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Review Article

The role of inorganic salts, heavy metals, fruits, vegetables and diet in nephrotoxicity

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ABSTRACT

Some inorganic salts and heavy metals are used in the treatment of various diseases but their increase uses may causes various chronic diseases. These therapies may cause potential toxicity that may be mainly renal toxicity caused by the ingestion of inorganic salts and heavy metals. The toxic effects of inorganic salts and heavy metals impaired renal function or renal health. This study provide knowledge and guide to encourage future toxicity studies, protection against these type of toxicities and their relation with diet particularly use of vegetables and fruits. This review has also presented evidence that many dietary and other factors can influence nephron activity. However, the evidence continues to shows that excessive heavy metals and inorganic salts intake play a leading role to causes serious renal health problems. The consumption of more natural foods, especially with high in fiber, salts like potassium, calcium, magnesium and some other potentially useful chemicals that may help reverse the biochemical and physiological damage caused by the typical unhealthy diet.

Key words: Nephrotoxicity, Inorganic salts, Heavy metals.

INTRODUCTION

In recent years, an increasing number of people have been suffering from renal problems. The goal of this article is to present information on the renal toxicity and renal benefits of natural diet, medicinal herbs and their relation with increase intake metals and heavy metals [1-10]. Specially, the herbal therapies appear most promising that encouraging the reduction of renal toxicity. Literature showed that some herbs are reported as toxic against renal function and some evidence of toxicity in animals or humans also reported. The most of the herbs and natural diet are potentially beneficial to the kidneys and inhibit or prevent renal toxicities. Some strong evidence of renal protection from toxic substances or drugs is reported in various researches. These natural diet and herbs are potentially effective against various other diseases like cardiovascular, diabetes, cancer etc. These natural diet and herbs have various active compounds that showed various actions like anti-oxidant, anti proliferative etc. They are being beneficial in renal disease or failure also [11-15].

MATERIAL AND METHODS

Nutrition and chronic kidney disease: In chronic kidney disease, diet is an important part of the treatment plan. The recommended diet may change over time if kidney disease gets worse. Some points are important to control or prevent renal toxicity caused by heavy metals or excessive inorganic salts ingestion. These points are a balance diet that including right amount of calories, proteins and other important nutrients such as sodium, phosphorus, calcium, potassium, fluids, vitamins and minerals. Some other factor that affect kidney health like staying at a healthy body weight, using special diet needs, vegetarian or low fat diets [11-15].

Toxicity from heavy metals and Adulterants within herbal extracts: Adulteration or contamination of herbal medicines appears to be common in countries that are lenient on the controls regulating their purity. In many cases, these may cause significant medical problems, especially in children [18-20]. While none of these resulted in acute renal toxicity, there is concern that these contaminants may have the potential to contribute to chronic or insidious health disorders [21].
Renal toxicities of medicinal herbs that contain heavy metals in their pharmaceutical products [22] like lead, arsenic and mercury were among the contaminants. Other reports of contamination include thallium intoxication caused by Chinese herbal medicine [23]. When pharmaceuticals are placed within herbal mixtures, they are normally meant to enhance the medicinal properties of the mixture; however, serious adverse consequences can result [19]. In some cases,

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heavy metals in Chinese and Ayurvedic medicines originate from the heavily polluted soil and irrigation water, as plants take up heavy metals through their roots [24]. Lead and cadmium levels in medicinal plants from India were highest in the leaves, and that herbal medicines using that part of the plant generally have higher environmentally induced heavy metal contents [25]. In other cases, the heavy metals or other adulterants are deliberately placed in the mixture. Within Chinese traditional medicines, small amounts of Realgar, a mineral containing mainly arsenic sulphide, and Cinnabaris, a mineral containing mainly mercuric sulphide, are deliberately used in some Chinese medicines [19]. It should be noted that adulteration of herbal remedies, indicating that efforts to control contamination may be helping. The possibility of accidental contamination during manufacturing, demands continued analysis of imported herbal medicines [19]. Cadmium toxicity resulting in acute tubulointerstitial nephritis in childrens [24].

