Chronic Renal Disease: Orthomolecular Ramifications

Richard P. Huemer, M.D.[1]

Introduction

Increasingly, human kidneys are under assault from environmental toxins as well as an array of diseases that place them at risk of ultimately failing. Eleven percent of American adults now show evidence of chronic kidney disease, with over 400,000 afflicted with end-stage kidney disease. Over a third of those cases are caused by diabetes, and the remainder by high blood pressure and other conditions, including genetic ones.[1]

Diabetes is epidemic, spurred in part by changing eating patterns and obesity. It currently kills more people than AIDS. The epidemic will worsen. The World Health Organization and the International Diabetes Foundation have predicted that by the year 2030, more than twice as many people worldwide will suffer from this devastating disease as now do.[2]

Physiology and Pathophysiology

Each kidney contains about one million nephrons, the functional units that filter about 200 quarts of blood daily. Urine is produced in the glomerulus, a part of the nephron consisting of a tuft of capillaries surrounded by a filter membrane. From there, the waste-laden filtrate flows through tubules where some substances are added and others reabsorbed to maintain the salt and water balance of the body. The entire system comprises one of the five channels of elimination.

The parts of the delicate kidney machinery are differentially susceptible to damage by various disease and toxins. The tubules may regenerate, but the glomeruli are believed not to. The glomerular filtration rate (GFR) serves as the main criterion of the stage of kidney disease, though not the sole one. GFR is commonly derived from a formula in which age, sex, race, and plasma creatinine are relevant variables.[3] GFR above 90 mL/min/1.73m^2 is normal. GFR below 15 denotes end-stage kidney disease.

Diabetes causes kidney disease by damaging blood vessels and impairing the microcirculation. Atherosclerosis does likewise; moreover, many diabetics have atherosclerosis. Sometimes, in a vicious cycle of causation, homocysteine in the blood causes atherosclerosis, causing kidney failure, which permits homocysteine to build up even higher, causing more atherosclerosis. This is not an uncommon scenario among diabetics.

Other causes of kidney damage are high blood pressure, toxic chemicals (including heavy metals and NSAID drugs), allergic drug reactions, autoimmunity (as in lupus and Goodpasture syndrome), polycystic kidney disease (a genetic condition), infections, kidney stone blockages, and physical trauma.

When kidneys fail, rising toxin levels may become apparent in other channels of elimination, i.e., the scent of urea on the breath, and the appearance of uremic "frost". The latter forms when urea and other nitrogenous wastes in the sweat crystallize on the skin.[4] Vital substances that the kidneys normally keep under control can build to lethal concentrations (e.g., potassium) or become unhealthily low (erythropoietin, vitamin D).

Great strides have been made in the care of kidney disease, but less so in its prevention, during the past half century. Tissue-typing has made kidney transplantation relatively commonplace, and the once-scarce dialysis machines are

1. 2755 West Avenue N, Palmdale, CA 93551 USA
e-mail:" rhuemer@yahoo.com

available to all who need them, thanks to Public Law 92-601.[5] Better drugs (such as furosemide) have been developed for stimulating the kidneys to produce urine, and there are new drugs for kidney-failure-related problems (like genetically-engineered erythropoietin for the anemia of chronic renal disease), and also for conditions (like diabetes and hypertension) that predispose to kidney disease.

Nutrition in Renal Disease

Kidney disease is one of the few specialized areas in which modern medicine has acknowledged a key role for nutrition. In fact, some dieticians have supplemental training in this area. Because protein metabolism yields nitrogenous wastes (urea and uric acid), control of dietary protein looms large in the management of failing kidneys. Too much protein increases the toxic burden that the kidneys must clear. The type of protein is also important. Proteins with a high biological value (that is, those with an amino acid balance resembling that of whey, casein or egg) are preferred, because they are thought to be utilized more efficiently. Confounding the whole protein issue is loss through the urine as albumin molecules slip through tiny defects in the damaged glomerular membranes.

