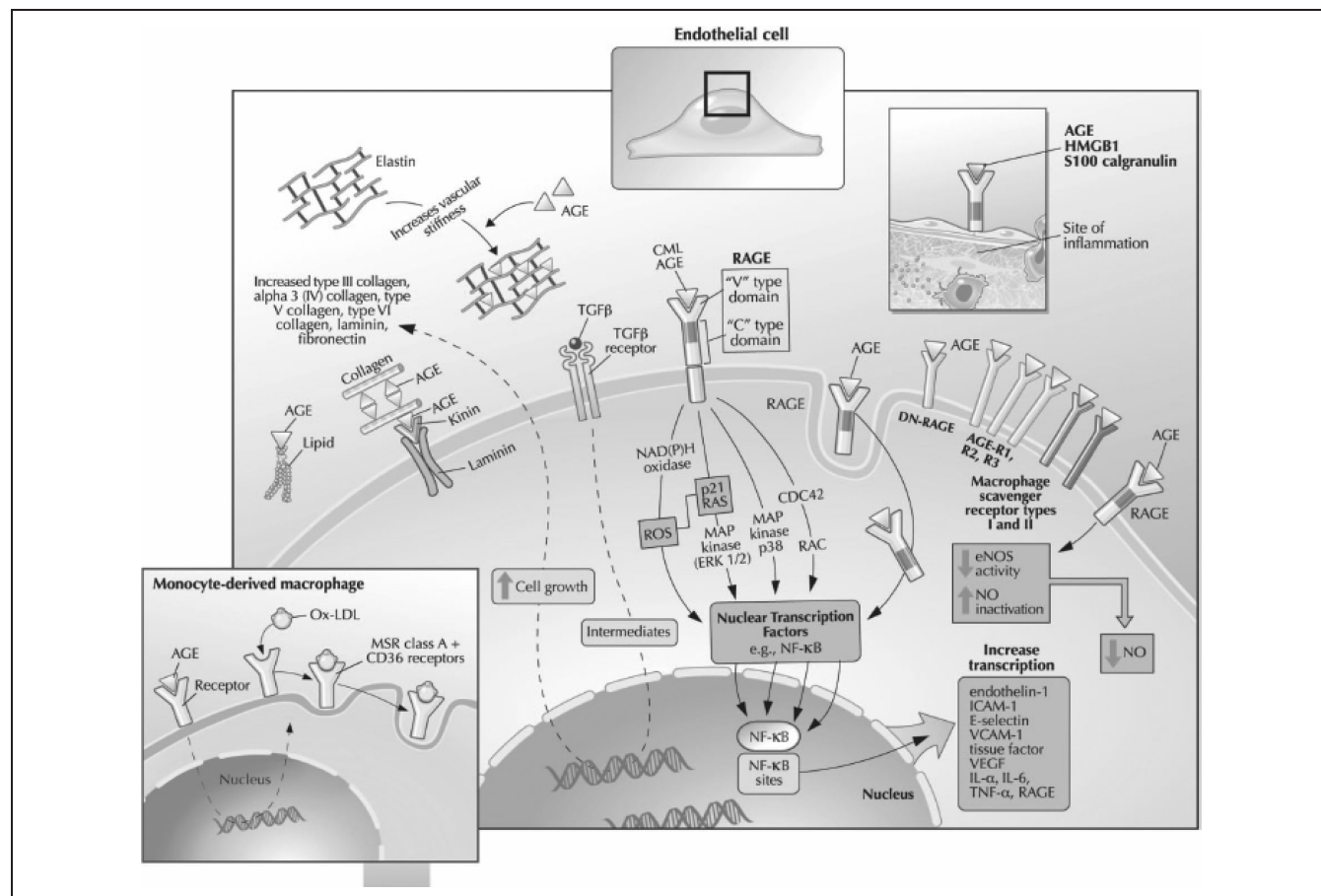


Figure 3 – AGE-RAGE interaction in human vascular endothelial cells.

and increases oxidative stress thus enhancing further production of AGEs, and (c) advanced age, due to long-lasting accumulation of AGEs in tissues. The exogenous route includes AGE uptake from foods containing AGEs. AGEs do not exist in nature, but are produced during thermal food processing, particularly when cooking is prolonged and contains a mixture of carbohydrates, lipids, and proteins. Food AGEs have similar oxidant and inflammatory attributes with endogenous AGEs and the most well studied are carboxymethyllysine and methylglyoxal. There is no proven direct relationship between AGE consumption from foods and future cardiovascular adverse effects, but increasing clinical and laboratory studies show that increased AGE ingestion may influence oxidative stress and thus play a role in atheromatosis.