Changing Diet: As a patient with chronic kidney disease, recommended diet may change over time, depending on how much kidney function has. The glomerular filtration rate (GFR) is the best way to track level of kidney function. The doctor can estimate GFR from the results of a simple blood test for creatinine along with age, sex and body size. If kidney disease progresses and GFR continues to decrease, the amount of protein, calories and other nutrients in diet will be adjusted to meet changing needs. If dialysis or a kidney transplant is needed eventually, diet will be based on the treatment option choose. The doctor can refer to a registered dietitian who will explain the changes need to make in diet and help choose the right foods [26-29]. As chronic kidney disease progresses, GFR number decreases.

1. Kidney damage (e.g., protein in the urine) with normal GFR 90 or above
2. Kidney damage with mild decrease in GFR 60 to 89
3. Moderate decrease in GFR 30 to 59
4. Severe reduction in GFR 15 to 29
5. Kidney failure Less than 15

Amount of calories: Get enough calories are important to overall health and well being. Calories are found in all the foods. They are important because they give energy, stay at a healthy weight. The proteins use in foods for building muscles and tissues. Because your recommended diet may limit protein, you may also be cutting down on an important source of calories. As a result, you may need to get extra calories from other foods. The dietitian may recommend using more simple carbohydrates. Other good sources of calories come from fats such as oils like, which are low in saturated fat and have no cholesterol. Maintaining a healthy weight is also important. People who have chronic kidney disease often need to gain weight or remain at their current weight. If you need to lose weight, your dietitian will teach you how to lose it slowly and carefully without risking your health [26-29].

Amount of protein: Getting the right amount of protein is important to your overall health. Your body needs the right amount of protein for, building muscles, repairing tissue and fighting infections. A diet that has controlled amounts of protein that may help decrease the amount of wastes in your blood and may help your kidneys to work longer. Protein comes from two sources. You will need to get some protein each day from both of these sources: animal sources, such as eggs, fish, chicken, red meats, milk products and cheese and plant sources, such as vegetables and grains [26-29].

Other important nutrients in diet: To feel best each day, may need to change the amounts of some of the following nutrients in diet that will help to plan meals to get the right amounts of each [30-35].

Sodium: Kidney disease, high blood pressure and sodium are often related. Therefore, you may need to limit the amount of sodium in your diet by select foods that are lower in sodium. Sodium is a mineral found naturally in foods. It is found in large amounts in table salt and in foods that have added table salt. You may need to limit the use of salt substitutes that are high in potassium. Try fresh or dried herbs and spices instead of table salt to enhance the flavor of foods. Also, try adding a dash of hot pepper sauce or a squeeze of lemon juice for flavor [6,20,27,33, 48,49].

Phosphorus: Kidneys may not be able to remove enough phosphorus from blood. This causes the level of phosphorus in blood to become too high. A high blood phosphorus level may cause skin to itch and the loss of calcium from bones. The bones can become weak and may break easily. Eating fewer foods that are high in phosphorus will help lower the amount of phosphorus in blood. Phosphorus is found in large amounts in the dairy products, such as milk, cheese, ice cream and dried beans, peas (such as kidney beans, split peas), lentils, nuts and peanut butter and beverages such as hot chocolate, beer and dark cola drinks[48-50,56]

Calcium: Calcium is a mineral that is important for building strong bones. However, foods that are good sources of calcium are also high in phosphorus. To keep your calcium and phosphorus levels in balance and to prevent the loss of calcium from your bones, you may need to follow a diet that limits phosphorus-rich foods and take phosphate. Using non-dairy creamers and recommended milk substitutes in place of milk is a good way to lower the amount of phosphorus in your diet. To take calcium supplements and a special prescription form of vitamin D [6,20,27,33, 56].

Potassium: Potassium is an important mineral in the blood that helps your muscles and heart work properly. Too much or too little potassium in the blood can be dangerous. Whether or not you need to change the amount of high-potassium foods in your diet depends on your stage of kidney disease and whether you are taking any medications that change the level of potassium in your blood [48-50,56].

Fluid: In general, you do not need to limit the amount of fluids you drink in the earlier stages of kidney disease. If your kidney disease gets worse, your doctor will let you know when you need to limit fluids and how much fluid is okay for you each day [15, 16, 34, 35].

Vitamins and minerals: Vitamins and minerals come from a variety of foods. If your diet is limited, you may need to take special vitamins or minerals. Certain vitamins and minerals may be harmful to people with chronic kidney disease. So check with your doctor before taking any herbal remedies as some of these may also be harmful to people with kidney disease. Cooking with herbs is a safe choice and can often be used instead of salt to flavor foods. Check with your doctor and dietitian about the right vitamins and minerals for you [6,9,12, 30-35].

