

# Pyridoxamine & Benfotiamine for Sugar and AGEing



## The Aging Process

We are the longest living mammals. The maximum life expectancy for humans is roughly 120 years and it is believed that our genetic potential should allow all of us to live over 100 years. Life expectancy has increased dramatically in the industrialized world during the 20th century from roughly 40-45 to nearly 75 years, but few make it to 90, never mind 100. The longest living group of humans is Japanese women with a life expectancy of 83 years. Living longer is not always better and many elders are plagued by degenerative diseases such as osteoporosis, cardiovascular problems, cancer, cataracts and arthritis. At present, the only methods known to increase lifespan are better lifestyle choices, and the prevention and treatment of disease, but what if we could influence the aging process itself?

The aging process is still largely a mystery. We age because natural selection chooses which genes will be propagated and which genes will be selected against. Unfortunately, genes that affect us after we have reproduced cannot be selected against and are passed on. Aging is a gradual decline in organ function, a loss of tissue structure and an accumulation of cellular damage. We all age differently; the timing, progression and consequences vary from person to person. The mechanism behind the aging process is not completely recognized but mounting research has provided clues, ideas and theories.

Free radicals are certainly part of this puzzle. They injure our tissues and every cell in our body is exposed to their damaging effect. Unfortunately, free radicals are by-

products of our breathing and completely preventing their formation is unrealistic. Antioxidants on the other hand quench free radicals and prevent some of the damage they induce.

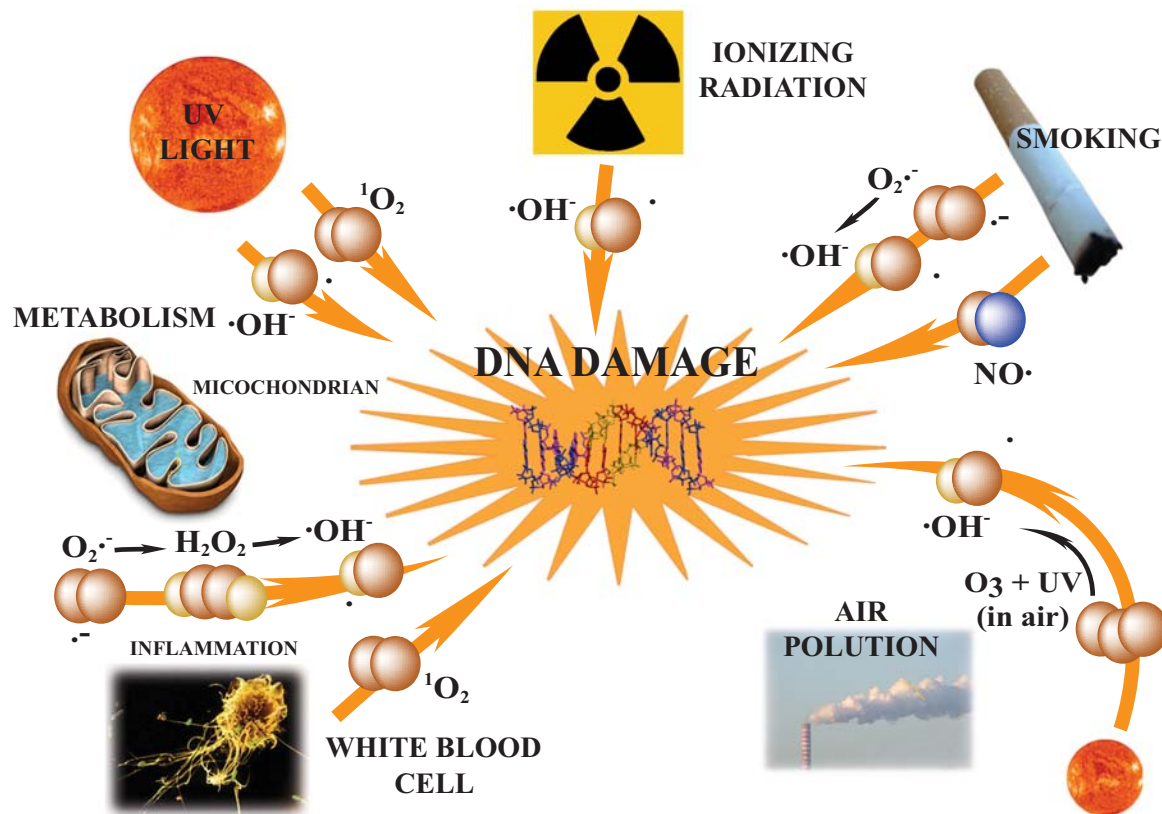
Another possibility that could limit lifespan is our cells ability to divide. It is thought that our cells might only be able to divide a certain number of times. That number might be programmed in our genome. Our cells losing their ability to partition would weaken our immune system and slowly lead to a loss of organ function and a breakdown of metabolic reactions.

Another chemical process that occurs in our body and leads to significant tissue injury and loss of function over time is known as the Browning Reaction, or the formation of Advanced Glycation End products (AGE) - the permanent glycation of proteins. It is the same reaction that occurs in the food we eat, toasted bread for instance becomes brown because of this reaction. In our body, the reaction occurs when protein and sugar molecules bind together. This results in loss of function and poor gene expression. Permanent protein glycation leads to the formation of cataracts, atherosclerosis, and other diseases common later in life. The Browning theory of aging was first brought forth in the 1980s by Monnier and Cerami.<sup>1</sup>



Glycation is especially rapid in diabetes because of the increased presence of glucose and is the reason why diabetes is sometimes referred to as "accelerated aging". For example, cataracts occur, on average, 10-15 years earlier in diabetics and are predictors of early death in such subjects.<sup>2-3-4</sup> Atherosclerosis, myocardial infarction, strokes, joint stiffness, reduced lung elasticity, hypertension, osteoarthritis and infections are all more common in diabetic patients.<sup>5</sup> Protein glycation is a process that occurs spontaneously, no enzymes are required and it ultimately leads to the formation of intermolecular cross-links. This leads to loss of function and increased stiffness and is

