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ADVANCED GLYCATION END PRODUCTS (AGES): IS THE SCIENTIFIC NEED TO TRAVEL BACK IN TIME TO REGAIN HEALTH NOW OBVIOUS?

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INTRODUCTION:

Advanced glycation end products (AGEs) are proteins or lipids that become glycated after exposure to sugars. AGEs may modify the extracellular matrix (ECM); modify the action of hormones, cytokines, and free radicals via engagement of cell surface receptors; and impact the function of intracellular proteins..AGEs block nitric oxide activity in the endothelium and cause the production of reactive oxygen species. AGEs cause microvascular and macrovascular complications by formation of cross-links between molecules in the basement membrane of the extracellular matrix and by engaging the receptor for advanced glycation end products (RAGE). Activation of RAGE by AGEs causes upregulation of the transcription factor nuclear factor-κB and its target genes. AGEs can be formed either endogenously or exogenously. Endogenously, advanced glycation takes place in all cell types via the Maillard reaction between reducing sugars and amino residues present in proteins, lipids, and DNA, resulting in loss of protein structure and function followed in some instances by cellular apoptosis. Transition to plant based antioxidant diet with traditional Indian cooking methods seems to confer multitude of health benefits.

DISCUSSION

AGEs are created through a nonenzymatic reaction between reducing sugars and free amino groups of proteins, lipids, or nucleic acids. This reaction is also known as the Maillard or browning reaction (5).Advanced glycation end products (AGEs) are compounds that are formed when protein or fat combine with sugar in the bloodstream. This process is called glycation. Human metabolic health implications of AGEs are significant.

There are three major types of AGEs: 1.Cross-linking fluorescent AGEs.2.Nonfluorescent cross-linking AGE.3.Nonfluorescent noncross-linking AGEs. Intracellular production of AGE precursors damages target cells by three general mechanisms: intracellular proteins modified by AGEs have altered function. Extracellular matrix components modified by AGE precursors interact abnormally with other matrix components and with matrix receptors (integrins) on cells. Plasma proteins modified by AGE precursors bind to AGE receptors on cells such as macrophages, inducing receptor-mediated ROS production. This AGE-receptor ligation activates the pleiotropic transcription factor nuclear factor-κB (NFκB), causing pathologic changes in gene expression.

These compounds naturally accumulate with age or formed as a result of cooking also especially at high temperatures. Advanced glycation end products (AGEs) form by the interaction of aldoses with proteins and the subsequent molecular rearrangements of the covalently linked sugars, eventuating in a diverse group of fluorescent compounds of yellow-brown color. This heterogeneous class of nonenzymatically glycated proteins or lipids is found in the plasma and accumulates in the vessel wall and tissues even in normal aging (1). There is enhanced formation of these products in diabetes mellitus. RAGE (Figure 1) a member of immunoglobulin family mediates the binding of AGEs to endothelial cells and mononuclear phagocytes. It interacts with a lactoferrin-like polypeptide that also binds AGEs, and appears to activate intracellular signal transduction mechanisms consequent to its interaction with the glycated ligand. RAGE expressed by ECs, mononuclear phagocytes, smooth muscle cells, mesangial cells, and neurons, indicating a potential role in the regulation of their properties in homeostasis and/or their dysfunction in the development of diabetic complications. In addition oxidant stress on cellular targets, resulting in changes in gene expression and the cellular phenotype occurs due to formation of intermediates of reactive oxygen species.

Body has antioxidant and enzymatic activities to deal with these issues to a certain extent. Increased production or consumption leads to accumulation of AGEs in the body. High levels have been implicated in the development of many diseases, like diabetes, heart disease, kidney failure, and Alzheimer's and premature aging (3).Modern cooking methods enhance the level of AGEs in food and these include barbecuing, grilling, roasting, baking, frying, sautéing, broiling, searing, and toasting (4). Dietary advanced glycation end products (dAGEs) are known to contribute to increased oxidant stress and inflammation. Dry heat promotes new dAGE formation by >10- to 100-fold above the uncooked state.