Special diet needs: You may need to make only a few changes in your diet to fit your needs as a kidney patient. If your doctor suggests that you eat less protein, your diet may need to include more carbohydrates or high-quality fats to give you enough calories [34,35]

Vegetarian diets: Most vegetarian diets are not rich in protein. Eating enough calories is an important way to use these smaller amounts of protein for important jobs like building muscle, healing wounds and fighting infection. Talk with dietitian about the best choices of vegetable protein with lower amounts of potassium and phosphorus. If you are not eating the right amount of proteins, calories and other nutrients. Dietitian will give you ideas about food choices that will help to improve your diet. If your kidney disease gets worse, and/or your nutritional health changes, you may need to have these tests more often. If your protein level continues to be low, you have a greater chance of getting an infection, being hospitalized and generally not feeling well [35,36].

GENERAL INFORMATION ABOUT FRUIT AND VEGETABLE

Low intake of fruit and vegetables is one of the main risk factors for disease. According to the World Health Organization, millions of lives worldwide could be saved each year if people ate enough fruits and vegetables. Certain types of heart diseases, Cancers, type II diabetes, obesity, kidney diseases etc. The WHO recommends consumption of fruit and vegetables in per day diet [35,36].

The Lifestyle: It is established scientific fact that people who eat lots of fruit and vegetables are less likely to get certain non-communicable diseases (e.g. cancer, heart disease, stroke, type II diabetes). Specific benefits have been identified for apples (protection against heart disease and certain cancers), cabbage and other cruciferous vegetables like broccoli (which may protect against certain cancers), tomatoes (protection against prostate cancer), and nuts (protective against heart disease and type II diabetes). Further individual benefits have been identified for kale, blueberries, raspberries, garlic, almonds and other fruits/vegetables.

HEALTH BENEFITS OF FRUIT AND VEGETABLES

It is not sensible to recommend specific "super" foods, since the scientific evidence strongly suggests that health benefits almost certainly result from the consumption of a wide range of different fruits and vegetables. However, a balanced diet that includes a wide variety of fruits and vegetables and minimal processed food would be expected to reduce the risk of a range of chronic degenerative illnesses. In addition, a diet rich in unprocessed food makes it easier for the body to regulate appetite, and usually helps people to avoid being overweight (fast-food diet increases the risk of obesity and type II diabetes). Fruits, vegetables and other plant foods tend to be rich in antioxidants and other phytochemicals. Antioxidants consumed in food inhibit damaging reactions within the human body and have a beneficial effect upon health. By reducing free-radical damage, antioxidants reduce inflammation, promote cardiac health, and reduce the risk of neuro-degenerative diseases like Alzheimer's and Parkinson's disease. Many studies also show that some plant phytochemicals are anti-proliferative – they slow or prevent the growth of some cancer cells. Recent research suggests that plant constituents increase sensitivity to insulin, which may help delay the onset of type II diabetes. Chronic inflammation may be the root cause of degenerative illnesses like heart disease. It is likely that eating fruit and vegetables regularly can prevent chronic inflammation, and this may contribute significantly to their beneficial effects. Studies show that taking antioxidant supplements (e.g. vitamin pills) does not protect health. By way of contrast, regular consumption of fruits and vegetables clearly has a beneficial effect upon health. Many different studies show beneficial effects for a range of different fruits, vegetables, oils, nuts and herbs. In summary, a diet rich in fruits and vegetables significantly reduces the risk of heart disease, stroke, type II diabetes, some types of cancer, obesity and Alzheimer's disease. This effect can

be further increased by including wholegrain foods, nuts and certain oils (e.g. omega-3 fatty acid) in the diet. The latest scientific evidence provides even greater support for the role fruits and vegetables play in helping to protect against all of these diseases that are associated with a decreased risk of such chronic diseases such as stroke, perhaps other cardiovascular diseases, kidney diseases, type-2 diabetes, and cancer in certain sites [35,36].

Role of fruits and vegetables: Fruits and vegetables have been recognized as a good source of vitamins, minerals and various nutritious and therapeutically important phytochemical. Research of the past 20 years has shown that fruits and vegetables not only prevent malnutrition but also help in maintaining optimum health through a host of chemical components that are still being identified, tested, and measured. They have been especially valuable for their ability to prevent vitamin C and vitamin A deficiencies.

