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 by 1997; 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 A1c (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., 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 ele-
vated 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 sig-
nificant exogenous source of highly
reactive AGEs. Food processing, heating
in particular, has a significant accelerat-
ing effect in the generation of glyco-
and lipoxidation products. Heat helps create
tasteful flavors that humans have learned
to enjoy. In recent decades, food manu-
facturers 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 impor-
tantly, its effective reduction by a restric-
tion 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 man-
agement of diabetic patients. Until effec-
tive 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 circulat-
ing AGEs by ~30% within a month with-
out a change in A1C. On the contrary,
short-term euglycemia or temporary nor-
malization 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 glyca-
tion reactions by inhibiting the conver-
sion 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 dis-
rupt already formed AGEs (e.g., AGE-
brakers) are also under active investiga-
tion. So far, animal and human studies
have been very encouraging. For exam-
ple, a significant reversal of vascular
inelasticity leading to improvement of
systolic hypertension and severe heart
failure has been reported with AGE-
brakers. 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 compli-
cations, mainly in the form of oxidative,
pro-inflammatory AGEs. Food common-
ly consumed after exposure to heat con-
tains a significant amount of pre-formed
AGEs, a fact that offers a new perspec-
tive 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 rec-
ommendations 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 diabet-
ic 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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