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REPORT

Guard Your Precious Proteins Against Premature Aging

By Steven Joyal, MD

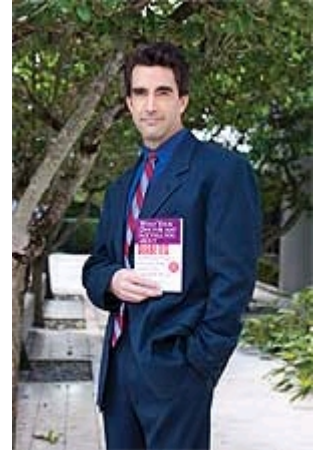
It may seem inconceivable, but scientists long ago learned why aging people suffer so many disorders related to their eyes, kidneys, brain, and vascular system.

While these pathological processes are accelerated in diabetics, they affect all aging people to one degree or another.

In a startling revelation, Steven Joyal, MD, lays out an innovative, but remarkably simple program to enable both diabetics and normal aging humans to avoid these horrendous biological consequences.

The article you are about to read is a summary of Dr. Joyal's new book titled *What Your Doctor May Not Tell You About Diabetes*.

In fact, this book contains vital information for every aging person. The reason is that most aging people suffer pre-diabetic pathologies and should therefore follow similar strategies to protect against common age-related diseases.



DIABETES IS A FORM OF ACCELERATED AGING

For decades, scientists have been trying to uncover the root causes of premature aging. The fact that diabetes is a form of accelerated aging comes as a surprise to most people. In fact, life expectancy for people with diabetes is four to eight years less than for non-diabetics. Both aging and diabetes share two important biological processes that damage the body: glycation, which results in damage to protein and lipid molecules, and oxidative stress, characterized by increased free-radical activity and damage to tissues by molecules like reactive sugar aldehydes. And many signs and symptoms of diabetes also commonly occur with aging, including:

- Cardiovascular ailments, such as heart attack, poor circulation in the legs, and atherosclerosis (a general term for several diseases characterized by thickening and hardening of the arteries), and stroke.
- Increased prevalence of certain types of cancer (pancreas, colon, and liver).
- Vision problems, including cataracts, glaucoma, and retinal degeneration.
- Impotence.
- Hearing loss.
- Memory loss or other cognitive impairment.
- Skin conditions, such as rashes, infections, thin skin, and discoloration.
- Loss of elasticity and flexibility of skin and other tissues.

Given that diabetes and aging share so many characteristics, it's not surprising that they also respond to many of the same prevention and treatment strategies.

GLYCATION AND GLYCOTOXINS: AGES AGE YOU FASTER

When patients hear that glycation is one of the major consequences of diabetes and a contributing factor in diabetic complications, their typical response is, "I've never heard of it. Is it something new?" When they hear that scientists have known about glycation since at least 1912 and of its major impact on diabetes and diabetic complications since the 1980s, their typical response is, "Why haven't I heard about it? Why isn't my doctor talking about it?"

Glycation is a biochemical process that involves a series of non-enzymatic reactions (those that don't require enzymes to make them happen) between proteins and/or certain lipids (fats) and glucose.

The result is the formation of toxic substances known as AGEs—advanced glycation end products—and ALEs—advanced lipoxidation end products.

If you've ever made toast, then you've experienced glycation firsthand. Toasting bread involves the Maillard reaction—the browning reaction that occurs when food is heated and cooked at high temperatures. This reaction is also commonly observed when we grill lamb chops, broil salmon steaks, and make French fries.



Levels of AGEs and ALEs increase as people grow older, and those levels are fueled by the foods we eat.

In the past, scientists underestimated the impact of food-derived glycotoxins' damage on human cells, organs, and tissues. Recent groundbreaking research, however, has uncovered startling evidence of the critical role that food-derived glycotoxins play in contributing to glycation in the body. Furthermore, recent research indicates AGEs play an important role in the aging process as well as in diseases such as diabetes, heart disease, kidney disease, cancer, Alzheimer's disease, and certain types of neuropathy.

Glycotoxin levels increase dramatically in people who have elevated blood glucose levels because these noxious substances thrive in high-glucose environments. Thus, glycotoxins are especially prevalent in individuals who have metabolic syndrome, prediabetes, or diabetes. Sites in the body that are especially susceptible to the accumulation of glycotoxins include the renal glomerulus (in the kidney), the retina (the membrane at the back of the eye that helps you see), and important blood vessels like the coronary arteries (the arteries that supply blood to the heart). We also know that glycotoxins play a significant role in causing chronic diseases that are associated with underlying inflammation, such as heart disease and neuropathy.

