

Renal Disease and Chinese Medicine

Written by: Travis Spire-Sweet, L.Ac.
The United States, along with other developed nations, is succumbing to a drastic increase in renal failure. The rate in increase of people reaching end-stage renal disease, (ESRD) glomerular filtration rate less than 20, is not proportionate to quality of care or treatment of the actual disease. To re-emphasize, there is no treatment for the actual disease, only management of symptoms with dialysis, transplant, or angiotensin converting enzyme (ACEi) therapy. ACEi, being the main form of preventative medicine, does not stop the progression of renal disease. "Current treatments are, in general, poorly effective and new therapeutic strategies or adjunct therapies that enhance the efficacy of current pharmaceutical agents are needed"¹. This exponential growth will continue as long as there is a rise in diabetes and hypertension, the leading contributors to ESRD.

The white flag has been raised in surrender to the numbers with no hope of reinforcements. However, Traditional Chinese Medicine has not only a chance of helping but can slow down the progression of renal disease, improve erythropoietin resistant anemia^{10,11,12,13}, improve sleep, fatigue, and depression in dialysis patients^{5,14,15}, and complements current ACEi and diabetes therapy¹⁶. Acupuncture and herbs can be effective because renal disease progresses slowly and even a small improvement over time provides years of benefit.^{17,18}

Chronic renal disease, no matter the cause, has the same histological changes and same disease progression¹⁹. From the infancy of renal disease there is an increase of transcription growth factor

beta (TGF-Beta) which leads to a cascade of inflammatory signals that further progresses to fibrosis and glomerular sclerosis, thus decreasing the number of nephrons, decreasing kidney function, and leading to ESRD. Angiotensin, which is part of the renin angiotensin system (RAS), is a polypeptide that circulates in the blood and causes vasoconstriction. An increase in angiotensin is often associated with CRF because the damaged kidney does not receive enough blood due to fibrosis and sclerosis of kidney tissue or artery. In response the kidney excretes renin that activates angiotensin and leads to vasoconstriction and increased systemic blood pressure. This increased blood pressure creates a negative feedback loop that increases mean arterial pressure (MAP) in the capillary beds of the kidney. This increased pressure on the capillary beds expands the vessels and destroys more of the kidney.

Not only does angiotensin increase blood pressure, but it also activates TGF-beta. The ability of ACEi to lower blood pressure and reduce one of the agonist of TGF-beta is one of the reasons why ACEi therapy is one of the first forms of treatment of kidney disease⁴.

Sympathetic nerve activity (SNA) in the kidney is 2.5x higher in a diseased state than a normal and the SNA leads to the progression of ESRD^{9,20}. As the kidney tissue becomes damaged proteinuria appears. These proteins filter through the glomerular capsule and then are reabsorbed later, increasing the rate of kidney decline. If diabetes is a

factor, glomerular filtration rate increases causing hyper-filtration, hypertrophy, and increased capillary hydrostatic pressure leading to hypertension. This is the start of diabetic nephropathy and from here the disease process is the same as all others, just the starting off point is different.²¹

How can acupuncture positively affect the disease mechanism of renal failure?

Hiromi Yamamoto of Japan showed that acupuncture on two points, one located below knee and the other medial posterior to ankle(KD-3 and ST-36), decreased sympathetic nerve activity in the kidney²². Dr. Brenner and Rector, leading nephrologist in the United States wrote "evidence from experimental studies indicated that sympathetic overactivity resulting from kidney disease may be accelerated in renal injury" and contributes to the progression of renal disease⁸. Josne Paterno showed that the same two acupuncture points on the ankle and shin lowers serum creatinine, proteinuria, glomerular sclerosis and tubulointerstitial fibrosis indices.²³ A secondary effect of one of the points studied above that may contribute to the shown effectiveness of acupuncture on CRF is the point below the shin. Stomach 36 when stimulated with acupuncture needles lowers blood pressure by modulating endothelial nitric oxide (eNOS) and neuronal nitric oxide (nNOS).²⁴

The second hand of Chinese medicine is herbal therapy.

