Life Extension Magazine October 2008

REPORT

Unique form of Vitamin B6 Protects Against Complications Related To Diabetes and Aging

By Laurie Barclay, MD

Every second, a destructive process called **glycation** occurs throughout our bodies.

Glycation occurs when sugars react with the body's proteins, resulting in the formation of non-functioning ***glycation end products.*** While **glycation** is a normal consequence of aging, it is far from desirable.

Cataracts that blur vision in the eye lens are an example of ***glycation*** reactions. More ominous, **glycation** is associated with the development of **atherosclerosis** and **kidney** failure. **Glycation end products** have been isolated from **Alzheimer's** lesions in the brain.

Collagen accounts for about a third of our total body proteins. **Glycation** causes the collagen in our **skin** and tissues throughout our bodies to **cross-link,** leading to unsightly characteristics of aging.

When meat is cooked, rapid **glycation** (or "browning") reactions occur as proteins combine with the sugars present. This same glycation process also happens at a slower rate to our **living proteins!**

The alarming phenomenon of our aging body slowly being cooked to death has motivated scientists to develop ways to block pathological ***glycation*** reactions.

Life Extension members gained access to the first validated anti-glycation nutrient when high-dose carnosine became available. Additional protection against glycation was shown in response to **benfotiamine**, a fat-soluble form of vitamin B1.

For over a decade, however, governmental regulatory issues blocked access to one of the most important anti-glycation agents...a unique form of vitamin B6 called **pyridoxamine.**

You may wonder why supplementing with more than one anti-glycating agent is desirable. The answer is that there are many chemical processes involved in the formation of **advanced glycation end products** in the body. By blocking multiple chemical pathways involved in glycation reactions, one can optimally slow this devastating degradation of our living proteins.

Pyridoxamine has been extensively studied and its multiple anti-glycation properties make it important to include in a science-based daily supplement program.

In this article, *Dr. Laurie Barclay* describes the unique ability that **pyridoxamine** has shown in preventing the formation of damaging **glycation end products** while averting common diabetic complications such as neuropathy, retinopathy, and kidney failure.

Protein degradation is a major contributor to aging and disease. Proteins are the substances most responsible for the daily functioning of living organisms. Once too many proteins lose their functional ability, the body becomes prone to degenerative diseases and premature aging.

Destruction to proteins can be caused by oxidation (as by free radicals) and protein-sugar reactions (glycation). ***Glycation*** occurs when sugars react with proteins in the body to form damaged, non-functioning structures. Many age-related diseases such as arterial stiffening, cataract, and neurological impairment are at least partially attributable to glycation.

Unique Form of Vitamin B6

Vitamin B6 is involved in hundreds of beneficial enzymatic reactions in the body. It may even help protect against certain cancers.[1]

While the benefits of conventional vitamin B6 (pyridoxine) are well documented, scientists have discovered a unique form of vitamin B6 called ***pyridoxamine*** that specifically interferes with toxic glycation reactions. This unique form of vitamin B6 offers hope in combating the ravages of **protein degradation** involved in normal aging and the accelerated glycation reactions suffered by diabetics.

It is well known that diabetics suffer premature vascular disease along with a host of other disorders related to blood glucose

imbalances. One reason is that excess blood glucose creates more glycation reactions in the body. It is thus imperative for diabetics to take extraordinary steps to protect against the formation of glycated end products (known technically as ***advanced glycation end products or AGEs***).

Glycation end products are linked to a range of diabetes-related conditions, particularly kidney disease (nephropathy), visual loss (retinopathy), and nerve damage (neuropathy).[2] One prominent anti-aging doctor described pyridoxamine as "the most potent natural substance for inhibiting AGE formation."[3]

Paul Voziyan, PhD, a research associate professor of medicine and biochemistry at Vanderbilt University Medical Center tells Life Extension, "Pyridoxamine can inhibit glycation reactions and formation of AGEs, known culprits that cause damage in diabetes."

