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Projected Cancer Risks From Computed Tomographic Scans Performed in the United States in 2007

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Arch Intern Med. 2009;169(22):2071-2077.

ESSENCE OF ARTICLE

“Results

Overall, we estimated that approximately 29 000 (95% UL, 15 000-45 000) future cancers could be related to CT scans performed in the US in 2007. The largest contributions were from scans of the abdomen and pelvis (n = 14 000) (95% UL, 6900-25 000), chest (n = 4100) (95% UL, 1900-8100), and head (n = 4000) (95% UL, 1100-8700), as well as from chest CT angiography (n = 2700) (95% UL, 1300-5000). One-third of the projected cancers were due to scans performed at the ages of 35 to 54 years compared with 15% due to scans performed at ages younger than 18 years, and 66% were in females. “

ARTICLE

Background

The use of computed tomographic (CT) scans in the United States (US) has increased more than 3-fold since 1993 to approximately 70 million scans annually. Despite the great medical benefits, there is concern about the potential radiation-related cancer risk. We conducted detailed estimates of the future cancer risks from current CT scan use in the US according to age, sex, and scan type.

Methods

Risk models based on the National Research Council's "Biological Effects of Ionizing Radiation" report and organ-specific radiation doses derived from a national survey were used to estimate age-specific cancer risks for each scan type. These models were combined with age- and sex-specific scan frequencies for the US in 2007 obtained from survey and insurance claims data. We estimated the mean number of radiation-related incident cancers with 95% uncertainty limits (UL) using Monte Carlo simulations.

Results

Overall, we estimated that approximately 29 000 (95% UL, 15 000-45 000) future cancers could be related to CT scans performed in the US in 2007. The largest contributions were from scans of the abdomen and pelvis (n = 14 000) (95% UL, 6900-25 000), chest (n = 4100) (95% UL, 1900-8100), and head (n = 4000) (95% UL, 1100-8700), as well as from chest CT angiography (n = 2700) (95% UL, 1300-5000). One-third of the projected cancers were due to scans performed at the ages of 35 to 54 years compared with 15% due to scans performed at ages younger than 18 years, and 66% were in females.

Conclusions

These detailed estimates highlight several areas of CT scan use that make large contributions to the total cancer risk, including several scan types and age groups with a high frequency of use or scans involving relatively high doses, in which risk-reduction efforts may be warranted.

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Redberg

Arch Intern Med 2009;169:2049-2050.

FULL TEXT

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J. Agric. Food Chem. All Publications/Website

Article

Chronic Dietary Kudzu Isoflavones Improve Components of Metabolic Syndrome in Stroke-Prone Spontaneously Hypertensive Rats

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J. Agric. Food Chem., 2009, 57 (16), pp 7268–7273

DOI: 10.1021/jf901169y

Publication Date (Web): July 22, 2009

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ESSENCE OF ARTICLE

“These results indicate that long-term dietary kudzu root extract supplementation can improve glucose, lipid, and blood pressure control in intact and ovariectomized SP-SHR.”

ARTICLE

Abstract

The present study tested the long-term effects of dietary kudzu root extract supplementation on the regulation of arterial pressure, plasma glucose, and circulating cholesterol in stroke-prone spontaneously hypertensive rats (SP-SHR). Female SP-SHR were maintained for 2 months on a polyphenol-free diet, with or without the addition of 0.2% kudzu root extract. Half of the rats in each diet group were ovariectomized, whereas the other half remained intact. Following 2 months on the diets, the 0.2% kudzu root extract supplementation (compared to control diet) significantly lowered arterial pressure (11–15 mmHg), plasma cholesterol, fasting blood glucose (20–30%), and fasting plasma insulin in both the ovariectomized and intact SP-SHR. These results indicate that long-term dietary kudzu root extract supplementation can improve glucose, lipid, and blood pressure control in intact and ovariectomized SP-SHR.

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http://www.uhmc.sunysb.edu/internalmed/nephro/webpages/Part_G.htm

CHRONIC RENAL FAILURE

Dr. Wadhwa

Objectives

- Learn about major etiologic causes of chronic renal failure
 - Understand the pathophysiology of nitrogen, potassium, sodium and water, acid-base, carbohydrates, lipids, and divalent ions metabolism in the course of chronic renal failure.
 - Understand the endocrine functions of the kidney and their pathology during chronic renal failure.
 - Learn the basic principles of drug metabolism in chronic renal failure.
 - Understand basic therapeutic strategies in chronic renal failure: hemodialysis, peritoneal dialysis, kidney transplantation.

Chronic renal failure (CRF) is defined as a permanent reduction in glomerular filtration rate (GFR) sufficient to produce detectable alterations in well-being and organ function. This usually occurs at GFR below 25 ml/min.

Four stages of decreased renal function may be visualized:

1. Silent – GFR up to 50 ml/min.
2. Renal insufficiency – GFR 25 to 50 ml/min.

3. Renal failure – GFR 5 to 25 ml/min
4. End-stage renal failure – GFR less than 5 ml/min.

Uremia (Azotemia) is a term applied to the manifestations of organ dysfunction seen in stages 3 and 4 as outlined above. Literally, uremia means urine in the blood. Azotemia, the accumulation of nitrogenous waste products, chiefly urea, in the blood is the hall mark of renal failure. It is a clinical syndrome resulting from retention of certain substances which are normally excreted into the urine and thus accumulate causing toxicity.