Moreover, failing kidneys have trouble maintaining blood pH and the balance of mineral salts in the body. Restriction of dietary potassium, phosphorus, and sodium is usually necessary to manage kidney disease. This is difficult for vegetarians, and a challenge even to omnivores, because many of the excluded foods are rich sources of phytochemicals and antioxidant vitamins.[6] In some cases an ion-exchange resin, sodium polystyrene sulfonate, is used to draw potassium into the bowels and thence out of the body via that channel of elimination.

Medical science also acknowledges the value of supplemental iron, calcium, and the hormonal form of vitamin D (1,25-dihydroxy cholecalciferol) in kidney disease. Calcium absorption depends on vitamin D, but the active (hormonal) form of vitamin D issues from healthy kidneys and is suppressed in kidney failure. Iron is used to treat the anemia associated with kidney disease. By and large, however, modern medicine brings its nutritional resources to bear on the later stages of kidney disease, and mostly focuses on macronutrients in the diet. Nutritional supplementation to preserve kidney health in chronic disease has not been the focus of clinical medicine, although clinical research has paid more attention to it.

Oxidative Stress and Renal Disease

Currently among researchers, there is keen interest in the contribution of oxidation, inflammation, and altered biomolecules to kidney disease. Damaging oxidative reactions are known to occur during dialysis, a fact that has led to the development and successful use of vitamin E-bonded dialysis membranes to diminish oxidation products and their consequences.[7] However, oxidation is even part of early kidney disease,[8] and it is intimately involved as a mechanism in experimental models of kidney disease in the laboratory.[9,10]

Part of the oxidation burden originates in inadequacy of the body's own antioxidant enzymes. At the same time increased superoxide production occurs (related to increased NADPH enzyme activity, and to high blood sugar in diabetics), there is diminished activity of the superoxide dismutase (SOD) enzyme.[6, 11] Other key antioxidant enzymes with reduced function in kidney disease are catalase and glutathione peroxidase.[12] This causes oxidative stress,[13] which in turn leads to inflammation (from NF-kappaB activation), shortened survival of red blood cells, cardiovascular disease, high blood pressure (due to undesirable oxidation of beneficial

nitric oxide), neurological disorders, and fibrosis. Oxidative stress is itself worsened by hypertension, diabetes, infections, and autoimmune disease–all of which are often associated with chronic kidney disease—as well as by dialysis and over-treatment with iron,[6] a pro-oxidant mineral. Vitamin E is able to protect the activity of the kidney's antioxidant enzymes.[9]

Oxidative stress and carbonyl stress (from excessive levels of carbonyl compounds, especially among diabetics) cause damaged biomolecules. More specifically, the types of damaged molecules are referred to as advanced glycation endproducts (AGEs), advanced lipoxidation endproducts (ALEs), and advanced oxidation protein products (AOPP).[14] The AOPP are said to be "exquisite markers" of oxidative stress, and are involved in monocyte activation.[15] The AGEs and AOPP cause release of cytokines (cellular control molecules), leading to alterations in the lipoproteins (such as LDL), inflammation, and increased risk of cardiovascular disease.[13,16] The best way to mitigate AGEs is to keep the blood sugar under control.[17]

Atherosclerosis and Homocysteine

Cardiovascular disease is intimately related with kidney failure. In this modern era of dialysis, more kidney patients die from their diseased blood vessels and heart than from anything else, even uremic poisoning.[13] The main cause is atherosclerosis. Major risk factors that independently predict atherosclerotic events, as studied in non-diabetic patients, are C-reactive protein (CRP, a marker for inflammation), fibrinogen (a blood-clotting protein), and the AOPP which arise from oxidative stress.[18] Another major risk factor, both for those with diabetes and those without, is homocysteine.

Homocysteine, an endogenously produced amino acid that is often referred to as a "non-traditional risk factor" for cardiovascular disease, has received a large share of blame for cardiovascular disease among kidney patients.[14] Low-normal concentrations (less than 7 micromoles/liter in blood), seem to be harmless but higher ones are not. Homocysteine can rise too high from a genetic defect (MTHFR gene polymorphisms), vitamin deficiency, inappropriate diet, protein loss, and inadequate food intake, all of which impair methylation reactions in the body–and of course also from inability of failing kidneys to excrete it.[19]