Some of the good things in herbs, fruits and vegetables: Vitamins, minerals, flavonoids- plant chemicals that act like antioxidants, saponins- plant chemicals that have a bitter taste, phenols- organic compounds in foods, carotenoids- vitamin A-like compounds, isothiocyanates- sulfur-containing compounds and several types of dietary fiber.

Foods high in sulfur: Algin (a gelatinous derivative of kelp or other seaweed, use a nutritional supplement) eggs, garlic, legumes (e.g. soy, beans, lentils, peanuts), onions, seaweeds.

Foods high in dietary fiber: Fruits, Legumes, Vegetables, Whole grains

Foods high in iron: Leafy vegetables (avoid those grown in cadmium-contaminated soils), Legumes, Meat, Iron-fortified cereals (Note: eating foods high in vitamin C improves iron absorption, except from meats).

Foods high in calcium: Calcium-fortified fruit juices, Leafy vegetables (avoid those grown in cadmium-contaminated soils), Milk and milk products (but beware of their protein content since excessive protein intake removes calcium from the body), Tofu (processed with calcium sulfate), Shellfish.

Foods high in anti-oxidants: Plants supply most of our dietary antioxidants: in general, the plant pigments such as those found in green yellow and red vegetables tend to be associated with antioxidants. Storage and processing tend to decrease antioxidants, but fermentation can increase them. Some common examples are leafy vegetables, carrots, tomatoes, citrus fruits, strawberries, teas (herbal and green) and algae.

Role of table salt and its toxicity: Salt is the most commonly used food additive. It improves the taste of many foods without adding calories. In larger amounts it also inhibits the growth of many microorganisms and has been used to preserve food. Salts contained 40% sodium and 60% chloride by weight i.e. 1 gram of salt has 400mg of sodium and 600mg of chloride.

Adequate intake (AI) for salt: Both sodium and chloride are essential nutrients for humans and all other animals. In February of 2004 the Food and Nutrition Board of the Institute of Medicine (IOM) released the new "Dietary Reference Intakes for Water, Potassium, Sodium, Choloride, and Sulfate". They stated that a Recommended Dietary Allowance (RDA) for sodium and chloride "could not be derived." "Hence an Adequate Intake (AI) is provided." The new guidelines do make it clear that the average human is consuming far more salt (sodium chloride) than is needed for good health. For young adults the new guidelines state that 1500 mg of sodium is an AI. The report lists hypertension, cardiovascular and kidney diseases as the major adverse effects of a toxic or excessive salt (sodium) intake. However, the report also notes evidence linking the toxic amount of salt in the diet to atrophic gastritis and stomach cancer and increased calcium loss in the urine, which contributes to kidney stone formation and osteoporosis. Lower AI for older because the toxicity of salt increases in older people. For those over 50 year the new AI is 1300 mg/day and for those over 70year the new AI is 1200 mg/day. The report also recommends humans roughly double their current potassium intake up to 4700 mg/day by eating a lot more fruits and vegetables as this helps reduce some of the toxic effects of salt. Thus, far fewer humans would die from cardiovascular disease and other illnesses linked to salt toxicity. There is no doubt that human beings evolved consuming a diet with far less salt than is now customary in modern societies. It seems likely then that the human body is biologically designed to handle far less salt than is now the norm in modern diets [39-46].

Salt toxicity creates an imbalance of electrolytes in the body: Other electrolytes besides sodium affect blood pressure and vascular disease. It was also about 2-3 times higher in potassium, calcium and magnesium as pricribed level. In rats, it has been shown that increasing potassium in the diet reduces deaths, cerebrovascular disease and increases life expectancy independently of its effects on blood pressure.

Sodium without Chloride appears less toxic: The human kidney quickly excretes excess sodium and chloride far less quickly when consumed together as it does when either is consumed alone. However, the human kidney's ability to excrete potassium is more limited because the level in blood is so much lower than

that of sodium and chloride. This requires metabolic energy to "push" the excess potassium into the kidney distillate. People with impaired kidney function or dialysis must avoid salt substitutes containing potassium chloride. In addition, the use of potassium supplements with angiotensin converting enzyme inhibitors, angiotensin antagonists and potassium-sparing diuretics can lead to a dangerous elevation of serum potassium levels. All of these drugs are frequently used to treat essential hypertension. Sodium without chloride has been shown to have far less tendency to raise blood pressure in people than salt.This means that other sodium salts such as sodium citrate would be far less likely to cause hypertension than salt and so would be far safer than table salt [47-50].