1. CAUSES OF CHRONIC RENAL FAILURE

Any disorder that permanently destroys nephrons can result in chronic renal failure. Most Common Causes of CRF are:

Diabetic nephropathy

Hypertensive nephrosclerosis

Glomerulonephritis

Interstitial nephritis

Polycystic kidney disease

About 100 to 150 per million persons in the U.S. develop CRF annually (0.010 to 0.015% per year); at an annual cost of \$25 – 35,000 per patient per year.

2. PATHOGENESIS

since the uremic syndrome resembles a systemic intoxication, the search for a putative uremic toxin has been the subject of intensive investigation. As yet, however, no single compound has been found to produce the clinical picture of uremia. Therefore it is more likely that multiple factors contribute to the pathogenesis of this syndrome.

2A. Retained Metabolic Products:

Many chemical compounds have been suspected to be responsible for the uremic syndrome. Some of these include:

Acetoin

Methylguanidine

Aliphatic amines

B2-Microglobulin

Amino acids

“Middle molecules”

Aromatic amines

Myoinositol

2,3-Butylene glycol

Creatinine

Other guanidines

Oxalic acid

Diamine oxidase

Gastrin Parathyroid hormone

(and fragments?)

Glucagon

Phenols

B2-Glucopein

Polyamines

Glucuronic acid

Pyridine derivatives

Growth hormone

Renin

Guanidinosuccinic acid

Retinol-binding protein

Indoles

Ribonuclease

Lipochromes

Urea

Uric acid

However, a distinct relationship between one or a combination of these substances and the entire syndrome has not been established in man. The toxic substances are responsible for the uremic syndrome is supported by:

1. Marked symptomatic improvement occurs after decreasing protein in the diet. This suggests that metabolites of protein are retained in renal failure and exert toxic effects.
2. Effective dialysis results in marked symptomatic improvement even though protein continues to be ingested. This suggests that toxic metabolites are removed by dialysis.
3. Uremic plasma seriously interferes with a variety of normal cell functions. The same plasma after dialysis has no adverse effects.

The relationship between toxic substances and uremia is exemplified by urea. When urea is present in high concentration in the body fluids, it may decompose spontaneously into ammonia and cyanate (Figure 2.1).

Cyanate is a potential toxin which combines irreversibly with normal proteins in cells and affects their functions. Cyanate administration in animals is followed by hypothermia, lethargy, anorexia, diarrhea, and seizures. However, there is little evidence that cyanate plays a role in uremic toxicity in man. Nevertheless, urea which is an end-product of protein metabolism, can decompose to substances with potential toxicity. This observation provides support for the chemical basis of the uremic syndrome.

Inferential evidence (mainly clearance data from dialytic therapy) suggests that molecules in the molecular weight range of 300-1500 daltons could be responsible for the uremic state. This has been termed the "Middle Molecule Hypothesis".

2B. Overproduction of Counter-regulatory Hormones:

Overproduction of parathyroid hormone in response to hypocalcemia and natriuretic hormone in response to volume overload could contribute to many aspects of the uremic state.

3C. Underproduction of Renal Hormones:

Decreased erythropoietin production causes anemia. Decreased 1-hydroxylation of vitamin D₃ contributes to bone disease. Clearly, these and other such deficiencies could play a role in the uremic state.

Undoubtedly, each of these factors plays a role in the development of the uremic syndrome. Later we shall look at the clinical manifestations of uremia. Let us turn for a moment to a manifestation of uremia at the cellular level.

3. CELLULAR DYSFUNCTION IN UREMIA

Hypometabolism and an abnormally low body temperature may be seen in patients with advanced, uncomplicated uremia. A characteristic feature of nearly every normal cell in the body is a very low concentration of sodium ions in the intracellular water compartment, e.g. in the muscle cells, about 10 mmol/L or less. In contrast, the concentration outside the cell is about 140 mmol/L. Under normal conditions sodium ions leak through the cellular membrane into the cell which increases sodium concentration inside the cell which activates the enzyme adenosine triphosphatase which promptly moves sodium from the cell into the extracellular space.

Two important events allow sodium transport: burning of glucose and consumption of oxygen. Removal of positively charged sodium ions from the cell accounts for production of a substantial portion of the body's heat. This process also leaves in its wake a negative charge, which in turn attracts and holds potassium ions inside the cell. Potassium is important for the proper functioning of a number of enzymes. The transport of sodium thus helps to concentrate potassium ions in the cell and to maintain normal body temperature (Fig. 3.7).

Deranged sodium transport in advanced uremia results in accumulation of sodium and chloride inside the cell, leading to accumulation of water and a fall in potassium concentration, with consequent defects in metabolic processes and a decline in heat production. A cell in which these changes take place has been referred to as the sick cell of uremia. Such changes have been found in RBC's, muscle cells and WBC's.

These changes can be reversed by adequate dialysis or successful renal transplantation.

Certain of the abnormal characteristics in the muscle cells of patients with advanced uremia can be reversed simply by removing protein from the diet and replacing it with optimal quantities of essential amino acids.

Besides the retention of salt and water in extracellular fluid, there is marked retention inside the cell. Although patients with end-stage renal disease may show no evidence of edema, one of the early changes commonly following initiation of dialysis therapy is a sharp decline in total body weight, which matches the loss of cellular salt and water. This loss corresponds in timing to correction of the derangement in sodium transport in nearly all cells.

