**REPORT**

**Innovative Strategies to Combat Kidney Disease**

By Julius Goepp, MD

You may be surprised to learn that until 2002, no standard definition for chronic kidney disease (CKD) existed within the medical community. Before then, conflicting classifications had created a state of confusion as to how many Americans were afflicted with this progressive, life-threatening condition.

Once proper categorization of the various phases of CKD was established, the stark and daunting scale of this modern epidemic emerged.

We now know that as many as 26 million Americans currently suffer from some form of chronic kidney disease. Aging individuals are especially vulnerable.

Yet public awareness of the threat remains low. When you consider that the risk of cardiovascular mortality in CKD sufferers is 30 times that of the general population, the steady increase in kidney disease rates seen today amounts to a public health disaster hidden in plain sight.

*Life Extension* has long emphasized the need for vigilance through regular testing (at least once a year) to monitor kidney health. In addition to the standard tests for creatinine, albumin, and BUN/creatinine ratio, certain individuals should insist their doctor test for cystatin-C, a largely overlooked blood marker which provides a far more precise measure of renal function. Optimal levels are less than .91 mg/L.

Individuals should also keep a record of their test results. Once any sign of disease is detected (such as an increase in creatinine), it is imperative that immediate steps be taken to halt its progress, as kidney function can decline precipitously and may be irreversible. Fortunately, many *Life Extension* members are already taking a variety of nutrients that support kidney health.

In this article, you will discover the most recent scientific advances in our understanding of how CKD unfolds, the specific risk factors that contribute to its progress, and how you can bring them under control.

You will also learn of safe, low-cost, natural interventions that have been shown to stop CKD in its tracks, long before end-stage renal disease (ESRD) renders dialysis or kidney transplant the only option.

**PYRIDOXAMINE OR PYRIDOXAL-5-PHOSPHATE: POTENT KIDNEY DEFENSE**

Since the formation of advanced glycation end-products (AGEs) is such a well-established factor in the onset and progression of kidney disease, nutrients that have been conclusively shown to mitigate the effects of these lethal agents constitute a front line, low-cost intervention.

A formidable AGE antagonist is the vitamin B6 compound pyridoxamine. A plethora of research confirms its power to halt formation of AGEs. Evidence has also emerged that pyridoxamine drastically limits formation of equally deadly advanced lipoxidation end products (ALEs)—another deadly catalyst for kidney disease.

A team of biochemists at the University of South Carolina were able to show that pyridoxamine traps the reactive molecules formed during lipid (fat) peroxidation and helps to “chaperone” them harmlessly into the urine.
Their colleagues subsequently found that neutralizing AGEs and ALEs can prevent kidney disease and lipid profile abnormalities in diabetic rats. They found that rats supplemented with pyridoxamine had lower levels of albumin (protein) in their urine, lower plasma levels of the waste product creatinine, and less dramatically elevated blood lipids than the placebo treated animals, all directly related to the reduction of AGE/ALEs.

They subsequently examined whether similar results could be obtained in obese animals that had not yet developed diabetes. Three groups of animals were studied:

1. lean (healthy) rats
2. obese rats without treatment
3. obese rats treated with pyridoxamine.

As expected, AGE and ALE formation underwent a two- to threefold increase in obese untreated rats compared to lean animals. Conversely, those increases were entirely absent in obese animals treated with pyridoxamine. Treated animals also experienced a smaller increase in plasma triglycerides, cholesterol, and creatinine levels, compared with the obese untreated rats.

In an equally compelling development, hypertension in animals treated with pyridoxamine also resolved, as did thickening of blood vessel walls. Untreated animals displayed urinary evidence of renal disease (albuminuria) that in contrast had been nearly normalized in supplemented animals. This provides powerful evidence of pyridoxamine’s multi-targeted protective effect against CKD.

In 2004, the same research team made a landmark discovery: while studying the relative effects of pyridoxamine along with a variety of additional natural antioxidants on the progression of kidney disease in diabetic rats, they decided to examine how these natural compounds stacked up against enalapril, a standard pharmaceutical intervention used to prevent CKD. Enalapril is an ACE inhibitor, one of a class of drugs commonly used to control blood pressure and kidney disease.