Possible symptoms of heavy metals toxicities: Heavy metal exposure can have symptoms that are chronic and subtle. Often the symptoms of heavy metal toxicity resemble those of other diseases. Heavy metal cause various health problems like, elevated risk of skin cancer, cancers of lung, liver, bladder, kidney and colon, anemia, neuropathy, hypertension, kidney or liver dysfunction etc. Children with pica (who may eat soil) are at highest risk for lead and arsenic exposure. In high cadmium soils, cadmium is taken up by leafy vegetables that may cause significant toxicity. The heavy metal toxicity in patients causes any age with anemia, neuropathy, cancer, hypertension, kidney or liver dysfunction, especially if they have two or more of these or also have cancer or other symptoms noted. There is no magic bullet for treatment, but you can make a difference by stopping or minimizing exposure is crucial, supplemental calcium citrate and vitamin D, and avoiding excess protein intake, decrease risk of lead toxicity along with preventing osteoporosis. Supplemental iron when needed (e.g. childhood and adolescence, pregnancy) can decrease lead uptake as well as prevent iron deficiency. Diets high in fiber and low in fat can decrease heavy metal risks along with their other benefits. Diets high in antioxidant plant foods and sulfur compounds may be protective against heavy metal toxicity in addition to other benefits such as decreasing risk of cancer [51-54].

Arsenic: Arsenic has a short half-life in the body (weeks) but its effects can be seen years after exposure has ceased. Sources of arsenic exposure are smoking tobacco, releases into the air and onto soils by smelting industry and natural contamination of some deep water wells, industrial exposure in the glass and micro electrics industry (gallium arsenide), use of wood preserved with chromated copper arsenic (CCA), Pesticides including some herbicides and fungicides, some paints, burning of fossil fuels in which arsenic is a contaminant [10-12,51,52].

Cadmium: Cadmium causes Kidney dysfunction, proteinuria, urinary tract problems; Sources of Cadmium exposure, Cigarette smoking (but not second-hand smoke); Releases into the air and onto soils by smelting operations and incineration of municipal waste containing plastics, ingestion of ni-cad batteries, foods grown on soils contaminated with smelting emissions, sewage sludge, chemical fertilizers, polluted groundwater, metal-plating industry wastes or cadmium pigments: leafy vegetables are especially noted for cadmium bio-concentration, industrial exposure in the battery, pigment and plastic industries. Cadmium has a very long half-life in the body (10 to 30 years) and can build up over a long time. Over 80% of the body burden resides in the kidneys [10-12,51,52].

Lead: Sources of lead exposure are leaded Paints, cans, plumbing fixtures, leaded gasoline, deterioration of leaded paint used in the past, Consumption of lead chips or paint dust (which tastes sweet) by children or developmentally delayed adults, soldering, as an occupational or hobby exposure; Vehicle exhaust, in soil and house dust; Ingesting leafy vegetables grown in lead contaminated soil; Storing acidic foods in improperly-glazed ceramics, lead crystal; Industries such as: battery manufacturing, demolition, painting and paint removal, and ceramics pose a significant threat to workers and communities; Releases into the air and onto soils by smelting operations.

These heavy metal may causes kidney Disease, including interstitial nephritis, tubular damage, Hyperuricemia (increased risk of gout), decline in glomular filtration rate and chronic renal failure. Lead may accumulate in bone and lie dormant for years, and then pose a threat later in life during events such as pregnancy, lactation, osteoporosis, and hyperthyroidism and hyperparathyroidism, which mobilizes stores of lead in bones [10-12, 51, 52].

Dietary suggestions that may help inhibit uptake of cadmium, arsenic and lead: Dietary factors affect heavy metal uptake. For example, an adequate level of dietary iron reduces uptake of cadmium and lead. Dietary calcium reduces the uptake of cadmium. Good habits that can reduce the intake and uptake of toxic metals include eating a balanced diet that is high in fiber, eating organic foods and avoiding foods grown with pesticides and artificial fertilizers or in contaminated soils. Including high sulfur foods such as onions, garlic, legumes, and eggs probably assists the body in blocking uptake and decreasing retention of many toxic metals. Using cast iron cooking vessels especially for cooking acidic foods (such as tomatoes) can add valuable iron to the diet. Providing 4-6 small meals per day to children because full stomachs are less likely to absorb lead [51-54].