## FORMATION OF FREE RADICALS



## BIOLOGICALLY SIGNIFICANT FREE RADICALS

### Reactive Oxygen Species:

$O_2^{\cdot -}$	Superoxide radical	$H_2O_2$	Hydrogen peroxide	$ONOO^-$	Peroxynitrite
$\cdot OH$	Hydroxyl radical	$^1O_2$	Singlet oxygen	$HOCl$	Hypochlorous acid
$ROO\cdot$	Peroxyl radical	$NO\cdot$	Nitric oxide	$\cdot$	Free electron

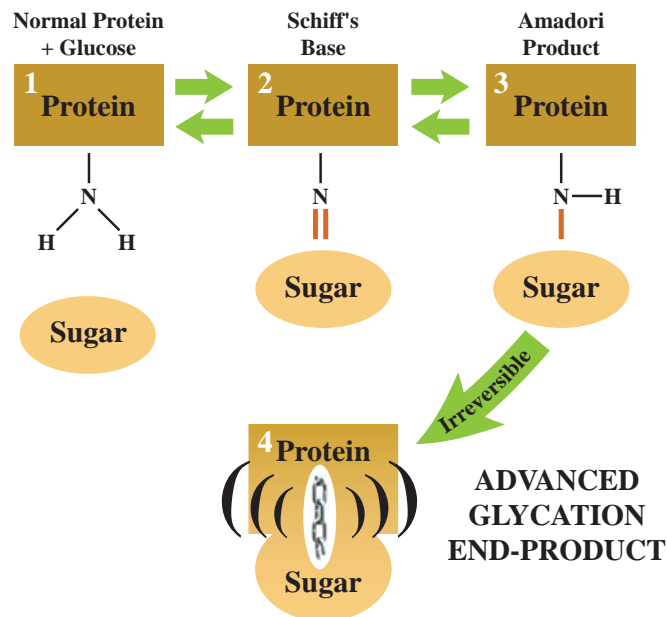
especially problematic for more vulnerable tissues such as the kidneys, capillary basement membranes and the cardiovascular and pulmonary systems.

## AGE and ALE formation

The French chemist L. C. Maillard first reported the formation of a yellow brown substance when he heated amino acids with sugars. That was in 1912 and the process is now known as the Maillard reaction, i.e. non-enzymatic glycation or the browning reaction. Non-enzymatic glycation does not occur only in foods, it is a common reaction that occurs in our body when proteins and sugar molecules bind together. This interaction was first observed in the 1970's when it was discovered that hemoglobin could be non-enzymatically bound to glucose. We also know that as hemoglobin ages and as blood glucose levels rise, the

degree of glycation increases.<sup>6</sup> It was later discovered that tissues that rejuvenate slowly such as collagen and crystallins are most vulnerable to AGE formation.<sup>7</sup> However the most damaging AGE reactions affect DNA; the blue print for the production of all proteins found in the human body. Once DNA has been affected, the appearance and configuration of proteins may be compromised. The damage is accelerated by hyperglycemia in diabetes, by hyperlipidemia in atherosclerosis and by oxidative stress in chronic disease. Glycation occurs when the free amino groups of lysine, hydroxylysine or arginine residues, as well as amino groups of phospholipids and guanyl nucleotides of DNA are spontaneously reduced by sugars such as glucose and its metabolic intermediates: triose phosphates, glyoxal and methylglyoxal.<sup>8-12</sup> Any tissue containing those residues and amino groups is prone to protein glycation. The initial reaction of a sugar molecule with a protein leads to the

## The formation of Advanced Glycation End-products



1. Proteins and sugar molecules are naturally present in organs and tissues
2. Abnormal attachment of a sugar molecule to a protein to form a Schiff Base
3. Appearance of Amadori product. Notice that what was a double bond is now a single bond - double bonds are much more reactive than single bonds which means that Amadori products are more stable than Schiff bases
4. Advanced Glycation End-product - the permanent attachment of a sugar molecule to a protein

formation of a Schiff base that rearranges itself to form a ketoamine. The covalent bonding of a sugar and an amino acid leads to the production of an Amadori product. Subsequent reactions lead to the formation of AGE.<sup>13</sup> A reaction similar to AGE formation can also occur through lipid peroxidation and metal-catalyzed glucose auto-oxidation (referred to as advanced lipoxidation end products or ALE).<sup>14,15</sup> The glycation of proteins to early glycation products is reversible. Schiff bases and Amadori products are produced through reversible reactions. However, AGE are stabilized through irreversible reactions such as rearrangement, dehydration and condensation.<sup>16</sup> Interestingly, of all the naturally occurring sugars, glucose has the slowest rate of glycation and AGE formation. The rate of AGE formation by sugars such as fructose, glucose-6-phosphate and glyceraldehyde-3-phosphate is far more rapid than for glucose.<sup>17</sup> For example, fructose-fed rats had blood glycated hemoglobin levels that were significantly higher (43%) than controls.<sup>18</sup>

Several factors contribute to protein glycation in the body. Smoking and diet are important contributors to AGE formation but there are still many unknowns and new AGE are still being discovered. Recent studies suggest that genetic factors also have an important influence on

circulating AGE levels.<sup>19</sup> Once AGE are formed, they remain in the tissue until the protein from which they are formed is degraded. Therefore, AGE accumulate most in tissues where protein turnover is slow. Such tissues include the crystallin in the lens of the eye and the collagen found in connective tissue.



## AGE and Longevity

It is difficult to understand the full extent of the impact AGE formation has on health because we do not have very good methods of identifying AGE. Many AGE are unstable in acids or alkaline solutions typically used to hydrolyze and study proteins. This makes it difficult to recognize and study them. Some AGE can only be identified after proteolysis of the protein. New AGE's are being discovered and it is clear that carbohydrates are not the only way proteins are chemically modified. For instance, advanced lipoxidation end products (ALE) are the result of the interaction of lipids and proteins. It is apparent that AGE formation is only a part of protein modification in tissues.