They found that pyridoxamine therapy was the most effective at preventing progression of kidney disease, followed by vitamin E and lipoic acid. Enalapril, the prescription drug, proved to be the least effective intervention. Pyridoxamine also limited lipid profile abnormalities and formation of AGEs and ALEs, offering a far broader spectrum of preventive effects than enalapril.

Researchers at the University of Miami advanced these findings by treating diabetic mice with both pyridoxamine and enalapril. Again they found that pyridoxamine alone provided substantial benefit, cutting albuminuria and damage to the glomeruli. Combining enalapril with pyridoxamine reduced kidney disease mortality in these animals as well, leading the researchers to suggest that the ACE-inhibitor (enalapril)/pyridoxamine combination might be useful.

A convincing body of research on pyridoxamine therapy in humans with CKD has also emerged in recent years. In 2007, a team of researchers at Harvard set out to determine optimal interventions to halt the progression of kidney disease in diabetics. They conducted two 24-week multicenter placebo-controlled trials in patients with known diabetic nephropathy—treatment of which is known to delay the onset of end-stage renal disease in diabetics. Doses of pyridoxamine ranged from 50 to 250 mg twice daily.

Pyridoxamine significantly inhibited the rise in blood levels of the waste product creatinine, one of the key biomarkers of kidney dysfunction and a predictor of kidney failure. Urinary levels of inflammatory cytokines were also significantly lower in the treated group compared to controls.

Pyridoxamine has been firmly established as a front line, safe, low-cost intervention in CKD caused or exacerbated by AGEs and ALEs. Further, this natural vitamin B6 compound has been shown to significantly improve outcomes of experimental kidney transplants and other forms of kidney disease.

It therefore borders on the criminal that in January of 2009, the FDA classified this potent, entirely safe CKD therapeutic as a drug, putting it out of reach for many Americans suffering from this deadly condition. No one should be forced to bear the outrageous burden of costly pharmaceuticals and their toxic side effects when a perfectly safe alternative exists.

Fortunately, there is another equally safe option available—another form of vitamin B6 known as pyridoxal-5-phosphate (P5P) that also exerts potent anti-AGE effects. It has been shown to prevent the progression of diabetic kidney disease in pre-clinical models. In fact, as far back as 1988, P5P was used by a German research group to reduce blood lipids in humans with chronic kidney disease.
Because of the tremendous blood flow and high concentration of metabolic toxins continuously circulating through the kidneys, they are the site of extraordinary oxidative stress, which is known to contribute to progressive kidney damage and its complications, such as high LDL and increased cardiovascular disease risk.\(^22\)

Coenzyme Q10 (CoQ10) \(\textit{fortifies}\) the body’s natural antioxidant capacity and reduces levels of oxygen free radicals, indicating its important defense against CKD. As it happens, CoQ10 has been used experimentally to control hypertension and kidney disease in laboratory animals \textit{since the early 1970s}.\(^23,24\)

Human studies have shown that CoQ10 levels substantially decline, while markers of oxidation such as malondialdehyde are dramatically \textit{elevated}, in kidney disease patients with even mild renal dysfunction.\(^41\) These decreased CoQ10 levels also make circulating \textit{lipoproteins} (such as LDL) more vulnerable to oxidative damage, which in turn increases risk for further cardiovascular damage, adding to the renal burden and substantially increasing the risk of kidney disease.\(^25\)

A team of European researchers published compelling evidence in 2001 of how effective such a nutritional intervention can be, studying a group of patients with established kidney disease.\(^26\) Subjects received antioxidant therapy with vitamin C, E, and riboflavin (vitamin B2) for one month before the addition of 2 months of CoQ10 therapy. Prior to supplementation, CoQ10 values in blood were just one-quarter of normal levels; they increased to nearly \textit{four times} the reference level following supplementation. The study was too brief to demonstrate any change in kidney function, but evidence from animal trials that same year showed that when CoQ10 levels were increased in tissues of diabetic rats, a reversal of markers of oxidative stress in kidney, heart, and liver resulted.\(^27\)