Goals for Healthcare Practitioners: Appropriate interventions in the case of heavy metal exposure include: Limit exposure, decrease absorption, decrease release of stored metals, protect vulnerable tissues, chelation therapy only for acute exposure [55-60].

1) Children with pica behavior (who eat dirt; about 10% of the population of 1-6 year-olds) are a very high risk group. Parents should be advised to ensure their children are not exposed to contaminated soils. Parents may wish to test and remediate the soils their children play in. Not smoking is especially valuable for those exposed to cadmium and arsenic. Leafy vegetables grown in cadmium contaminated soils may be an important source of cadmium toxicity.

2) A healthy diet can help reduce uptake. Mineral nutrition is especially important, particularly iron and calcium nutrition. Calcium citrate and vitamin D supplementation may be appropriate. Iron supplementation may be needed during periods of high need such as childhood and pregnancy. Excessive protein intake (more than 1.5 grams protein per kilo of lean body mass per day) is not advised except in special circumstances such as pregnancy. Foods high in fiber limit the uptake of heavy metals. A low-fat diet reduces cadmium uptake. Including high-sulfur foods in the diet may limit cadmium effects.

3) Release of lead from bones may be reduced by standard methods to reduce the risk of osteoporosis, such as weight-bearing exercise, adequate calcium and vitamin D intake, and other treatment such as hormone therapy. Arsenic does not stay in the body; it is readily excreted within weeks. However, the damage caused by arsenic is permanent and may not be evident for decades.

4) The kidneys are protected through adequate consumption of water. Bones and kidneys are aided through avoiding excess protein intake. Many heavy metals act in part through creation of free radicals in the cellular environment. A diet high in anti-oxidants can mitigate some of these effects.

5) Acute and massive exposure of young children leading to extremely toxic levels of lead or cadmium may require chelation therapy. It is not indicated in other situations and carries serious risks since it removes calcium and iron and other nutrients from the body.

CONCLUSIONS

This review has presented evidence that many dietary and other factors can influence nephron activity. However, the evidence continues to favor excessive heavy metals, dietary salt and other agents. Salt Intake and many other agents, are playing a leading role in causes other serious health problems. The long-term benefits of reducing salt intake for reducing not only CVD risk but also the risk of osteoporosis, kidney stones and stomach cancer. To consume a more natural foods diet high in fiber, potassium, calcium, magnesium and other potentially useful chemicals that may help reverse the biochemical and physiological damage caused by the typical unhealthy diet. Salt appears to be a serial killer which has escaped indictment and prosecution thanks in large part to a public relations campaign for awareness to those of people who'd like to be accurately informed about how what they eat impacts their health. Herbal extracts may exert renal toxicity through their inherent properties. If found to have some degree of toxicity, in a manner similar to that which is presently performed for nephrotoxic pharmaceutical agents. Importantly, the inherent properties of the herb are not the only source of herb-associated renal disorders, as herb–drug interactions, and contaminants within the mixture are all issues of concern. Strict controls on the presence of adulterants within herbal medicines, labelling of dosages and contraindications, and manufacturing techniques must be maintained to ensure the safety of those consuming herbal medicines.

REFERENCES

1. Jha V, Chugh KS. Nephropathy associated with animal, plant, and chemical toxins in the tropics. Sem Nephrol 2003; 23: 49–65.
2. Solez K, Daugirdas J, Gregory MC *et al*. Is 'Chinese herbs nephropathy' a prejudicial term? Am J Kidney Dis 2001; 38: 1141–2.
3. Vanherweghem LJ. Misuse of herbal remedies: The case of an outbreak of terminal renal failure in Belgium (Chinese herbs nephropathy). J Altern Complement Med 1998; 4: 9–13.
4. Liu SY, Woo SO, Koh HL. HPLC and GC-MS screening of Chinese proprietary medicine for undeclared therapeutic substances. J Pharm Biomed Anal 2001; 24: 983–92.
5. Wei L, Chen B, Ye R, Li H. Treatment of complications due to peritoneal dialysis for chronic renal failure with traditional Chinese medicine. J Tradit Chin Med 1999; 19: 3–9.
6. Ascherio A, Rimm EB, Hernan MA *et al*. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 1998; 98:1198-204.
7. Bass DA, Hickock D, Quig D, Urek K. Trace element analysis in hair: factors determining accuracy, precision, and reliability. Altern Med Rev 2001; 6:472-81.
8. Dahl NV. Herbs and supplements in dialysis patients: Panacea or poison? Semin Dial 2001; 14: 186–92.