AGE concentrations correlate with age but not with lifespan and some have criticized the glycation theory of aging based on this observation. The levels of AGE in the proteins of old short-lived animals cannot be compared to the levels of AGE found in old long-lived animals. It is important to

understand that AGE bioaccumulate in tissues with slower protein turnover times. AGE formation might be similar in different tissues - for instance, in skin and collagen - but the half life for collagen is 120 years versus 15 years for skin. It is therefore not surprising that the levels of the AGE/ALE compounds CML, CEL and pentosidine are three times higher in human articular collagen versus skin collagen of the same age.<sup>20</sup> Therefore, AGE concentration in tissues correlates with age but not life span. However, AGE may influence longevity through another injurious mechanism; their impact on our genome.



*The Giant Tortoise is the longest living animal with a maximum lifespan of 200 years.*

In a paper published in the Annals of the New York Academy of Sciences, John W. Baynes puts forth a very interesting explanation for the apparent discrepancy between tissue concentration of AGE and longevity.<sup>21</sup> AGE could exercise their effect on longevity through their action on DNA. There is evidence to support that DNA can be glycosylated by AGE and ALE<sup>22,23</sup> which explains why patients with end-stage renal failure who have increased levels of AGE have a high incidence of DNA damage.<sup>24</sup> DNA damage occurs through the interaction of AGE and ALE with groups found on the amino portion of adenine and guanine residues found in the DNA matrix. The formation of AGE in the genome would alter the DNA sequence and would lead to cellular apoptosis, necrosis, chronic diseases and increased rates of cancer. The impact of AGE on DNA is relative to the rate of glycation but the consequences would be influenced by the efficiency of DNA repair - a process that is less efficient in shorter-lived species. Although AGE formation contributes to DNA damage, it is the efficiency with which the organism can repair and reverse this damage that controls the rate of the aging process and the longevity of the animal.<sup>25</sup> In humans and other long-lived organisms, the damage associated with the Maillard reaction is averted more efficiently through complex protection mechanisms. The availability of metal ions that



*Chocolate discs with multi-colored coating - 75% sugar content.*

promote glycation reactions is restricted, detoxification pathways remove and inactivate reactive intermediates and antioxidant mechanisms prevent injury induced by reactive sugars. In other words, there are two important factors in the maintenance of biological integrity: the rate at which injury is incurred and the organism's efficiency at recovering from this onslaught. Short-lived species incur less damage throughout their life span but they are short-lived because they cannot repair this damage as effectively as long-lived organisms.

## The bitter truth about sugar

There is growing evidence that suggests that the accumulation of Advanced Glycation End products is involved in a variety of diseases and degenerative disorders.<sup>26,27</sup> AGE are formed in surplus in diabetes, renal failure and with advancing age.<sup>28</sup> We have known for years that continuous cellular exposure to excess glucose prevents normal growth,<sup>29</sup> which leads to significant tissue dysfunction and has been related to several degenerative diseases. The increased presence of carbonyl compounds and glycosylated proteins lead to the inhibition of key cellular enzymes. These include: glyceraldehyde-3-phosphate dehydrogenase (GAPDH)-an important enzyme in glycolysis and apoptosis which may be involved in Alzheimer's and prostate cancer progression, glutathione reductase - an enzyme that recycles glutathione and lactate dehydrogenase - involved in cellular energy production.<sup>30</sup> The formation of Advanced Glycation End-products is especially prevalent in diabetes and has been related to the development of diabetic complications such as vascular disease, retinopathy and impaired wound healing. Elevated glucose levels lead to the binding of sugar molecules to albumin. This interferes with the normal functioning of the protein and contributes to diabetic

complications.<sup>31</sup> Even short periods of hyperglycemia appear to be sufficient to increase the formation of  $\alpha$ -oxoaldehyde, a significant product in early glycation.<sup>32</sup> AGE are toxic to neurons and may be an important factor in the development of diabetic neuropathy because they activate the enzyme nitric oxide synthase, which may cause the death of neurons.<sup>33</sup> Furthermore, AGE negatively affect energy production and lead to decreased cellular ATP levels, increase glucose consumption and lactate production in neurons.<sup>34</sup>

Diabetic patients are at an increased risk for cardiovascular disease. They are predisposed to certain risk factors such as hypertension and abnormal blood lipid profiles. The presence of AGE in the vasculature was shown to be related to hypertension and the long-term administration of an AGE inhibitor reduces blood pressure.<sup>35</sup> In addition, epidemiological evidence demonstrated that hyperglycemia is a risk factor for heart disease: the lower the blood sugar levels, the lower the cardiovascular disease risk.<sup>36</sup> Diabetic blood vessels contain more AGE,<sup>37</sup> display fewer Receptor of Advanced Glycation End-product (RAGE)<sup>38</sup> and produce more proinflammatory cytokines.<sup>39</sup> Diabetic patients were shown to have, on average, a 12.6% increase in AGE plasma levels and up to 46.5% increases when faced with kidney damage.<sup>40</sup> This has serious implications for atherosclerosis because glycation impedes normal cellular growth and prevents the normal healing of blood vessels.<sup>41</sup> In a study on diabetic animals, an AGE cross-link breaker prevented the development of arteriole plaque by 30% and an AGE inhibitor led to a 40% reduction in plaque formation.<sup>42</sup> Similarly, diabetic patients were shown to have higher levels of glycated LDL cholesterol, an especially harmful type of cholesterol, thought to be a useful indicator of heart disease risk.<sup>43</sup>