By 2004, definitive demonstration of CoQ10 in human kidney disease patients was demonstrated by researchers working with transplant recipients.\(^28\) Such individuals undergo tremendous oxidative stress and typically have marked disturbances in lipid profiles as a result. The European group provided their patients with CoQ10 supplements of \textit{30 mg} three times per day for four weeks, and monitored levels of oxidation factors (such as \textit{malondialdehyde}), levels of natural antioxidant enzymes in the body, and lipid profiles.\(^28\)

Significant improvements were seen after just four weeks, with reduction in LDL, increase in beneficial HDL, and a decrease in presence of inflammatory cells. These results suggest a potentially dramatic improvement in both quality of life and survival rates for patients whose disease has progressed to the point of kidney failure requiring transplantation or dialysis. They also bode well for those with early-stage kidney disease.

Animal studies have also shown that CoQ10 can protect kidney tissue from numerous \textit{nephrotoxic drugs}, including \textit{gentamicin}, a powerful antibiotic with a notorious propensity for causing kidney damage.\(^33,34\) These findings are significant both because they offer protection in patients who might be exposed to such drugs, and because of what they teach us about CoQ10’s potent ability to combat the extreme oxidative stress that the kidney faces as it deals with a variety of foreign chemicals.
damage and dysfunction. As the body’s primary filtration system, it must “process” roughly 200 quarts of blood per day, rendering about 2 quarts of waste products and water. The fundamental structural unit of the kidney is the nephron. These high-pressure filtering mechanisms govern the removal of waste products and toxins, control blood pressure and volume, and regulate levels of electrolytes and metabolites in the blood. A healthy kidney contains approximately 800,000 to 1 million nephrons.

Housed within each nephron is a front-line filtration element called the glomerulus, a miniscule capillary coil. (The two together resemble an incandescent light bulb containing a convoluted filament.) The endothelial cells of the glomerular capillaries act as the direct physical exchange between the kidney and the bloodstream. Waste products and water are combined to form urine, while blood cells and protein remain in the circulatory system.

The kidney’s tight control of water and mineral flow, and its role in maintaining healthy blood pressure and mineral balance, rely on the optimal functioning of nephrons and glomeruli. For this reason, one of the primary markers of kidney function is the glomerular filtration rate (GFR), a measure of the volume of fluid the kidney is able to process at any given time.

The glomerular filtration rate; plasma concentrations of the waste substances creatinine, urea, and nitrogen (blood urea nitrogen or BUN); and levels of protein in the blood and urine are the most commonly used measures to determine the presence of CKD. Rapidly rising creatinine usually signals imminent kidney failure. There should be no protein in the urine if your kidneys are functioning optimally.

It should be noted that BUN and creatinine may not increase above the normal range until 60% of total kidney function is lost. This is why certain aging individuals should ask their doctors to test for cystatin-C in the blood. Cystatin-C is a protein produced by virtually all cells and tissues in the body. Because it is formed freely and at a near-constant rate—as opposed to albumin, which may fluctuate with dietary protein intake—plasma cystatin-C serves as a more accurate biomarker of renal function.

CKD may be categorized in one of 5 stages. Stage 1, the mildest, is defined only by the persistent presence of protein in urine (GFR may be normal); in each successively higher stage, GFR declines, until Stage 5 is reached, defining end-stage renal disease (ESRD), or kidney failure. ESRD is irreversible and results in death without dialysis or kidney transplant.
**REPORT**

Innovative Strategies to Combat Kidney Disease

By Julius Goepp, MD

**SILYMARIN**

Silymarin is extracted from milk thistle (*Silybum marianum*), a plant rich in the flavonolignans silychristin, silydianin, silybin A, silybin B, isosilybin A and isosilybin B, which are collectively known as the *silymarin complex*.

This safe, natural compound has a long history as a traditional therapy for liver and kidney conditions. It has been used in Western medical practice for more than a quarter of a century as the treatment of choice for the serious kidney injury resulting from severe mushroom poisoning, owing to its potent antioxidant and nephron-protective effects. In fact, we’ve known since 1979 that kidney injury by mushroom poisoning in animals pre-treated with silymarin can be almost entirely prevented. These effects make it a natural choice for protection against drug-induced kidney damage, since so many drugs can act like poisons, exerting extreme oxidant stress on kidney tissue.