Animal-derived foods that are high in fat and protein are generally AGE-rich and prone to new AGE formation during cooking. In contrast, carbohydrate-rich foods such as vegetables, fruits, whole grains, and milk contain relatively few AGEs, even after cooking. Aminoguadine is known to inhibit formation odd AGEs. Significantly reduced by cooking with moist heat, using shorter cooking times, cooking at lower temperatures, and by use of acidic ingredients such as lemon juice or vinegar. Higher-fat and aged cheeses, such as full-fat American and Parmesan, contained more dAGEs than lower-fat cheeses, such as reduced-fat mozzarella, 2% milk cheddar, and cottage cheese. High-fat spreads, including butter, cream cheese, margarine, and mayonnaise, was also among the foods highest in dAGEs, followed by oils and nuts. Whereas cooking is known to drive the generation of new AGEs in foods, it is interesting to note that even uncooked, animal-derived foods such as cheeses can contain large amounts of dAGEs. This is likely due to pasteurization and/or holding times at ambient room temperatures (eg, as in curing or aging processes) (6).

Grains, legumes, breads, vegetables, fruits, and milk were among the lowest items in dAGE, unless prepared with added fats. For instance, biscuits had more than 10 times the amount of dAGEs found in low-fat

breads, rolls, or bagels. The heat-induced new AGE formation in olive oil was completely prevented in the presence of the AGE inhibitor, amino guanidine, but only partly blocked by the anti-oxidant BHT. New AGE formation in cooked meat was also inhibited following exposure to acidic solutions (marinades) of lemon juice and vinegar.

Advanced glycation end products (AGEs) and its cell receptor (RAGE) and soluble receptor (sRAGE) has been implicated in chronic limb ischaemia also. AGE-RAGE axis inclusive of AGE, RAGE, and sRAGE has been implicated in atherosclerotic stenosis and restenosis. Serum and tissue levels of AGE, and expression of RAGE are elevated, and the serum levels of sRAGE are low in CLLI. It is known that AGE, and AGE-RAGE interaction increase the generation of various atherogenic factors including reactive oxygen species, nuclear factor-kappa B, cell adhesion molecules, cytokines, monocyte chemo attractant protein-1, granulocyte macrophage-colony stimulating factor, and growth factors. sRAGE acts as antiatherogenic factor because it reduces the generation of AGE-RAGE-induced atherogenic factors. The formation of AGEs on the surface of diabetic erythrocytes mediates their interaction with endothelial cells (ECs) leading to binding and induction of vascular dysfunction. Enhanced binding of diabetic erythrocytes to ECs can be blocked by pre incubation of erythrocytes with anti-AGE IgG or preincubation of ECs with antibodies to the receptor for AGE (RAGE). Immunoblotting of cultured human ECs and immunostaining of normal/diabetic human tissue confirmed the presence of RAGE in the vessel wall.

Binding of diabetic erythrocytes to endothelium generated an oxidant stress, as measured by production of thiobarbituric acid-reactive substances (TBARS) and activation of the transcription factor NF-kappa B, both of which were blocked by probucol or anti-RAGE IgG. The extensive contact of diabetic erythrocytes bearing surface-associated AGEs with vessel wall RAGE could be important in the development of vascular complications (2). Appearance of thiobarbituric acid–reactive substances (TBARS) and activation of NF-κB, mononuclear phagocytes are also affected by oxidative processes resulting from the presence of AGEs.

In addition, AGEs found on the surface of erythrocytes can bind to RAGE, increasing TBARS levels and activating NF-κB. The source of ROS on diabetic erythrocytes is most likely AGEs bound to the erythrocyte surface, because engagement of RAGE by antibodies does not produce oxidant stress. AGE and its interaction with RAGE can induce AF through alteration in cellular protein and extracellular matrix. AGE and its interaction with RAGE induce atrial structural and electrical remodeling (8).