WHAT YOU NEED TO KNOW: PROTECTING AGAINST DIABETIC COMPLICATIONS WITH PYRIDOXAMINE

- Pyridoxamine is a specialized form of vitamin B6 easily converted in the body to pyridoxal 5-phosphate (PLP), the active form of the vitamin.
- Pyridoxamine may therefore offer hope in combating the ravages of aging in general and of diabetes in particular.
- Pyridoxamine may help prevent diabetic complications by blocking formation of advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs) underlying loss of structure and function accompanying aging.
- AGEs are implicated in diabetes-related conditions including kidney disease (nephropathy), visual loss (retinopathy), and neuropathy.
- Animal models have shown benefits of pyridoxamine in these conditions, and evidence from clinical trials is promising.
- Pyridoxamine has been described as "the most potent natural substance for inhibiting AGE formation."
- Pyridoxamine may enhance the effects of other compounds thought to preserve kidney function, including CoQ10 and silymarin.

The Biochemistry of Glycation

Glycation occurs in a series of several slow biochemical reactions, some, but not all, of which are reversible. The first step entails reactions of sugar molecules with amino acids or lipids to form "early" glycation products known as Amadori products.[4] Unlike most body processes, this initial step does not involve enzymatic reactions and can be readily reversed.

Preventing this crucial first step in glycation therefore seems like a reasonable target in controlling or preventing the pathological processes that can result in advanced glycation end product (AGE) formation. Once the Amadori product is oxidized, this step is not reversible. At this point, glycation end products are as difficult to reverse as it would be to turn rusted metal back to its shiny, new condition, once the iron has oxidized.

AGEs do their dirty work by binding to receptors on the cell surface known as receptors for advanced glycation end products (RAGEs). When AGEs bind to RAGEs, more free radicals are produced, and other damaging processes associated with chronic inflammation are unleashed.[5]

Although we think of inflammation as being important primarily in conditions such as infection and arthritis, it is also a key process underlying aging and chronic diseases including diabetes and atherosclerosis.

Pyridoxamine Fights Glycation

Over a decade ago, a group of researchers confirmed that pyridoxamine can inhibit glycation reactions and AGE formation, awakening interest in further, more extensive investigation of the mechanism of action of this form of vitamin B6.[27]

"We now know that pyridoxamine can inhibit three processes critical in development of diabetic complications," Prof. Voziyan says." Firstly, pyridoxamine can sequester glucose and reactive products of glucose and lipid degradation, thus inhibiting formation of advanced glycation and advanced lipoxidation end products."

"Secondly, pyridoxamine can scavenge catalytic metal ions, thus inhibiting toxic oxidative reactions; and thirdly, pyridoxamine can react with free oxygen radicals, thus preventing them from damaging biologically important macromolecules such as proteins and DNA," Prof. Voziyan explains. "Since these mechanistic studies were performed either in [the laboratory] or in animal models, we do not yet know which of these mechanisms are responsible for the therapeutic effects of pyridoxamine in humans. It is likely that all three are important."[4,6-8]

Sushil K. Jain, PhD, professor of pediatrics, physiology, biochemistry and molecular biology and chief of pediatric research at Louisiana State University Health Sciences Center in Shreveport, tells Life Extension that "pyridoxamine can scavenge toxic free

radicals being produced in excess by high glucose and ketone levels in diabetic patients, and pyridoxamine can increase the utilization of glucose."

In essence, pyridoxamine utilizes a two-pronged approach: it causes glucose to be metabolized more quickly, effectively reducing high glucose levels, while it consumes toxic free radicals produced by high levels of glucose and ketones (chemicals produced when fat is burned for energy) accompanying diabetes.

WANT SOME AGING WITH THAT CRÈME BRÛLÉE?

Although it is a culinary delight to see and smell white sugar sprinkled atop creamy custard turn to golden brown by the heat of a blue flame, be forewarned that there is a high price to pay for eating it.

This "browning" reaction is also evident when we heat a slice of bread in the toaster or when we barbecue meat over hot coals. Known as the Maillard reaction, the browning that occurs when foods are heated or cooked in high heat reflects chemical structures being changed in a process referred to as glycation, which creates **advanced glycation end products** (AGEs). Specifically, the heat causes a sugar molecule to attach to a protein or lipid, giving rise to AGEs and *advanced lipoxidation end products* that are fundamentally involved in aging.[6,9,10]

It is no coincidence that the organ failure accompanying diabetes, particularly poorly controlled diabetes, resembles that seen in aging, except that it occurs sooner and proceeds at a faster pace. Glycation is a common enemy in both conditions, giving rise to AGEs implicated in blindness, kidney failure, nerve damage, cardiovascular disease, and stroke, largely through their effect on small (microvascular) and large (macrovascular) blood vessels.[6]

Controlling glycation is therefore vital to help protect against aging and particularly against diabetes, which can be considered to be a form of accelerated aging.