4. PATHOPHYSIOLOGY

The most intriguing aspect of CRF is that compensatory mechanisms allow loss of 90% of GFR before manifestations of the uremic syndrome are evident. Thus a variety of adaptations compensate for the decreased GFR and allow a new steady state of external balance to exist, but on the other hand contribute to the uremic syndrome. In spite of these adaptations, the hallmark of CRF is the loss of flexibility in responding to challenges to external load of solutes and water. The adaptations include

4A. Intact Nephron Hypothesis:

Nephrons functioning in diseased kidneys maintain glomerulo-tubular balance. That is, filtration and net excretion of various substances are coordinated. (e.g. with normal renal function, usually 50-60% of filtered urea is reabsorbed from the tubules. In CRF it may fall to 30% to maintain balance).

4B. The Magnification Phenomenon:

although nephrons in diseased kidneys function homogeneously, they alter their handling of given solutes as needed to maintain balance of these solutes. That is, nephrons can magnify their excretion of a given solute. (e.g. tubular creatinine excretion is < 10% with normal renal function. In CRF it may increase to 30%).

4C. Trade-off Hypothesis:

The mechanisms that are magnified to maintain individual solute control may have deleterious effects on other systems. This trade-off is seen in the increased parathyroid hormone (PTH) secretion seen in CRF which enhances renal phosphorus excretion. PTH has been implicated in the pathogenesis of many disturbances of uremia (sleep, sex, bone, disease, anemia, lipidemia, vascular disease). The corollary of the trade-off hypothesis is the concept of proportional reduction of solute, that is, reduction of solute intake (e.g. phosphorus) in proportional to decrements in GFR could prevent the compensatory changes (e.g. increased PTH) which may contribute to the development of uremia.

5. SOLUTE HANDLING IN CHRONIC RENAL FAILURE

5A. Creatinine and Urea Balance.

Although creatinine is secreted and urea is reabsorbed through tubules, balance depends on their rates of filtration. Balance (rate of filtration) is maintained by allowing plasma concentrations to rise until renal excretion equals production. Urea reabsorption falls with the solute diuresis per nephron and thus the blood urea nitrogen need not rise as much as expected to maintain balance. Creatinine secretion is enhanced and thus excretion also is balanced to production at a plasma concentration less than anticipated.

In addition, urea is metabolized in increased amounts by gut bacteria as the blood urea nitrogen rises and creatinine production is reduced by metabolic suppression.

The figure shows the affect of a single decrease in GFR on creatinine balance. Note that CRF is consists of multiple decreases in GFR over time. If production of creatinine is assumed constant, then this figure illustrates the change in creatinine balance. The top panel shows a decrease in GFR of 50%. The excretion of creatinine falls with accumulation in total body reflected by an increase in serum creatinine (lower panel). A new steady state was reached when excretion again equaled production of creatinine.

This occurred at the expense of an elevated serum creatinine and total body creatinine. Another way of visualizing this new steady states is that the product of the new serum cr and new GFR must equal the product of the old serum cr and Old GFR (if creatinine production remains stable).

5B. Water Balance:

In order to maintain water balance, the fraction of water reabsorbed by the kidney must decrease. Thus, an increased flow per nephron ensues. With progressive CRF, the ability to excrete a water load is compromised and the patient may develop hypo-osmolarity. Urine concentration ability of the kidney becomes fixed around 300 mosm/kg of water and thus the patient is also susceptible to dehydration if water intake is lowered. Thus, a CRF patient is prone to both excess and deficit of water. Nocturia develops early in CRF because of decreased concentrating ability of urine during sleep.

5C. Sodium Balance:

In order to maintain sodium balance, the fraction of sodium reabsorbed must be decreased, thereby increased excretion of sodium fraction because of decreased GFR. A humoral natriuretic factor in CRF helps to increase sodium excretion.

In CRF, the kidneys are unable to reduce sodium excretion rapidly in response to a sudden decrease in intake or extrarenal losses (e.g. G.I. loss). Thus, major increase in sodium intake results in edema and major decreases in intake or increases in extrarenal losses result in volume depletion. The hallmark of CRF is the loss of flexibility in responding to challenges to external load of solutes and water.

While normal subjects can excrete sodium promptly following a sodium load with minimal effect on ECF, in CRF subjects delayed excretion results in ECF expansion. While normal subjects on salt restricted diet reduce urine Na to 20 mEq in 48 hours, CRF subjects may require 1-2 weeks for similar sodium conservation and thus are prone to sodium depletion. This is illustrated in fig. 9.5.

5D. Potassium Balance:

Increased tubular secretion of potassium helps maintain potassium balance until renal failure is severe. In normal subjects, 90% of potassium is excreted in urine and 10% in stool. In advanced CRF, fecal excretion of potassium increases to 50% of the potassium load. Thus, plasma potassium and body potassium are maintained on normal dietary intake. However the patient is susceptible to hyperkalemia from sudden potassium loads.

5E. Calcium and Phosphorus Balance:

Decreased GFR leads to a sequence of events outlined in the syllabus in the section of Ca and P metabolism. A trade-off occurs in the development of secondary hyperparathyroidism in that the elevated PTH increases phosphate excretion but contributes to bone disease and perhaps other system dysfunction as described earlier.

5F. Hydrogen Ion Balance:

CRF is associated with a continuous positive balance (retention) of hydrogen ions due to a decrease in the tubular ammonia production to excrete hydrogen in (Fig. 13.3).

Retained anions such as SO_4 and PO_4 contribute to acidosis. The bottom line is that bone serves as a sump for excess hydrogen ion and plasma HCO_3 concentration is preserved at only a modestly reduced concentration (about 15 mmol/L). However, flexibility is lost and severe acidosis may occur from small challenges.