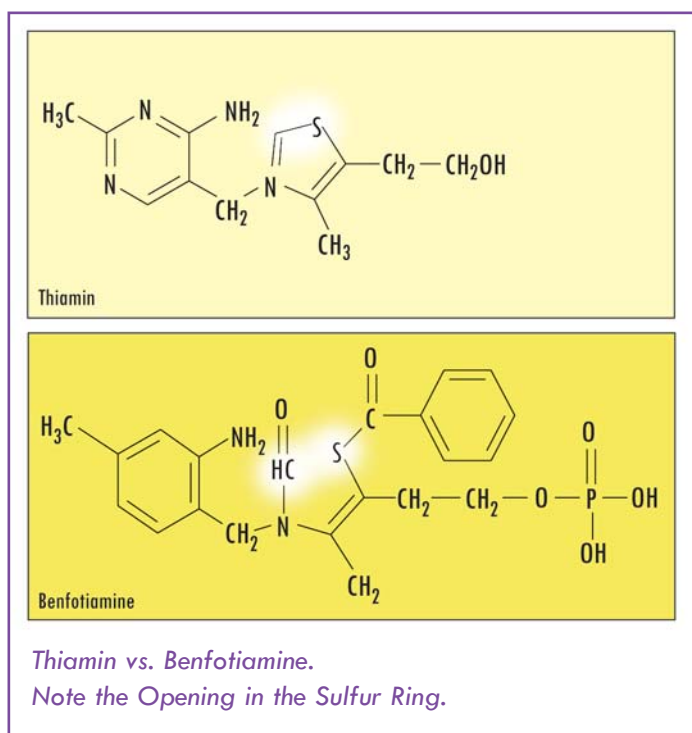
Another common pathology where AGE formation appears to have a significant impact is Alzheimer's disease (AD), a degenerative brain disorder currently affecting 4.5 million Americans.<sup>44</sup> Accumulation of AGE leads to cellular cytotoxicity and since AGE levels are higher in AD, it is possible that they may contribute to the cell death seen in AD.<sup>45</sup> It has also been shown that nucleotide (the building blocks for DNA and RNA) glycation leads to mutations and programmed cell death.<sup>46</sup> AGE formation promotes protein aggregation that is linked to amyloidoses such as Alzheimer's disease<sup>47</sup> and familial amyloidosis.<sup>48</sup> The finding that patients with diabetes have a significantly higher risk of developing Alzheimer's disease supports the involvement of AGE formation in Alzheimer's.<sup>49</sup>

In human cartilage, the presence of AGE increases 50 fold between the age of 20 and 80.<sup>50</sup> The strength of connective tissue comes from the intermolecular collagen crosslinks. AGE formation in the collagen matrix prevents such crosslinks and the accumulation of AGE in cartilage leads to increased stiffness and brittleness.<sup>51</sup> Moreover, AGE hinders normal tissue turnover. In cartilaginous tissues for instance, AGE prevents proteolytic degradation, which promotes the further accumulation of AGE.<sup>52</sup> This partly explains why the most important risk factor for the development of osteoarthritis is the age of the individual; the older the tissue, the more AGE.

The glycation of collagen is also an important factor in the loss of bone quality seen with advancing age.<sup>53</sup> Studies have shown that AGE accumulation in the cartilaginous portion of the bone matrix leads to a 40% decrease in cellular proliferation,<sup>54</sup> interferes with cellular adhesion to the extracellular matrix and obstructs genetic expression.<sup>55</sup> As AGE increases in cartilage, proteoglycans and collagen synthesis in articulations decrease.<sup>56</sup> A recent study has shown that with increasing AGE levels in articular tissue, osteoarthritis severity also increases.<sup>57</sup> The trial demonstrated that with increasing AGE concentrations, glycosaminoglycan loss was also increased, repair was impeded and the uptake of new proteoglycans into the collagen matrix was reduced. In this study, damaged knees were injected with ribose to increase AGE formation. The release of glycosaminoglycans was increased by a factor of four and there was a 40% increase in articular damage. Ribose injections led to a significant augmentation in cartilage degeneration.<sup>58</sup> AGE also promotes chronic inflammation through its effect on cytokines and free radical production.<sup>59</sup>

*A recent study has shown that with increasing AGE levels in articular tissue, osteoarthritis severity also increases*

It is unequivocal that AGE are associated with age-related disorders such as arteriosclerosis, inflammatory disorders, diabetes, arthritis and neurodegenerative conditions. After all, AGE leads to protein denaturation, genetic mishaps, enzyme inactivation and an inadequate or misdirected immune response. Research into anti-AGEing compounds and newer therapies to address and prevent glycation and lipoxidation may prevent age-related disorders and might prove useful for the treatment and prevention of conditions for which adequate therapies are currently lacking.



## Preventing Glycation

The prevention of glycation would lead to significant improvement and a reduction of complications seen in diseases such as diabetes where the formation of AGE leads to significant health problems. More importantly, because no level of AGE in any bodily tissue should be considered harmless; thwarting this process would lead to health improvements and would fend off the loss of function seen in aging.

We possess an enzymatic defense against protein glycation but this defense system is imperfect as glycation occurs under normal physiological states. The enzymes involved in the prevention of glycation are glyoxal I, specific aldehyde reductases, dehydrogenase isoenzymes, amadoriase and fructosamine 3-deoxyglucosone. It is important to realize that free radicals and oxidative stress promote glycation because the depletion of glutathione and NADPH by oxidants reduces the activity of glyoxalase I. Also, some aldehyde reductase are NADPH dependent.<sup>60</sup>

Several natural compounds and pharmaceutical drugs have been investigated for their possible efficacy in the prevention of protein damage by sugars or lipids. Unfortunately, test tube experiments are often misleading because it is difficult to differentiate between inhibition of carbohydrate auto-oxidation and AGE inhibition. Fortunately, there is reason to be optimistic: clinical studies have clearly demonstrated that protein glycation and lipoxidation can be avoided.