The first thing any doctor is going to tell a patient with renal disease is DO NOT TAKE any Chinese supplements or herbs, they lead to kidney failure and possibly cancer. There is logical concern for this, many over the counter Chinese patent medicines in the 80's and 90's contained unlabeled medication, heavy metals, and unspecified herbs.^{25,26,27} Aristolochia species, like fang ji and mu tong, along with aristolochic acid containing herbs like xi xin, are to be avoided in renal disease. Aristolochic acid can build up in even a healthy kidney and causes acute kidney failure. This type of kidney failure is known as aristolochic acid nephropathy and before that its common name was Chinese herb nephropathy, hence the idea that all Chinese herbs cause kidney failure.¹ Then there is ephedra (Ma Huang) which increases blood pressure and can cause kidney stones.^{25,26,27} The amount of ephedra being taken as a dietary supplement for weight loss was close to 40-50 times more than a normal Chinese medicinal dose. Another specific herb that comes up is licorice (Gan Cao) which can cause pseudoaldosteronism, increases blood pressure, and can lead to hypokalemia.^{25,26,27} The metabolism of herbs in renal failure is completely different than a healthy individual, the duration the herbs are in the system is longer especially if the herb is secreted in the urine. Just be aware that the metabolic imbalance in the body changes what is absorbed in the intestines, and the first pass effect into the liver is modified. In general, depending on the GFR, dose in smaller doses. Another concern that comes up is with

CYP450 enzyme system in the liver and how herbs either interact or effect the metabolism of other medications.⁹ Simple rule of thumb is formulas with Bupleurum (Chai hu) especially Xiao Chai Hu Tang, appear to be the strongest at being metabolized by the CYP450 system.²⁶

Knowing the worries of Chinese medicine and herbal therapy here are a few positives:

Safflower, (Hong Hua) inhibits the SMAD2,3 inflammatory cascade by activating smad7, the inhibitor of SMAD2,3, in the kidney. (SMAD2,3 are downstream activators for fibrosis and glomerular sclerosis which are activated by TGF-beta, so even if TGF-beta is high it can't effect the kidney because the downstream signals are blocked)²⁸

Angelica and Astragalus (Dang Gui Bu Xue Tang), is cooked and dosed in a 5:1 ratio. Any other ratio have shown to be significantly less biochemically active than the 5:1 decoction. These two herbs must also be cooked together, when added separately after cooking the strength of the formula is diminished. Dang Gui Bu Xue Tang lowers proteinuria, which has shown to be a leading contributor to the progression of renal failure. The formula also improves microvascular insufficiency in a damaged kidney by increasing vascular endothelial growth factor (VEGF) which decreases the rate of capillary loss in kidney failure. The astragalus part of the formula when combined with ACEi, increases the ability the medication has in lowering TGF-beta. ACEi often has the side effects of chronic

dry cough and astragalus limits the amount of ACEi needed therefore decreasing the severity and even the occurrence of dry cough.^{10,13,16,25,29,30,31,32,33,34}

Notoginseng (San Qi) has been shown to have the ability to prevent epithelial to myofibroblast transition (EMT) in damaged kidney tissue. This is basically the conversion of function epithelial into a fibroblast extra cellular matrix (ECM) depositing cell. So even though the kidney may be damaged, San Qi prevents the epithelial cells from becoming non-functional. This function is achieved by inhibiting alpha smooth muscle actin (alpha-SMA) positive myofibroblast. It is these alpha-SMA fibroblast that respond to increased TGF-beta and deposit extra cellular matrix (ECM).³⁵ These fibroblast go through apoptosis in the presence of San Qi.³⁶ Reactive oxidative species (ROS) play another role in tubulointerstitial damage by activating TGF-beta. San Qi inhibits nicotinamide adenine dinucleotide phosphate (NADPH) which is a major source of the ROS produced in the kidney.³⁷

Cordyceps Sinensis (Dong Chong Xia Cao) a parasitic fungus can be given orally as a tea with protective benefits against chronic renal failure.³⁸ The pharmacological effects of cordyceps lower serum creatinine (Scr), lower inflammatory cytokines like TGF-Beta, decrease BUN, proteinuria, and inhibit mesangial cell proliferation.^{25,39} In a clinical study of CRF a course of treatment with cordyceps was able to lower BUN by 25% and improve anemia by increasing hemoglobin by 13%.⁴⁰

Generally this is the first and foremost used Chinese herb for renal failure due to its ability to protect the kidney, having near zero side effects, and being non-nephrotoxic at very high dosages.