Changes in dietary AGEs parallel changes in insulin sensitivity, oxidative stress, and hormonal status in women with PCOS, and therefore lowering the concentration of AGEs in food may improve these variables

The average AGE consumption in New York is thought to be around 15,000 AGE kilo units per day. Therefore, a high-AGE diet is often referred to as anything significantly above 15,000 kilo units daily. When you eat a diet rich in plant foods, such as fruits, vegetables, legumes and whole grains, and consume low-fat dairy and less meat, the AGE levels will likely be lower.

In fact when you prepare meals with moist heat, such as soups and stews, again the consumption level of AGEs will be low. TABLE 1 shows some common food level of AGEs expressed as kilounits per lit. Slow cooking and cooking on ceramic or earthen ware have shown benefits.

Fresh whole foods are better as they are low in absorbable Ages. it C and quercetin hinders AGEs formation. So does natural plant phenols. Resveratrol significantly inhibited AGEs-induced TGF-beta1 mRNA increases in a dose-dependent manner (7). Models for treatment of chronic limb ischaemia (CLI) suggest lowering AGE levels through reduction of dietary intake of AGE, prevention of AGE formation and degradation of AGE, suppression of RAGE expression, blockade of AGE-RAGE binding, elevation of sRAGE by up regulating sRAGE expression, and exogenous administration of sRAGE, and use of antioxidants(8). Diet full of colorful fruits, vegetables, herbs, and spices may help protect against the damaging effects of AGEs. Regular exercise and an active lifestyle have been shown to reduce the amount of AGEs in the body (9,10).

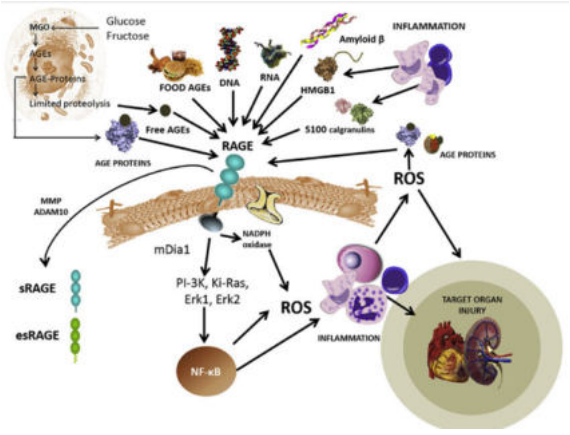
CONCLUSION

Optimal management strategies would revolve around lowering AGE levels through reduction of dietary intake of AGE, prevention of AGE formation and degradation of AGE, suppression of RAGE expression, blockade of AGE-RAGE binding, elevation of sRAGE by up regulating sRAGE expression, and exogenous administration of sRAGE, and use of antioxidants. Healthier cooking methods, limiting foods high in AGEs and eating more antioxidants and regular exercise is the way forward for better health. May be a return to vegan diet with more natural food and minimal cooking low and slow would be the ideal as our ancestors did. Need we return back in time to regain our health?

Table 1.

- **1 fried egg:** 1,240 kU/l
- **1 scrambled egg:** 75 kU/l
- **2 ounces (57 grams) of toasted bagel:** 100 kU/l
- **2 ounces of fresh bagel:** 60 kU/l
- **1 tablespoon of cream:** 325 kU/l
- **¼ cup (59 ml) of whole milk:** 3 kU/l
- **3 ounces of grilled chicken:** 5,200 kU/l
- **3 ounces of poached chicken:** 1,000 kU/l
- **3 ounces of French fries:** 690 kU/l
- **3 ounces of baked potato:** 70 kU/l
- **3 ounces (85 grams) of broiled steak:** 6,600 kU/l
- **3 ounces of braised beef:** 2,200 kU/l

Figure 1



Receptor for Advanced Glycation End Products (RAGE) Is a Key Pathway for Inflammatory Complications

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