WHAT YOU NEED TO KNOW: DIABETES AND ACCELERATED AGING

- Both aging and diabetes share two important biological processes that damage the body: glycation, which results in damage to protein and lipid molecules, and oxidative stress, characterized by increased free-radical activity and damage to tissues.
- Glycation is a biochemical process that involves a series of non-enzymatic reactions (those that don't require enzymes to make them happen) between proteins and/or certain lipids (fats) and glucose, which result in the formation of dangerous glycotoxins called advanced glycation end products (AGEs).
- Foods in the fat and meat (protein) groups contain thirty-fold and twelve-fold higher AGE content, respectively, than foods in the carbohydrate group. On the other hand, fresh fruits, vegetables, whole grains, raw nuts, and other unprocessed, unrefined foods have low levels of glycotoxins.
- Glycotoxins are also formed during food production and preparation. Foods prepared under high heat (such as broiling, frying, hot-oven roasting, and barbecuing) are loaded with glycotoxins.
- Preparing food at temperatures less than 250°F avoids the formation of dietary glycotoxins. Such methods use liquids and lower cooking temperatures and include poaching, steaming, braising, stewing, and slow cooking (as in a crockpot cooker).
- The damage wrought by glycation can be prevented with specific nutrients. Benfotiamine helps prevent the nerve and blood vessel damage—and the resulting complications—that are caused by glycation.
- Carnosine is an antioxidant that acts as a shield against sugar molecules, thus preventing glycation. Carnosine also stimulates enzymes and other substances to eliminate damaged, glycated proteins, thus helping to reduce the impact

of diabetic complications.

HOW GLYCOTOXINS ARE FORMED IN FOOD

Food-derived glycotoxins are formed during a series of chemical reactions that occur between glucose and the proteins, lipids, and nucleic acids derived from food. Glycotoxins trigger cells to send messages that lead to the production of inflammatory substances called cytokines, which cause tissue damage in the body. Experimental studies show that this is exactly what happens in glycotoxin-induced vascular (blood vessel) damage often seen in diabetes. Hemoglobin A1c (HbA1c) is an AGE that is created when glucose molecules bind to hemoglobin, a protein in blood. Measurement of this factor in the blood is very helpful in monitoring the level of glycation damage in prediabetes and diabetes.

An important strategy to reduce the level of glycation damage is to keep blood glucose levels within a healthy range (below 100 mg/dL premeal or after a fast). We also know from extensive research in this area that fasting blood sugar readings in the 70 to 85 mg/dL range appear optimal for disease prevention and longevity.

Glycotoxins are also formed during food production and preparation. Food manufacturers use various heating processes to enhance flavor, color, and texture; to improve food safety (sterilization and pasteurization); and to extend shelf-life. Unfortunately, glycotoxins are a byproduct of these processes. Foods as varied as cola drinks, baked goods, caramel, and brewed products contain glycotoxins.

Foods high in fat and protein (such as meat and poultry) typically have the highest glycotoxin levels. How you prepare your food (or have it prepared for you if you eat out) can also have a significant impact on the formation of glycotoxins.



Glycotoxins are especially harmful to people with diabetes, in whom these molecules are associated with retinopathy (glycotoxins accumulate in the retinal blood vessels), neuropathy (they accumulate in peripheral nerves, resulting in nerve damage), kidney failure (they are found in kidney tissue), heart disease, and blood vessel disease.

High blood glucose levels also invite damage from another source—oxidative stress.

OXIDATIVE STRESS

You may remember from high-school chemistry that molecules are composed of atoms, which in turn each consist of a nucleus, protons, neutrons, and electrons. The atoms of a molecule are held together by chemical bonds. When these bonds are broken—which occurs naturally as part of metabolism, for example—highly reactive molecules called free radicals can be produced. Exposure to environmental toxins (pollution, food additives, radiation, pesticides, and cigarette smoke, for example) also stimulates the production of free radicals.

The body can often ward off the damage these free radicals may cause by sending in antioxidants, substances to prevent the oxidative damage that free radicals can inflict on the body's tissues. If, however, the body is under stress, which can be caused by failing to follow a diet that contains enough antioxidants (in other words, lots of fresh fruits and vegetables), the body may not be able to neutralize these damaging molecules. When this happens, the end result may be damage to the body's cells, tissues, and organs. This damage has been associated with several complications of diabetes, including injury to the heart and blood vessels. In addition, free-radical damage is a well-known cause of the accelerated aging of tissues in the body.