Broad-Spectrum Protection

In addition to its role in preventing formation of advanced glycation (AGE) and advanced lipoxidation end products (ALE),[9,10] pyridoxamine performs many vital functions of theoretical and practical benefit in both conditions.

"It is claimed that the benefits of pyridoxamine are due to prevention of protein damage by glycation," Professor Paul J. Thornalley, from the Protein Damage and Systems Biology Research Group, Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, University Hospital, Coventry, UK, tells Life Extension.

"Pyridoxamine is, however, a form of vitamin B6 and the supplementation is expected to primarily increase the vitamin B6 pool in the body," Prof. Thornalley says. "Some studies have found that diabetes is associated with a deficiency of vitamin B6 in the body. Pyridoxamine is expected to correct this, and the benefits accrued from pyridoxamine therapy may also be due to this."

Work done by Prof. Jain and colleagues has shown that pyridoxamine also promotes activity of enzymes, known as sodium-potassium ATPase and calcium ATPase, which are needed for nerve cells to transmit impulses to one another. This effect of pyridoxamine helps explain why it could be particularly useful in diabetic neuropathy. By inhibiting oxygen free radical production, pyridoxamine prevents reduction of sodium-potassium ATPase activity caused by high blood sugar.[8]

"Activities of sodium-potassium ATPase and calcium ATPases are vital for the normal function of neurons," Prof. Jain says. "The activity of these enzymes is low or diminished in diabetic patients. Supplementation with pyridoxamine prevents decrease in activity of these ATPases in cells."

Prof. Voziyan also points out that "along with other forms of vitamin B6, pyridoxamine participates in many important natural metabolic reactions as an enzyme cofactor."

To be biologically active, pyridoxamine is first converted by the body to pyridoxal 5-phosphate (PLP).[11] Pyridoxine, which is the form of B6 primarily used in currently available supplements, is biochemically of no value to the human body until it is first converted to PLP.

Although the vitamin B6 activity of all three naturally occurring forms (pyridoxamine, pyridoxine, and pyridoxal) is comparable because the body contains enzymes that convert one form to another, the ability of pyridoxamine to inhibit glycation and AGE formation is superior to that of the other two forms (pyridoxine and pyridoxal).

"Regarding pyridoxamine and preventing secondary complications of diabetes, …the compound is able to scavenge the deleterious aldehydes which are thought to mediate these changes," Dr. Hipkiss says.

Aldehydes are harmful chemicals, given off as byproducts of certain metabolic reactions in the body, which increase free radicals that wreak havoc in many tissues, culminating in disease and injury. Research by Prof. Voziyan and colleagues showed that pyridoxamine reacts rapidly with damaging aldehydes, thereby preventing chemical modification of tissue proteins and

AGE/ALE formation.[6]

Even apart from its effect on AGE formation, pyridoxamine may hold promise in diabetes by reversing another of the most fundamental culprits underlying the disorder and its complications: beta-cell dysfunction.[12] Beta cells are the specialized cells within the pancreas that secrete insulin, which is deficient in patients with diabetes.

In an experimental model of diabetes, hamsters treated with pyridoxamine for four weeks had fasting blood sugar and glucose tolerance test results similar to those of control animals without diabetes. Even more amazingly, insulin secretion improved and beta cells began to regenerate and grow in pyridoxamine-treated diabetic animals.[12]

Life Extension Magazine October 2008

REPORT

Unique form of Vitamin B6 Protects Against Complications Related To Diabetes and Aging

By Laurie Barclay, MD

Pyridoxamine Protects Against Kidney Damage

“There is experimental evidence that pyridoxamine supplementation can be helpful in preventing and delaying diabetic complications,” Prof. Jain says.