Chinese rhubarb root (Da Huang) has been used for thousands of years as the main way to treat kidney disease. The confusion between American rhubarb root, often seen in pies, compared to the Chinese rhubarb root can be attributed to Christopher Columbus' eager ambition in believing he had landed in the east Indies and had found the famous and valuable Chinese medicinal rhubarb.⁴¹ Its strong cathartic action is thought to detoxify the blood by increasing the excretion of waste products through the large and small intestine.²⁵ In small doses, starting at 1g per day and increasing to the tolerance of the patient,³⁹ rhubarb lowers protein urea, lowers BUN (a nitrogen by product that is supposed to be excreted by the kidney but builds up in CKD), decreases glomerular sclerosis but not tubulinterstitial fibrosis, decrease mesangial cell proliferation, and lowers methylguanidine (MG) and guanidinosuccinic acid (GSA), two uremic toxins.^{25,39,42} The medicinal benefit of this root was observed in a 151 patient control trial comparing captopril (ACEi) therapy in combination with rhubarb, without the root, and a control taking neither. The group receiving both captopril and rhubarb showed significantly better serum parameters than the other groups.⁴³ Aqueous extract of rhubarb root have also been used in the form of an enema that functioned like dialysis before dialysis was invented. These enemas were

shown to improve quality of health in patients with renal failure. Chang Chuan Chinese Medical College used an enema with rhubarb to treat 1,000 CRF patients with an effective rate of 87.7%.⁴⁴

Salvia miltiorrhiza (Dan Shen) is a very active and safe ACEi which contributes to its activity in ameliorating the progression of renal disease^{45,46}. The inhibition of angiotensin II is what enables salvia to lower renal TGF-beta along with reducing blood pressure. The reduction in blood pressure appears to be two fold. One acting as an ACEi and the second by activating renal arterial eNOS, which is a vasodilator.⁴⁷ Other researched renal protective mechanisms deal with its ability to lower protein urea, BUN, Scr, and inhibit ROS by increasing SOD and catalase.^{36,37,38,40} Lately salvia's ability to act as a xanthine oxidase inhibitor has led to increased interest in its future role as an alternative to allopurinol, a medication that causes severe nephrotoxicity at normal dosages in patients with current renal failure.^{48,49,50}

Overall the use of acupuncture and the herbs safflower, astragalus, angelica, notoginseng, cordyceps, rhubarb, and salvia can significantly ($P>0.05$) lower renal SNA, lower TGF-beta, ameliorate renal fibrosis and glomerular sclerosis, prevent EMT, inhibit SMAD2,3, and alpha-SMA, causes apoptosis of fibroblasts, inhibit ROS and NADPH, lower creatinine, BUN, decrease proteinuria, inhibit xanthine oxidase, and act as an ACEi.

PREVENTION

Acupuncture and herbs gives us the tools to combat chronic kidney fail-

ure. The strength of TCM has always been its preventative abilities. In the Yellow Emperor's Inner Canon, Suwen, Chapter 2 it states: "Treating an illness after it has begun is like suppressing a revolt after it has broken out. If someone digs a well when thirsty, or forges weapons after becoming engaged in battle, one cannot help but ask, "Are not these actions too late?"⁵¹

How can acupuncturist help in preventing Kidney disease? First we must go back to the leading causes of CRF. Those being diabetes and high blood pressure.

Diabetic nephropathy is characterized by infiltration of glycoproteins in kidney tissue, increased oxidative stress caused by lipoperoxidation, decrease in free radical scavenging enzymes, vascular damage, advanced glycation end products (AGEs), proteinuria, and polyuria.