Mushroom poisons (mycotoxins) are among the most deadly natural toxins known. Their kidney toxicity is surpassed only by some of the most aggressive chemotherapy agents. Physicians have therefore looked to silymarin as a potential “renoprotective” agent for patients undergoing chemotherapy.

Silymarin is also protective against several classes of nephrotoxic drugs, in particular *cisplatin* and *Adriamycin®,* two of the most potent chemotherapeutic drugs—but also two of the most damaging to the kidney owing to oxidative damage and severe inflammation. Researchers around the world have found that silymarin and its components reduce and often entirely prevent the kidney damage caused by these drugs.

Silymarin's ability to protect against the oxidative stress produced by potent drugs suggests that it may be useful in protecting against more subtle, chronic injury by free radicals, particularly those generated by chronic blood glucose elevations. German researchers, for instance, have found that silymarin could entirely prevent injury to renal cells incubated with elevated glucose concentrations while blocking production of oxidative stress markers.

Silymarin's protective power also extends to ischemia/reperfusion injury (restoration of blood supply following restriction of blood flow). Turkish researchers demonstrated that they could completely prevent visible and functional damage to kidney structures exposed to this kind of injury by pre-treating animals with silymarin. Studies such as these have huge implications for the general population, because they suggest that by maintaining optimal antioxidant function through supplementation, we may be able to prevent much (if not most) of the chronic oxidative damage to which our kidneys are exposed daily.

**RESVERATROL**

The considerable advance in our understanding of the cyclical relationships between oxidative stress, endothelial dysfunction, inflammation, atherosclerosis, and chronic kidney disease points to resveratrol as an intervention in the chain of events that ultimately lead to renal failure.

Italian researchers are among the leaders in resveratrol research, and early in this century one group published remarkable research demonstrating the impact of resveratrol on preserving kidney structure and function in rats exposed to ischemia/reperfusion injury.

Japanese and Indian urologists followed that up in 2005 and 2006 with reports detailing the mechanisms by which resveratrol combats oxidative damage following reperfusion, markedly reducing kidney dysfunction. Overwhelming bacterial infections (sepsis) are a common cause of kidney failure in the intensive care unit and following surgery or trauma. Turkish physiologists demonstrated that resveratrol can reduce or prevent both kidney and lung injury in septic rats.
Resveratrol’s unmatched antioxidant and anti-inflammatory potential has been tapped in studies of its ability to prevent drug-induced kidney damage as well. Nephrotoxicity in rats exposed to the antibiotic gentamicin was significantly reduced and more rapid healing of injured kidney tissue was attained using resveratrol, with dramatic reduction in markers of oxidant injury. A team of toxicologists in Brazil demonstrated its kidney protective power against cisplatin, the powerful chemotherapy agent responsible for so much drug-induced kidney damage. Finally, Indian pharmacologists were successful in protecting animal kidneys from damage caused by another common chemotherapy and immune suppressant drug cyclosporine A by pre-treating the animals with resveratrol.

Since diabetes is the leading cause of kidney disease—and because the damage it inflicts is largely mediated by free radical production resulting from destructive alteration of proteins by glucose (glycation)—researchers have explored resveratrol as a preventive in diabetic kidney damage. Promising work has come from Indian pharmacologists, who’ve shown that they could significantly attenuate kidney damage in rats with experimentally induced diabetes—even 4 weeks after the diabetes was induced!

In the researchers’ own words, “The present study reinforces the important role of oxidative stress in diabetic kidney disease and points towards the possible antioxidative mechanism being responsible for the renoprotective action of resveratrol.”

Like resveratrol, lipoic acid is a powerful antioxidant with few known side effects. Lipoic acid has been successfully employed in the laboratory to block the oxidative damage caused by ischemia/reperfusion injury, thereby opening the door to another effective treatment for this common cause of acute kidney failure. For example, in 2008 researchers showed that they could reverse all adverse effects on renal function and lab abnormalities produced following experimental ischemia/reperfusion injury in animals. Lipoic acid has been comprehensively studied worldwide for its power to prevent or mitigate drug-induced kidney damage. We know that lipoic acid is an effective kidney-protective agent against damage inflicted by Adriamycin®, the immunosuppressive drug cyclosporine A, and even against acute toxic doses of the pain reliever acetaminophen. In studies of protection against cyclosporine toxicity, lipoic acid also helped to normalize blood lipid abnormalities.