Common methods of food processing include heating, sterilizing, or microwave, all of which tend to accelerate the nonenzymatic addition of nonreducing sugars to free NH₂-groups of proteins and lipids. This process, also known as “browning” of foods, is largely responsible for the color and flavor of cooked foods that most people are drawn to (Charissou and others 2007). Researchers at the Department of Geriatrics, Mount Sinai School of Medicine have determined that AGEs are mostly found in foods cooked at very high temperatures (Uribarri and others 2007). This includes foods that have been fried, barbecued, broiled, or cooked in the microwave. Increased AGE levels were observed in industrial highly processed foods from animal products like frankfurters, bacon, and powdered egg whites, compared to their unprocessed forms. In all categories, exposure to high temperatures raised the AGE level for equal food weights. The temperature level appeared to be more critical than the duration. Furthermore, microwaving increased AGE

content more rapidly compared to conventional cooking methods (Parliment 1993).

Virtually any food exposed to extreme heat conditions can scorch the natural sugars in food and create these glycotoxins. This also applies for many prepacked foods that have been preserved, pasteurized, homogenized, or refined, such as white flour, cake mixes, dried milk, dried eggs, dairy products, including pasteurized milk, and canned or frozen precooked meals. While it may be impossible to totally avoid glycotxin consumption, it is possible to reduce their content by changing the way food is prepared, and thus steaming, boiling, poaching, stewing, stir-frying, or using a slow cooker is strongly advised. These methods not only cook foods with a lower amount of heat, they also retain foods moisture during the cooking process and researchers have proved that water and moisture inhibit the reactions forming AGEs.

Food composition, cooking temperature, method, and duration can influence AGE formation in many ways. Foods rich in proteins and fats are potential free-oxygen radical sources through lipid oxidation, thus imposing the organism on excess oxidative stress promoting further AGEs formation. This process is accelerated by increased temperature, low humidity, and the presence of trace metals. This procedure takes place when meat is cooked with fat, either animal or plant (butter, margarine), due to the presence of trans-saturated fatty acids. Fortunately, only 10% of AGEs is absorbed by intestinal cells and of that 30% is excreted by the kidneys while 70% is stored in various tissues (Koschinsky and others 1997). Healthy mice received high AGE content food for 6 mo resulting in the appearance of DM II whereas no diabetes was reported when they received foods with same composition and calories, but less AGEs

though they had increased plasma AGEs at the beginning of the study (Sandu and others 2005). According to Vlassara and others, consumption of foods rich in AGEs leads to production of inflammatory cytokines, like TNF- α and C-reactive protein, while other studies proved that low AGE diet prevented diabetic nephropathy in mice (Lin and others 2003).

In diabetic mice, persistent consumption of AGEs increased the incidence of nephropathy compared to diabetic mice that received food with less AGEs. These studies support the opinion that AGE complications are independent and rather additive to hyperglycemia (Cai and others 2007). Increased AGE formation was measured in meat fat fried for > 1 h with soya oil. Smoking is another source of AGEs, because dry heating of tobacco leaves destroys chlorophyll and oxidates carotinoids, thus creating a favorable environment for AGE production. When diabetics were placed on high AGE diet for 2 weeks they increased plasma AGE levels by 65%. At the same time another group of diabetics received low AGE diet resulting in decrease of their plasma levels by 30% (Uribarri and others 2003). According to Uribarri and others, most individuals in the United States consume 16000 kU AGEs per day (Vlassara and others 2002).

Foods containing carbohydrates, like beans, dairy products, fruits, and vegetables, have low AGE concentrations, whereas snacks and biscuits contain large amounts of AGEs. This happens because industrial manufacturing uses products of animal origin (for example, eggs). Heat assists in creating tasteful flavors that humans have grown accustomed to enjoying. In recent decades, food manufacturers have been using this knowledge to boost the flavor of natural foods by incorporating synthetic AGEs into foods. Certain biscuits contain up to 1000 units AGEs per serving, while certain types of processed grains have 600 AGEs per serving. On the other hand, bread, even when toasted, contains similar calories with a meal of corn flakes—it has only 30 AGE units per serving. Obviously, in this instance the cause is not the food itself, but the food industry chemical preparation of meals.

Precooked foods usually served in fast food restaurants, like hamburger, French fries, dressings, and fried chicken, are cooked at temperatures above 230 °C, leading to increased production of AGEs. Certain pastries, like enriched croissants, are produced by application of high pressures during heating and fermentation in order to produce the desirable form. This process causes deconstruction, dehydration, depolarization, and crosslinking between the carbohydrates and the amino acids, promoting their oxidation. Cooking duration plays an important role. One hour boiling of chicken breast in 230 °C generates 1000 AGE units, while frying in oil for 15 min created 5250 AGE units, while 90 g of chicken breast forms 9000, 6700, 4300, and 1000 AGE units when they are cooked by frying, grill, steam, and water boiling, respectively (Goldberg and others 2004).

Various AGE concentrations in common foods appear in Table 1. Fatty foods, such as cheese creams, butter, margarine, mayonnaise, olive oil, and dry fruits contain higher amounts. In the category of animal products most AGEs are seen in yellow cheese, the bovine steak, eggs, and to a lesser degree in milk and fish. In the carbohydrate category most AGEs were found in processed cereals and in bread snacks bread and grains, while the least were recovered from fresh fruits and unprocessed vegetables.