How much pathology truly arises from homocysteine? It can be argued that an underlying process of inflammation is responsible for dysfunction of the inner vascular linings and for oxidative stress, and not homocysteine per se.[20] However, homocysteine is capable of causing such vascular dysfunction by means of decreased nitric oxide and increased oxidation products.[21,22]

Control of homocysteine demands efficient methylation. Vitamins B_6, B_{12}, and folate are crucial to this process. Milligram doses of folate may be required. Vitamin B_{12} is thought to be most efficiently absorbed by injection, but large daily oral (buccal or sublingual) doses are more convenient and recent evidence indicates that they are absorbed better than previously supposed. Trimethyl glycine (betaine) also supports methylation, and may be taken in doses of 500 to 2,500 mg daily, or more, to suppress homocysteine.[23]

Endogenous Antioxidants

In addition to producing several antioxidant enzymes, our bodies manufacture other antioxidant substances, including glutathione, alpha lipoic acid (ALA), and coenzyme Q10 (CoQ10). The amino acid N-acetylcysteine (NAC), a precursor to glutathione, is known to prevent oxidative injury to the kidneys, and it has recently been shown to inhibit a destructive oxidative response that AOPP induces in white blood cells.[15]

NAC is the acetylated form of cysteine, a sulfur-containing amino acid produced

endogenously from methionine. Its metabolic derivative taurine has been studied as a blood pressure-lowering agent, in rats and humans. In humans, six grams a day for as few as 7 days resulted in measurably decreased blood pressure.[24] Possible explanations and related benefits include abatement of sympathetic nervous system activity, control of calcium ion flux, membrane stabilization, detoxification (bile channel), and antioxidant activity.[25]

With respect to CoQ10, rather remarkable results have been achieved by researchers in India in a randomized, double-blind trial in patients with end-stage kidney disease.[26] The 48 patients in the treatment group received 60 mg of CoQ10 three times a day for 12 weeks. Compared to the placebo group, which showed no improvement, the CoQ10 group had increased urine output and GFR, and reduced creatinine and blood urea nitrogen. The improvement in GFR, as measured by the creatinine clearance test, is quite remarkable because it implies that the glomeruli, thought to be irreplaceable, had undergone healing during the therapy.

Other effects of the CoQ10 therapy were decreased markers of oxidative damage: thiobarbituric acid reactive substances (TBARS), diene conjugates, and malondialdehide (MDA). Moreover, antioxidant vitamins C and E, and beta carotene, showed significant increases, perhaps because fewer of their molecules were expended in quenching free radicals. This carefully-done study is not listed in MedLine.

CoQ10 is involved in the generation of energy within the mitochondria. Another key substance in this process is carnitine, an amino acid that transfers fatty acids into the mitochondria for fuel. Vitamin C is needed for its manufacture. Carnitine becomes depleted in people with uremia, and supplementing it results in decreased cardiac complications and muscle symptoms, and improvements in exercise tolerance and anemia.[27] The most effective form is acetyl-L-carnitine.

Carnitine improves mitochondrial function, but because it promotes oxidation, researchers at the Linus Pauling Institute[28] have added alpha lipoic acid (ALA) to obtain its energy-enhancing benefits without free-radical side effects. Over and above that effect, ALA protects rats against kidney damage artificially induced by temporary interruption of blood supply to the kidney (reperfusion injury).[29] Moreover, in rats made experimentally diabetic, it protects against kidney damage through improved blood sugar control, as well as by its antioxidant action.[30]

Ascorbate and Bioflavanoids

Vitamin C deserves special mention. There is some concern that too much ascorbate will induce excessive oxalate in the urine of people who are prone to oxalate kidney stones; however additional vitamin B_6 can counteract this potential problem.[31] Vitamin C favors absorption and utilization of iron, which is important for controlling the anemia of chronic kidney disease, in conjunction with the hormone erythropoietin.[32]

The smallest blood vessels are subject to damage in hypertension and diabetes, which how these diseases destroy kidneys. Indeed, diabetes has been described as being, at its core, a disease of the micro-vasculature. This is most obviously true in the eye, where the pathologic changes are visible, but is quite apparent also in the kidneys. Natural substances can protect tiny vessels to a degree that drugs cannot.