Nephrologists at Georgetown University are examining lipoic acid in the context of diabetic kidney disease. Their results show it can improve renal function in diabetes by lowering sugar levels. They have also recently demonstrated that lipoic acid lowers protein loss in urine and improves kidney structure and function in diabetic laboratory animals by reducing oxidative stress.

In yet another compelling study, Korean researchers recently showed that they could improve kidney patients’ responses to the vasodilator (blood vessel relaxer) nitric oxide (NO) by supplementing them with lipoic acid. Loss of endothelial responsiveness to NO is a cause of vascular disease in diabetics, and a chemical called asymmetric dimethylarginine (ADMA) is a sensitive marker and predictor of cardiovascular outcome in patients with end-stage renal disease. Fifty patients on hemodialysis were treated with lipoic acid 600 mg per day for 12 weeks. Levels of the marker ADMA remained unchanged in the control group, but fell significantly in the lipoic acid group, suggesting that lipoic acid may reduce the risk of cardiovascular complications in this group of patients.

**RISKS TO KIDNEY HEALTH**

Given the toxic, high-pressure conditions involved in renal function and the delicacy of the kidney’s structural components, it comes as no surprise that an array of near-constant internal and external insults may take a severe toll on the glomeruli and other parts of the kidney. Their incremental damage and destruction leads to the progressive decline in renal function seen in aging humans.

These internal and external insults include:

- **Hypertension.** Over time, chronic high blood pressure inflicts damage to the endothelial cells lining the kidney’s blood vessels, including those within the glomeruli. The result is a familiar cascade of events that leads to the thickening of blood vessel walls and reduction in blood flow seen in atherosclerosis. Reduced blood flow is in turn directly translated into lower GFR. Pressure damage to the glomeruli also diminishes their filtration capacity, permitting large protein
molecules such as albumin to pass into urine instead of remaining in circulation. (This is why urine albumin levels are used to detect kidney disease.)

- **Elevated serum glucose.** Diabetes is now the leading cause of CKD.61 Experts predict even greater increases in CKD if rates of diabetes incidence continue to rise steeply.62 It should be noted, however, that high blood sugar poses a threat to kidney health even in non-diabetic individuals. Chronic exposure to glucose degrades and destroys kidney cells through the formation of advanced glycation end products (AGEs)—molecules generated through the pathologic binding of glucose to proteins in the body. AGEs cause primary structural proteins in the cells to cross-link and become non-functional, increasing oxidative stress, inflammation, and directly damaging kidney tissue.63-66 It has been established that even early-stage insulin resistance is associated with CKD.67

- **Excess fatty tissue.** Body fat contributes to the development of CKD through production of inflammatory cytokines specific to adipose (fatty) tissue called adipokines. Along with AGEs and oxidative stress, adipokines exacerbate the inflammation commonly found in people with CKD.67 For this reason, metabolic syndrome—co-occurring insulin resistance, hypertension, and abdominal obesity—represents a perfect storm for the development of CKD. A 2007 study found that metabolic syndrome occurs in 30.5% of individuals with stage 4 or stage 5 chronic kidney disease.68 Metabolic syndrome increases the risk of chronic kidney disease, even before diabetes manifests.69

- **Protein over-consumption.** Ingesting an excessive amount of protein, particularly meat, may tax the kidneys to the point of distress. The extraordinary increase in individuals adhering misguidedly to high-protein diets in order to lose weight has had the unintended consequence of boosting rates of kidney damage and disease. Meat consumption also results in high AGE production and the consequent inflammatory injury to kidney tissue.69 A prudent approach to dietary protein is thus encouraged by most experts, particularly in people who already have some degree of CKD.

