

Orentreich  
Foundation for the  
Advancement of  
Science, Inc.

# VitalLongevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

June 2005

## GLUCOSE TOXICITY

Our last VitaLongevity (March 2005) stressed the anti-aging benefits of lowering insulin levels using both nutritional methods and key supplements. Lower glucose levels resulting from these strategies provide an added reward: reduced formation of advanced glycation end products or AGEs. Toxic in excess, glucose directly damages proteins, lipids, and other cellular constituents by attaching itself to these molecules through the non-enzymatic process of glycation.

Temperature and the level of glucose drives the rate of glycation and ultimately the abundance of AGEs. Other sugars also perform glycation; notably, fructose reacts more readily with proteins than does glucose (Figure 1), but glucose circulates at the highest level of any of the sugars and causes the most damage. The initial events of glycation can be reversed, that is, a lower glucose level will allow the sugar and protein to separate. But over time, in the presence of chronically elevated glucose, e.g., diabetes, the glycation products become more complex, irreversible, and detrimental—they become AGEs.

Not surprisingly, along with the growing recognition of glucose toxicity, the recommended normal fasting blood glucose level keeps getting revised downward, recently dropping from 110 to <100 mg/dL; some believe that optimal fasting glucose should be <86mg/dL. Excessive after-meal glucose surges pose even greater hazards; levels above 200 mg/dL, for example, triple the risk of AGE-associated retinopathy in persons with normal fasting glucose. Glycosylated (glycated) hemoglobin (HbA1c), a protein in red blood cells, serves as a measure of average glucose levels over the previous 3 months. HbA1c should be under 6%, the lower the better.

### Glycation Damage

AGEs cause problems in numerous ways but primarily by inhibiting specific functions of proteins. Some glycated proteins clump abnormally and precipitate in such delicate tissues as tubules and tiny blood vessels of the kidney, the first organ to be impaired in diabetes. Reactive AGEs facilitate cross-linking between structural proteins (primarily collagen) in blood vessels and skin, resulting in vascular

stiffness (arteriosclerosis) and hypertension and in inelastic and wrinkled skin, respectively. AGEs induce circulating platelets, antibodies, and lipoproteins to stick to blood vessel walls, beginning the process of fatty streak formation (atherosclerosis) and vessel occlusion. AGEs also react with their own receptor, RAGE, producing reactive oxygen species (ROS) and subsequent oxidative damage to proteins. ROS themselves greatly speed AGE formation, creating a vicious cycle (Figure 2). Youthful and calorie-restricted organisms engage in high rates of protein turnover, getting rid of clinker proteins and debris as quickly as possible. Cellular junk consisting of, among other things, glycated, misfolded proteins accumulates in aged organisms and impedes its own elimination; cataract formation is one example. The breakdown products of AGEs, also highly reactive, lead to second and third generations of AGEs and further life-shortening events such as heart attacks and strokes.

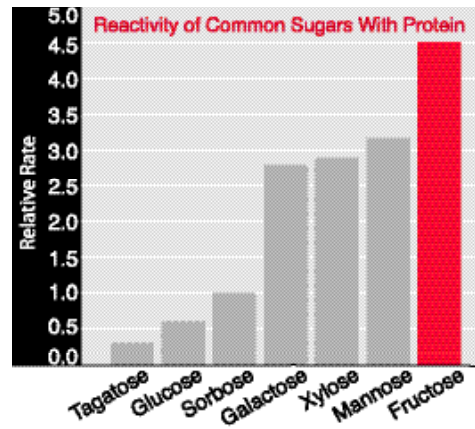


Figure 1. Adapted from: Bunn HF, Higgins PJ. Reaction of monosaccharides with proteins: possible evolutionary significance. *Science* 1981;213:222-4, by permission of the publisher.

### Food Sources of AGEs

Food cooked at high temperatures undergoes the same glycation and AGE formation as occurs in our bodies but at a much faster rate. Visible browning indicates the presence of AGEs, most

being yellow-to-brown in color. You add to your burden of AGEs by eating seared, fried, or broiled foods. Although microwave ovens don't brown foods, the localized, intense heat creates large amounts of colorless AGEs. We absorb about 10% of ingested AGEs, 1/3 of those being excreted in urine, the rest available to do harm. The AGE content of the Western diet rose sharply in the past five decades due to changes in methods of food preparation and such additives as caramelized sugars in cola.

### Skin AGEs

Skin is a bellwether for damage occurring elsewhere in the body. For example, poorly controlled diabetics exhibit prematurely aged skin; the reasons for this go beyond simple AGE cross-linking of collagen and elastin or sallowness due to browning. A complex chain of AGE-induced events establishes a self-inciting micro-inflammatory cycle that interferes with the structure and function of skin. Of note, common environmental stressors that contribute to skin aging—sun exposure, pollution, hypoxia, smoking, trauma, and infections—provoke the same inflammatory process.