Food Item	AGE Content
Beef boiled for 1 hour	22 kU/g
Beef broiled for 15 minutes	60 kU/g
Fried chicken breast	61 kU/g
Broiled chicken breast	58 kU/g
Raw tofu	8 kU/g
Broiled tofu	41 kU/g

kU/g: units of AGEs per gram of food

OXIDATIVE STRESS AND METABOLISM

There are many different types of free radicals, but those that play a critical role in cardiovascular and metabolic problems are called superoxide radicals and peroxynitrite. Research has shown that hyperglycemia (high levels of glucose in the blood) promotes the formation of free radicals, especially superoxide radicals, and therefore oxidative stress as well.

Situations that can promote oxidative stress include:

- Hyperinsulinemia (high insulin levels).
- Elevated fasting and postmeal (postprandial) levels of triglycerides and cholesterol.
- Elevated levels of superoxide, which in turn generate highly reactive peroxynitrite and can trigger many damaging events in the body, including heart, kidney, blood vessel, and eye problems
- Repetitive episodes of ischemia (lack of blood flow and oxygen to tissue), which occurs in diabetes patients who have coronary artery disease and peripheral vascular disease.

Oxidative stress, in turn, stimulates the development and progression of complications from diabetes. Some research even suggests that oxidative stress serves as a key trigger for diabetes.

In fact, sophisticated experiments on insulin resistance show that repeated exposure of insulin-resistant tissue to oxidative stress can result in hyper-glycemia.

As we can see, therefore, reducing food-derived glycotoxins in the diet as well as oxidative stress can have a significant, positive impact on our health.

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AN ANTI-GLYCATION EATING PLAN

An innovative, easy-to-follow eating plan that reduces the negative impact of age-accelerating dietary glycotoxins in the body is essential. Overall, foods in the fat and meat (protein) groups contain thirty-fold and twelve-fold higher advanced glycation end product (AGE) content, respectively, than foods in the carbohydrate group. On the other hand, fresh fruits, vegetables, whole grains, raw nuts, and other unprocessed, unrefined foods have low levels of glycotoxins.



A key factor in the formation of food-derived glycotoxins is temperature. Foods high in protein and fat (such as animal products like beef, pork, poultry, fish, seafood, and lamb) as well as foods high in fructose that are cooked, heated, or processed at high temperatures are loaded with glycotoxins. High-temperature cooking methods should be used sparingly—certainly not every day and only a few times a week if possible. Instead, preparing food at temperatures less than 250°F minimizes the formation of dietary glycotoxins. Such methods use liquids and lower cooking temperatures and include poaching, steaming, braising, stewing, and slow cooking (as in a crockpot cooker).

Be on the lookout for foods that are broiled, barbecued, grilled, fried, or oven roasted—these cooking methods use high temperatures and dry cooking conditions, which generate high levels of dietary glycotoxins. Here's a quick comparison of different cooking methods and the resulting glycotxin content of some common foods.

Although broiling is believed to be a “healthier” cooking method than frying, it doesn't make much difference whether you broil or fry a chicken breast; you will end up with about the same amount of glycotoxins: 58 kU/g and 61 kU/g, respectively. The AGE content of beef boiled for one hour is 22 kU/g, while broiling beef for just fifteen minutes results in a value of 60 kU/g, roughly triple the glycotxin content. This is because the temperature involved in boiling beef is much less than for broiling beef.

Typically, beef is broiled at temperatures that exceed 500°F. Boiling, on the other hand, is a cooking method that uses water and does not exceed a temperature of 212°F. When it comes to tofu, the choice between raw (8 kU/g) and broiled (41 kU/g) is quite dramatic—broiling generates about five times the glycotxin level. In comparison, fresh fruits and vegetables barely make the charts for dietary glycotoxins (apples 0.13 kU/g, bananas 0.01 kU/g, and carrots 0.1 kU/g).

DIETS HIGH IN GLYCOTOXINS INDUCE ENDOTHELIAL DYSFUNCTION AND INFLAMMATION

A group of non-smoking patients were divided into two groups: one group consumed a diet high in glycotoxins, the other a diet low in glyco-toxins. Results from the six-week study, published in Proceedings of the National Academy of Sciences in 2002, showed that patients in the high-glyco-toxin group had a 35% increase in serum levels of C-reactive protein (a marker of inflammation), an 86% increase in serum tumor necrosis factor-alpha levels (an important inflammatory cytokine), and a 20% decrease in endothelial function. Patients in the low-glycotxin group, however, showed a decrease in these signs of inflammation.