## The Nutritional Shield

Most degenerative processes in the human body can be delayed or prevented through better nutrition and wiser lifestyle choices. Better nutritional and lifestyle habits remain the best approach to prevent disease and they are partly responsible for the extended lifespans seen in recent years. It should be no surprise that two powerful anti AGEing products are in fact vitamins. Benfotiamine (a form of vitamin B<sub>1</sub>) and pyridoxamine (a form of vitamin B<sub>6</sub>) have been studied extensively for their ability to prevent the formation of AGE and ALE. The results speak for themselves.

## Benfotiamine

Thiamine, also known as vitamin B<sub>1</sub>, was initially recognized as an anti-beriberi factor. Beriberi comes from a Sinhalese word meaning extreme weakness. The disease was primarily seen prior to the 19th century. Casimir Funk isolated the anti-beriberi factor from rice in 1912. It was the first compound referred to as a vitamin; an amine essential for life, hence its designation as vitamin B<sub>1</sub>. The chemical formula for vitamin B<sub>1</sub> was recognized by Robert R. Williams in 1931, and was named thiamine. The body's thiamine stores are small (only 30 mg) and because the vitamin has a central role in energy production, most stores are located in muscles.<sup>61</sup> The active form of the vitamin is thiamin pyrophosphate (TPP). Common indications for the vitamin include the treatment of nerve disorders, and the prevention of deficiency in disorders such as alcoholism, cirrhosis, gastrointestinal disease, increased carbohydrate intake, hyperthyroidism and infection.<sup>62</sup> In a more recent study, thiamine supplementation in 120 young adult women improved decision time and mood.<sup>63</sup> The vitamin is also useful for the prevention and for the treatment of heart failure.<sup>64</sup>

Thiamine is needed for several enzymatic reactions in the human body. The most important being the vitamin's involvement in pyruvate dehydrogenase (an enzyme important in energy production), transketolase (an enzyme involved in lipid, glucose and branched chain amino acid metabolism and also for the production and maintenance of the myelin sheath surrounding nerve cells), and 2-oxo-glutarate dehydrogenase (involved in the synthesis of acetylcholine, GABA and glutamate).

Benfotiamine is a newer, highly absorbable, fat-soluble source of vitamin B<sub>1</sub>. It has similar application to thiamin but it is roughly 5 times more absorbable than regular thiamine and can pass directly through cell membranes. It is better assimilated, enters tissues with more ease and has longer periods of tissue retention.<sup>65</sup> It is thiamine's newer cousin and was developed in Japan in the 1950's for the treatment



# ORTHO • CORE

## SUPPLEMENT FACTS:

Serving Size: 9 Capsules

### Phytonutrient Complex

Calcium D-Glucarate	15 mg
Chlorophyllin Complex	300 mg
Trans-resveratrol (Chirally Pure)	1.8 mg
Indole-3-Carbinol (I3C)	20 mg
Sulforaphane	7.1 mg

**Phytonutrients** selected from evidence in human research – not just animal and test-tube studies, at doses based on epidemiology, not a roll of the dice.\*

### Vitamins

#### Vitamin A Complex

Retinol (palmitate)	500 IU
Natural-Source Mixed Carotenoids:	
Alpha-carotene	1332 IU
Beta-carotene	9990 IU
Cryptoxanthin	25 IU
Lutein	6.7 mg
Lycopene	18 mg
Zeaxanthin	545 mcg

Most multis either have *no* preformed **Vitamin A**, or thousands of IUs – enough to jeopardize your bone health. **Ortho•Core** get the balance right.\*

**Natural beta-carotene** and other carotenoids, biochemically distinct from the usual synthetic form.\*

We don't skimp on the **lycopene**: 18 mg reflects the high intakes in diets associated with the health of the prostate and other tissues.

#### Vitamin B Complex

B <sub>1</sub> (Thiamine)	9 mg
B <sub>2</sub> (Riboflavin)	2.5 mg
B <sub>3</sub> (Niacin from Inositol Hexanicotinate)	115 mg
B <sub>5</sub> (d-Ca Pantothenate)	100mg
B <sub>6</sub> (Pyridoxine)	25 mg
B <sub>12</sub> (Cyanocobalamin)	24 mcg
Folic Acid	800 mcg
Biotin	300 mcg
Pyrroloquinoline quinone (PQQ)	30 mcg
Choline (Bitartrate)	500 mg
Inositol	100 mg

**B-Complex Vitamins** in data-driven amounts instead of arbitrary 50 mg increments.\*

**Inositol hexanicotinate**, *not* niacinamide! Gives you the benefits of niacin without the flush and without inhibiting the *Sirtuin* cell defense enzymes.\*

**PQQ**, the newest discovery in the B enzyme cofactor group!\*

#### Vitamin C Complex

Vitamin C (Magnesium Ascorbate)	400 mg
Mixed Citrus Bioflavonoids	100 mg
Quercetin	65 mg
Vitamin D <sub>3</sub> (Cholecalciferol)	1000 IU

**A Full 1000 IU of Vitamin D**, as now recommended by many authorities for optimal health.\*

\*These statements have not been evaluated by the Food and Drug Administration.  
This product is not intended to diagnose, treat, cure, or prevent any disease.