In studies of diabetic or obese rats, pyridoxamine protected against kidney damage, as well as against development of retinopathy and neuropathy in diabetic rats. Compounds found in the urine of these rats confirmed that pyridoxamine was acting as an AGE/ALE inhibitor.[9]

Rats made diabetic by administration of a drug known as streptozotocin tend to develop kidney disease, similar to nephropathy seen in diabetic patients. Interestingly, pyridoxamine limited AGE formation and development of nephropathy in streptozotocin-diabetic rats without affecting control of blood sugar.[13]

Lipids appear to be an important source of AGEs in the diabetic rat, based on findings that pyridoxamine lowers lipids. Blood levels of cholesterol and triglycerides increase in proportion to AGEs in skin collagen.[13] In Zucker rats, pyridoxamine lowered levels of cholesterol and triglycerides, inhibited AGE formation, and protected against kidney and blood vessel damage.[13]

Zucker rats given pyridoxamine in their drinking water, but not the untreated controls, had lowering of high blood pressure and less thickening of blood vessel walls associated with atherosclerosis. Even more amazing was that markers of kidney damage decreased in the pyridoxamine-treated rats. Blood creatinine levels decreased, as did leakage of total protein and of a specialized protein known as albumin into the urine, nearly returning to levels seen in nonobese rats.[13]

Similarly, in streptozotocin-diabetic rats, pyridoxamine significantly blocked the increase in albumin found in the urine, and of blood levels of creatinine and lipids.[14]

Pyridoxamine was as effective as aminoguanidine in correcting these abnormalities reflecting diabetic complications.[14] However, pyridoxamine, but not aminoguanidine, improves insulin secretion, glycemic control, and beta-cell regeneration in diabetic animals.[12]

“Therapeutic effects of pyridoxamine in complications of diabetes were investigated in animal models and in clinical trials,” Prof. Voziyan says. “The most substantial data are available on pyridoxamine’s effects in diabetic nephropathy. In several different animal models, pyridoxamine inhibited increase in albuminuria and serum creatinine; pyridoxamine also ameliorated characteristic pathologic lesions such as increase in glomerular volume and expansion of mesangial matrix.”

In other words, pyridoxamine corrected not only functional markers of diabetic kidney damage, such as albumin in the urine and creatinine in the blood, but also anatomical markers. The glomerulus acts as a filter to control which beneficial compounds are retained in the blood and which waste products are excreted into the urine passing through each nephron, or urine collection unit within the kidney.

Blood volume within the glomerulus, which is an intricate web of capillaries (small blood vessels) surrounding each nephron, is increased in diabetic nephropathy.[15] Pyridoxamine appears to reduce this increase in glomerular volume.

Another pathological change in diabetic nephropathy is that material within the glomerulus known as mesangial matrix progressively expands, ultimately blocking glomerular capillaries and hence reducing filtration of blood through the nephrons. One key factor leading to expansion of the mesangial matrix is abnormal glycation of matrix proteins, which interferes with their degradation and turnover.[16]

Not surprisingly, therefore, by preventing AGE formation, pyridoxamine is uniquely poised to prevent expansion of the mesangial

matrix, an important marker of diabetic nephropathy.[7]

In streptozotocin-induced diabetic rats, PLP (an active form of pyridoxamine) significantly reduced evidence of nephropathy, namely albumin in the urine, glomerular hypertrophy, mesangial expansion, and accumulation of AGEs. Pyridoxamine itself had similar effects, although PLP was more effective.[17]

Shedding further light on the mechanisms of action of pyridoxamine in protecting kidney function are studies in a rare genetic disorder that results in overproduction of oxalate, leading to kidney stone formation and end-stage renal disease early in life. In an experimental model of this disorder, pyridoxamine cut urinary oxalate excretion by half, compared with untreated animals, and significantly reduced kidney stone formation.[18]

Another kidney disease in which pyridoxamine may be therapeutic is chronic allograft nephropathy, which occurs when the immune system attacks a transplanted kidney. In an animal model of this condition, pyridoxamine improved kidney function and reduced structural damage by inhibiting AGE formation.[19]

Pyridoxamine Protects Against Nerve and Eye Damage

“In diabetic animal models, pyridoxamine demonstrated relevant therapeutic effects in the retinal vasculature and in the peripheral nerves,” Prof. Voziyan says.

