



## Fights the “Caramelization of the Flesh”

**Advanced Glycation Endproducts**, or “**AGEs**” as they’re appropriately called, are the end result of the complex chemical process through which the structure of proteins is warped by exposure to sugars or by other, much more reactive molecules. AGE chemistry is the cause of the “browning” you see when you roast a chicken or make toast, but the same “browning” chemistry is at work in your body every day of your life.

In your arteries.

In your kidneys.

In your heart, your eyes, your skin, your nerves. In every cell, the sugar that your body uses for fuel is busily at work at this very moment, *caramelizing* your body through exactly the same chemical processes that caramelize onions or peanut brittle. Slowly, imperceptibly, uncontrolled reactions with sugars and other molecules create chemical handcuffs which gum up your proteins, deactivate your enzymes, trigger unhealthy biochemical signaling in your cells, and damage your DNA. Aging you.

Make that: AGEing you.

The results: slow loss of function, disease, aging, and ultimately an early grave. AGEs transform the supple grace of youth into “crusty” old age, through exactly the same chemical process by which they form the crust on a

loaf of bread.

Glycation math is simple: more sugar equals more AGEd proteins. As a result, people with **diabetes** – whose bodies don’t keep blood sugar levels under proper control – begin to feel the effects of glycation at much younger ages than do people with more normal blood sugar levels.<sup>1,2</sup>

But while the complications suffered by people with diabetes are linked to their high blood sugar levels, that doesn’t mean that having “normal” blood glucose will save you from the destructive power of AGE. Rather, **watching people with diabetes is like watching “normal” aging played on fast-forward.** The damage to the nerves, their fine blood vessels, the retinas, and the other organs, which all too often desecrates the bodies of diabetics, is ultimately suffered by all of us, as the insidious chemistry of glycation slowly overpowers the structure and function of our bodies. The difference between people who have diabetes and the rest of us lies simply in the time it takes for the AGE burden **Uncontrolled reactions with sugars create chemical handcuffs which gum up your proteins.**

It’s no surprise, then, that you’ll find AGEs

at the crime scene in people with cardiovascular disease. **The atherosclerotic gunk in the hearts of people with heart disease is thick with AGEs, even if they aren’t diabetic.**<sup>3</sup> In one recent study,<sup>4</sup> scientists tested the amount of AGE in the serum of 48 men with normal fasting blood sugar levels, and compared it with the number of blood vessels leading into their hearts which were significantly narrowed by atherosclerotic plaque.

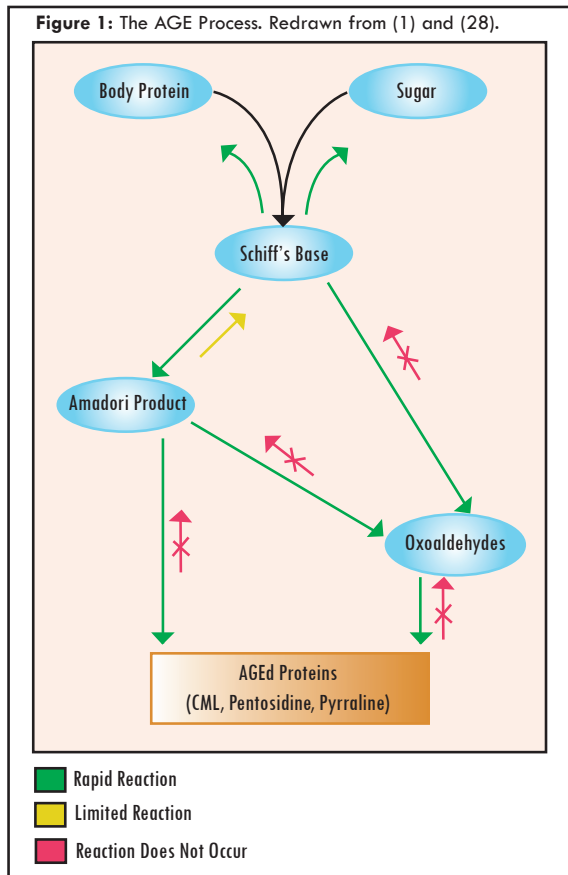
Not only did the researchers find that **serum AGE levels were two-thirds higher in nondiabetic people with coronary artery disease than in people without it,** but a highly significant correlation was revealed between a person’s level of AGE and the *number* of narrowed arteries he or she had. In other words, **the more AGE a person had in his or her serum, the more of the heart’s arteries were clogged with atherosclerotic gorp.**



The take-home message is clear: **AGEs are a clear and present danger to your health – even if you aren’t diabetic. No level of AGE should be considered “healthy,” “normal,” or “safe.”**

## Two Ways to AGE

There are two major ways that AGEs can form inside the body. One way is through a simple series of chemical reactions known as the “Maillard Pathway.” This is the same series of reactions that cause food to brown when it’s



cooked, and food chemists have known about it for a century. Maillard chemistry begins when a sugar molecule gets stuck to a protein, forming what’s called a **Schiff’s base**. But Schiff’s bases are highly unstable, so they never get the chance to build up in the body. They therefore either rearrange their structures into the more stable form of an **Amadori product**, or else break apart again, into the original protein and sugar molecules.

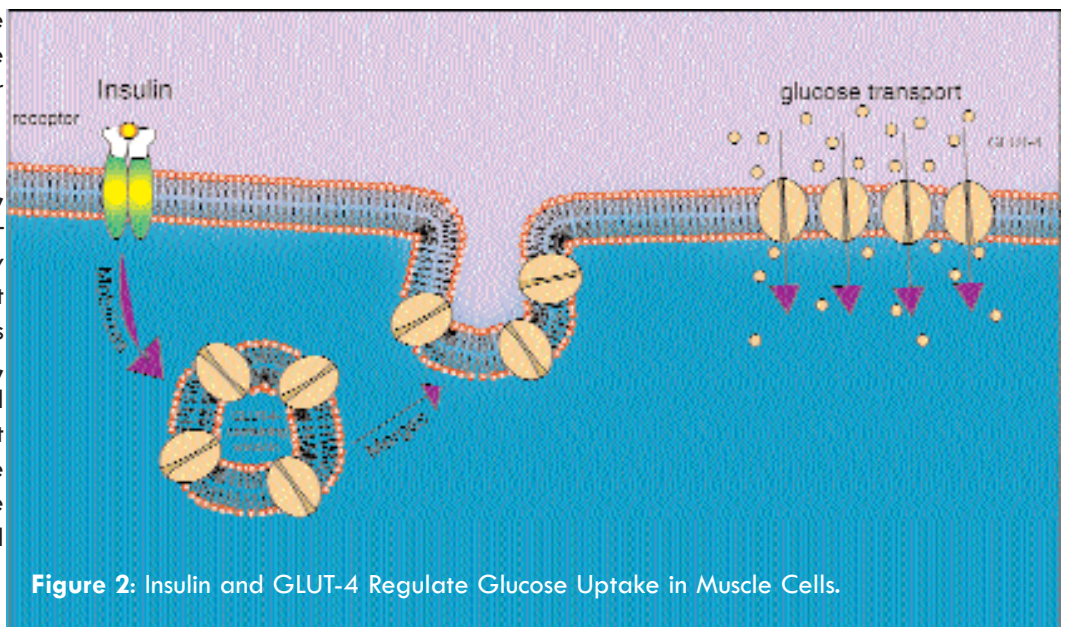
If an Amadori product is formed, it can then go on to form AGEs – either *directly*, or *indirectly* through the **oxaldehydes** that form when Amadori products break down (see **Figure 1**). Thus, the early stages in the Maillard reaction are easily reversed, but each successive step in the pathway makes it more and more likely that a full-blown AGE will be formed.