AGE Reduction by Diet

Diets low in AGEs are not lacking flavor or nutritious components. It has been proven that a 50% reduction in AGEs ingested with foods, decreases their plasma levels by 30% within a month, but leaves glycated hemoglobin values unaffected (Peppas

and others 2003). In addition to these, hypoglycemic drugs that lower blood glucose do not lead immediately to a proportional reduction of plasma AGEs, implying that their presence is related to the duration of hyperglycemia and to mean HbA1c values of past years. Cooking with monosaturated fatty acids (like olive oil) is preferred, due to their ability to delay the absorption of carbohydrates. They also strongly advise consumption of foods with low glycemic index, like beans, vegetarian soups, and apples that are highly antioxidative. Marinating foods in olive oil, cider vinegar, garlic, mustard, lemon juice, and dry wines slows AGE formation. Researchers also calculated food AGEs in diabetics compared to healthy individuals and defined 16000 units as a safe limit of AGE consumption. People consuming more AGEs are considered to be in greater risk than those on low AGE diets. Of course, these values are not consistent, and thus large prospective studies are required in order to define nutritional guidelines concerning the minimum AGE daily intake.

Rytine is a natural flavonoid substance found in high concentration in tomato juice, with the ability to inhibit AGE formation

Table 1—AGE content of common foods (AGEs denote carboxymethyllysine-like immunoreactivity, assessed by ELISA).

Food	AGEs (kU/g)
Olive oil	16.68
Fast food beef	54.17
Bacon	90.22
Pink steak	54.25
Chicken breast — fried	61.22
Chicken breast — boiled	11.23
Smoked salmon	5.71
Oil cooked tuna	17.4
White fat cheese	84.23
Yellow nonfat cheese	14.5
Egg boiled for 10 min	18.6
Egg fried with margarine	41.1
White bread	1.51
Whole grain bread	1.10
Toast bread	6.07
Pie crust	5.4
Beans boiled for 1 h	2.9
Spaghetti boiled for 12 min	2.42
Glycopotatoes fried for 10 min	0.72
Boiled potatoes for 30 min	0.17
Fast-food fried potatoes	15.2
Vanilla biscuit	32.2
Small fried potatoes	28.8
Club-sandwich	12.2
Popcorn	1.34
Apple	0.12
Banana	0.08
Broccoli	2.20
Fried carrots	0.10
Mushrooms	2.6
Onion	0.35
Tomato	0.23
Vanilla ice cream	0.35
Full fat milk	0.04
Nonfat milk	0.07
Infant milk	4.86
Maternal milk (fresh)	0.05
Nonfat yogurt	0.32
Honey	0.08
Fresh orange juice	0.003
Processed orange juice	0.056
Spaghetti with tomato sauce	9.34
Spaghetti with cheese	40.69
Pizza	68.24
Coffee instant	0.047
Cola like	0.065
Tea	0.019

in vitro for a long period of time (Kiho and others 2004). Other studies in experimental models of diabetic atheromatosis confirmed that the reduction of food AGEs offered an important protection against the development of nephropathy and arterial stent restenosis. In diabetic patients a diet poor in AGEs for 6 wk decreased C-reactive protein by 20%, whereas a diet rich in AGEs increased C-reactive protein by 35%. Diabetics have more AGEs due to high protein diets, but if they alter their diet so as to consume steam cooked and boiled foods along with avoiding overheated grilled meals, they may manage to decrease food AGE intake by 50% (without any caloric or nutrient restriction). Ideally, foods cooked under 250 °C for 1 h are more desirable and food industries must be forced to label AGE content and invest in inventing food procedures that produce less AGEs.

Conclusions

AGE consumption reduction can be achieved in 3 ways: (1) the daily choice of foods with a low AGE content, (2) healthier cooking methods so as to minimize the production of AGEs, and (3) high antioxidant intake to delay AGE formation. No specific or exhaustive diets are advised. On the contrary, common dietary principles should be recommended to all diabetics, in order to increase patient compliance. Diabetics should be informed about the direct relationship between AGEs and atheromatosis independent of their blood glucose levels. Despite the fact that many drugs are used for AGE inhibition or degradation their efficacy on humans is strongly doubted. Thus diabetics are advised to prepare their meals by steam cooking or boiling in water rather than grilling and frying foods. Cooking at lower temperatures is the safest and most effective method of dietetic prevention of cardiovascular complications in diabetes.

In conclusion, dietary AGEs are significant contributors to plasma AGEs in humans. Sustained reduction in AGE intake may result in effective suppression of inflammatory molecules in diabetes, eventually leading to prevention or delay of atherosclerosis evolution. Further clinical studies are needed to establish specific AGE-based nutritional guidelines as part of complementary nonpharmacological interventions for the diabetic population. While large randomized studies to discover the ideal AGE lowering or inhibiting drug are pending, it is wise to keep in mind what Hippocrates said almost 2000 yr ago: "Prevention is the best treatment." This is the most realistic and cost-effective approach.

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