6. PROGRESSION OF CHRONIC RENAL FAILURE

A variety of chronic renal diseases progress to end-stage renal disease, including chronic glomerulonephritis, diabetic nephropathy, and polycystic kidney disease. Although the underlying problem often cannot be treated, extensive studies in experimental animals and preliminary studies in humans suggest that progression in chronic renal disease may be largely due to secondary factors that are unrelated to the activity of the initial disease. These include systemic and intraglomerular hypertension, glomerular hypertrophy, the intrarenal precipitation of calcium phosphate, hyperlipidemia, and altered prostanoid metabolism (table).

Secondary factors and progression of chronic renal failure

- Intraglomerular hypertension and hypertrophy
- Phosphate retention, with interstitial CaPO_4 deposition
- Increased prostaglandin synthesis
- Hyperlipidemia, especially in the nephrotic syndrome
- Metabolic acidosis
- Proteinuria
- Tubulointerstitial disease
- Retained “uremic” toxins
- Filtered iron in nephrotic syndrome

The major histologic manifestation of these secondary causes of renal injury is focal segmental glomerulosclerosis. Thus, glomerular damage and proteinuria typically occur with progressive renal failure.

6A. INTRAGLOMERULAR HYPERTENSION AND GLOMERULAR HYPERTROPHY

In animal models, for example, a rise in intraglomerular pressure, due either to the compensatory response to nephron loss or to primary renal vasodilatation (as in diabetes mellitus), appears to play an important

role in the progressive glomerular scarring. The mechanisms by which intraglomerular hypertension might promote glomerular injury are incompletely understood. At least two factors may be involved:

- Direct endothelial cell damage, similar to that induced by systemic hypertension

- Increased pressure-induced movement of circulating macromolecules (such as

IgM and fibrinogen and complement metabolites) through the fenestrated endothelial cells into the subendothelial space in the glomerular capillary wall. The characteristic accumulation of these “hyaline” deposits can progressively narrow the capillary lumens, thereby decreasing glomerular perfusion and filtration.

An increase in glomerular size, as well as intraglomerular pressure, also may occur in these settings. This change can contribute to glomerular injury both by increasing wall stress and by causing detachment of the glomerular epithelial cells from the glomerular capillary wall.

Non-hemodynamic factors also may be important in the development of secondary glomerulosclerosis. Marked nephron loss in experimental animals can lead to glomerular cell proliferation, macrophage influx and accumulation of extracellular matrix components (leading to narrowing of the capillary lumens).

How these changes occur is not well understood, but cytokines such as platelet-derived growth factor and transforming growth factor- β (TGF- β) may play a contributory role. Experimental studies, for example, suggest that TGF- β may contribute to increased extracellular matrix production and the development of glomerulosclerosis in a variety of renal diseases.

Thus glomerulosclerosis results from the glomerular hypertension itself or from increased glomerular capillary flow and filtration (fig. 16-7).

In addition to processes affecting the glomeruli, secondary tubulointerstitial disease also is commonly seen. This change is often under-appreciated, but both the glomerular filtration rate and long-term prognosis are more closely related to the degree of tubulointerstitial, rather than glomerular injury.

6B. OTHER SECONDARY FACTOR -- Identification of the role of these secondary factors is important clinically because they can be treated, possibly preventing or at least minimizing further renal injury. Dietary protein restriction and the use of anti-hypertensive agents (particularly angiotensin converting enzyme inhibitors) have been most widely studied. In addition to the potential importance of intraglomerular hypertension and glomerular hypertrophy, the following factors also may contribute to secondary renal injury:

Phosphate retention -- A tendency to phosphate retention is an early problem in renal disease, beginning as soon as the glomerular filtration rate starts to fall. In addition to promoting bone disease, the excess phosphate also may contribute to progression of the renal failure. This may occur at least in part by phosphate precipitation with calcium in the renal interstitium, leading to an increase in renal calcium content even before the plasma creatinine concentration exceeds 1.5 mg/dL (132 μ mol/L). The calcium

phosphate salts may then initiate an inflammatory reaction, resulting in interstitial fibrosis and tubular atrophy.

These problems can be minimized by decreasing phosphate intake or by the use of oral phosphate binders. It has been suggested, for example, that the efficacy of protein restriction may be related in part to a concurrent decline in phosphate intake.

Altered prostanoid metabolism -- Glomerular prostaglandin production tends to be increased in glomerular disease. This response may represent an appropriate intra-nephronal adaptation, since the ensuing renal vasodilatation helps to maintain the GFR in the presence of an often marked reduction in glomerular capillary permeability induced by the underlying disease. This adaptation is reversed by an NSAID, leading to renal vasoconstriction and a subsequent fall in intraglomerular pressure. These changes are manifested clinically by reductions in glomerular filtration rate (usually by about 20 percent) and protein excretion (often by more than 50 percent) in many patients with chronic glomerular disease.

Non-randomized studies suggest that long-term therapy in responders (those with a substantial decline in proteinuria) may be associated with a lesser rate of progression to end-stage renal disease.

Hyperlipidemia – Hyperlipidemia is common in patients with chronic renal disease, particularly those with the nephrotic syndrome. In addition to accelerating the development of systemic atherosclerosis, experimental studies suggest that high lipid levels also may promote progression of the renal disease. The major evidence in support of this hypothesis are the observations in experimental animals that cholesterol loading enhances glomerular injury and that reducing lipid levels with a drug such as lovastatin slows the rate of progressive injury.