Maillard reactions are the best-known way for AGEs to form in the body, and they are responsible for the buildup of a lot of the AGEs in your heart and blood vessels. But scientists have recently come to understand *another* pathway of AGE formation – a distinctly *biological* pathway, which only occurs *within* your cells because of the body’s metabolism of carbohydrates.<sup>5,6</sup>

When blood sugar levels climb, the body releases the hormone **insulin**, which signals muscle and fat cells to open their cellular “doors” (known as **Glucose Transporter type 4 (GLUT-4)**) to more glucose (see **Figure 2**). As long as blood sugar levels, insulin levels, and cellular responsiveness to insulin’s signals are optimally coordinated, the body can keep its blood sugar balance.

But even in healthy people, blood sugar levels surge in the first couple of hours after a meal, as incoming carbohydrate is broken down into sugar and released into the bloodstream more quickly than muscle and fat cells take it in. And as we **AGEs are a clear and present age (and even danger to your health more so in conditions like type 2 diabetes and metabolic syndrome X)**, the coordination between insulin and GLUT-4 at the cellular level breaks down – a condition known as **insulin resistance**. As a result, sugar levels *within* muscle cells can remain stable or low, even as sugar levels *in the blood* soar.

At the same time, however, the concentration of sugar inside some kinds of cell climbs to dangerously high levels when blood sugar levels rise. In these cell types, the movement of sugar into the cell is *not* regulated by insulin. Examples of such cells include nerve cells, the cells that make up the fine blood cells of the retina of the eye and the filtering units



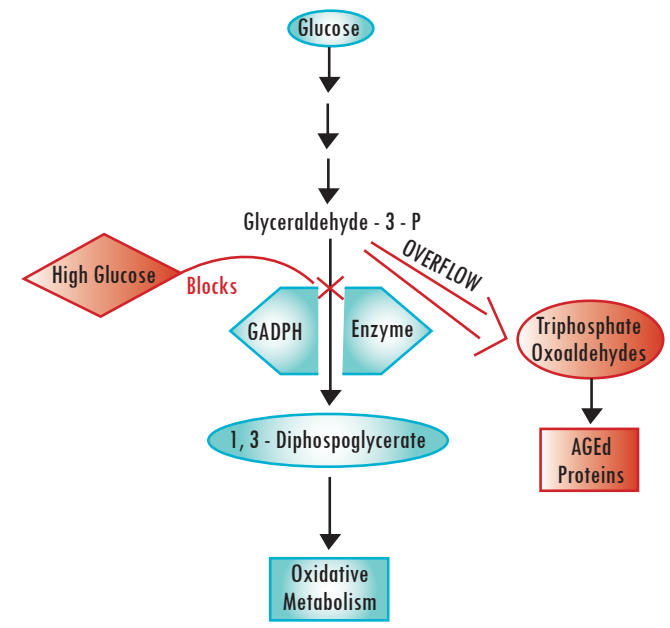
**Figure 2: Insulin and GLUT-4 Regulate Glucose Uptake in Muscle Cells.**

(glomeruli) of the kidney, and some other organs. As a result, when your blood sugar levels increase, your nerve and fine blood vessel cells are also flooded with glucose.

The resulting high sugar levels within these cells cause a logjam in the normal cellular metabolism of glucose. This backlog results in a buildup within the cell of super-reactive glucose-metabolic intermediates known as **triosephosphates**.<sup>5,6</sup> Under these conditions, the excess **triosephosphates attack the surrounding proteins, lipids, and DNA, forming oxoaldehydes** (see Figure 1) and causing AGE damage from within the heart of the cell.

You can think of the process by which excess glucose forms AGE in these cells like an overflowing sink. When the taps are only half-on, water (blood sugar and its metabolites) easily passes through the drain (the enzyme GADPH). But when the water comes in too quickly, it can exceed the capacity of the drain (high blood sugar actually *deactivates* GADPH), and the water overflows the sink, creating a mess (AGEd proteins). See Figure 3.

**Figure 3:** Oxoaldehydes Build Up, AGE Formed When Glucose Metabolism Goes Awry. Redrawn from (5,6,7,83).



of your health – and ultimately, of your very life – as you age. So in addition to maintaining healthy blood sugar levels, it makes sense to look at ways of *directly* fighting the chemical assault that causes AGEing in your body.

Because of the involvement of AGEs in the ravages of diabetes, multinational drug companies have long sought out drugs that could interfere with the AGE process. The first, and most researched, of these AGE-blocker drugs was **aminoguanidine**. Aminoguanidine prevents the formation of AGEs by sopping up oxoaldehydes,<sup>8,9</sup> which are formed (again) either through

the breakdown of Amadori products (Figure 1) or through the overloading of cellular glucose-metabolizing machinery (Figure 3).

**There's just NO evidence**

**that most of these "AGE-blocking"**

Two decades of research have shown that this is an effective strategy.

**ingredients have any effect on**

**AGEing in your body.**

**Aminoguanidine powerfully reduces the AGE burden in many organs, and fights off AGE-induced structural and functional damage, in living, breathing organisms.** Giving diabetic lab animals aminoguanidine in their drinking water dramatically reduces AGE-induced damage and loss of function in their kidneys,<sup>10-12</sup> in their nerves,<sup>13,14</sup> in the retinas of their eyes,<sup>15,16</sup> and in their arteries.<sup>17</sup>

Of equal importance for those of us who are not afflicted with diabetes, aminoguanidine has also been proven to prevent the AGE-damage which accompanies "normal" aging, preventing loss of kidney function,<sup>18,19</sup> stiffening of the arteries<sup>19,20</sup> and cardiac hypertrophy (the enlargement of the heart which accompanies most forms of heart disease).<sup>19,20</sup>

Unfortunately, while preliminary human trials suggested that human diabetics would reap similar benefits, the same studies found evidence that **aminoguanidine may cause a drug-induced autoimmune disorder** similar to the way that the antibiotic minocycline leads some users to develop a lupus-like syndrome.<sup>1</sup> Trials in Europe were simply shut down when the major sponsors pulled out,<sup>21</sup> and it seems that further work with aminoguanidine has been abandoned. Other drug companies are scrambling to develop AGE-fighting drugs of their own, with such

**To sum up:**

1. High blood sugar levels cause high levels of glucose to build up within neurons and fine blood vessel cells.
2. High levels of glucose cause a logjam within the cellular glucose-processing pathway, as the input of glucose creates more highly-reactive intermediates (triosephosphates) than other enzymes in the pathway can process.<sup>5,6</sup>
3. The built-up triosephosphates quickly react with proteins to form oxoaldehydes ... and oxoaldehydes aggressively form AGEs.<sup>5,6</sup>
4. AGEs cause cellular dysfunction and the complications of diabetes, and contribute to the aging process.<sup>1,2</sup>

So there's the problem. The question is: what can you do about it?

**AGE-Blocker Drugs**

If your blood sugar levels are high, then a key part of controlling AGE levels is to bring them into a safer range. But even if your blood sugar levels are "normal," AGEing is one of the ringleaders in the gang of vandals that rob you

marketing-challenged names as ALT-946, OPB-9195, 2,3 DAP, and A717. In the next few years, you can expect to see these drugs work their way out of the world's research institutes and into local pharmacies.