Formulated with a broad spectrum of vitamins, minerals, and phytonutrients whose role in supporting your health is backed by scientific research *in humans*, **Ortho•Core** is the most advanced, balanced, and comprehensive core nutritional supplement ever! Optimal forms and science-driven dosing make **Ortho•Core** a solid cornerstone on which to build your unique nutritional supplement regimen.\*

<b>Vitamin E Complex</b>	100 mg
Tocopherols:	90 mg
alpha-tocopherol	22 IU
beta-tocopherol	1.5 mg
gamma-tocopherol	52 mg
delta-tocopherol	22 mg
Tocotrienols	10 mg
alpha-tocotrienol	3 mg
beta-tocotrienol	0.1 mg
gamma-tocotrienol	6 mg
delta-tocotrienol	1.3 mg
<b>Vitamin K<sub>2</sub> (As Menatetrenone (MK-4))†</b>	500 mcg
<b>Minerals</b>	
Boron (Citrate)	1.8 mg
Calcium (Citrate-Malate, D-Glucarate)	300 mg
Chromium (Picolinate)	100 mcg
Copper (Citrate)	1.5 mg
Iodine (Potassium Iodide)	150 mcg
Lithium (Orotate)†	1000 mcg
Magnesium (Citrate, Aspartate, Oxide, Ascorbate)	210 mg
Manganese (Glycinate)	2.3 mg
Molybdenum (Na Molybdate)	45 mcg
Selenium (Se-Methylselenocysteine)	200 mcg
Silicon (Na Metasilicate)	50 mg
Strontium	1.5 mg
Vanadium (Citrate)	18 mcg
Zinc (Citrate)	11 mg
<b>Biotransformation Conjugates</b>	
Acetic acid	100 mg
Glycine	400 mg
Taurine	500 mg
Trimethylglycine (TMG HCl)	500 mg
N-Acetylcysteine (NAC)	200 mg

The the **Complete E-Complex**, instead of a reliance on overweighted “natural” alpha-tocopherol or “mixed tocopherol” ratios that drive other E vitamers out of your tissues and rob you of their benefits.\*

**Boron** is not just for women! Recent epidemiological and experimental studies link this mineral to healthy prostate cell growth and differentiation.\*

**Lithium** is a mineral, not a drug. Recent research has revealed lithium’s neuroprotective powers and has shown that dietary lithium intake supports normal mood balance.\*

**Magnesium** blended for good bioavailability\* with reasonable capsule count.

**Selenium** as *Se-methylselenocysteine* (SeMC): the most vigilant form of this guardian of cellular health.\*

**Silicon, Strontium, and Vanadium:** missing from most multis, these minerals’ nutritional significance is rapidly emerging.\* Dosages reflect what’s found in good diets and mineral-rich drinking water.

**Zinc and Copper** in the balance needed for health. Unbalanced zinc supplementation usurps copper’s biochemistry, with long-term consequences for your health.\*

**Biotransformation Conjugates** needed to depolarize and excrete activated xenobiotic chemicals.\*

† USA version only

of vitamin B<sub>1</sub> deficiency.<sup>66</sup> This modern form of the vitamin holds promise against a new threat, AGE/ALE formation. Benfotiamine can prevent protein glycation/lipoxidation and lessen the damage they cause to cellular structures. These properties are unique to benfotiamine and are not seen with regular thiamine. The vitamin exhibits antioxidant activity and, based on its structure, is considered an AGE breaker.<sup>67</sup> Studies performed on human umbilical vein cells cultured in a high glucose environment demonstrated that the addition of benfotiamine to the solution reduced AGE production to levels similar to the ones expected under normal physiological glucose.<sup>68</sup>

Thiamin, however, does not prevent AGE generation in diabetic rats.<sup>69</sup> In a study performed on diabetic rats where nerve conductivity and nerve glycoxylation were assessed with thiamine and benfotiamine supplementation, the results clearly showed that benfotiamine is a superior AGE inhibitor. Three months after diabetes induction, nerve conductivity dropped by 10.5% and the glycation product CML rose by 3.5 fold and deoxyglucosone AGE formation was increased by 5.1 fold. After six-months of supplementation with benfotiamine, nerve conduction velocity was almost normal. Thiamine supplementation also improved nerve impulse transmission but not to the extent of benfotiamine. More importantly, benfotiamine completely prevented diabetes induced CML products whereas thiamine did not significantly reduce AGE levels.<sup>70</sup> Another study in 14 patients suffering from diabetic polyneuropathy (nerve damage manifesting as pain, tingling, or numbness) showed that a combination of benfotiamine and vitamin B<sub>6</sub> for 6 weeks significantly reduced pain from an intensity of 8.2 to a score of 2.3. Also of significance, supplementation led to enhancement in vibratory sensitivity and general improvements in 93% of cases.<sup>71</sup>

Another study examined benfotiamine's effect on diabetic red blood cells. The results are impressive: 40% reductions in CML levels and intracellular methylglyoxal derived AGE dropped by almost 70%.<sup>72</sup>

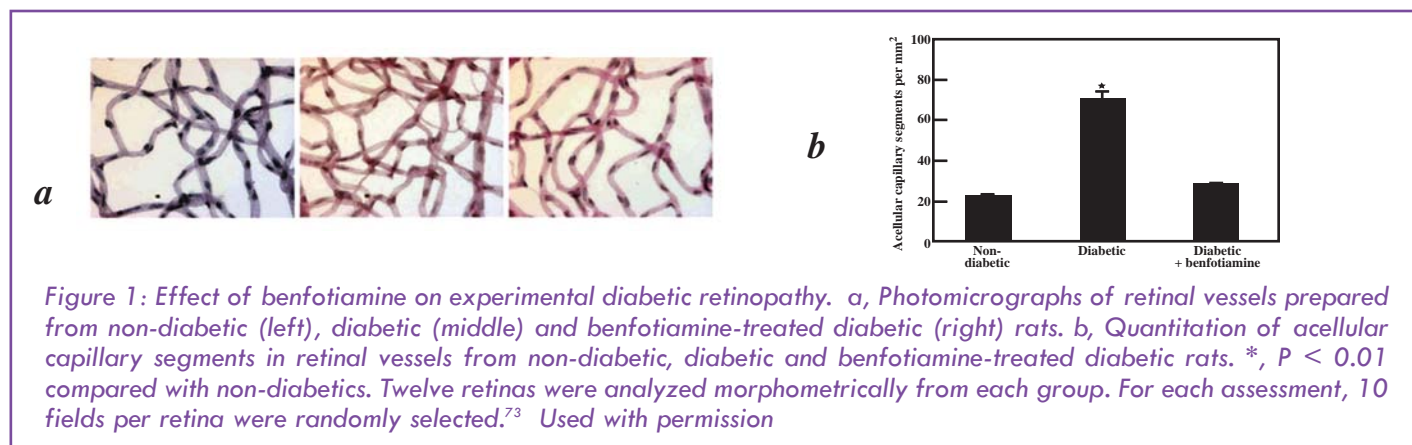
Benfotiamine corrected defective cellular replication and reduced AGE generation. The vitamin also prevented diabetic retinopathy in diabetic rats preventing an increase in the number of acellular capillary segments in the retina (see figure 1).<sup>73</sup> Acellular capillary segments are the result of the vascular endothelium no longer being able to proliferate and repair itself.<sup>74</sup>