The factors responsible for the lipid effects are incompletely understood. In different animal models, a high cholesterol intake may be deleterious in association with a rise in intraglomerular pressure, while lipid-lowering agents may be beneficial without affecting glomerular hemodynamics. These disparate observations suggest that mechanisms other than intraglomerular pressure alone may play a contributory role. It has been shown experimentally, for example, that hyperlipidemia activates the mesangial cells (which have LDL receptors), leading to increased production of fibronectin (a component of the extracellular matrix) and of a chemo-attractant for monocytes. Both of these changes could contribute to glomerular injury. In addition, HMG CoA reductase inhibitors such as lovastatin may act independent of plasma lipid levels by directly inhibiting mesangial cell proliferation.

The applicability of these findings to human disease is unproven, since there are no studies evaluating the possible protective effect of lowering lipid levels. However, both increased mesangial lipid deposition and enhanced expression of LDL-receptors on mesangial and epithelial cells have been demonstrated in patients with chronic glomerular diseases. Mesangial phagocytosis and increased traffic of macromolecules through the more permeable glomerular capillary wall could be responsible for the lipoprotein deposition; in addition, the increase in receptors could promote lipid accumulation even in the absence of hyperlipidemia. Whether the deposited lipid contributes to the glomerular injury is uncertain.

Metabolic acidosis and increased ammonium production – As the number of functioning nephrons declines, each remaining nephron excretes more acid (primarily as ammonium). The local accumulation of ammonia can directly activate complement, leading to secondary tubulointestinal damage (at least in

experimental animals). On the other hand, buffering the acid with alkali therapy prevents the increase in ammonium production and minimizes the renal injury.

Although the renal protective effect of alkali therapy unproven in humans, there are other reasons (prevention of osteopenia and muscle wasting) why correction of the acidemia might be desirable. Sodium bicarbonate is preferred to sodium citrate in this setting, since citrate leads to a marked increase in intestinal aluminum absorption, possibly promoting the development of aluminum toxicity; this is most likely to occur in those patients treated with aluminum-containing antacids to bind dietary phosphate. The effect of citrate may be mediated both by keeping aluminum soluble (via the formation of aluminum citrate) and by binding of calcium in the intestinal lumen; the ensuing fall in free calcium then may lead to increased permeability of the tight junctions between the cells and a rise in passive aluminum absorption. Bicarbonate, on the other hand, does not produce these effects and therefore does not increase aluminum transport.

Anemia – Progressive anemia, due largely to erythropoietin deficiency, is a common complication of advanced renal disease. Experimental studies suggest that this may be a protective adaptation, since anemia leads to reduced vascular resistance which lowers both systemic blood pressure and intraglomerular pressure. Prevention of anemia in animals is associated with reversal of these changes and enhancement of the glomerular injury.

These observations may have clinical relevance, since anemia can now be corrected in predialysis patients by the administration of recombinant erythropoietin. Preliminary observations on a relatively small number of patients suggest that, although correction of the anemia with erythropoietin does raise the systemic blood pressure in advanced renal failure, there does not seem to be any acceleration of rate of progression.

Proteinuria – It has been suggested that proteinuria itself may contribute to disease progression, both by overloading the mesangium with macromolecules and by promoting tubulointerstitial disease. It is possible, for example, that a marked increase in protein filtration and subsequent proximal reabsorption leads to tubular cell injury and the release of lysozymes into the interstitium. Thus, reversing intraglomerular hypertension with protein restriction or antihypertensive therapy may be beneficial both by diminishing hemodynamic injury to the glomeruli and by reducing protein filtration (which is in part dependent upon the intraglomerular pressure).

Tubulointerstitial disease – All forms of chronic renal failure are associated with marked tubulointerstitial injury (tubular dilatation, interstitial fibrosis), even if the primary process is a glomerulopathy. Furthermore, the degree of tubulointerstitial disease is a better predictor of the glomerular filtration rate and long-term prognosis than is the severity of glomerular damage in almost all chronic progressive glomerular diseases, including IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, and lupus nephritis.

The mechanism by which the tubulointerstitial disease occurs is not well understood. As described above, both calcium phosphate deposition and metabolic acidosis with secondary interstitial ammonia accumulation may play a contributory role. There is also evidence that an active immunologic process is involved, beginning early in the course of the disease and in some cases being an extension of the

inflammatory process in the glomeruli. In some experimental models of renal disease, corticosteroid therapy can ameliorate the tubulointerstitial damage (without effect on the glomerular injury).

However, even effective therapy of the interstitial inflammation may not prevent progressive injury. In this setting, healing may be associated with interstitial fibrosis mediated in part by the release of cytokines such as transforming growth factor- β .

Retained toxins – Dialysis of nonuremic animals with glomerulosclerosis preserves the glomerular filtration rate and slows the rate of further glomerular damage. This observation suggests that retention of ultrafiltrable toxins during the course of progressive renal disease contributes to secondary glomerular injury. How this might occur is not clear.

Iron toxicity – Increased glomerular permeability can result in the filtration of the normally nonfiltered iron-transferrin complex. Dissociation of this complex in the tubular lumen leads to the release of free iron which can promote tubular injury by promoting the formation of hydroxyl radicals.

7. CLINICAL MANIFESTATIONS OF CRF

Clinical Manifestations:

The symptoms and signs which constitute the uremic syndrome are summarized below:

Neurological Disorders: Fatigue, lethargy, sleep disturbances, headache, seizures, encephalopathy, peripheral neuropathy including restless leg syndrome, paraesthesia, motor weakness, paralysis.

Hematologic Disorders: Anemia, bleeding tendency – due in part to platelet dysfunction.

