

Introduction to Clinical Medicine - Chronic Kidney Disease

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Chronic renal disease failure is a common disease. It affects every aspect of someone's life, from what they eat and drink, to their energy level, to where they can travel, to how long they live.

Patients with chronically impaired renal function can be divided into two groups. First are the patients with renal function impaired to the degree that they require renal replacement therapy. One type of renal replacement therapy is dialysis. Another treatment option is renal transplantation. A second group is those with some degree of renal insufficiency, but not enough to require dialysis. This is termed chronic kidney disease (CKD).

ESRD affects over 200,000 people in the U.S. Average life expectancy is decreased by ~60-70%, regardless of age. Patients with ESRD spend an average of ~7 days a year in the hospital. Cardiovascular disease and gastrointestinal bleeding are common. Average health care costs exceed \$68,000 per year per patient

Caring for the patient with chronic renal disease involves several components. One component involves identifying and treating the underlying disease. Then, interventions to slow the rate of worsening should be considered. A third component involves providing medical support for the patient requiring renal replacement therapy, also known as dialysis.

Stages of CKD

| Stage | Description | GFR (ml/min/1.73m ²) | % of adult population |
|-------|------------------------------------|-------------------------------------|--------------------------|
| 1 | Kidney Damage with Normal or ↑ GFR | ≥90 | 3.3% |
| 2 | Kidney damage with mild ↓ GFR | 60-89 | 3.0% |
| 3 | Moderate ↓ GFR | 30-59 | 4.3% |
| 4 | Severe ↓ GFR | 15-29 | 0.2% |
| 5 | Kidney failure | < 15 (or dialysis) | 0.2% |

Causes of CKD

The most common causes of CKD include: hypertension, diabetes, primary glomerulonephritis, secondary glomerulonephritis, polycystic kidney disease and multiple myeloma. Evaluation of the patient with chronic kidney disease should include consideration of each of these; *the most effective therapies are based upon treating the underlying cause.*

Diabetes is responsible for causing end-stage renal disease in ~40% of patients with stage V chronic kidney disease. In general, the progression of diabetes diabetic nephropathy is fairly predictable (Figure 1). Diabetic nephropathy is fairly uncommon in patients with diabetes duration less than five years. However, the duration of diabetes in those with adult onset diabetes may be difficult to determine.

Most patients with diabetic nephropathy have end-organ damage from their diabetes in sites other than the kidneys. Diabetic retinopathy is very common. Atherosclerotic peripheral vascular disease is very common, as is neuropathy.

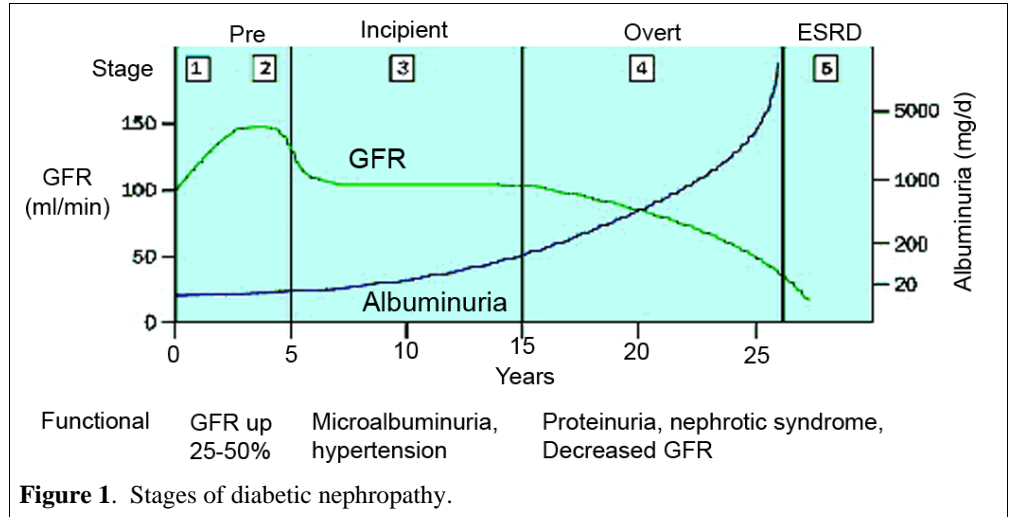


Figure 1. Stages of diabetic nephropathy.

Most patients with diabetic nephropathy will, by the time they develop decreased GFR, excrete at least 1 g per day of proteinuria. The early stages, incipient diabetic nephropathy, can be screened for by quantitative urine protein tests. The presence of microalbuminuria is highly predictive of progression to covert diabetic nephropathy and interventions should be started at the time of incipient diabetic nephropathy.

Chronic hypertension is the second most common cause of chronic kidney disease, and recent evidence suggests that may have a becoming more common in diabetic nephropathy. Since most patients with chronic tape kidney disease have some degree of hypertension, this diagnosis should be one of exclusion after evaluating other possible diagnoses.