Benfotiamine's effectiveness in the prevention of AGE formation may be related to the normalization of glycolysis. Accelerated glycolysis leads to the production of more intermediate metabolites such as glyceraldehyde-3-phosphate (G-3-P) and fructose-6-phosphate, which are highly reactive with proteins (G-3-P is 200 times more reactive to proteins than glucose).<sup>75</sup> Also, in hyperglycemic states, the mitochondria releases an excessive amount of superoxides - reactive oxygen compounds that can cause significant damage to cells. Those superoxide then inhibit the glycolytic enzyme GAPDH which forces glycolysis metabolites into four other glucose pathways, causing hyperglycemic damage. Benfotiamine activates the enzyme transketolase, which transforms glucose metabolites before they can interact with proteins.<sup>76</sup>

Benfotiamine has been used for more than 12 years in Europe and has an impeccable safety record. It is an important ally in the fight against glycation/lipoxidation and has proven to be an effective vitamin for diabetics and shows promise as an anti-aging therapy.

## Pyridoxamine

Vitamin B<sub>6</sub> is important for numerous metabolic functions. The vitamin is needed for over one hundred enzymes involved in the metabolism of proteins,<sup>77</sup> for the production of neurotransmitters, antibodies and red blood cells. Common indications for vitamin B<sub>6</sub> include the treatment of homocystinuria<sup>78</sup> (a metabolic abnormality characterized by excessive amounts of the amino acid homocysteine in the

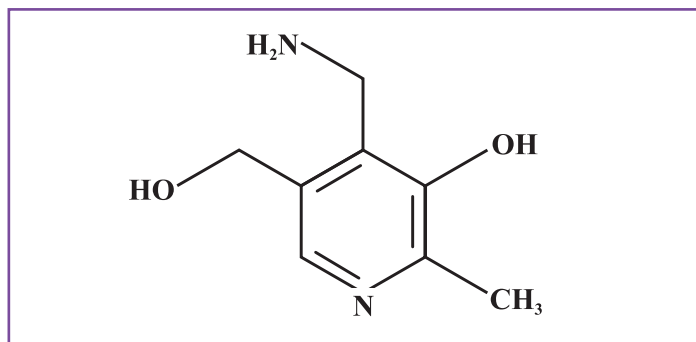


**Table 1: Evidence of Inadequate Vitamin B<sub>6</sub> Nutritional Status in Developed Countries**

	<u>Number of participants in study</u>	<u>% Deficient</u>
Young women embarking on contraceptive study	129	0.8-13.2
Elderly men undergoing prostate surgery	94	4.3-8.5
Preschool children	35	9
Breast-fed infants	84	10
Pregnant adolescents	122	17
Hospitalized elderly subjects	153	19
Hospital patients	650	25
Men, various ages	617	25
Free-living elderly subjects	198	27
Hospitalized elderly subjects	102	28
Pregnant women	458	42
Adolescent girls	127	68
Low-income pregnant women	127	68

Source: Bender DA. Non-nutritional uses of vitamin B<sub>6</sub>. Br J Nutr. 1999 Jan;81(1):7-20. Review.

urine), premenstrual syndrome,<sup>79</sup> imbalances due to oral contraceptives (oral contraceptives can impair vitamin B<sub>6</sub> status),<sup>80</sup> and impaired glucose tolerance in pregnancy.<sup>81</sup> It also has exhibited immuno-stimulating properties.<sup>82,83</sup> General signs of a vitamin B<sub>6</sub> deficiency include, microcytic and hypochromic anemia, depression, dermatitis and confusion.<sup>84</sup> There are several forms of vitamin B<sub>6</sub>: pyridoxine, pyridoxal and pyridoxamine. Vitamin B<sub>6</sub> deficiency is common and varies depending on demographics. (See Table 1)



Pyridoxamine

Pyridoxamine is a form of vitamin B<sub>6</sub>. It is both an AGE inhibitor and an AGE breaker. Pyridoxamine traps AGE/ALE and it cleaves the model AGE crosslink phenylpropanedione.<sup>85</sup> Pyridoxamine is thought to trap reactive carbonyl-precursors to AGE that are a result of oxidative and non-oxidative chemistry. Pyridoxamine performs this function more efficiently than other forms of vitamin B<sub>6</sub>.<sup>86</sup> Pyridoxamine is extremely reactive with 1,4-Dicarbonyl compounds, which exhibit toxicity through their

reactivity with lysyl residues. A reaction that leads to the formation of AGE.<sup>87</sup> Pyridoxamine binds to carbonyl compounds at a rate that is 2300 times faster than N-acetyllysine, which means that it is far better at binding carbonyl compounds than lysine. Lysine will be spared if pyridoxamine is present in sufficient amounts.

Pyridoxamine can also bind to methylglyoxal, another dicarbonyl compound involved in AGE formation. This reaction leads to the formation of a methylglyoxal-pyridoxamine dimer. It was shown that with proper supplementation, plasma pyridoxamine could reach levels sufficient to react with all the methylglyoxal present in plasma.<sup>88</sup> Additionally, it has recently been suggested that pyridoxamine might cleave AGE because it was shown that it could cleave phenylpropanedione, a model for permanently glycated proteins.<sup>89</sup> This is a significant finding; pyridoxamine can prevent AGE and ALE formation, but it also appears to have the capability to reverse some of the damage already incurred to bodily proteins.