Cardiovascular Disorders: Pericarditis, hypertension, congestive heart failure, coronary artery disease, myocardial pathology.

Pulmonary Disorders: Pleuritis, uremic lung.

Gastrointestinal Disorders: Anorexia, nausea, vomiting gastroenteritis, GI bleeding, peptic ulcer.

Metabolic-Endocrine Disorders: Glucose intolerance, hyperlipidemia, hyperuricemia, malnutrition, sexual dysfunction and infertility.

Bone, Calcium, Phosphorus Disorders: Hyperphosphatemia, hypocalcemia, tetany, metastatic calcification, secondary hyperparathyroidism, 1,25-dihydroxy vitamin D deficiency, osteomalacia, osteitis fibrosa, osteoporosis, osteosclerosis.

Skin Disorders: Pruritus, pigmentation, easy bruising, uremic frost.

Psychological Disorders: Depression, anxiety, denial, psychosis.

Fluid and Electrolyte Disorders: Hyponatremia, hyperkalemia, hypermagnesemia, metabolic acidosis, volume expansion or depletion.

Some of the important manifestations are elaborated below:

7A. Anemia:

Anemia is universal as GFR falls below 25 ml/min.; in certain disorders it may occur with mild renal insufficiency. Several factors contribute:

- a. Erythropoiesis is markedly depressed, mainly due to reduced erythropoietin production; in addition, there may be reduced end-organ response to erythropoietin with reduced heme synthesis.
- b. Red cell survival is shortened with a mild to moderate decrease in red cell life span, possible due to a “uremic” toxin.
- c. Blood loss is common in uremic patients, possibly secondary to abnormal coagulation due to decreased platelet function.
- d. Marrow space fibrosis occurs with osteitis fibrosa of secondary hyperparathyroidism resulting in decreased erythropoiesis.

7B. Hypertension:

Hypertension occurs in 80% to 90% of patients with renal insufficiency. Several factors contribute:

- a. Expansion of extracellular fluid volume; this may arise because of reduced ability of the kidney to excrete ingested sodium.
- b. Increased activity of the renin-angiotensin system is common; many patients with advanced renal failure have renin levels that are not completely suppressed by the elevated blood pressure.
- c. Dysfunction of the autonomic nervous system occurs with insensitive baroreceptor sensitive and with increased sympathetic tone.
- d. Possible diminished presence of vasodilators: there may be decreased renal generation of prostaglandins or of factors in the kallikrein-kinin system.

7C. Altered Calcium and Phosphorus Metabolism (Renal Osteodystrophy):

- a. As GFR decreases there is a slight retention of phosphorus; this phosphorus retention can lead to hypocalcemia, which stimulates PTH. The latter causes phosphaturia, with restoration of serum phosphorus and calcium toward normal. However, this occurs only at the expense of elevated serum PTH levels. This cycle repeats itself in progressive renal failure with PTH levels increasing progressively. Ultimately, the renal tubule can no longer respond to higher levels of PTH with a further decrease in phosphorus reabsorption. When this occurs, hyperphosphatemia develops, hypocalcemia may become prominent and PTH level can increase to very high levels. High PTH levels cause bone disease with severe osteitis fibrosa.
- b. Altered vitamin D metabolism occurs secondary to decreased renal mass or to phosphate retention, with decreased synthesis of 1,25 (OH)₂ D₃. This deficiency leads to: 1. Diminished intestinal absorption of calcium, 2. decreased calcemic response of the skeleton to PTH, 3. impaired suppression of PTH

secretion for any increase in serum calcium level, and 4. altered collagen synthesis. With advanced renal failure, these events can lead to secondary hyperparathyroidism and osteomalacia.

c. Skeletal resistance to the calcemic action of PTH develops; thus an increased PTH is required to maintain serum calcium at any level.

d. Finally, accumulation of aluminum from aluminum binding antacids may contribute to the bone disease.

8. MANAGEMENT OF CHRONIC RENAL FAILURE

8A. Treatment of primary renal disease:

The primary disease can be responsible for the continuous deterioration in renal function. It is important to recognize and to treat the primary renal disease. (e.g. certain disorders such as crescentic glomerulonephriti, membranous glomerulonephronpathy or analgesic nephropathy are potentially treatable or can be stabilized).

8B. Treatment of reversible aggravating factors:

The progression of the decrease in GFR may be documented by plotting the reciprocal of the serum creatinine ($1/S_{cr}$) against time. Conceptually, this means that GFR (nephrons) is being lost at a constant rate. A relatively linear course should be displayed. Deviation from this course should alert one to the presence of disorders which can acutely worsen renal function as shown below.

These factors aggravate the progression of renal failure and are known as reversible aggravating factors. The appropriate treatment of these factors can reverse or stabilize renal function to its pre exacerbation level. Various reversible factors are:

1. Salt and water depletion leading to hypovolemia
2. Systemic or renal infection
3. Accelerated hypertension
4. Nephrotoxic drugs
5. Urinary obstruction
6. Acute heart failure
7. Hypercalcemia

8C. Treatment of secondary factors to prevent or slow the progression of renal disease:

Human studies that are currently under way should determine the efficacy of treating at least some of these secondary hemodynamic and metabolic abnormalities in an attempt to preserve renal function. If these modalities are effective, the benefit is likely to be greatest if begun before a great deal of

irreversible scarring has occurred. Thus, protective therapy may have the greatest impact if initiated relatively early in the course, before the plasma creatinine concentration exceeds 1.5 to 2 mg/dL (132 to 176 mmol/L).