- **Drugs.** The nephrotoxic side effects of many commonly used medications comprise another significant causative factor in CKD. Chief among the mechanisms by which drugs cause kidney damage are oxidative stress and adverse alterations in cellular energy management. So-called “analgesic nephropathy” involves destruction of the active regions of the kidney by overuse of pain relievers, usually used in combinations of two or more, including the common over-the-counter medication acetylsalicylic acid (Tyleno®,®) as well as non-steroidal anti-inflammatory medications (NSAIDs) including high-dose aspirin, and ibuprofen (Advil®, Motrin®).70-73 Chemotherapy agents have also been shown to significantly impair renal function.74,75 Please note that acetylsalicylic acid inflicts kidney damage via a different mechanism than pain relieving drugs like ibuprofen.

## OVERCOMING CKD-INDUCED FATIGUE

**L-carnitine,** an amino acid-derived nutrient crucial to cellular energy management, can play a vital role in kidney disease prevention and management.68,87 Carnitine deficiency is itself a known causative factor in the development of kidney disease. Conversely, patients with kidney disease frequently develop carnitine deficiency, especially those on dialysis. Carnitine therapy is known to lead to improvements in many kidney-disease-associated complications including cardiovascular disease, anemia, decreased exercise tolerance, weakness, and fatigue.67

As noted earlier, CKD sufferers are at very high risk for developing cardiovascular complications, including heart attacks and heart failure. This is thought to be in part related to massive oxidative stress induced by kidney disease, and partly to inadequate energy management in cardiac tissues induced by carnitine deficiency.88 The frequent result of these interrelated factors is a massive deterioration in energy, exercise tolerance, quality of life—and perhaps even longevity.89

As early as 1998 scientists in Kentucky discovered that supplementation with L-carnitine could improve patient-reported general health, vitality, and physical function in people on dialysis.90 In 2001, research by clinicians at Los Angeles Medical Center showed that L-carnitine, given intravenously to dialysis patients, could reduce fatigue and preserve exercise capacity.91 A literature review by nephrologists at Vanderbilt University in 2003 indicated that L-carnitine supplementation should be used to improve red blood cell count in dialysis patients whose anemia doesn’t respond to therapy with the hormone erythropoietin.92 Finally, more data from Italy demonstrate that L-carnitine supplements can help suppress levels of the inflammatory marker C-reactive protein, potentially reducing cardiovascular risk in dialysis patients.93
Innovative Strategies to Combat Kidney Disease

By Julius Goepp, MD

ADDITIONAL NUTRIENTS THAT MAY BENEFIT CKD

**Folic acid** is well known for its capacity to reduce levels of the metabolite *homocysteine*, which is strongly associated with cardiovascular disease and dramatically elevated in individuals with kidney disease or kidney failure.94-97

**Omega-3 fatty acids** have been shown to help correct cardiovascular risk factors98-100 and to improve kidney function in patients with established kidney disease.101,102 Research published in 2009 suggests that diets rich in omega-3s may actually prevent kidney disease.103,104

Through powerful antioxidant effects, **vitamin E** may help prevent CKD onset, and **vitamins E and C** may mitigate development of cardiovascular and other complications in patients with chronic kidney disease.105-110

SUMMARY

Chronic kidney disease (CKD) is rapidly approaching epidemic proportions, with up to 26 million Americans suffering from some form of kidney disease. Kidneys must filter 200 quarts of blood every day. The high-pressure and toxin-rich environment to surrounding renal function renders these delicate, highly complex organs especially vulnerable to damage, dysfunction, and disease.

**High blood pressure, elevated blood sugar, NSAIDs** (such as ibuprofen), **certain medications**, and **high-protein diets** are the most common threats to kidney health. The potentially lethal insults they inflict include oxidative stress, production of advanced glycation and lipoxidation end products (AGEs and ALEs), inflammation, and an excessive filtration burden that taxes renal function over time.

Nutrients such as **pyridoxal-5-phosphate (P5P)** fight AGEs and ALEs. **CoQ10, silymarin, resveratrol, and lipoic acid** are also clinically supported, potent interventions. Omega-3 fatty acids help quell inflammation, contributing to enhanced kidney health. A host of additional nutrients complement these actions, including folic acid (folate) and vitamins C and E.

*If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.*

References


56. Chander V, Tirkey N, Chopra K. Resveratrol, a polyphenolic phytoalexin protects against cyclosporine-induced nephrotoxicity through nitric oxide dependent mechanism. Toxicology. 2005 May;210(1):55-64.