But are there not any safe, *natural* anti-AGEing nutrients? A number of supplements are marketed as “AGE-inhibitors.” But while many of the herbs and other nutrients thrown into these supplements inhibit AGEing *in a test tube*, **there's no evidence that most of these “AGE-blocking” ingredients have any effect on AGEing in your body.** We briefly discuss some examples in the sidebar, **What Won't Work.** But you probably get the point. *Your body is not a test tube!* Health food store shelves are awash with supposed “anti-AGE” formulations, but nearly none of these products work *in the body* the way that they do “under glass.” At the end of the day, **it's sheer bluff to claim that a supplement can inhibit the AGE process until it's been put to the test in a living, breathing organism.**

### TPP: Our Hero ... in Chains!

There is a nutrient that could, in theory, pack a potent wallop against the AGE onslaught: **Thiamin Pyrophosphate (TPP)**, the active coenzyme form of the B-complex vitamin *thiamin*. In 1996, researchers showed that TPP could step in to stop AGE formation at the most important point in the process: the late, irreversible conversion of Amadori products into full-blown AGEs (see **Figure 1**).<sup>49</sup> What's more, TPP could theoretically have a *two-pronged* AGE-inhibiting effect in the body, because boosting TPP in cells stressed by high glucose concentrations could open up an important biochemical “safety valve” in the normal metabolism of blood sugar through an enzyme known as **transketolase**. Activating transketolase allows the body to shunt excess triosephosphates into a safe alternative metabolic pathway, preventing the logjam that leads to the buildup of triosephosphates and the formation of AGE. It's like opening up the overflow plate in your sink: the excess water (glucose metabolites) are safely drained away before they reach a level where they can overflow (see **Figures 3 and 4**).

### It's Not the Stuff in Your Multi!

Unfortunately, this does *not* mean that loading up on regular thiamin (vitamin B<sub>1</sub>) will free you from glycation's sticky shackles. The problem is that **your body's ability to absorb and metabolize thiamin itself is very limited.** The conventional form of thiamin cannot pass directly across cell membranes: it requires a special shuttle system to pump it across the intestinal wall and (later) into the cell. There's enough room on the shuttles to ensure that you'll absorb the relatively low doses typically found in food, but the much higher doses found in a typical multivitamin or “B-50” pill are well in excess of this transport system's capacity. While a small amount of additional absorption occurs via diffusion

into the fluid that bathes the cells, this adds little to total bioavailability: no matter how much thiamin you take, you don't materially increase plasma levels beyond what you get from the first 12 milligrams of the dose.<sup>50-53</sup>

Even greater problems occur in getting thiamin *into the cells* to do its job. While some thiamin crosses the intestinal wall through diffusion into the fluid surrounding the cells of the intestinal tract, the cells themselves (except for red blood cells) cannot absorb conventional thiamin except through the active transport system.<sup>53,53a</sup> The severity of the limits of this system can be seen when you bypass the limited intestinal absorption of thiamin by *injecting* it directly into the blood. When 5 milligrams are injected, most of the dose is taken up by the cells, and the kidneys will excrete only 25% of the original dose. But increasing the dose does not increase the cellular absorption. The more thiamin you inject, the more ends up simply passing out through the urine, and at 100 milligrams or more, **100%** of the additional thiamin is passed out of the urine.<sup>54</sup> Thiamin is one case where the old skeptic's taunt is true: you really *are* flushing most of your supplement down the toilet!

You might think that you can get around this problem by taking supplements containing TPP *itself*, instead of plain old thiamin. Unfortunately, as part of the normal cellular absorption process, specific enzymes actually strip TPP of its phosphate groups.<sup>53,55,56</sup> As a result, **you get no additional AGE-battling benefit from taking preformed thiamin pyrophosphate** instead of standard thiamin. In fact, when you take supplements based on TPP *itself*, studies show that thiamin levels and biological activity are actually *lower* than if you take the same amount of regular thiamin!<sup>57</sup>

So how can you *meaningfully* boost your body's supply of this potent anti-AGEing nutrient?

### Benfotiamine: the TPP Solution

Fortunately, an *effective* way to boost thiamin pyrophosphate was found nearly fifty years ago by Japanese scientists.<sup>58</sup> These researchers discovered an unique class of thiamin-derived compounds present in trace quantities in roasted crushed garlic, and later in other vegetables from the *Allium* genus (such as onions, shallots, and leeks). Because of the connection to *Allium* vegetables, these rare thiamin compounds were named **allithiamines**.

Where thiamin itself has a closed “**thiazole**” ring at its key sulfur group, allithiamines have a unique opening at this location in their structure (see **Figure 5**). This simple structural difference makes allithiamines able to pass *directly* through cell membranes, allowing them to readily cross the intestinal wall and be taken straight into the cell, bypassing the hurdles faced by thiamin or preformed

# What *Won't* Work

## “Test-Tube Only” Ingredients

While **thyme extract**,<sup>22</sup> **inositol**,<sup>23</sup> **acetyl-L-carnitine**,<sup>24</sup> **taurine**,<sup>25</sup> and a whole host of **antioxidants** (including **n-acetyl-cysteine (NAC)**<sup>26</sup> and **flavanoids**, such as **quercetin**,<sup>22</sup> **resveratrol**,<sup>27</sup> and others) are valuable supplements in their own right, they aren't AGE-fighters. Yes, these nutrients *do* inhibit the Maillard browning process – in beakers at food chemistry labs. But none of them has yet been shown to fight AGE *in a living organism*. And there's plenty of reason to believe that they will *not* do so, because the chemistry of the stove top – or the lab bench – is so totally unlike what happens in living systems.<sup>28</sup>

Chemical conditions important to the AGE process differ in very important ways between the body and the test tube, and these distinctions translate into discrepancies in *how* AGEs come into being, *how much* AGE is produced, and even *which* AGE compounds are formed – an important consideration, when you realize that while some AGEs are stiffening your arteries even as you read this article, others exist in only tiny trace quantities, or don't exist *at all* outside of the artificial conditions of the lab.<sup>28</sup>

In particular, the concentration and distribution of key players in AGE chemistry – such as sugar, antioxidants, free radicals, and “transition metals” like iron and copper – as well as the temperature at which glycation-related reactions are allowed to happen, can all alter the course of the AGEing process. There's a yawning chasm separating the body's balance of these factors from what you'll see in a beaker heating over a Bunsen burner. These differences mean that test-tube AGE chemistry distorts the way that AGE chemistry actually plays out in the body, creating results in the lab which don't reflect what's going on in your cells and tissues.<sup>28</sup> The bottom line: the fact that something prevents the “browning” of compounds in a test tube is no guarantee that it will have any effect on the slow caramelization of your body's proteins and DNA. **It's meaningless to claim that a supplement can inhibit the AGE process until it's been put to the test in living things.**

## Trivial Dosages

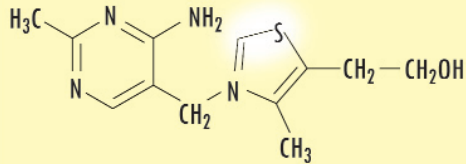
Other so-called “AGE-fighting” formulas include valid ingredients at meaningless dosages. For instance, there is a perfectly good study<sup>29</sup> to show that **curcumin** supplementation significantly reduces AGE cross-linking in the skin and tails of diabetic rats. But the **dosage used to get an anti-AGE effect was 200 milligrams of curcumin per kilogram of body weight** – equivalent, in an average adult person, to **14 000 milligrams of curcumin!**

Normally, the dose of a nutrient or drug needed to create some effect in the human body is proportionately less in humans than it is in rodents, because of our slower metabolisms.<sup>30-32</sup> But curcumin is a well-established exception. Studies show that curcumin has a very low bioavailability in humans,<sup>33-38</sup> largely because enzymes in the colon tend to convert it into versions of the molecule which are harder for the body to absorb.<sup>38,39</sup> And humans deactivate even *more* curcumin than rodents do,<sup>38</sup> with the result that **in humans, curcumin doesn't consistently appear in your blood or plasma until you get up to daily doses exceeding 2 000 milligrams**<sup>33,35-40</sup> – and that's 2 000 milligrams of *curcumin*, remember, not of raw *turmeric*, which is only about 3% curcumin by weight.