In a study from Queen’s University of Belfast in Northern Ireland, diabetic rats given pyridoxamine for 29 weeks had dramatically reduced development of retinal damage, whereas those given other antioxidants, namely vitamin E and lipoic acid, did not. Pyridoxamine protected against a wide variety of pathological changes in the diabetic retina, including blockage of small blood vessels, altered gene and protein expression, and accumulation of immunologically active AGE/ALEs.[20]

A laboratory study from Case Western Reserve University in Ohio showed that pyridoxamine prevented AGE formation in the lens, further supporting its benefits in protecting against the visual loss accompanying aging and diabetes. The same study showed that pyridoxamine reduced oxidative stress and AGE formation in red blood cells and plasma proteins from diabetic rats.[22]

“Pyridoxamine supplementation has shown benefit in prevention of diabetic nephropathy and retinopathy in experimental diabetes using high-dose supplementation,” Prof. Thornalley says.

Human Studies With Pyridoxamine

Pyridoxamine has shown promise for treatment of diabetic nephropathy, not only in animal models of diabetes, but also in phase 2 clinical trials with diabetic patients.[23]

“Pyridoxamine efficacy was also investigated in patients with type 1 and type 2 diabetes and overt nephropathy,” Prof. Voziyan says. “In these clinical trials, pyridoxamine significantly reduced the rise in serum creatinine.”

Phase 2 clinical studies of pyridoxamine in patients with kidney disease from type 1 or 2 diabetes were conducted at several specialty centers and were led by a group from the prestigious Joslin Diabetes Center at Harvard Medical School.[23] One trial used a dose of 50 mg pyridoxamine given twice daily, whereas the second trial used doses of 250 mg twice daily.

When results from both trials were combined, pyridoxamine significantly decreased AGE formation, as expected. Even more promising was a reduction in the change from baseline in blood levels of creatinine, suggesting a protective effect on kidney function compared with placebo. However, there were no differences compared with placebo in excretion of albumin into the urine.[23]

Because of its role in combating AGE formation as well as oxidative stress, pyridoxamine is a novel approach being studied clinically for its possible contribution in treatment of diabetic nephropathy and other forms of chronic kidney disease.[24]

Pyridoxamine May Complement Other Kidney-Protecting Compounds

One of the advantages of using pyridoxamine to support kidney function is that its multiple mechanisms of action are likely to allow it to safely enhance the effects of other therapies—including pharmaceuticals and nutritional supplements—that may protect the kidney from injury related to diabetes or other chronic conditions. Two renal-protective agents identified by Life Extension are CoQ10[21] and silymarin.[25]

Pyridoxamine may be used in concert with prescription therapies used in the management of conditions associated with diabetes. “Both animal studies and clinical trials have shown that pyridoxamine therapy is effective even when used together with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are standard anti-hypertensive treatments in diabetes,” Prof. Voziyan says. “This shows that pyridoxamine therapy provides additional benefits compared to existing standard treatments.”

To minimize the formation of advanced glycation end products in your body, avoid foods cooked higher than 250 degrees, especially high-fat, grilled meats and caramelized sugars. Optimally control blood glucose levels. Supplementation with

pyridoxamine, antioxidants and other anti-glycating compounds such as carnosine and benfotiamine would be expected to further assist in protecting against glycation-induced protein damage.

COQ10 MAY REDUCE NEED FOR DIALYSIS

Chronic kidney failure has been linked to free radical damage and antioxidant deficiency. Coenzyme Q10 (CoQ10) is a potent antioxidant and could therefore be helpful in chronic kidney disease.

A randomized, double-blind, placebo-controlled trial compared the effect of CoQ10 (180 mg per day) vs. placebo for 12 weeks in patients with kidney failure, some of whom already required dialysis. Compared with placebo, CoQ10 reduced serum creatinine and blood urea nitrogen, which are elevated in kidney disease. Compared with placebo, CoQ10 increased creatinine clearance and urine output, showing improved kidney function.[21]

In patients on chronic dialysis, CoQ10 decreased the need for dialysis. At the end of the study, twice as many patients who received placebo instead of CoQ10 required dialysis. About 80% of the patients given CoQ10 had a positive response to treatment. The researchers suggest that higher doses might result in even greater improvement in those patients, and/or benefit in patients who did not respond to 180 mg CoQ10 per day.[21]

The researchers concluded that CoQ10 supplementation improves kidney function in patients with kidney failure regardless of dialysis status, and that it may delay or prevent the need for dialysis. Patients receiving CoQ10 had marked increases in the antioxidant vitamins E and C and beta-carotene, as well as considerable decreases in markers of oxidative stress such as thiobarbituric acid reactive substances and malondialdehyde.[21]

Clinical Implications

A large portion of people over age 65 suffer less than optimal kidney function. Metabolic syndrome, pre-diabetes, and type 2 diabetes afflict an unprecedentedly high percentage of the aging population.