CHOOSE GLYCOTOXIN-FREE FOODS

Glycotoxins found in foods cooked or otherwise prepared under high heat (such as broiling, grilling, and frying) accumulate in tissues and organs throughout the body. But they also remain there for a very long time. Although the rate of absorption of food-derived glycotoxins is not very high, the body's ability to remove them (through excretion) is limited. Studies show, for example, that although about 70% of the glycotoxins you eat escape being absorbed by the digestive tract (the body does have ways to resist these invaders), only 33% of the absorbed glycotoxins show up in the urine over a 48-hour period. This means that the glycotoxins are deposited in tissues of the body, where they can wreak havoc. So, to help you get started on your anti-glycation eating program, let's look at how to choose and prepare glycotxin-free foods.

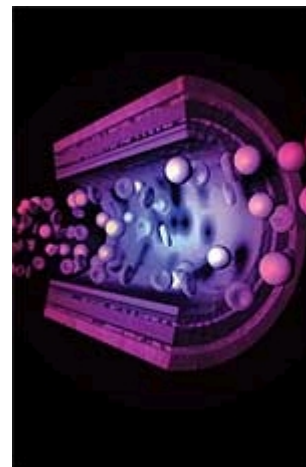
WHAT'S COOKING

When it comes to eating to prevent diabetes, please remember that it's not only what you eat that's important, it is how it is prepared. For example, if you have diabetes, given a choice between roasting, grilling, or poaching salmon, which cooking method should you select if you want to help avoid the food-derived glycotoxins that promote nerve and blood vessel damage, both of which cause and contribute to major complications of diabetes? If you guessed poached salmon, you're right.

Cooking foods using intense heat and without water or other liquids, such as broth or wine, causes the sugars to bind non-enzymatically with proteins (collagen and elastin fibers) to form glycotoxins. Visual evidence of this chemical reaction is the browning reaction seen in food cooked under high, dry heat. The cookies and cake in the oven, the chicken on the grill, and the potatoes in the frying pan are all browning and manufacturing AGEs and ALEs, increasing your risk of developing cardiovascular complications and speeding up the aging process itself.

Whether or not you already have high blood glucose levels, which typically accelerate the biochemical reactions that lead to glycation inside the body, eating foods that are cooked with high heat adds food-derived glycotoxins, which further adds fuel to the fire in terms of glycation. Cooking meats at high temperatures also creates other health hazards, such as the formation of gene-mutating toxins—carcinogens—that significantly increase the risk of cancer.

Cooking with liquids, for example steaming or poaching, inhibits the non-enzymatic attachment of sugar and fat to proteins. "The idea that how I cook my food can have such a tremendous impact on my diabetes is just incredible to me," says Jean, a 51-year-old court clerk. "I was so excited when I learned about glycation and glycotoxins, and how broiling, barbecuing, and grilling are damaging my health. It was enough to make me change how I cook and what I order when I eat out, and now I feel much more in control of my diabetes and my life."



EATING OUT

Following an anti-glycation eating plan when dining out is easy!

One tip is to always verify how a particular menu item is prepared. If you don't see what you want, ask if a particular item can be made for you. For example, ask if a grilled fish dish can be poached instead. Request steamed vegetables instead of roasted or grilled vegetables. Choose poached chicken instead of the broiled steak or stir-fried chicken. Here are some other tips to consider when eating out:

- Don't stop at fast-food establishments. Most items in fast-food restaurants are loaded with glycotoxins. Examples of foods very high in diabetes-accelerating and premature aging-promoting glycotoxins include grilled hamburgers, fried chicken, deep-fried onion rings, and French fries.
- Call ahead and ask if the restaurant's chef can prepare a specific entrée for you using low-temperature cooking methods that use liquid, like braising, poaching, and stewing.
- Be creative. If the restaurant does not have a suitable entrée, order items from the appetizer, soup, salad, and side dish sections of the menu.
- Bring your own dressing or condiments. Your freshly made olive or flaxseed oil dressing can be the perfect topping for your restaurant salad as opposed to unhealthy commercial salad dressings.
- Start your meal with broth-based soup or a leafy green salad spritzed with olive oil and vinegar.

What Your Doctor May Not Tell You About Diabetes also provides details of specific nutrients that can help prevent the damage caused by glycation.