Pyridoxamine can prevent the formation of glycation end products from free sugars but can also reverse the early stages of glycation.<sup>90</sup> Pyridoxamine is known as an Amadorin because it can interrupt protein glycation in its latest stage - once the protein and the sugar molecules have formed an Amadori adduct but not an AGE molecule. Supplementation with pyridoxamine is especially beneficial for diabetics. It is a promising treatment for the prevention and improvement of nephropathy as seen in type 1 and type 2 diabetic animals.<sup>91</sup> Pyridoxamine's capacity at preventing the formation of AGE avoids cellular damage

and prevents the chemical modifications of tissue proteins seen with aging. Pyridoxamine prevents lipid peroxidation and glycosylation of hemoglobin and increases the sodium-potassium ATPase activity in cells exposed to elevated glucose levels.<sup>92</sup> Proper functioning of the sodium-potassium pump is essential for the normal activity of nerve and muscle cells. An in vitro study showed that pyridoxamine is a powerful free radical scavenger and that it could inhibit the formation of superoxide radicals seen with 30 mM and 50 mM solutions of glucose by 97 and 96 percent respectively.<sup>93</sup> Vitamin B<sub>6</sub> also prevented increases in levels of hemoglobin A1c<sup>94</sup> and lipid peroxidation in red blood cells exposed to a high glucose environment. Pyridoxamine not only inhibited the formation of AGE/ALE, but it also demonstrated a strong lipid lowering effect in rats<sup>95</sup>, retarded the development of renal disease,<sup>96</sup> and delayed the onset of retinopathy.<sup>97</sup> It has been suggested that lipid derivatives in the form of CML and CEL are a significant source of protein modification. In obese rats, pyridoxamine reduced the presence of those compounds in skin collagen.<sup>98</sup> The prevention of glycation/lipoxidation by pyridoxamine is not related to glycemia because pyridoxamine has no effect on blood glucose levels<sup>99</sup>. It is clear that

pyridoxamine offers protection against the formation of AGE/ALE, which safeguards bodily proteins and prevents a wide range of pathologies seen with the normal aging process.

Pyridoxamine's absorption was carefully studied. The vitamin is absorbed through passive diffusion with 35% efficiency and has a plasma half-life of 2-3 hours. Vitamin B<sub>6</sub> has been demonstrated to be safe in dosages up to 200 mg per day.<sup>100</sup>

## Getting through the door

This is all very complicated, but really quite simple. All proteins have a specific function and that function relates to their structure. If the protein becomes glycated, the structure changes and the function is lost. Imagine the protein structure as being a door with the function of letting people through. The key to the lock would represent the sugar molecule. Pyridoxamine and Benfotiamine can prevent the key from entering the lock by intercepting dicarbonyl intermediates which are precursors to the formation of AGE.

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# Another Orthomolecular Breakthrough for Diabetics

Not producing enough or the cellular inability to utilise insulin, wreaks havoc on the body. The usefulness and effectiveness of natural and nutritional interventions for those whose blood sugar levels have gone astray should not be overlooked.

Ortho•Glucose™ contains isohumulones, hops, cinnamon, corosolic acid and chromium picolinate in doses supported by clinical research in type II diabetic patients. These nutrients and plant extracts have been shown to reduce blood sugar levels, potentiate the action of insulin and improve glucose utilization. But most importantly, Ortho•Glucose diminishes the risk of complications associated with diabetes.

**Ortho•Glucose is the ideal choice for those trying to regain normal carbohydrate metabolism and striving to achieve normal blood glucose levels.**



These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Where pyridoxamine stands apart is in its ability to remove the key once it has entered the lock - when protein glycation has occurred. Once the door is locked and the key is gone as in AGE formation, the only way through the door is to dismantle it. This is known in the body as protein or tissue turnover.



If you think that AGE/ALE formation is not a concern because your blood sugar levels are normal, you are mistaken. It is well known that circulating levels of Hb A<sub>1c</sub> - the product of the non-enzymatic glycation of hemoglobin with glucose - is normally roughly 4% of total hemoglobin. This level is 3-5 times higher in diabetics, but 4% is clearly a concern. If 4% of our weight is constituted of damaged tissue, it means that the average man carries 7lbs of dead weight, in this case comprised of harmful compounds that impede tissue function, stimulate inflammation, promote cellular dysfunction and lead to genetic mayhem. Furthermore, this example utilized glucose, a molecule that is far less reactive than other sugar molecules when it comes to protein glycation - that is why it was chosen through natural selection as the blood sugar molecule - any other sugar compound would probably have caused too much glycation for life to be maintainable. There are several molecules capable of non-enzymatic reactions with proteins. Sugars and lipids can interact with amino acid residues and new glycation reactions are constantly being discovered. It is likely that the total body burden of damaged proteins far exceeds 4%.

When it comes to aging, there are still many unknowns. One thing is clear, pyridoxamine prevents one of the key processes thought to be involved in aging and it also prevents a reaction that leads to the loss of function in our cells, tissues and organs. Glycation prevention was also shown to be a significant help in preventing the complications related to diabetes, a state of rapid AGE/ALE formation.

It has been said that life is the prevalence of the biological over the chemical. Glycation is the perfect example; it is a spontaneous, chemical and detrimental reaction occurring in our body without the control of enzymes. Our body's response to it is to trap reactive sugar molecules and prevent the permanent glycation of proteins. Pyridoxamine

and Benfotiamine feed those reactions and offer protection against tissue damage associated with AGE/ALE formation in the body. They are a useful ally in the treatment and prevention of a wide range of conditions including diabetes, atherosclerosis, renal failure, inflammation and neurodegeneration. Finally and perhaps above all, they lead the way as new anti-aging therapies.

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