Diabetes can dramatically accelerate the biology of human aging. The horrific degenerative diseases caused by diabetes include stroke, heart attack, lower- limb amputations, blindness, kidney damage, and painful neuropathy. Better methods to protect against diabetic complications are urgently needed.[26]

Advanced glycation end products underlie many of the complications of diabetes as well as the aging process itself. Glycation—a non-enzymatic reaction between sugars and amino acids—alters the structure and function of essential proteins, setting the stage for a host of degenerative diseases.

Fortunately, a unique form of vitamin B6 can help prevent the formation of ***advanced glycation end products*** (AGEs) and has been shown in laboratory and clinical studies to help avert complications of diabetes such as neuropathy, retinopathy, and kidney damage. Known as **pyridoxamine**, this novel form of vitamin B6 offers critical protective benefits not only for individuals with diabetes, but for everyone seeking to prevent many of the deleterious effects of aging.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370

SILYMARIN MAY IMPROVE FAILING KIDNEY FUNCTION

Silymarin is an herbal preparation extracted from *Silybum marianum* (milk thistle) and *Cynara cardunculus* (artichoke thistle) seeds and fruits. In a rat model of acute renal failure caused by insufficient blood flow to the kidney, silymarin had a protective effect.[25]

Animals with this type of kidney damage, known as ischemia/reperfusion injury, had significant increases in serum urea, creatinine, and cystatin C levels, as well as in tissue malondialdehyde, and protein carbonyls. Animals that received silymarin before ischemia/reperfusion injury had a much lower rise in these markers of kidney damage and oxidative stress.[25]

The researchers concluded that silymarin protects the kidneys against ischemia/reperfusion injury, which may "provide a basis for the development of novel therapeutic strategies for protection against the damages caused by ischemia/reperfusion."[25]

References

1. Theodoratou E, Farrington SM, Tenesa A, et al. Dietary vitamin B6 intake and the risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2008 Jan;17(1):171-82.

2. Nawale RB, Mourya VK, Bhise SB. Non-enzymatic glycation of proteins: a cause for complications in diabetes. Indian J Biochem Biophys. 2006 Dec;43(6):337-44.

3. Perricone N. Ageless Face, Ageless Mind. New York, New York: Ballantine Books; 2007.

4. Chetyrkin SV, Mathis ME, Ham AJ, et al. Propagation of protein glycation damage involves modification of tryptophan residues via reactive oxygen species: inhibition by pyridoxamine. Free Radic Biol Med. 2008 Apr 1;44(7):1276-85.

5. Ahmed N, Thornalley PJ. Advanced glycation endproducts: what is their relevance to diabetic complications? Diabetes Obes Metab. 2007 May;9(3):233-45.

6. Voziyan PA, Metz TO, Baynes JW, Hudson BG. A post-Amadori inhibitor pyridoxamine also inhibits chemical modification of proteins by scavenging carbonyl intermediates of carbohydrate and lipid degradation. J Biol Chem. 2002 Feb 1;277(5):3397-403.

7. Chetyrkin SV, Zhang W, Hudson BG, Serianni AS, Voziyan PA. Pyridoxamine protects proteins from functional damage by 3-deoxyglucosone: mechanism of action of pyridoxamine. Biochemistry. 2008 Jan 22;47(3):997-1006.

8. Jain SK, Lim G. Pyridoxine and pyridoxamine inhibits superoxide radicals and prevents lipid peroxidation, protein glycosylation, and (Na+ + K+)-ATPase activity reduction in high glucose-treated human erythrocytes. Free Radic Biol Med. 2001 Feb 1;30(3):232-7.