ANTI-GLYCATION NUTRIENTS

To help protect yourself against the damaging consequences of glycation, there is one supplement that is especially important: benfotiamine. Few people have heard about this special variation of vitamin B1 that has been shown to prevent nerve and blood vessel damage—and the resulting complications—that are caused by glycation. What Your Doctor May Not Tell You About Diabetes highlights many experimental studies that show the benefit of benfotiamine in relieving pain due to the nerve and inflammatory damage wrought by glycation, helping alleviate oxidative damage, and preventing glycation-induced damage to the all-important endothelium in blood vessels. One example is a recent study that shows how benfotiamine significantly improves blood flow and reduces oxidative stress in patients who are given meals high in food-derived glycotoxins.

What Your Doctor May Not Tell You About Diabetes also presents a study recently published in Diabetes Care that points to the amazing effect of benfotiamine in preventing glycotxin-induced inflammation, endothelial dysfunction in the vascular system, and oxidative stress in human patients. In this important study, patients were given a heat-processed test meal with a high level of dietary glycotoxins and then supplemented with 1,050 mg of benfotiamine daily. Benfotiamine significantly reduced glycotxin-induced damage to the vascular system in these patients. Yet another impressive study in patients with painful peripheral neuropathy shows that 100 mg of benfotiamine given four times daily significantly improves neuropathy scores, with the greatest effect being a reduction in pain in these patients. This recent study confirms the results of a 1999 study, which showed significant improvements in neuropathy scores after only three weeks in patients suffering from painful peripheral diabetic neuropathy. These patients received up to 320 mg of benfotiamine daily, with greater benefits seen in the high-dose group.

Benfotiamine provides tremendous benefit by stopping the accumulation of sugar-derived compounds called triosephosphates that can damage blood and nerve cells. Benfotiamine also activates a key enzyme called transketolase, which renders these triosephosphates harmless, thus inhibiting the damaging action of glycation.

Benfotiamine supplementation therefore holds promising potential for patients who have diabetic neuropathy, diabetic retinopathy, and kidney disease and no side effects have been reported from its use.

Another important supplement for protecting against glycation-induced damage is carnosine. Carnosine is a molecule (dipeptide) composed of two amino acids—beta-alanine and histidine. Carnosine is valuable because it helps inhibit accelerated aging by interfering with glycation, thus protecting against glycation-induced damage and acting as an anti-oxidant to fight oxidative stress.

By binding to protein molecules, carnosine acts as a shield against sugar molecules, thus preventing glycation. Carnosine can also stimulate enzymes and other substances to eliminate damaged, glycated protein, thus helping to reduce the impact of diabetic complications. Evidence of carnosine's anti-glycation abilities has emerged from several studies. In one recent example involving human cells, carnosine was shown to protect kidney cells against damage from high glucose levels. In another, investigators noted that carnosine and its two precursors—beta-alanine and histidine—may help inhibit the development of atherosclerosis caused by high levels of glycation in diabetes. When carnosine was compared with the anti-glycating drug aminoguanidine in cell culture studies, the supplement proved to be as effective, probably because it inhibits glycation earlier in the process than the drug does.

COOK TO YOUR HEALTH AND MINIMIZE GLYCOTOXIN FORMATION FROM FOOD

DO: Marinate foods in liquids and seasonings: lemon juice, dry wine, broth, olive oil, cider vinegar. Feel free to add herbs and spices, including garlic, mustard, thyme, sage, tarragon, and others. Marinating foods can help delay the reactions that lead to glycotxin formation.

DO: Eat foods prepared using low-heat cooking methods that employ water or liquid, like poaching, stewing, braising, boiling, steaming, slow-cooker cooking, and so on. Include a raw vegetable salad (and fruit) every day.

AVOID: Broiling, frying, hot-oven roasting, grilling, and barbecuing.



While healthy people usually take 1,000 mg a day of carnosine in two divided doses (500 mg two times daily), diabetics may consider taking 1,000 mg of carnosine two to three times a day.

SUMMARY

As we age, all of us face an onslaught of damage from oxidative stress and glycation. Whether you have diabetes, want to prevent diabetes, or want to minimize the age-accelerating impact upon your body from free-radical damage and glycation, What Your Doctor May Not Tell You About Diabetes provides a wealth of information including a comprehensive, integrated plan that includes nutritional supplements, an anti-glycation eating plan, pharmacologic options (when appropriate), and lifestyle modification to help you combat several insidious factors of aging to live healthier and longer.

Steven Joyal, MD, is the Vice President of Scientific Affairs at the Life Extension Foundation.

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