Glomerulonephritis, both primary and secondary should be evaluated in patients with chronic kidney disease. If an underlying glomerulonephritis is identified, and aggressive treatment of his underlying problem a result in either stabilization or even improvement and reversal of their chronic kidney disease.

Autosomal dominant polycystic kidney disease is responsible for approximately 7% of cases of end-stage renal disease. This is an autosomal dominant genetic disorder that results in the replacement of the renal parenchyma with



Figure 2. Kidney in autosomal dominant polycystic kidney disease. A normal kidney is shown in the center.

innumerable renal cysts. The renal ultrasound is highly effective screening tool for autosomal dominant polycystic kidney disease. Because this is an autosomal dominant genetic condition with essentially 100% penetrance, an accurate family history may be very helpful in identifying patients who are likely to have polycystic kidney disease. However, a negative family history does not exclude this diagnosis as there is a remarkably high spontaneous mutation rate in the PKD1 and PKD2 genes which are responsible for autosomal dominant polycystic kidney disease.

In some cases, the diagnosis can be suggested by physical examination. The kidneys may become so enlarged with the renal cysts that they may become football-sized or larger. In this case, they are frequently palpable on abdominal examination.

The history may also be helpful; many patients have recurrent urinary tract infections that lead to severe infections and/or recurrent severe flank pain due to spontaneous hemorrhages into the renal cysts.

Autosomal dominant polycystic kidney disease is not a renal-limited disease. Intracranial aneurysms are present in ~4% of patients. If the person has a positive family history for intracranial aneurysms or intracranial hemorrhage, they may have as much as a 10% risk. Hepatic, pancreatic, and ovarian cysts are very common. Recurrent abdominal pain due to diverticulitis is common and there is evidence of an increased risk of cardiac valvular disease.

Multiple myeloma is a plasma cell tumor. In some cases the monoclonal immunoglobulins that are produced are nephrotoxic and can result in progressive renal dysfunction. In many of these cases, the patient is relatively asymptomatic and comes to medical attention only during medical evaluation of their chronic kidney disease. A classic finding is a negative urine dipstick for protein but a positive urine protein quantitative assay. Remember, the urine dipstick is an enzymatic assay for albumin, and will not detect light chains or heavy chains in the urine.

Slowing the progression of chronic renal insufficiency

A common theme that you will see in medicine throughout your career is that all too often adaptive processes that are beneficial in the short-term are detrimental in the long-term. One example is that an epinephrine surge in response to stress is beneficial in the short-term, in that it may help the individual respond to the specific circumstances. However, long-term epinephrine release leads to hypertension, cardiac arrhythmias, increased risk of stroke or heart attack, and even clinical depression.

The body's responses to chronic renal insufficiency are similar, evoking short-term beneficial maneuvers that are detrimental in the long-term. Indeed, these responses can themselves lead to further renal disease and worsening of the renal insufficiency, completely independent of the initiating disease that lead to the renal insufficiency.

Four interventions appear to interrupt these responses, and appear to slow the progression of chronic renal insufficiency. Of course, one should also treat the underlying cause of the renal disease.

First, strict *blood pressure control* is essential. If only one therapy can be instituted, blood pressure control should be the one. Blood pressure control alone probably decreases the rate of renal loss by $\sim 2/3$. The desired blood pressure goal is $\sim 125/75$.

Second, the *renin-angiotensin system* plays an important role in the progression of chronic kidney disease. Accordingly, inhibiting the renin-angiotensin system, either with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, slows the progression of chronic kidney disease. In most cases, there's more evidence for beneficial effects of angiotensin converting enzyme inhibitors.

Dietary protein restriction is the third therapy that should be considered. Amino acids increase GFR, beneficial in the short-term, but detrimental in the long-term. However, many patients with renal disease spontaneously eat a low-protein diet as a complication of underlying chronic illness. Dietary protein restriction should be undertaken only after assessing protein intake and considering the potential benefit to the patient, which includes decreasing compliance with other therapies because of the difficulty of dietary compliance.

Last, hyperlipidemia, especially elevated LDL levels, should be treated. Animal studies clearly show that elevated LDL levels increase the rate of loss of GFR, whereas decreasing LDL is protective. The exact mechanism through which LDL is detrimental has not been completely elucidated.

Caring for the patient with ESRD

Patients with ESRD require one of three therapies to maintain life, hemodialysis, peritoneal dialysis or renal transplantation. A patient with no renal function who receives none of these therapies will typically die within approximately two weeks. Each of these modalities requires special considerations by physicians.

Hemodialysis

Hemodialysis is the most common form of renal replacement therapy. Patients come for dialysis three times a week for sessions that last ~ 4 hours. Blood is withdrawn from their body, run through the hollow, semi-permeable fibers of a dialysis cartridge and returned to their body. Dialysis fluid is present on the other side of the fibers. Diffusion of solutes and other molecules between blood and dialysis fluid allows removal of compounds normally removed by the kidneys and addition to the blood of molecules that the kidney is not providing. Blood is typically run through the dialysis machine at a rate of ~ 450 ml/min.