9. Craig W, Beck L. Phytochemicals: Health Protective Effects. Can J Diet Pract Res 1999; 60:78-84.
10. Ernst E, Coon JT. Heavy metals in traditional Chinese medicines: A systematic review. Clin Pharmacol Ther 2001; 70: 497–505.
11. Foote J, Cohen B. Medicinal herb use and the renal patient. J Renal Nutr 1998; 8: 40–2.
12. Wojcikowski K, Johnson D, Gobe G. Medicinal herbal extracts–renal friend or foe? Part one: The toxicities of medicinal herbs. Nephrol 2004; 9, 313–8.
13. Nortier JL, Martinez MC, Schmeiser HH *et al*. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). New Eng J Med 2000; 342: 1686–92.
14. Nortier JL, Vanherweghem JL. Renal interstitial fibrosis and urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). Toxicology 2002; 181–182: 577–80.
15. The Upcoming 2005 Dietary Guidelines: Fruits and Vegetables: Chronic Disease Fighters Dietary Guidelines Advisory Committee Report. January 2005.
16. Jorgensen K. Survey of pork, poultry, coffee, beer and pulses for ochratoxin A. Food Addit Contam 1998; 15: 550–4.
17. Hilepo JN, Bellucci AG, Mossey RT. Acute renal failure caused by 'cat's claw' herbal remedy in a patient with systemic lupus erythematosus. Nephron 1997; 77: 61.
18. Ko RJ. Adulterants in Asian patent medicines. New Eng J Med 1998; 339: 847.
19. Ernst E. Serious adverse effects of unconventional therapies for children and adolescents: A systematic review of recent evidence. Eur J Pediatr 2003; 162: 72–80.
20. Hollenberg NK, Martinez G, McCullough M, *et al*. Aging, acculturation, salt intake, and hypertension in the Kuna of Panama. Hypertension 1997; 29:171-6.
21. Gillum RF. Will persons on low sodium diets become iodine deficient? Am Heart J 1982; 103: 1084-5.
22. Zurovsky Y, Haber C. Antioxidants attenuate endotoxin- generation induced acute renal failure in rats. Scand J Urol Nephrol 1995; 29:147-54.
23. Howard H, Berger A. Alopecia and Sensory Polyneuropathy from thallium in a Chinese herbal medication. JAMA 1992; 268: 3430–1.
24. Cheng S. Heavy metals in plants and phytoremediation. Environ Sci Pollut Res 2003; 10: 335–40.
25. Dwivedi SK, Dey S. Medicinal herbs: A potential source of toxic metal exposure for man and animals in India. Arch. Environ. Health 2002; 57: 229–31.
26. Zhang DN. Treatment of chronic renal failure with 'serial recipes for renal failure': A report of 64 cases. J Tradit Chin Med 1989; 9: 159–62.
27. Meneely GR, Ball COT. Experimental epidemiology of chronic sodium chloride toxicity and the protective effects of potassium chloride. Am J Med 1958; 25:713-25.
28. Milner LS, Wei SH, Houser MT. Amelioration of glomerular injury in doxorubicin hydrochloride nephrosis by dimethylthiourea. J Lab Clin Med 1991; 118: 427–34.
29. Pedraza-Chaverrí J, Maldonado PD, Barrera D, Cerón A, Medina-Campos ON, Hernández-Pando R. Protective effect of diallyl sulfide on oxidative stress and nephrotoxicity induced by gentamicin in rats. Mol Cell Biochem 2003; 254:125-30.
30. Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. Circulation 1975; 52:146-51.
31. Ophir O, Peer G, Gilad J, et al. Low blood pressure in vegetarians: the possible role of potassium. Am J Clin Nutr 1983; 37:755-62.
32. Kwok TC, Chan TY, Woo J. Relationship of urinary sodium/potassium excretion and calcium intake to blood pressure and prevalence of hypertension among older Chinese vegetarians. Eur J Clin Nutr 2003; 57:299-304.
33. Geleijnse *et al*. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. Br Med J 1994; 309:436-40.
34. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride, and sulfates. 2004. Chapter 6. p. 247-392.
35. Gillman MW *et al*. Protective effect of fruits and vegetables on the development of stroke in men. JAMA 1995; 273: 1113-7.
36. Reginster F, Jadoul M, Van Ypersele de Strihou C. Chinese herbs nephropathy presentation, natural history and fate after transplantation. Nephrol Dial Transplant 1997; 12: 81–6. 10
37. Sacks FM, *et al*. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med 2001; 344: 3-10.
38. Kilgore WW, Li MY. Food Additives and Contaminations. In: Doull J, Khassen CD, Amdur MD, eds. Cassarett and Doulls, Toxicology: The Basic Science of Poisons, 2nd ed. New York: Macmillian, 1980:593-607.
39. Klag MJ *et al*. The contribution of urinary cations to the blood pressure differences associated with migration. Am J Epidemiol 1995; 142: 295-303.