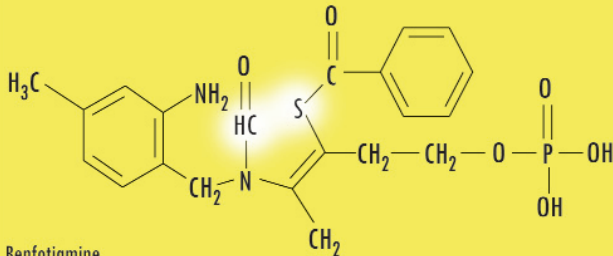
Accordingly, the medical researchers who are running a Phase I clinical trial of curcumin in people at high risk for cancer or with pre-malignant tumors instruct their patients to start off with a gram (1000 mg) of the phytochemical and then work their way up to *eight* grams from there.<sup>36</sup> The trial has already yielded exciting preliminary evidence of a protective effect of curcumin.

One way around this bioavailability problem is to **combine curcumin with piperine**, an phytochemical found in small amounts in black pepper. One study showed that **piperine increases the bioavailability of curcumin in humans by a whopping factor of twenty**.<sup>40</sup> But one thing is for sure: a few hundred milligrams of plain curcumin is not going to protect anyone from the slow stiffening of the body's tissues caused by AGE cross-links.

Likewise, some formulas marketed as anti-AGE nutrients include trivial doses of the remarkable anti-aging peptide **Carnosine**. It's actually unclear whether **Carnosine**, taken orally, can actually reduce AGE in the body.<sup>28</sup> But **if you want to get any benefits from Carnosine, you'll need to take doses of about a gram or more**. Careful studies have established that human-equivalent doses of up to 500 mg of **Carnosine** a day have no effect on **Carnosine** levels in the muscles and the brain<sup>41,42</sup> and don't offer any protection against AGE-associated loss of arterial flexibility.<sup>43</sup> Higher doses *do* allow the body to increase its **Carnosine** stores,<sup>41,44</sup> protect the arteries against stiffness,<sup>43</sup> and (at human-equivalent doses of 945 mg a day) provide powerful neuroprotective<sup>45-47</sup> and “anti-aging”<sup>48</sup> benefits – but cynical or ignorant formulators shy away from such doses, since **Carnosine** is both bulky and expensive.



Thiamin



Benfotiamine

**Figure 5: Thiamin vs. Benfotiamine (an Allithiamin).** Note the Opening in the Sulfur Ring.

thiamin pyrophosphate. Once inside the cell, the ring is closed and the basic thiamin “backbone” is converted into TPP,<sup>54,57</sup> which is then available to activate the transketolase “safety valve” (see **Figure 6**). As a result, your body absorbs allithiamines better than thiamin itself, and levels of thiamin and TPP remain higher for longer.<sup>53,54,57,59-62,64-68</sup>

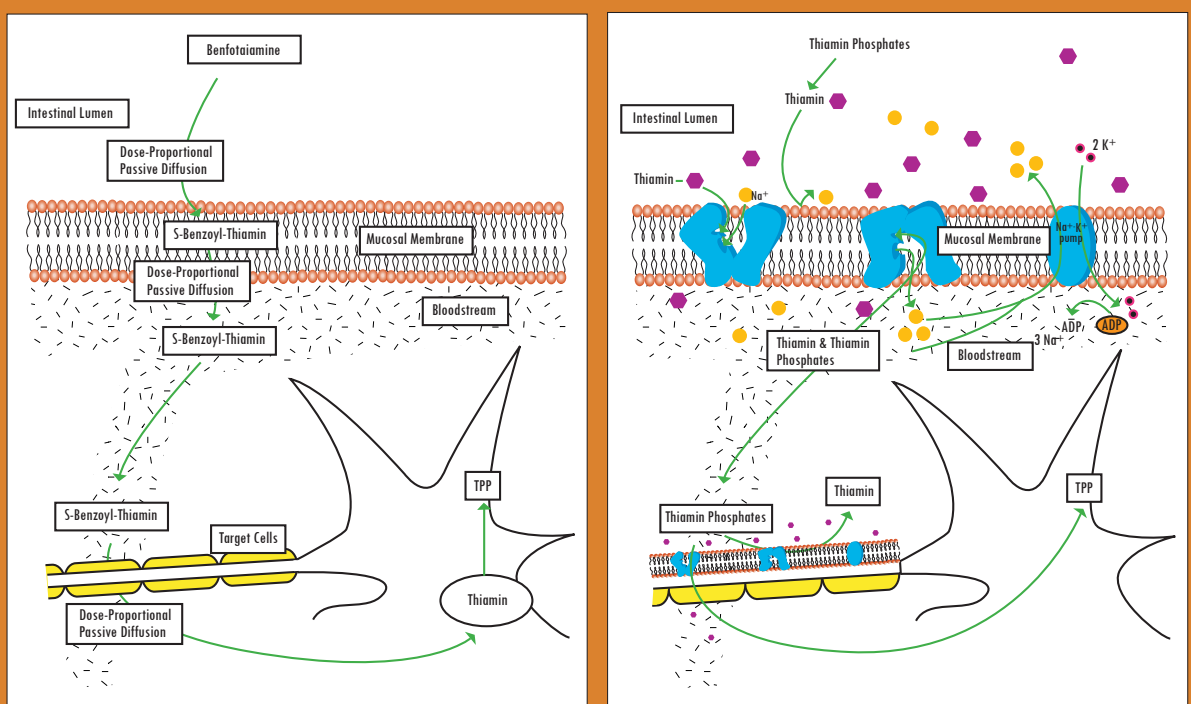
The most effective member of the allithiamine family – and the *only* one with proven AGE-battling powers – is **Benfotiamine (S-benzoylthiamine-O-monophosphate** – see **Figure 5**). Thiamin absorption from **Benfotiamine** is about five times as great as from conventional thiamin supplements (see **Figure 7**).<sup>64,65</sup> And because of its much greater access to the cells of the body *other* than red blood cells, the effect is even more impressive at the tissue level: brain and muscle, for instance, take in *five- to twentyfive-fold* as much thiamin in the form of **Benfotiamine** as they do of an equal amount of regular

thiamin.<sup>65</sup>

In fact, **Benfotiamine** is not just more readily-absorbed than a basic thiamin supplement, but is even more bioavailable than the other *allithiamines*, including **thiamin tetrahydrofurfuryl disulfide/TFD**<sup>54,66</sup> (which, confusingly, you may find sold under the name “allithiamin,” as if this term referred to TFD specifically and not to a *class* of nutrients). Yet **Benfotiamine** is actually *less* toxic than conventional thiamin supplements!<sup>67</sup>

By effectively increasing levels of thiamin *itself*, **Benfotiamine dramatically boosts AGE-fighting thiamin pyrophosphate and cell-shielding transketolase activity in your body.**