Lipoperoxidation is when a unsaturated lipid (cellular membrane) is attacked by a free radical. The free radical cleaves a H+ group and creates a lipid radical. The lipid radical shortly thereafter comes into contact with a water molecule and forms lipid peroxide.

This cycle repeats itself over and over very quickly if there are no free radical scavengers such as SOD, catalase, or glutathione to bind to the free radical and break it down. The increase in need of antioxidants caused by hyperglycemia creates a low amount of those free scavengers showing up in blood work because they are bound to a free radical. It's these free radicals that cause vascular damage by bombarding cellular

membranes. AGEs are formed when a sugar (glucose) comes into contact with an amine group in protein. If a visual is better, it's the same process that happens when making maple syrup. These AGEs have receptors on the kidney called receptor for advanced glycation end products (RAGE). This binding causes inflammation in the kidney. The kidney plays a role in the metabolism and excretion of AGEs. This role is diminished in diabetic disease. High renal concentrations of glucose stimulates protein kinase c (PKC). PKC activates TGF-beta which stimulates cyclin-dependent kinase p27^{kip1}. P27^{kip1} causes cell arrest at the G1 phase in the cell cycle. This arrest leads to cellular hypertrophy of mesangial and tubular cells in the kidney.

The first line of defense in treating diabetes is lowering serum glucose by decreasing glycogenesis, increase

pancreatic sensitivity to glucose, increase uptake of glucose by tissue and adipose cells, and by decreasing

Visit the AAM website at
www.missouriakupuncture.org
for charts/graphs and references.

intestinal absorption of glucose. Second line of defense is creating a cellular environment that can handle the increased oxidative stress induced by hyperglycemia. That can be done by increasing the amount of catalase, SOD, and glutathione being produced by the body or by inhibiting the formation of AGEs and free radicals. Most secondary symptoms such as nephropathy, neuropathy, retinopathy from diabetes is related to this oxidative damage.

Previous experiments with acupuncture and the pancreas has revealed that the right spleen channel actually stimulates the pancreas while the left spleen channel stimulates the spleen. Points such as Sp-3 and Sp-6 on the right are effective at activating and increasing the sensitivity of

the pancreas to insulin. Ear seeds placed on kidney, endocrine, and shenmen increase free radical scavenging enzymes (catalase, and SOD). The treatment was done on diabetic patients and a

control. The three ear points were massage 12 seconds a piece 3 times per day for 20 days. By doing this the amount of serum catalase was doubled and the amount of SOD was significantly increased⁵². We have previously mentioned how St-36 and Kd-3 decreased renal sympathetic activity and inhibited TGF-beta.

Radix ginseng (Ren Shen), Scutellaria baicalensis (Huang Qin), and Rehmannia glutinosa (Shou Di Huang) increase insulin receptor substrate-2 (IRS2) which helps maintain beta cell function in the pancreas. Beta cells are the cells responsible for excretion of insulin.

They also increases pancreas duodenum homeobox-1 (PDX-1) which is responsible for beta cell proliferation.⁵³ When Huang Qin is combined with metformin it increases the anti-diabetic effect by increasing SOD, catalase, glutathione peroxidase (GPx), and decreasing lipid peroxidation.⁶³

Schisandra chinensis (Wu Wei Zi), Poria cocos (Fu Ling), Rhizoma alismatis (Ze Xie), Dioscorea opposita (Shan Yao) increase glucose absorption in the intestinal tract, Wu Wei Zi, Shan Zhu Yu, Ze Xie increase glucose uptake in adipose and fibroblast cells.⁵⁴

Warm and Tonify the Spleen Decoction (Wen Pi Tang) inhibit AGEs, and increase AGE clearance. Da Huang, a chief herb in Wen Pi Tang, was shown to be the most active in inhibiting AGEs by 98.1% at a dosage of 25ug/ml.⁵⁵

