Chronic Kidney Disease (CKD) — Pathophysiology and Diagnosis

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The kidneys are our body’s central metabolic organs. They regulate water and electrolyte balance and are responsible for the removal of potentially toxic substances and medications. Many common diseases can lead to damaged kidneys and an impairment of their function. Chronic renal failure is a systemic disease with significant effects on the body. This article examines the mechanisms and processes of chronic kidney disease.

Definition of Chronic Kidney Disease

Determination of Chronic Kidney Disease

Chronic renal failure is defined as an irreversible decrease of not only glomerular and tubular function but also endocrine renal function. It presents as pathologically disturbed excretory and incretionary renal function. This damage has to have been exhibited for longer than 3 months.
Epidemiology and Etiology of Chronic Kidney Disease

Causes and Distribution of Chronic Kidney Disease

The incidence of chronic renal failure is approximately 10 cases per 100,000 people. In industrialized nations alone, tens of thousands of people are dependent on dialysis because of the widespread contributory causes of chronic kidney failure in these countries.

The most common cause of chronic renal failure by a significant margin is diabetic nephropathy (Kimmelstiel-Wilson syndrome, diabetic glomerulosclerosis), at 30–40% of cases. Approximately 20% of patients suffer from hypertensive nephropathy.

Glomerulonephritis is responsible for almost 15% of cases and primarily affects younger people. Polycystic kidney disease and tubulointerstitial nephritis are each responsible for approximately 10% of cases. Congenital obstructive urinary flow disorders, chronic-recurrent nephrolithiasis, or amyloidosis can permanently damage the kidneys and lead to chronic renal failure.

Pathophysiology of Chronic Kidney Disease

The Pathophysiological Processes of Chronic Kidney Disease

Chronic renal failure is caused by a progressive decline of all kidney functions, ending with terminal kidney damage. During this time, there is modulation and adaptation in the still-functional glomeruli, which keeps the kidneys functioning normally for as long as possible. The remaining glomeruli, therefore, experience a rise in pressure through hyperfiltration.

The release of various cytokines and growth factors leads to hypertrophy and hyperplasia. At the same time, the function of the glomeruli suffers due to the excessive
demands on them, leading to increased permeability and proteinuria. Increased protein concentrations in the proximal tube system are direct nephrotoxins and can further impair kidney function.

There are four phases of chronic renal failure:

1. Reduction in Excretory Function

Breakdown of excretory function is the consequence of an accumulation of endogenous and extraneous substances. This leads to changes in pharmacokinetics and an increase in the concentration of various medications. Breakdown occurs when the remaining glomeruli are confronted by a surplus of waste products, leading to osmotic diuresis. There is a reduction in the maximal concentrating capacity of the kidney. In order to filter the physiological quantity of dissolved substances, the nephrons produce between 3 and 4 times as much urine during renal failure, resulting in an accumulation of waste substances.

2. Reduction in Incretory Renal Function

Because the kidney plays a part in the regulation of many important hormonal cycles, chronic renal failure also has endocrinal consequences. Through a shortage of erythropoietin, there is a reduction in erythrocyte synthesis, which leads to renal anemia; uremia then leads to a reduction of functional erythrocytes due to hemolysis or hemorrhages.

Vitamin D production is also impaired, and phosphate excretion is reduced. Secondary hyperparathyroidism and the associated renal osteopathy ('high-turnover' osteopathy) develop as a result of hyperphosphatemia. Parallel to this, other pathomechanisms lead to a disruption in bone metabolism: osteomalacia occurs due to a disruption of mineralization, and adynamic bone disease occurs due to a reduction in bone cell activity (particularly in dialysis patients).

3. Over-hydration and the Disruption of Electrolyte Balance

As long as the glomeruli can manage to compensate, diuresis and fractional sodium excretion rise. If the glomerular filtration rate noticeably drops, then the ability to compensate is exhausted, leading to increased retention of water and electrolytes.

Hypertension, pulmonary edema, and peripheral edema result from overhydration. Water and salt excretion are thereby inextricably linked. Diuretics can aid in water and salt excretion where critical glomerular damage is present. Early loss of salts as a result of the disturbance in the resorption process can actually be made worse by the use of diuretics.
Thus, as the glomeruli adapt to compensate, the tubular transport mechanisms also adapt in order to prevent hyperkalemia through increased potassium secretion. Hyperkalemia only develops as a result of hyperstimulation of the resorption capacity. As many patients are treated with calcium-sparing diuretics due to previous conditions, it is vital to refer to patient’s medication history and adapt the treatment plan accordingly.

Acidosis also rises alongside hyperkalemia. The kidneys can no longer sufficiently eliminate accumulating protons due to a strongly reduced glomerular filtration rate. This metabolic acidosis leads to increased bone calcium release and strengthening renal osteopathy, an increase in gastrointestinal problems, and the impairment of protein metabolism.

4. Toxic Organ Damage as a Result of Retention of Urinary Excreted Metabolites
Toxic organ damage can be explained under the umbrella term ‘uremic syndrome.’ The rise in urinary excreted metabolites in the blood is called azotemia. These metabolites include urea, creatinine, beta-2 microglobulin, parathyroid hormone, among others. Uremic syndrome (uremia) principally describes a systemic disruption of all organ functions, especially the circulatory system, central nervous system, blood, and membranes.