Despite the lack of conclusive evidence, many physicians have already begun using some of the above modalities in patients with progressive renal disease. Current recommendations might include:

□ □ Treatment of hypertension at any stage of the disease, preferably beginning with an angiotensin converting enzyme inhibitor or possibly diltiazem or verapamil. Concurrent diuretic therapy will often be necessary in patients with fluid overload.

The optimal level of blood pressure control is uncertain, but diastolic pressures of < 80 mmHg may be desirable. Even normotensive patients should be treated if they have proteinuria, which is a marker for possible hemodynamically-mediated glomerular injury. The aim of therapy in this setting (or in patients with overt hypertension) is to diminish protein excretion, which may be a marker for reduced intraglomerular pressure and improved glomerular permselectivity.

□ □ The optimal level of protein intake has also not been determined but it may be reasonable to restrict intake to 0.8 to 1 g/kg of high biologic value protein in mild to moderate disease (plasma creatinine concentration less than 2.0 mg/dL { 176 mmol/L}) and to 0.6 to 0.7 g/kg in more advanced renal insufficiency. This should be accompanied by phosphate restriction and , if present, treatment of hyperphosphatemia with calcium carbonate or calcium acetate.

□ □ If present, both hyperlipidemia and metabolic acidosis (plasma bicarbonate concentration less than 21 meq/L with a reduced extracellular pH) should probably be treated. In addition to possible renal protection, these modalities also may diminish systemic atherosclerosis and muscle and bone breakdown, respectively.

8D. Treatment of end stage renal failure:

When GFR falls below 5 ml/min, the patient usually can not live without renal replacement therapy. Renal replacement therapy includes dialysis and kidney transplantation as illustrated below:

Various social or medical factors influence decisions about peritoneal or hemodialysis, and transplantation in the treatment of end-stage renal failure. It should also be noted that none of the above are panaceas and each, modality is associated with complications and failures.

[http://www.patient.co.uk/doctor/Chronic-Renal-Failure-\(CRF\).htm](http://www.patient.co.uk/doctor/Chronic-Renal-Failure-(CRF).htm)

Chronic Renal Failure (CRF)

See related article Chronic Kidney Disease and its Management.

Chronic renal failure is usually taken to be synonymous with stage 4 (severe impairment) chronic kidney disease (CKD) or stage 5 CKD (established renal failure) - see the Assessing Renal Function article for information about glomerular filtration rate (GFR).

The 5 stages of Chronic Kidney Disease (CKD)¹

eGFR (estimated GFR) STAGE

>90 ml/min/1.73m² with another abnormality* Stage 1 CKD - without another abnormality, regard as normal

60-89 ml/min/1.73m² with another abnormality* Stage 2 CKD - otherwise regard as normal

30-59 ml/min/1.73m² (moderate impairment) Stage 3 CKD

15-29 ml/min/1.73m² (severe impairment) Stage 4 CKD

<15 ml/min/1.73m² (established renal failure) Stage 5 CKD

*e.g. already known to have proteinuria, haematuria (but no urological cause), microalbuminuria (in diabetes), polycystic disease or reflux nephropathy

Management

All stages of CKD²

- Regular measurements of kidney function and other laboratory tests depending on the severity of kidney impairment.
- General health advice: smoking cessation, weight loss, aerobic exercise, limiting alcohol intake, limiting sodium intake.
- Avoidance of nephrotoxins, e.g. IV radiocontrast agents, NSAIDs, aminoglycosides.
- Cardiovascular prophylaxis:
 - o For patients with 10 year risk of cardiovascular disease of greater than 20%, consider aspirin treatment (if BP is below 150/90 mmHg) and lipid-lowering drug therapy.
 - o Blood pressure monitoring: blood pressure should be measured at least annually.
 - o Control of hypertension: hypertension should be tightly controlled. The threshold for initiation of anti-hypertensive medication:
 - If urine protein/creatinine ratio (PCR) is below 100 mg/mmol: threshold 140/90 mmHg, target 130/80 mmHg.
 - If urine PCR is above 100 mg/mmol: threshold 130/80 mmHg, target 125/75 mmHg.
- ACE inhibitor or angiotensin receptor blocker to be started:

- o If urine PCR is above 100 mg/mmol.
- o In diabetic patients with micro-albuminuria.
- o Serum creatinine and potassium should be checked before starting medication, two weeks after starting, and after subsequent increases in dose. If creatinine increases by more than 20% or fall in GFR of more than 15%, repeat creatinine, check potassium and refer for specialist opinion on whether to stop treatment or to investigate for renal artery stenosis.
- o If hyperkalaemia is present (serum K above 6 mmol/l): stop relevant drugs, eg. NSAIDs and potassium-retaining diuretics; check diet and proprietary treatments, e.g. LoSalt. If hyperkalaemia persists the ACE or ARB should be stopped.

Additional management for CKD stage 3 includes²

- Annual measurement of haemoglobin, potassium, calcium and phosphate.
- If Hb below 11 g/dL and other causes excluded, treat with erythropoiesis stimulating agents to maintain Hb 11-12 g/dL depending on the patient's functional needs.
- Request renal ultrasound in patients with lower urinary tract symptoms, refractory hypertension, unexpected progressive fall in GFR.
- Immunise against influenza and pneumococcus.
- Review all prescribed medication regularly to ensure appropriate doses.
- Avoid nephrotoxic drugs including NSAIDs wherever possible.
- Check parathyroid hormone concentration when Stage 3 is first diagnosed: if raised, check serum 25-hydroxyvitamin D and if low, treat with ergocalciferol or cholecalciferol with calcium supplement (not calcium phosphate). Repeat PTH after 3 months and refer if still raised.