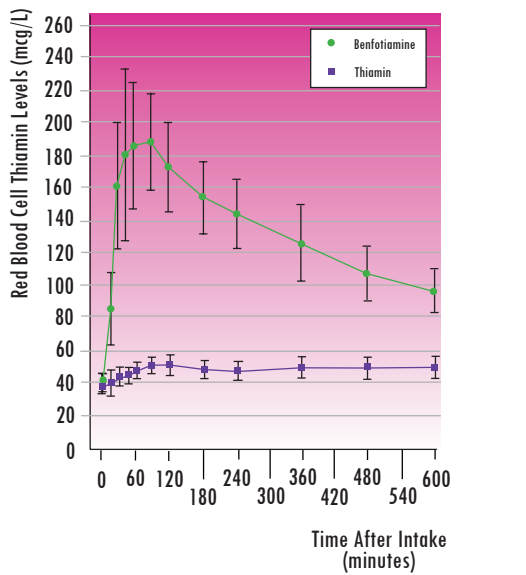
In one study,<sup>50</sup> **Benfotiamine boosted peak TPP levels in red blood cells by one hundred and twenty times as much as the same amount of standard thiamin.** This astonishing result is more dramatic than what has been seen in whole-body studies, but all studies agree that there is an impressive advantage to taking **Benfotiamine** instead of regular thiamin supplements as a way of raising AGE-shielding TPP. More typical were the results of another study,<sup>68</sup> in which the blood TPP levels of 20 dialysis patients were analyzed before and after they had taken each of two thiamin supplements: thiamin mononitrite (the form used in most thiamin pills) or **Benfotiamine**. Those who took **Benfotiamine kept their blood thiamin pyrophosphate levels consistently higher over the next 24 hours**, so that they experienced a *total* blood TPP exposure which was 430% of that seen in those who took conventional thiamin supplements.



**Figure 6: Absorption of Benfotiamine vs. Thiamin.** Redrawn from (63).

Even 24 hours later, TPP levels in the red blood cells of the patients who had taken a single dose of **Benfotiamine** were still almost double those in patients who had taken the standard thiamin supplement.<sup>68</sup> The differences become all the more impressive when you realize that there was nearly *half again* (1.43 times) as *much* thiamin in the standard (100 milligram) thiamin supplement as there was in the **Benfotiamine** preparation!

**Figure 7:** Red blood cell thiamin levels from regular thiamin vs. **Benfotiamine**. Redrawn from (64).



An even more important advantage of **Benfotiamine** is its effect on transketolase, the enzyme that provides a “safety valve” for the destructive AGE-precursors formed in the cell when sugar levels are high. Megadoses of regular thiamin supplements fail to increase the activity of this critical enzyme above the baseline level provided by a basic, RDA-type level of intake.<sup>54,66</sup> But **unlike conventional thiamin supplements, Benfotiamine effectively boosts transketolase activity.**<sup>54,66</sup>

**Benfotiamine’s** TPP-boosting abilities have been used clinically to treat disorders where restoring the activity thiamin-based enzymes is critical to recovery.<sup>69,71</sup> But with the discovery of TPP’s “Amadorin” activity, and the critical importance of transketolase activity in the safe metabolism of AGE-forming reactive intermediates when blood sugar levels are high, the focus of recent scientific studies has shifted. As we’ll see, **Benfotiamine has been proven in clinical trials to restore nerve function in diabetic neuropathy**, the AGE-related nerve damage which is all too common in people with diabetes.<sup>72-79</sup> And exciting new evidence is being amassed that the proven benefits of **Benfotiamine** in diabetic neuropathy also extend into other forms of AGE-related damage.

### Benfotiamine Blocks AGE

One of the first studies to test **Benfotiamine’s** ability to

lower the AGE burden,<sup>80</sup> whose full results were only recently released,<sup>81</sup> was a head-to-head comparison of its effects against those of a regular thiamin supplement. The

### Unlike conventional thiamin supplements, **Benfotiamine** effectively boosts transketolase activity.

study used four groups of lab animals. One group was composed of normal, healthy rodents; the second group was made up of rodents with untreated experimental diabetes; and there were two groups of diabetic animals who received equal megadoses of thiamin in their diet – in the form of either conventional thiamin, or as **Benfotiamine**.

At the beginning of the study, scientists tested the animals’ levels of both blood sugar and **HbA<sub>1c</sub>** (glycated hemoglobin – an Amadori product used to measure a person’s overall blood sugar levels over the course of a few months). Six months after the onset of diabetes, these measures were taken again, and their nerve cells were tested for the AGEs **N-ε-(carboxymethyl)lysine (CML)** and of AGEs derived from an oxoaldehyde known as **imidazolone**.

While all groups of rodents began the study with similar blood sugar levels, diabetic animals’ blood sugar was three to four times as high as the healthy animals’ at three months, and edged up still more by the end of the study. Likewise, all animals’ HbA<sub>1c</sub> began at similar levels, but was more than doubled by diabetes. No supplement significantly affected these measures of blood sugar levels and control.

But looking at the animals’ AGE levels (and consequent nerve damage) showed how powerful **Benfotiamine** can be – despite the *ineffectiveness* of conventional thiamin supplementation. Predictably, the nerves of unsupplemented diabetic animals were disturbingly burdened with AGE: their CML levels were three-and-a-half times as high as the control animals’, and their levels of the oxoaldehyde were a whopping *five times* as great.

Preventatively supplementing diabetic animals with thiamin “did not significantly affect” neural AGE levels,<sup>80</sup> any more than it had affected blood glucose or HbA<sub>1c</sub>. But in striking contrast, **Benfotiamine supplements**

**Benfotiamine** has been proven **caused “a major inhibition of imidazolone-type AGE formation,”**<sup>80</sup> their nerves containing 62% less of this AGE than those of the unsupplemented diabetic controls. Even more impressively, first-strike **Benfotiamine supplements** “completely prevented” diabetes-induced increases in the AGE CML!<sup>80</sup>

In a later study, scientists also tested the effects of thiamin and **Benfotiamine** supplements *after* diabetes had fully set in and complications begun.<sup>81</sup> Even at this late stage in the

**Benfotiamine supplements**  **completely prevented**  **diabetes-induced increases in AGE.**

disease, **Benfotiamine** still slashed levels of the oxoaldehyde to just under half of what was seen in the unsupplemented diabetic animals (and also to levels lower than those of the thiamin-treated group). Likewise, CML levels in animals receiving **Benfotiamine** supplements were found to be one-third less than in the untreated diabetics (although the difference was not strong enough to meet statistical standards), while regular thiamin supplements provided no protection *at all* against this AGE.

And when **Benfotiamine** blocks AGE formation, it rescues nerves otherwise ravaged by these molecular vandals. After three months of diabetes, the unsupplemented group had suffered a reduction of 10.5% in **nerve conduction velocity (NCV)**, the speed at which the nerves deliver electrical messages. At this point in the study, animals who had received either kind of thiamin supplement were somewhat better off as compared to the unsupplemented animals.

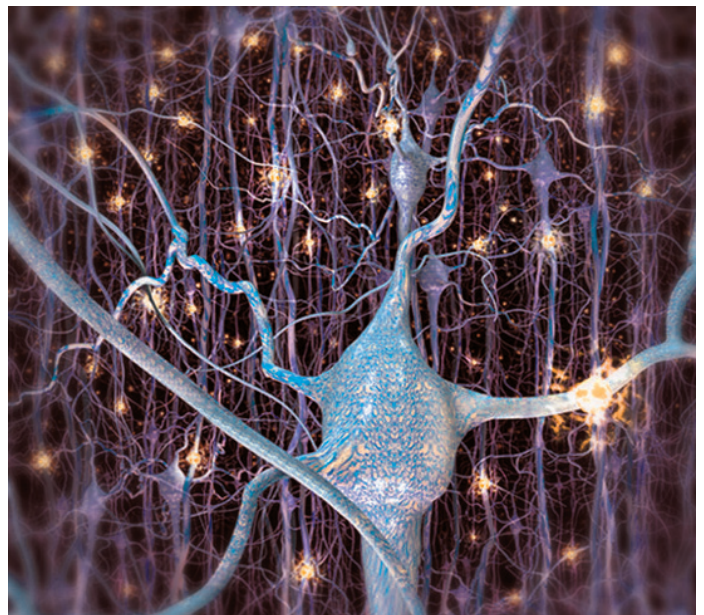
But after initially progressing, the group that had received regular thiamin supplements stopped making headway, remaining stuck at a plateau level they had reached at three months. By contrast, the group that consumed **Benfotiamine** continued to recover more and more of their nerve function as the study continued. Six months after beginning treatment, **the Benfotiamine-supplemented group's nerves were signaling as well as the healthy, nondiabetic group's** – as well, in fact, as they had *before* the onset of diabetes!