Shou Di Huang decreases diabetic kidney lesions, inhibit TBA-reactive substance which is a lipid peroxidation product, decreases BUN, serum glucose, and renal glucose.⁵⁶ Shou Di Huang also enhances liver glucokinase which phosphorylates a glucose molecule turning it into glucose-6-phosphate. It stimulates secretion of insulin and decreases hepatic glycogen content.⁵⁷

Eight Ingredient Pill with Rehmannia (Ba Wei Di Huang Wan) suppressed proteinuria in a 25 week study, inhibited fibronectin, TGF-beta, renal lipid peroxidation by lowering TBA-reactive substance, increased renal SOD, and was shown to be able to prevent diabetic kidney damage by reducing renal oxidative injury.⁵⁸

Radix astragali (Huang Qi) reduces fasting serum glucose, reduces albuminuria levels, reverses glomerular hyper-filtration rate, and ameliorates pathological changes seen in early diabetic nephropathy.⁵⁹

High proteinuria is often seen in diabetic and non-diabetic nephropathies. The rate of GFR is closely predictable with the level of proteinuria. Showing that a patient with low proteinuria would have a slower progression of renal failure than a similar patient with a high level of proteinuria. Cinnamon and Poria Decoction (Gui Zhi Fu Ling Wan) when given in diabetes decreases kidney weight by preventing renal hypertrophy, decreases TGF-beta, fibronectin, AGEs and proteinuria.^{60,61} Huang Qi also increases SOD, reduces proteinuria, and oxidative renal damage.⁶²

The next leading cause of CKD that can benefit from the preventative abilities of Chinese medicine is high blood pressure. With high blood pressure there is essential and secondary hypertension. Essential hypertension is where the cause of the increase in blood pressure is not known which accounts for over 90% of diagnosed hypertension. Secondary hypertension are cases when the cause of high blood pressure is caused by another medical condition. Examples of secondary hypertension are complications from diabetes, polycystic kidney disease, renovascular hypertension caused by stenosis of renal artery, Cushing's syndrome, thyroid problems, and a long list of others.

Acupuncture of St-36, Zusanli, is effective at lowering blood pressure by inducing eNos which dilates blood vessels.²⁴ Kd-3, Taixi, combined with St-36 lowers blood pressure, inhibits TGF-beta and attenuates the progression of renal disease.²³ KD-3 combined St-36 decreases sympathetic nerve activity in the kidney thereby reducing blood pressure.²²

When it comes to herbs there are three main players with renal disease. We have already spoken of Dan Shen and its ACEi ability and renoprotective properties.^{36,37,38,40,48,49,50} Two other herbs are Herba apocyni veneti (Luo Bu Ma) and Tribulus terrestris (Bai Ji Li). Luo Bu Ma

lowers blood pressure in essential, 5/6 nephrectomized, and NaCl induced hypertension by inhibiting ACEi and acting as a slight diuretic.⁶⁴ It was also shown to decrease BUN in the 5/6 nephrectomized model. Bai Ji Li has a smooth muscle relaxant effect, ACEi activity in the heart, aorta, kidney, clipped kidney, lung, and blood.^{65,55}

Other herbs such as Ligusticum (Chuan Xiong), Gastrodia (Tian Ma), and Gynostemma (Jiao Gu Lan) are beneficial at lowering blood pressure but they do not have a direct effect on the kidney. Hong Hua, even though it is great for kidney disease, only has minor hypertensive effect.²⁸

These findings validate the long history of use of traditional Chinese medicine in the treatment and prevention of renal disease. The multi-targeted approach that can be taken with the combination of herbal therapy and acupuncture is well beyond the current approach of western medicine but does not undermine current pharmaceutical therapy. Unfortunately the heavy curtain of aristolochic acid species causing Chinese herb nephropathy still lingers today. This combined with the patients frantic and desperate search for a quick cure to their kidney disease online can lead to negative results. Just type in "kidney disease cure" on Google and you will find days' worth of miracle herbal decoctions that you can conveniently buy. An informed licensed acupuncture and herbalist does have the ability to help those with chronic renal failure, to help those 30 million Americans who might someday walk into your clinic and ask, "Does Chinese medicine help kidney failure?"

Visit

www.missouriacupuncture.org
for the full article.