Additional management for CKD Stages 4-5 includes²

- Care of all patients with stage 4 or 5 CKD should be discussed formally with a nephrologist even if it is not anticipated that renal replacement therapy will be appropriate. Exceptions may include:
 - o Patients with another terminal illness.
 - o Patients with stable function in whom all the appropriate investigations and management interventions have been performed and who have an agreed and understood care pathway.
 - o Patients in whom further investigation and management is clearly inappropriate.
- 3-monthly tests: serum creatinine (for eGFR), Hb, calcium, phosphate, bicarbonate, parathyroid hormone.
- Dietary assessment.

- Immunisation against hepatitis B.
- Investigation and treatment of phosphate retention and hyperparathyroidism.
- Correction of acidosis.
- Timely provision of dialysis access depending on treatment choice.

Renal replacement therapy

Indications for renal replacement therapy (haemodialysis, peritoneal dialysis, chronic ambulatory peritoneal dialysis or renal transplantation) include:

- Serum creatinine greater than 500 mmol/L.
- Symptoms: pericarditis, encephalopathy, peripheral neuropathy, intractable gastrointestinal symptoms, failure to thrive and malnutrition.
- Severe metabolic acidosis: bicarbonate less than 12 mmol/L.

Complications

- Anaemia: left ventricular hypertrophy, fatigue, impaired cognitive functioning
- Coagulopathy
- Hypertension: left ventricular hypertrophy, heart failure, stroke, cardiovascular disease
- Calcium phosphate loading: cardiovascular and cerebrovascular disease, arthropathy, soft tissue calcification
- Renal osteodystrophy: disorders of calcium, phosphorus and bone, most commonly osteitis fibrosa cystica
- Bone changes of secondary hyperparathyroidism: bone pain and fractures
- Neurological: uraemic encephalopathy, neuropathy including peripheral neuropathy
- Dialysis amyloid: bone pain, arthropathy, carpal tunnel syndrome
- Fluid overload: pulmonary oedema, hypertension
- Malnutrition: increased morbidity and mortality, infections, poor wound healing
- Glucose intolerance due to peripheral insulin resistance

Management of complications

- Water and electrolyte balance:

- o Patients with chronic kidney disease pass normal volumes of urine. Precise restriction of fluid intake is only required for patients with oliguria. The usual recommendation is for a daily intake equal to the daily urinary output plus 500 mL (for insensible losses).
- o Patients should avoid binge drinking and be vigilant in replacing extra fluid losses in hot weather and during episodes of diarrhoea or vomiting.
- o Severe acute volume overload may require high dose loop diuretics or dialysis.
- o Dietary restriction to 60 mmol/day each of sodium and potassium is appropriate but compliance is greatly improved with sensible and flexible dietary advice.
- o Loop diuretics (with the addition of a thiazide diuretic if resistant) improve sodium balance and blood pressure.
- o Hyperkalaemia is treated with dialysis if the potassium level rises above 7 mmol/L. Otherwise treatment is directed towards the cause, e.g. excess fruit, chocolate or coffee, gastrointestinal haemorrhage, acidosis or tissue necrosis. Hyperkalaemia with the GFR still above 10 mL/min may be due to hyporeninaemic hypoaldosteronism in patients with diabetes, hypoadrenalism or as a result of treatment with ACE inhibitors.
- Anaemia:
 - o Erythropoietin is given with iron. The serum ferritin is monitored throughout treatment and iron is stopped if the ferritin level becomes too high, e.g. above 500 mcg/L.
 - o Early erythropoietin therapy may prevent left ventricular hypertrophy.
 - o The timing for initiation of treatment remains uncertain. The haemoglobin level is usually maintained at or above 11 g/dL.
- Acidosis:
 - o Chronic acidosis aggravates hyperkalaemia, inhibits protein synthesis and accelerates calcium loss from bone.
 - o Treated with sodium bicarbonate as long as the patient can tolerate the increased sodium load. Additional sodium may cause fluid overload and worsen hypertension.
- Hyperphosphatemia:
 - o Occurs late in chronic kidney disease.
 - o Treated with dietary restriction, dietary phosphate binders and calcium carbonate.
- Hypocalcaemia:
 - o Prescribe calcium supplements, with or without calcitriol.
- Hyperparathyroidism:

- o Reduce hyperphosphataemia by diet and phosphate binders.
 - o Prescribe 1,25-dihydroxycholecalciferol and maintain a normal calcium level.
 - o Secondary hyperparathyroidism starts early in chronic renal failure and is difficult to treat when it becomes established.
 - o Secondary hyperparathyroidism may lead to tertiary hyperparathyroidism if not treated effectively.
 - Malnutrition:
 - o Must be avoided, although protein restriction can slow progression of renal failure.
 - o Restriction of dietary protein slows the progress of glomerulosclerosis in residual nephrons in animal experimental models.
 - o There remains controversy as to the benefits of protein restriction for treatment. Although patients are advised against high-protein diets, low-protein diets are not usually recommended and the emphasis is to maintain good nutrition.
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 2. The Renal Association; UK Guidelines for the management of Chronic Kidney Disease. June 2005.
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Internet and further reading

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Acknowledgements EMIS is grateful to Dr Colin Tidy for writing this article. The final copy has passed scrutiny by the independent Mentor GP reviewing team. ©EMIS 2008.

DocID: 1959

Document Version: 20

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