The long half-life of skin collagen (15 years) allows AGE accumulation to exceed protein turnover, making skin particularly vulnerable to glucose toxicity. The rate of collagen-AGE formation in non-diabetics is about 3.7% per year. Over time, the self-assembly of collagen becomes impaired and fibers become disordered, turning brown. But it's another vulnerable target, the cells lining cutaneous blood vessels (endothelial cells), that is responsible for starting the inflammatory cascade. As shown in Figure 2, endothelial cells present RAGE to circulating AGEs. Via the AGE-RAGE interaction, a cell adhesion molecule (ICAM-1) is produced. ICAM-1 recruits circulating immune cells that begin producing ROS and secreting enzymes that degrade the structural support proteins of the skin. This degradation process inflicts random damage on bystander cells that react by secreting other inflammatory molecules (prostaglandins and leukotrienes). These molecules in turn cause resident mast cells (cells typically involved in allergy response) to release histamine and tumor necrosis factor-alpha (TNF- $\alpha$ ) both very inflammatory and capable of activating more endothelial cells lining adjacent capillaries. These cells respond by making and dumping more ICAM-1. Thus, a smoldering, low-grade but chronic state of inflammation begins. The result: thin, wrinkled, inelastic skin that heals very slowly.

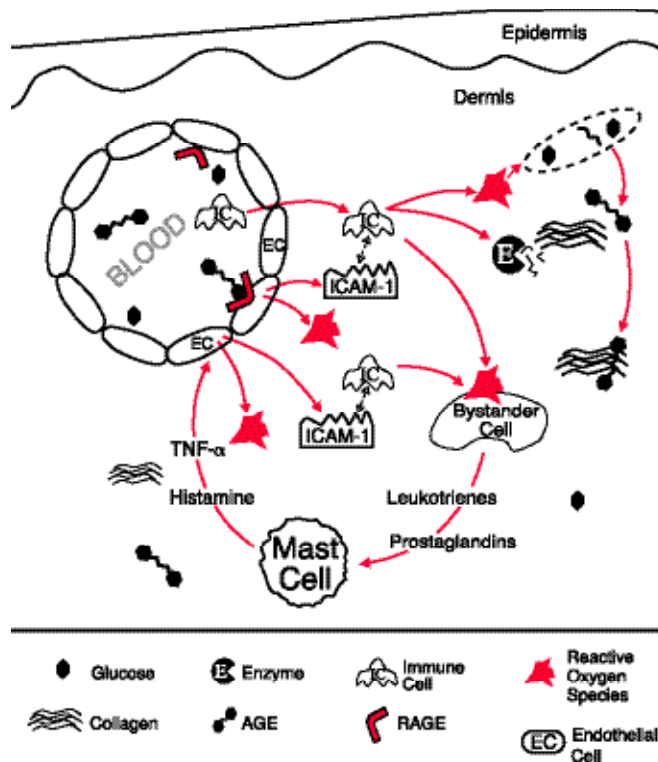


Figure 2.

fibers such as glucomannan and psyllium to your diet to slow its absorption. Eat your fruit whole, not juiced, for this reason as well. Limit pre-made AGEs by eating raw or minimally cooked foods when possible. Pre-packaged foods exposed to high heat during preservation, such as canned or frozen meals, as well as pasteurized dairy products, contain high levels of AGEs. Using a slow-cooker instead of the microwave oven allows a lower cooking temperature and creates moisture that helps delay the glycation reaction.

Consider using artificial sweeteners, e.g., Splenda® or Equal®, in lieu of sugar and avoid products containing high-fructose corn syrup. Two supplements, both safe and effective, can be considered:

**Carnosine**, a natural antioxidant, inhibits glycation and also reacts with glycated proteins, disarming them of their ability to cross-link. Carnosine also rejuvenates senescent dermal cells (fibroblasts) that produce collagen. For these reasons, carnosine helps keep skin and connective tissue supple and elastic. Long-lived cells contain high levels of carnosine, but its level declines with age. A dose of 400 to 1000mg twice daily is recommended.

**Benfotiamine**, a lipid-soluble form of the water-soluble vitamin thiamine (B<sub>1</sub>), counteracts AGE formation by blocking the absorption of excess glucose into cells, thus protecting against glucose toxicity. The main beneficiaries of its activities are endothelial cells; benfotiamine was shown to prevent retinopathy in diabetic rats. The recommended dose is 100 mg twice daily.

No one should rely solely on supplements to avert glucose toxicity. Incorporating just a few of the suggestions presented here as well as those we discussed previously into your daily routine will go a long way to improving your chances of living a long and healthy life.

## What to Do?

Don't stew in your own juice for starters. We can't avoid entirely the slow-cooking process of aging but we can reduce the main ingredient, glucose, by selecting foods with a low glycemic index (GI) (see <[www.prevention.com](http://www.prevention.com)>). GI indicates the effect each carbohydrate-containing food has on blood glucose levels. You can further blunt the after-meal increase in blood glucose by adding soluble

## INFORMATION FOR DONORS

The Orentreich Foundation for the Advancement of Science, Inc., was founded in 1961. OFAS is a non-profit institution dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. It is duly registered with the US Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

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