Specialized blood vessels must be present in the patient for *hemodialysis access*. These are surgically

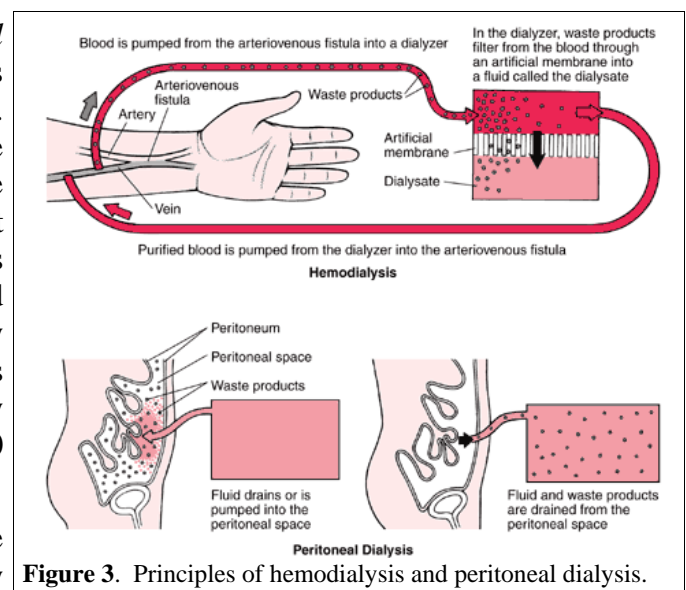


Figure 3. Principles of hemodialysis and peritoneal dialysis.

created large diameter, high-flow vessels, either an arteriovenous fistula, using native vessels, or a synthetic graft, placed between native vessels. The purpose of this specialized vessel is to allow a blood vessel large enough for the high rates of blood flow required for hemodialysis. This hemodialysis access is critical for life. Patients should be instructed not to allow either blood draws from that arm or blood pressure to be measured in that arm. A sign to this effect should be placed at the head of the bed of every hospitalized dialysis patient. The dialysis access should be used only by specialized trained dialysis nurses, and should not be used for drawing blood or for giving intravenous medications.

Most patients with ESRD make little-to-no urine. Because fluid ingested is only removed at the thrice-weekly dialysis sessions, they must *limit their fluid intake* to prevent edema development, particularly pulmonary edema, and to prevent worsening of their hypertension.

Phosphate intake must also be limited. Phosphate is excreted only by kidneys, and is poorly removed by dialysis. To prevent its build-up, ESRD patients must take medications that bind phosphate in the GI tract before it is absorbed. In addition, dietary phosphate ingestion should be limited.

The number of circulating RBC's is regulated by *erythropoietin*, a hormone produced only in the kidney in adults. In the absence of renal erythropoietin production patients develop a normochromic, normocytic anemia. Genetically-produced human erythropoietin is available, and routinely used to replace endogenous erythropoietin production.

Infections should receive extra attention in patients who have ESRD. ESRD alters temperature regulation, so that these patients do not mount the normal febrile response to an infection. *Even a low-grade temperature, 37.5°C, should be considered as a sign of a serious infection.* Moreover, ESRD suppresses the immune system, making infections potentially more difficult to treat.

Cardiovascular disease is the most common cause of death in patients suffering from ESRD. A high level of suspicion for ischemic heart disease should be maintained at all times.

Renal Transplantation

Renal transplantation is the preferred treatment for stage five chronic kidney disease for the majority of patients. For most people, it results both on a better quality of life and for longer life expectancy.

The major problem of renal transplantation is the need for life-long immunosuppression to prevent rejection of transplanted kidney. This makes patient were susceptible to infections. A very high level of suspicion should be maintained in all renal transplant patients for infection in the

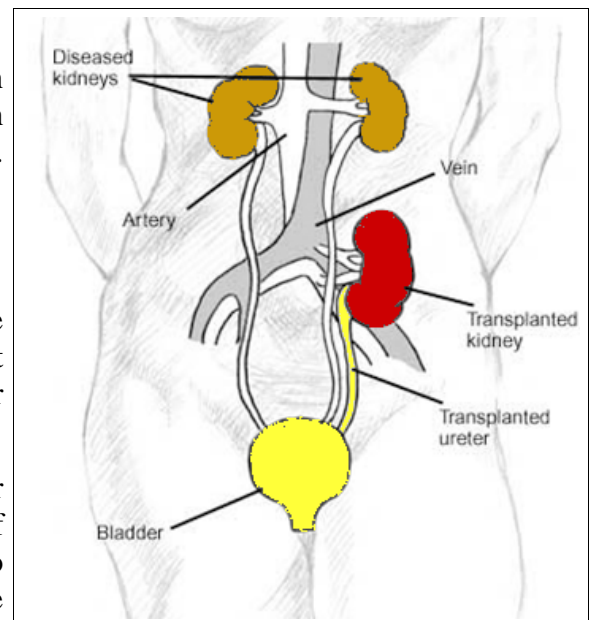


Figure 4. Example of placement of renal transplant kidney.

face of even low-grade fevers, and infection should be aggressively treated.