### Safe and Effective In Humans

But the proof of **Benfotiamine's** ability to protect your cells and proteins from AGE and restore the function of AGEd tissues is not confined to lab rats. As we mentioned earlier, **many randomized, double-blind, placebo-controlled human trials have proven that Benfotiamine powerfully supports nerve function in diabetic neuropathy.** In one trial,<sup>73</sup> 24 people suffering with diabetic neuropathy took either **Benfotiamine** tablets (plus doses of common B<sub>6</sub> and B<sub>12</sub> similar to those used in multivitamins) or a look-alike dummy pill, spread out into three doses a day for twelve weeks. The total daily dose used was 320 milligrams of **Benfotiamine** during the first two weeks, followed by 120 milligrams a day for the remainder of the trial. (The dose used in most trials, and

commonly prescribed by European physicians, is 320 milligrams a day, divided into four equal doses). Before and after the trial, the function of patients' nerve cells were tested using nerve conduction velocity (NCV) and **vibratory perception threshold** (which tests the nerves' sensitivity by determining the lowest level at which vibrations applied at key nerve sites are first felt).

At the end of the trial, **the vibration perception threshold had "clearly" improved by 30% in those who had taken the Benfotiamine supplements, while it had worsened in the placebo group** by 5% at one site and by 32% at another; in this small a group of people, the result was not strong enough to be judged "significant" in the statistical sense. At the same time, **people taking Benfotiamine experienced statistically significant improvements in nerve conduction velocity from the feet, even as this aspect of nerve function deteriorated in those taking the look-alike pills!**<sup>73</sup>



The power of **Benfotiamine** to improve vibratory perception threshold<sup>74,76-79</sup> and nerve conduction velocity<sup>76</sup> have been confirmed in other trials. Clinical trials have also shown that **Benfotiamine supports nerve function in diabetics as measured by many other methods.** For instance, **Benfotiamine users consistently experience significant relief of their diabetic nerve pain**<sup>74,76-81</sup> (see **Figure 8**), along with an increased ability of the nerves to detect an electrical current,<sup>72,74</sup> respond to electrical stimulation,<sup>76</sup> and regulate the heartbeat.<sup>76</sup> Similarly, **Benfotiamine prevents** this loss of control from happening in the first place in diabetic dogs.<sup>8</sup>

One controlled clinical trial<sup>78</sup> was especially revealing,

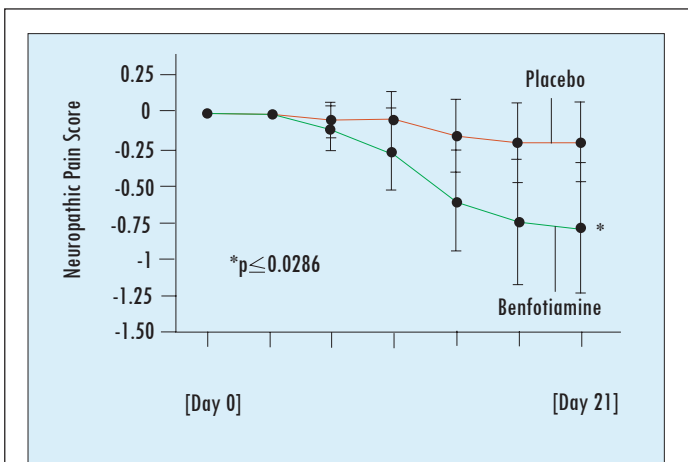
because it put **Benfotiamine** head-to-head against a megadose of conventional thiamin. Forty-five diabetics suffering with painful diabetic neuropathy were first assessed for severity of diabetic nerve pain using a visual analog scale, and tested for vibration perception thresholds. They were then randomly selected to take either **Benfotiamine** (400 milligrams a day for the first three weeks, followed by 150 milligrams a day for the next nine weeks) or 600 milligrams of conventional thiamin a day for the entire three month study. Both groups also received B<sub>6</sub> and B<sub>12</sub> supplements. At the end of the trial, both groups were re-assessed.

The results were crystal clear. After three months, the nerve torture of people taking megadose thiamin supplements had not significantly changed. Yet **users of Benfotiamine**

**Users of Benfotiamine experienced a dramatic 88% relief of their neuropathic pain.**

**experienced a dramatic 88% relief of their neuropathic pain.** And when vibration perception threshold was re-examined, it was found that **the nerves of Benfotiamine users became 60% more responsive**, while people who relied on a megadose of regular thiamin again gained no significant benefit.<sup>78</sup>

The bottom line: people taking **Benfotiamine** gain real benefits in the functioning of their nerves and in the relief of



**Figure 8: Benfotiamine** reduces nerve pain in diabetic neuropathy. Redrawn from (77).

their pain, while conventional thiamin – even at megadose levels – gets you nowhere. And the benefits of **Benfotiamine** are not the result of changes in blood sugar levels (either fasting,<sup>74</sup> or after a meal,<sup>74</sup> or averaged over several months (as measured by HbA<sub>1c</sub>)<sup>72,73,78</sup>) or other improvements in metabolic benchmarks.<sup>74</sup> They are the

direct results of **Benfotiamine's** AGE-fighting, metabolic-balancing powers.

### More Anti-AGEing Protection

A recent study in human type I diabetics<sup>83</sup> provides more direct proof that **Benfotiamine protects humans from AGE just as it does experimental animals.** The study began by testing the patients' levels of HbA<sub>1c</sub> (as a measure of overall exposure to blood sugar and Amadori products), the AGE **CML**, and the oxoaldehyde **methylglyoxal** within their red blood cells. Then the sufferers took high-dose **Benfotiamine** supplements for four weeks, after which they were tested again.

At the end of the study, **Benfotiamine had beaten back CML levels by 40%, and cut methylglyoxal levels by nearly 70%**<sup>83</sup> And, as you'd expect, these results came purely from *direct* AGE-fighting: HbA<sub>1c</sub> was unaffected by the supplement.

These results are especially important because this way of measuring AGE is turning out to be an important and relatively easy way of testing AGE-related disease risk in humans: levels of CML within red blood cells are closely associated with diabetics' odds of developing retina damage – *independently* of their age, how long they have been diabetic, or their blood sugar level as assessed with HbA<sub>1c</sub>. The scientists who discovered this relationship have therefore concluded that **levels of CML within blood cells predict risk of diabetic retina damage** (retinopathy).<sup>84</sup>

Having shown that the level of CML in your blood cells tells you your odds of suffering diabetic retinopathy, and that **Benfotiamine** reduces red blood cell CML in humans,<sup>83</sup> scientists at the Albert Einstein College of Medicine's Diabetes Research Center asked the next, obvious, and exciting question: might **Benfotiamine** protect you against the retinal damage caused by decades of high blood sugar?