40. Krishna GG, Kapoor SC. Potassium depletion exacerbates essential hypertension. Ann Intern Med 1991; 115:77-83.
41. Schmieder RE, Messerli FH, Garavaglia GE, et al. Dietary salt intake: a determinant of cardiac involvement in essential hypertension. Circulation 1988; 78: 951-6.
42. Mascoli S, Grimm R, Launer C, et al. Sodium chloride raises blood pressure in normotensive subjects. Hypertension 1991; 17: 21-6.
43. Mitchell AR. The clinical biology of sodium. Oxford: Elsevier Science 1995:108. 36
44. Seals DR, *et al*. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. J Am Coll Cardiol 2001; 38:506-13.
45. Kurtz TW, Al-Bander H, Morris RC. 'Salt sensitive' essential hypertension in man. N Engl J Med 1987;317: 1043-8.
46. Lonati L, Cuspidid C, Sampieri L, et al. Ultrasonographic evaluation of cardiac and vascular changes in young borderline hypertensives. Cardiology 1993; 83:298-303.
47. Beauchamp GK, Bertino M, Engleman K. Failure to compensate decreased dietary sodium with increased table salt usage. JAMA 1987; 258:3275-8.
48. Godlee F. The food industry fights for salt. Br Med J May 18, 1996; 1239-40.
49. Blais CA, Pangborn RM, Borhani NO, et al. Effect of dietary sodium restriction on taste responses to sodium chloride. Am J Clin Nutr 1986; 44:232-43.
50. Denton D, Weiseinger R, Mundy NI, et al. The effect of increased salt intake on blood pressure of chimpanzees. Nat Med 1995;1:1009-16.
51. Mandal BK, Chowdhury TR, Samanta G et al. Impact of safe water for drinking and cooking on five arsenic-affected families for 2 years in West Bengal. India Sci Total Environ 1998; 218: 185–201.
52. Heavy Metals Remediation Committee of the Vashon-Maury Island Community Council, 2003
53. Subat-Dezulovic M, Slavic I, Rozmanic V, Persic M, Medjimurec B, Scukanec-Spoljar M. Drug-induced acute tubulointerstitial nephritis: A case with elevated urinary cadmium. Pediatr Nephrol 2002; 17: 382–5.
54. Frisch M, Schwartz BS. The pitfalls of hair analysis for toxicants in clinical practice: three case reports. Environ Health Perspect 2002; 110(4):433-6.
55. Ernst E. Harmless herbs? A review of the recent literature. Am J Med 1998; 104: 170–8.
56. Graudal NA, Galloe AM, Gawed P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride: a meta-analysis. JAMA 1998; 279: 1383-91.
57. Nosaka K, Takahashi T, Nishi T, Imaki H, Suzuki T, Suzuki K, Kurokawa K, Endou H. An adenosine deaminase inhibitor prevents puromycin aminonucleoside nephrotoxicity. Free Rad Biol Med 1997; 22:597–605
58. Tobian L, Lange J, Ulm K, Wold L, Iwai J. Potassium reduces cerebral hemorrhage and death rate in hypertensive rats, even when blood pressure is not lowered. Hypertension 1985; 7: I110-14.
59. Law M, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I-Analysis of observational data among populations. BMJ 1991; 302:811-15.
60. Yang CS, Lin CH, Chang SH, Hsu HC. Rapidly progressive fibrosing interstitial nephritis associated with Chinese herbal drugs. Am J Kidney Dis 2000; 35: 313–18.