9. Metz TO, Alderson NL, Thorpe SR, Baynes JW. Pyridoxamine, an inhibitor of advanced glycation and lipoxidation reactions: a novel therapy for treatment of diabetic complications. Arch Biochem Biophys. 2003 Nov 1;419(1):41-9.

10. Onorato JM, Jenkins AJ, Thorpe SR, Baynes JW. Pyridoxamine, an inhibitor of advanced glycation reactions, also inhibits advanced lipoxidation reactions. Mechanism of action of pyridoxamine. J Biol Chem. 2000 Jul 14;275(28):21177-84.

11. Higuchi O, Nakagawa K, Tsuzuki T, et al. Aminophospholipid glycation and its inhibitor screening system: a new role of pyridoxal 5'-phosphate as the inhibitor. J Lipid Res. 2006 May;47(5):964-74.

12. Takatori A, Ishii Y, Itagaki S, Kyuwa S, Yoshikawa Y. Amelioration of the beta-cell dysfunction in diabetic APA hamsters by antioxidants and AGE inhibitor treatments. Diabetes Metab Res Rev. 2004 May;20(3):211-8.

13. Alderson NL, Chachich ME, Youssef NN, et al. The AGE inhibitor pyridoxamine inhibits lipemia and development of renal and vascular disease in Zucker obese rats. Kidney Int. 2003 Jun;63(6):2123-33.

14. Degenhardt TP, Alderson NL, Arrington DD et al. Pyridoxamine inhibits early renal disease and dyslipidemia in the streptozotocin-diabetic rat. Kidney Int. 2002 Mar;61(3):939-50.

15. Bilous RW, Mauer SM, Sutherland DE, Steffes MW. Mean glomerular volume and rate of development of diabetic nephropathy. Diabetes. 1989 Sep;38(9):1142-7.

16. Abrass CK. Diabetic nephropathy. Mechanisms of mesangial matrix expansion. West J Med. 1995 Apr;162(4):318-21.

17. Nakamura S, Li H, Adijiang A, Pischetsrieder M, Niwa T. Pyridoxal phosphate prevents progression of diabetic nephropathy. Nephrol Dial Transplant. 2007 Aug;22(8):2165-74.

18. Chetyrkin SV, Kim D, Belmont JM, et al. Pyridoxamine lowers kidney crystals in experimental hyperoxaluria: a potential therapy for primary hyperoxaluria. Kidney Int. 2005 Jan;67(1):53-60.

19. Waanders F, van den BE, Nagai R, et al. Renoprotective effects of the AGE-inhibitor pyridoxamine in experimental chronic allograft nephropathy in rats. Nephrol Dial Transplant. 2008 Feb;23(2):518-24.

20. Stitt A, Gardiner TA, Alderson NL, et al. The AGE inhibitor pyridoxamine inhibits development of retinopathy in experimental diabetes. Diabetes. 2002 Sep;51(9):2826-32.

21. Singh RB, Kumar A, Niaz MA, et al. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in patients with end-stage renal failure. J Nutr Environ Med. 2003 Mar;13(1):13-22.

22. Nagaraj RH, Sarkar P, Mally A, et al. Effect of pyridoxamine on chemical modification of proteins by carbonyls in diabetic rats: characterization of a major product from the reaction of pyridoxamine and methylglyoxal. Arch Biochem Biophys. 2002 Jun 1;402(1):110-9.

23. Williams ME, Bolton WK, Khalifah RG, et al. Effects of pyridoxamine in combined phase 2 studies of patients with type 1 and type 2 diabetes and overt nephropathy. Am J Nephrol. 2007;27(6):605-14.

24. Swaminathan S, Shah SV. Novel approaches targeted toward oxidative stress for the treatment of chronic kidney disease. Curr Opin Nephrol Hypertens. 2008 Mar;17(2):143-8.

25. Turgut F, Bayrak O, Catal F, et al. Antioxidant and protective effects of silymarin on ischemia and reperfusion injury in the kidney tissues of rats. Int Urol Nephrol. 2008 Mar 27.

26. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/#allages. Accessed August 4, 2008.

27. Booth AA, Khalifah RG, Hudson BG. Thiamine pyrophosphate and pyridoxamine inhibit the formation of antigenic advanced glycation end-products: comparison with aminoguanidine. Biochem Biophys Res Commun. 1996 Mar 7;220(1):113-9.