By putting **Benfotiamine** to the test in a new study in diabetic laboratory animals,<sup>85</sup> it appears that these scientists have answered their question in the affirmative. For in these animals, **Benfotiamine prevents AGE-related diabetic retinal damage.**

In this study,<sup>85</sup> scientists first tested the ability of thiamin and **Benfotiamine** to activate the transketolase enzyme – the key to **Benfotiamine's** anti-AGE powers – in cultured cells. Similarly to what has been seen in “in vivo” studies in humans,<sup>54</sup> regular thiamin caused only a 20 percent increase in this enzyme's power – while **Benfotiamine** boosted enzyme activity by a remarkable 400 percent.

The researchers then gave one group of diabetic rodents **Benfotiamine** supplements, and left another group

**Benfotiamine supplements normalized AGE levels**

unsupplemented, keeping a third group of nondiabetic animals as a control group.<sup>85</sup> Nine months later, they examined the animals' eyes, testing the level of AGE in their retinas, examining metabolic abnormalities of the cells, and looking for **acellular capillaries**. Acellular capillaries are the dead husks left behind when the cells of the tiny blood vessels of the eye die. Because these dead cells can no longer deliver blood to the retina, they are both a *cause* and a *marker* of damage to the eye – damage which is common in diabetics because of their high blood sugar levels, and which makes diabetics *25 times more likely to go blind* than people with more normal levels of blood sugar.

As in other studies, **Benfotiamine** had no effect on the high blood sugar levels of the diabetic animals, as measured by HbA<sub>1c</sub>. Nor did it reduce the diabetics' obesity. But what it *did* do for the diabetic animals was astonishing.

The first finding was that **Benfotiamine supplements normalized AGE levels in the diabetics' retina**. While unsupplemented diabetic animals suffered a burden of 279 units of AGE in their retinas, **Benfotiamine**-supplemented animals had only 94 units' worth – a level not distinguishable from the 72 units in the normal, healthy animals. **Benfotiamine** also normalized several key metabolic parameters in the diabetic animals' cells (dangerously elevated membrane **protein kinase C** and hyperactive hexosamine pathway, and hyperglycemia-associated overactivation of the inflammatory **NF-kappaB** messenger).<sup>85</sup>

But most important of all, **Benfotiamine prevented the AGE-associated retinal damage**. After nine months of diabetes, diabetic animals had suffered three times as many acellular capillaries as were found in healthy animals. But with the protection afforded by **Benfotiamine**, the number of acellular capillaries in the supplemented diabetics was indistinguishable from that of their normal, healthy cousins (**Figure 9**)!<sup>85</sup> Combined with the human study on CML levels within red blood cells,<sup>84</sup> the evidence suggests that **Benfotiamine's** vigorous abilities as an AGE-fighter will make it vital support for the health of *human eyes*, just as it's already proven to be for human nerves.

And there's *another* AGE-related disease that researchers believe **Benfotiamine** may fight: the loss of **kidney function** which accompanies "normal" aging, and which is accelerated by diabetes. The levels of CML and imidazolone within red blood cells – already shown to be a good marker of risk of diabetic retina damage<sup>84</sup> – are considerably higher in diabetic patients on dialysis than they are in healthy people.<sup>86</sup> And as we've seen, **Benfotiamine** has an impressive capacity to take on these AGEs in humans.<sup>83</sup>

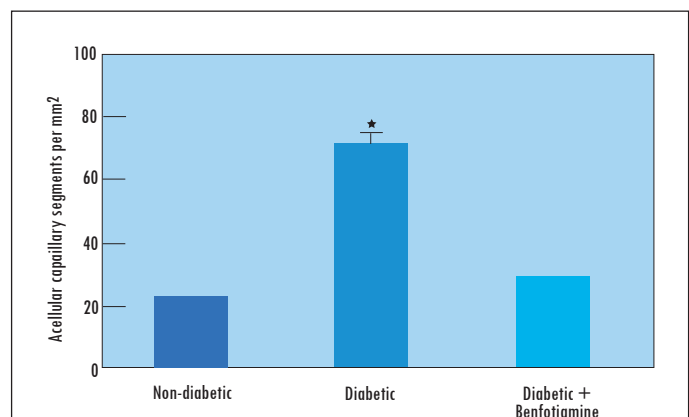
Benfotiamine prevented the AGE-associated

Dr. Paul Thornalley of the University of Essex has just completed a study designed to see if **Benfotiamine** will protect diabetic rodents against kidney damage.<sup>87</sup> When he initiated his study, Dr. Thornalley was so confident of the success of the project that his sober scientific predictions sounded like

arrogance: **"It is expected that thiamin and Benfotiamine will prevent the development of diabetic nephropathy ... This study has an outstanding chance of success."**<sup>87</sup>

Just as we were going to press, the results of this study were revealed. In this study,<sup>88</sup> researchers compared three groups of diabetic, insulin-treated laboratory animals with a fourth group of healthy animals which was kept as a control group. One group of diabetic animals received no treatment except the insulin; a second group received **Benfotiamine** at a dose similar to that used in human clinical trials; and a third received a 'megadose' of **Benfotiamine**, *ten times* higher than the standard dose. The animals then had their kidney function tested every six weeks for nearly six months.

The results have vindicated Dr. Thornalley's confidence. **Benfotiamine dramatically reduced diabetic kidney disease**, delaying or avoiding **hyperfiltration** (the disease-related increase in blood flow through the fine blood vessels of the kidneys that actively filter the blood) and reducing the loss of **albumin** in the urine by 76% (healthy kidneys filter out albumin, which is a protein in the blood).<sup>88</sup> Even more promisingly, the standard dose of **Benfotiamine** was just as effective as the 'megadose,' so that we might expect to see the same results in humans at doses that have *already* proven effective in human clinical trials for neuropathic pain. A second study is now underway to see if **Benfotiamine** will actually improve kidney function in diabetic animals with *pre-existing* kidney damage,<sup>88a</sup> as it has already been shown to do in the nerves of diabetic



**Figure 9: Benfotiamine Prevents AGE-Related Retinal Damage in Experimental Diabetes.** Redrawn from (85).

animals and humans.

### The End of an AGE

**These are not test-tube studies.** The results experienced when taking **Benfotiamine** occur not merely in labs, but in *lives*: in the bodies – and in the health – of living things, from experimental animals to human beings. This unique thiamin delivery system shields real-life, living, breathing bodies from the AGE assault, extending its protection all the way up from the biochemical level to the actual health and well-being of users of **Benfotiamine** supplements.

And the fact that **Benfotiamine** can defend you from the threat of AGE *without* influencing blood sugar levels makes their powers all the more arresting. After all, there are many ways to support healthy sugar levels, from lifestyle choices like exercise, weight loss, and a healthier diet;<sup>89</sup> to nutrients like **R(+)-lipoic acid**<sup>90</sup> and (for diabetics) **chromium picolinate**;<sup>91</sup> and on to herbs like **banaba extract (colosolic acid)**<sup>92,93</sup> and (once proper standardization is established – see “Setting the Standard” in this issue of *Advances*) **American ginseng (*Panax quinquefolius L.*)**.<sup>94</sup> **Benfotiamine**, however, attacks the AGE problem *head-on, whatever* your blood sugar levels are. **Benfotiamine** can thus fight AGE *above and beyond* what can be accomplished by maintaining or restoring healthy blood glucose levels.

For our entire evolutionary history, AGEs have robbed people of their health, warping proteins and spreading inflammation and tissue dysfunction through the bodies of diabetics and healthy people alike. In **Benfotiamine**, we finally have a *proven* way to protect tissues from the AGE assault.