Many years ago, Dr. Albert Szent-Györgyi, the Nobel laureate who discovered the chemical nature of vitamin C, became aware that an additional healing factor was present in crude vitamin C extracts, and that it protected the tiniest blood vessels. He dubbed it vitamin P. Today we know vitamin P as a class of polyphenolic compounds called bioflavonoids, and we know they possess antioxidant and anti-inflammatory activities.

One of the most ubiquitous of the bioflavonoids, and one of the most potent, is quercetin. It is found in green tea, red wine, garlic, onions, cabbage, citrus fruits, apples, and a great many other foods.

Quercetin has protected rats' kidneys in various experimental situations. In one situation, a kidney is damaged by temporarily shutting off its blood supply; one consequence is harmful influx of calcium into cells.[33] Pre-treatment with quercetin reduced the damage, reduced TBARs, and restored depleted antioxidant enzymes.[34] In the another type of experiment, a muscle-destroying dose of glycerol produced less oxidative stress, less dysfunction, and less tissue damage when quercetin was administered.[35] A different bioflavonoid, naringin, also proved effective in the two experimental situations.[36,37]

Moreover, in rats artificially made diabetic, the usual markers of oxidative stress and kidney dysfunction were significantly attenuated in animals that received quercetin orally during the development of their diabetic kidney disease.[38]

Although flavonoids are effective anti-inflammatory, antioxidant, and vascular protective substances, they do not seem to have caught clinical researchers' interest. An exception is a three-year study at the University of California, San Francisco, in which diabetic patients were treated with a polyphenol-enriched, low-iron-available, carbohydrate-restricted diet; compared with those on the standard low-protein diet, the patients on the special diet had less elevation of creatinine, and significantly fewer adverse outcomes (deaths or kidney transplants).[39]

Other natural substances possess anti-inflammatory activity, and so may help stabilize failing kidneys. Among them are curcumin (from the spice turmeric), Boswellia herb (source of a natural 5-lipoxygenase inhibitor), and fish oils, especially DHA and EPA.

Benefits of Nitric Oxide

The discovery that nitric oxide dilates blood vessels is relatively recent, and a boon to Pfizer, whose drug sildenafil permits nitric oxide to persist longer in the body. One might suppose that sildenafil could lower blood pressure by dilating arteries—and indeed it does, but not to a clinically useful degree.[40] (However it is useful in a special situation, pulmonary hypertension.)[41] It has been speculated that moderate wine consumption might benefit kidney patients through the actions of polyphenols, such as quercetin and resveratrol, that stimulate nitric oxide production and inhibit the endothelin-1 pathway.[42] The safest, most natural way to increase nitric oxide is by ingesting the amino acid L-arginine, which yields nitric oxide through the action of the nitric oxide synthase enzyme. Arginine has potential value in kidney disease,[43] both as a precursor to nitric oxide and as a way to overwhelm harmful arginine analogs like ADMA (asymmetric dimethyl arginine), which are part of the toxic burden of uremia.[44]

Nitric oxide has the power to inhibit AGEs.[45] Other substances with the potential to prevent damaged biomolecules include carnosine and aminoguanidine, which inhibit crosslinking.[46] Both have been studied in experimental animals and/or human trials.[47-49] Although they look promising, it would seem desirable to break the crosslinks instead of merely inhibiting their formation. Drugs based on thiazolium salts can actually do this. The one furthest in clinical development is alagebrium chloride, which entered phase 2 clinical trials early in 2005.[50]

Conclusion

Kidney disease is quite prevalent and likely to become more so, given the rising incidence of diabetes and hypertension, conditions which underlie most of it. Regardless of whatever environmental factors initiate kidney disease, the root

causes of kidney failure lie in the inflammatory and oxidative responses that perpetuate and extend the injury to the organ's delicate structures. The natural pharmacopoeia offers a panoply of antioxidant, anti-inflammatory, and vascular-protective agents to help preserve kidney function and mitigate kidney damage.

Although an orthomolecular therapeutic regimen must necessarily be individualized, the available literature indicates special relevance to kidney disease of the following nutritional substances: CoQ10, vitamin E, vitamin C, quercetin, betaine, NAC, ALC, ALA, curcumin, L-arginine, and green tea.

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