Glucose, Advanced Glycation End Products, and Diabetes Complications: What Is New and What Works

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Editor's note: *This is one in a series of articles from the various professional section councils of the American Diabetes Association. This installment is from the Council on Complications.*

The incidence of diabetes, particularly type 2 diabetes, is increasing at an alarming rate. Worldwide, about 124 million people had diabetes by1997; by 2010, this number is estimated to reach 221 million. Because of the large number of severe pathologies complicating the clinical course of diabetes, one can easily speculate on the huge economic and psychosocial impact of diabetes across age groups and geographical regions.

A large number of studies have focused on the factors involved in the pathogenesis of diabetic complications, most seeking effective therapies, but the exact cellular or molecular basis of these complications has not yet been fully elucidated. Hyperglycemia is still considered the principal cause of diabetes complications. Its deleterious effects are attributable, among other things, to the formation of sugar-derived substances called advanced glycation end products (AGEs). AGEs form at a constant but slow rate in the normal body, starting in early embryonic development, and accumulate with time. However, their formation is markedly accelerated in diabetes because of the increased availability of glucose.

AGEs are a heterogeneous group of molecules formed from the nonenzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids. The initial product of this reaction is called a Schiff base, which spontaneously rearranges itself into an Amadori product, as is the case of the well-known hemoglobin A_{1c} (A1C). These initial reactions are reversible depending on the concentration of the reactants. A lowered glucose concentration will unhook the sugars from the amino groups to which they are attached; conversely, high glucose concentrations will have the opposite effect, if persistent. A series of subsequent reactions, including successions of dehydrations, oxidation-reduction reactions, and other arrangements lead to the formation of AGEs. Several compounds, e.g., $^{\epsilon}$*N*-carboxymethyl-lysine, pentosidine, or methylglyoxal derivatives, serve as examples of well-characterized and widely studied AGEs.

A key characteristic of certain reactive or precursor AGEs is their ability for covalent crosslink formation between proteins, which alters their structure and function, as in cellular matrix, basement membranes, and vessel-wall components. Other major features of AGEs relate to their interaction with a variety of cell-surface AGE-binding receptors, leading either to their endocytosis and degradation or to cellular activation and pro-oxidant, pro-inflammatory events.

A large body of evidence suggests that AGEs are important pathogenetic mediators of almost all diabetes complications, conventionally grouped into micro- or macroangiopathies. For instance, AGEs are found in retinal vessels of diabetic patients, and their levels correlate with those in serum as well as with severity of retinopathy.

Aminoguanidine, an inhibitor of AGE formation, is shown to prevent retinopathy in diabetic animals. Also, it is known that AGEs accumulate in peripheral nerves of diabetic patients and that the use of anti-AGE agents improves nerve conduction velocities and neuronal blood flow abnormalities.

The characteristic structural changes of diabetic nephropathy, thickened glomerular basement membrane and mesangial expansion, are accompanied by accumulation of AGEs, leading to glomerulosclerosis and interstitial fibrosis. Prolonged infusion of nondiabetic rats with AGEs has led to the development of similar morphological changes and significant proteinuria. Here again, AGE inhibitors such as aminoguanidine prevented diabetic nephropathy in diabetic animal models and were recently shown to do the same in one clinical trial on diabetic patients.

Atherosclerosis is significantly accelerated in diabetic patients and is associated with greater risk of cardiovascular and cerebrovascular mortality. Animal and human studies have shown that AGEs play a significant role in the formation and progression of atherosclerotic lesions. Increased AGE accumulation in the diabetic vascular tissues has been associated with changes in endothelial cell, macrophage, and smooth muscle cell function. In addition, AGEs can modify LDL cholesterol in such a way that it tends to become easily oxidized and deposited within vessel walls, causing streak formation and, in time, atheroma. AGE-crosslink formation results in arterial stiffening with loss of elasticity of large vessels. This arterial stiffness has recently been shown to be reversed

by the administration of another anti-AGE class of compounds called AGE-breakers.

In addition to those endogenously formed, AGEs can also be introduced in the body from exogenous sources. Tobacco smoke, for example, is a well-known exogenous source of AGEs. The combustion of various pre-AGEs in tobacco during smoking gives rise to reactive and toxic AGEs. Serum AGEs or LDL-linked AGEs are significantly elevated in cigarette smokers. Diabetic smokers, as a result, are reported to exhibit greater AGE deposition in their arteries and ocular lenses.

More importantly, recent studies have provided evidence that diet is a significant exogenous source of highly reactive AGEs. Food processing, heating in particular, has a significant accelerating effect in the generation of glyco- and lipoxidation products. Heat helps create tasteful flavors that humans have learned to enjoy. In recent decades, food manufacturers have been using this knowledge to boost the flavor of natural foods by incorporating synthetic AGEs into foods. Consequently, the AGEs content of the Western diet has increased vastly in the past 50 years, as has the quantity of food consumed.

A significant proportion (~10%) of ingested AGEs is absorbed with food. There is apparently a direct correlation between circulating AGE levels and those consumed. Studies in animals have demonstrated an important relationship between high dietary AGE intake and development or progression of diabetes-related tissue damage, e.g., vascular and renal. In all instances, this was prevented by dietary AGE restriction.

A similarly significant contribution to the human body AGE pool by diet was demonstrated recently. More importantly, its effective reduction by a restriction of dietary AGEs was associated with a significant suppression of circulating levels of vascular disease markers (e.g., adhesion molecules) as well as of inflammatory mediators.

This new evidence suggests that modulation of food-AGE content could become an important ingredient of the therapeutic armamentarium in the management of diabetic patients. Until effective and safe drugs become available, physicians and dieticians can, for instance, advise increased reliance on fresh foods, cooked by brief applications of heat, in the presence of ample water or humidity. A diet designed to be low in AGEs is apparently not lacking in taste, while not requiring compromises in important nutrients. Such a regimen can decrease AGE intake by more than 50%; this in turn was shown to reduce circulating AGEs by ~30% within a month without a change in A1C. On the contrary, short-term euglycemia or temporary normalization of A1C are not sufficient means for reducing serum AGEs; instead this requires extended periods of time, e.g., months or years.

Anti-AGE drugs are also being intensively studied. Aminoguanidine was the first drug designed to inhibit glycation reactions by inhibiting the conversion of early products to AGEs. Animal studies proved that aminoguanidine was beneficial for many diabetes-related complications. While promising, the drug required further testing. Additional drugs that inhibit AGE formation or disrupt already formed AGEs (e.g., AGE-breakers) are also under active investigation. So far, animal and human studies have been very encouraging. For example, a significant reversal of vascular inelasticity leading to improvement of systolic hypertension and severe heart failure has been reported with AGE-breakers. Other pharmacological approaches are still in early stages of development.

In conclusion, current evidence points to glucose not only as the body's main short-term energy source, but also as the long-term fuel of diabetes complications, mainly in the form of oxidative, pro-inflammatory AGEs. Food commonly consumed after exposure to heat contains a significant amount of pre-formed AGEs, a fact that offers a new perspective on food as a major environmental risk factor. It may be necessary, for instance, to restructure our guidelines to include methods of food preparation along with or in addition to routine recommendations about food quantity and composition.

It is reasonable to consider that good glycemic control, in combination with a careful diet in terms of reduced AGE consumption, should be among the new goals for optimal management of diabetic patients. Addressing dietary habits from a new perspective, while difficult, could achieve the best long-term effects as novel drug interventions become available for clinical use in the future.

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