## The Bottom Line

**Advanced Glycation Endproducts, (AGEs)** are proteins whose structure has been warped by exposure to sugars or by other, much more reactive molecules. AGE chemistry is the cause of the “browning” in roast chicken skin or on toast, but the same “browning” chemistry is at work in your body every day of your life. AGE reactions create chemical handcuffs which gum up your proteins, deactivate your enzymes, trigger unhealthy biochemical signaling in your cells, and damage your DNA. Aging – or *AGEing* – you.

### Two Ways to AGE

There are two major ways that AGEs can form inside the body. One way is through a simple series of chemical reactions known as the “Maillard Pathway.” But more recently, scientists have come to understand *another* pathway of AGE formation, which only occurs *within* your cells because of the body’s metabolism of carbohydrates.

When blood sugar levels rise, *some* key kinds of cells – including **nerve cells (neurons)** and the cells that make up the fine blood **cells of the retina of the eye** and the filtering units (**glomeruli**) of the kidney – are also flooded with glucose. The resulting high sugar levels within these cells cause a logjam in the normal cellular metabolism of glucose. This backlog results in a buildup within the cell of super-reactive glucose-metabolic intermediates known as **triosephosphates**. And once that happens, the excess **triosephosphates attack the surrounding proteins, lipids, and DNA, causing AGE damage from within the heart of the cell.** It’s these cells are thus the most vulnerable to the complications of diabetes.

There *is* a nutrient that could, in theory, pack a potent wallop against the AGE onslaught: **Thiamin Pyrophosphate (TPP)**, the active coenzyme form of the B-complex vitamin *thiamin*. Boosting TPP in cells stressed by high glucose concentrations opens up an important biochemical “safety valve” in the normal metabolism of blood sugar through an enzyme known as **transketolase**. Activating transketolase allows the body to shunt excess triosephosphates into a safe alternative metabolic pathway, preventing the logjam that leads to the buildup of triosephosphates and the formation of AGE.

But neither conventional thiamin, nor supplements containing TPP *itself*, effectively boost TPP in your cells.

### Benfotiamine: the TPP Solution

Fortunately, an *effective* way to boost thiamin pyrophosphate in your cells does exist: **Benfotiamine**. **Benfotiamine** is the most potent of the **allithiamines**, an unique class of thiamin-derived compounds present in trace quantities in roasted crushed garlic *Allium* vegetables.

**Benfotiamine's** unique open-ringed structure makes it able to pass *directly* through cell membranes, readily crossing the intestinal wall and being taken straight into the cell.

As a result, your body absorbs **Benfotiamine** better than thiamin itself, and levels of thiamin and TPP remain higher for longer. Brain and muscle, for instance, take in *five- to twentyfive-fold* as much thiamin in the form of allithiamines as they do of an equal amount of regular thiamin. And **Benfotiamine** is even more bioavailable than the other *allithiamines*, including thiamin tetrahydrofurfuryl disulfide/TTFD. Yet **Benfotiamine** is actually *less toxic* than conventional thiamin supplements!

By effectively increasing levels of thiamin *itself*, **Benfotiamine dramatically boosts AGE-fighting thiamin pyrophosphate and cell-shielding transketolase activity in your body.**

### Shielding Nerve Structure

While most “anti-AGE” supplements rely on test-tube “browning” experiments as the “evidence” of efficacy, **Benfotiamine has been proven in multiple real-world human and animal studies to reduce AGE formation and support tissue structure and function in diabetics.**

In clinical trials in people suffering with diabetic nerve damage, **Benfotiamine** has been proven to improve **vibratory perception threshold** and **nerve conduction velocity**. Clinical trials have also shown that **Benfotiamine users experience a 50% reduction in diabetic nerve pain**, along with an increased ability of the nerves to detect an electrical current, respond to electrical stimulation, and regulate the heartbeat. Similarly, **Benfotiamine prevents** this loss of control from happening in the first place in diabetic dogs.

In one critical human clinical trial, a B-vitamin combination using **Benfotiamine** as its thiamin source was put head-to-head with a B-complex supplement that included a megadose of conventional thiamin. **Benfotiamine** proved its effectiveness on several of these key parameters, while the standard thiamin pill failed.

These benefits are not due to changes in blood sugar levels (either fasting, or after a meal, or averaged over several months (as measured by HbA<sub>1c</sub>), or improvements in metabolic benchmarks. They are the *direct* results of **Benfotiamine's** AGE-fighting, metabolic-balancing powers.

### Benfotiamine in Other Vulnerable Tissues

More recently, new studies have begun to document **Benfotiamine's** ability to shield other tissues from AGE damage. One just-published study tested the ability of

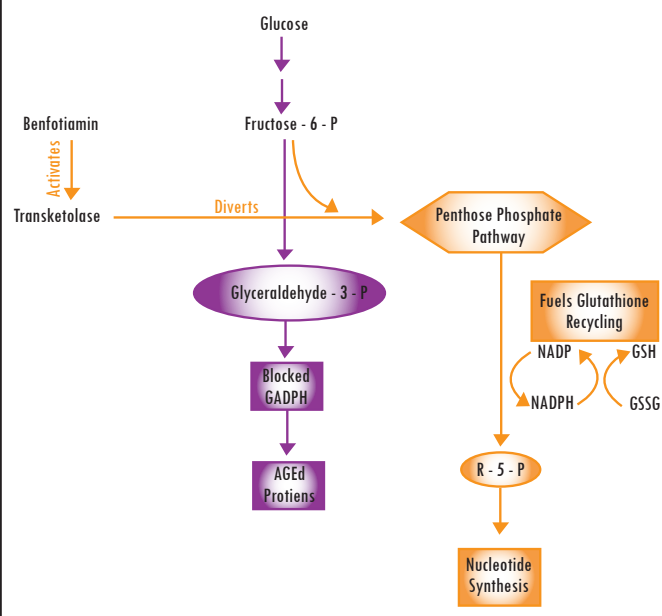
thiamin and **Benfotiamine** to protect diabetic rodents' retinas from the ravages of AGE. The study found that **Benfotiamine supplements normalize AGE levels in diabetics' retinas**, as well as several key metabolic parameters within the diabetic animals' cells. More importantly, the study found that **Benfotiamine prevents AGE-associated retinal damage**. With the protection afforded by **Benfotiamine**, the number of acellular capillaries in the supplemented diabetics was indistinguishable from that of their normal, healthy cousins!

And there's *another* AGE-related disease that researchers believe **Benfotiamine** may fight: the loss of **kidney function** which accompanies “normal” aging, and which is accelerated by diabetes. Dr. Paul Thornalley of the University of Essex has just completed a study designed to see if **Benfotiamine** will protect diabetic rodents against kidney damage. Both megadose thiamin and **Benfotiamine** caused clear-cut reductions in the leakage of protein through the animals' kidneys – with **Benfotiamine** showing itself to be the superior intervention. A second study is now underway to see if **Benfotiamine** will actually improve kidney function in diabetic animals with *pre-existing* kidney damage, as it has already been shown to do in the nerves of diabetic animals and humans.

### The End of an AGE

**These are not test-tube studies.** The results experienced when taking **Benfotiamine** occur not merely in labs, but in *lives*: in the bodies – and in the health – of living things, from experimental animals to human beings. In **Benfotiamine**, we finally have a *proven* way to protect tissues from the AGE assault.

**Figure 4:** Transketolase Opens the Pentose Phosphate Shunt, Preventing AGE Formation. Redrawn from (83).



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# Z e n

# i n a B o t t l e

Green tea was first brought to Japan by the earliest Buddhist monks from China. They found that the steaming brew lent a tranquil focus to their meditations. Now science has uncovered the molecular secret to their state of restful attention. It's an unique, neurologically-active amino acid called **L-Theanine**, found almost exclusively in the true tea plant.

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