Clinically, many symptoms of chronic renal failure can be detected via the skin. Patients often have macules (‘café au lait’ spots), are conspicuously pale, and have a gray, dirty-looking complexion. They often complain of pruritus. Internal membranes are also affected, leading to pericarditis, peritonitis, and pleurisy.

Uremia can also lead to hemolysis with anemia. Simultaneously, thrombocyte and leukocyte dysfunctions or deficiencies can arise.

People with chronic renal failure have a generally increased risk of atherosclerosis with an elevated cardiovascular risk. This leads to media calcification caused by calcium phosphate and to intima calcification through inflammatory factors and cholesterol plaques. Hypertension is common, along with edemas and pulmonary congestion.

Impairments of the central nervous system are indicated by a reduction in vigilance, from general drowsiness to uremic coma. Seizures can occur. Uremia also causes polyneuropathy with paresthesia.

Symptoms of Chronic Kidney Disease

Clinical Presentation of Chronic Kidney Disease

Chronic renal failure often begins with generalized symptoms such as tiredness, loss of appetite, and headaches. Further early indicators are polyuria, newly emerging or worsening hypertension, or peripheral edemas. Depending on the etiology, there can also be flank pain or fever.

As the disease progresses, increased tiredness, paleness, headaches, visual disturbances, and a severe loss of renal capacity become noticeable. Uremic gastroenteropathy leads to a loss of appetite and nausea. Pruritus occurs and muscle fibrillations become apparent.

In the final stages, renal failure leads to oliguria or anuria, dyspnea, vomiting, uremic encephalopathy with a severe reduction in vigilance, and increased susceptibility to bleeding.

Diagnosis of Chronic Kidney Disease

Detection of Chronic Kidney Disease

Diagnosis is primarily based on a detailed medical history, taking particular note of underlying diseases and medications. Clinical examination and laboratory tests complete
the diagnosis. Imaging procedures (i.e., sonography, computed tomography, and magnetic resonance imaging scans) can provide helpful supporting information. A renal biopsy can be ordered to confirm the diagnosis.

Most importantly, clinical laboratory testing of the glomerular filtration rate serves to determine the National Kidney Foundation disease stage.

**For diagnosis, but above all, as the disease progresses, regular electrolyte measurements are crucial.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description of renal function</th>
<th>GFR</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Increased risk of renal failure</td>
<td>&gt; 90</td>
<td>There is an underlying illness which can lead to kidney damage.</td>
</tr>
<tr>
<td>1</td>
<td>Renal damage with normal function</td>
<td>&gt; 90</td>
<td>Pathological indications in the blood – or urinary testing – without causing disease.</td>
</tr>
<tr>
<td>2</td>
<td>Renal damage with mild loss of kidney function</td>
<td>60 – 89</td>
<td>Pathological indications in the blood – or urinary testing – without causing disease.</td>
</tr>
<tr>
<td>3</td>
<td>Renal damage with moderate loss of kidney function</td>
<td>30 – 59</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Renal damage with severe loss of kidney function</td>
<td>15 – 29</td>
<td>Kidney function decompensates, uremia can manifest itself, and renal replacement therapy should be discussed and prepared for.</td>
</tr>
<tr>
<td>5</td>
<td>Complete kidney damage and kidney failure</td>
<td>&lt; 15</td>
<td>Renal replacement therapy is absolutely necessary.</td>
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</table>

**Important:** For diagnosis, but above all, as the disease progresses, regular electrolyte measurements are crucial!

**Therapy of Chronic Kidney Disease**

The most important and primary goal is the maintenance of normal renal function.

The underlying renal disease should be treated and risk factors and nephrotoxic substances (e.g., the use of nonsteroidal anti-inflammatory drugs, nicotine, aminoglycosides, and X-ray contrast medium) should be modified or removed.

Water and electrolyte balance should be monitored and compensated for. The simplest way to measure water retention is by regular weighing of the patient. If water balance is normal, a fluid intake of around 2 liters per day is recommended. A diuretic will optimize the elimination of urea.

Loop diuretics are recommended for more advanced renal failure. If over time, the diuretic effect begins to weaken, diuretic resistance may be present; this can be overcome by sequential nephron blockade in which loop diuretics are combined with thiazide. The resultant loss of electrolytes must be closely monitored and replaced, however.

Symptoms of hyperkalemia should be monitored. A low-potassium diet is recommended and potassium-sparing diuretics should not be prescribed. If renal acidosis occurs, serum bicarbonate values of < 22 mmol/L can be counterbalanced by the administration of bicarbonate.

Arterial blood pressure needs to be adjusted to low-normal values. The guideline rate is
130/80 mm Hg. If significant proteinuria of > 1 g/24h is present, a target blood pressure of 125/75 mm Hg is recommended. Hypertension can cause additional damage to the kidneys and indicates a poor prognosis. Adequate regulation of blood pressure can often be achieved by undertaking combined antihypertensive therapy, during which angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers should be avoided due to their nephroprotective properties.

As renal failure is accompanied by a change in pharmacokinetics, appropriate medication adjustments must be made in order to avoid intoxication.

Renal anemia can be improved with synthetic erythropoietin. Depending on the blood parameters, iron supplements can also be necessary, particularly if dialysis is underway and blood loss is occurring, as this is often accompanied by iron deficiency.

Prophylaxis and treatment for renal osteopathy are achieved by the lowering of phosphate levels and compensation for a vitamin D deficiency. Phosphate binders are used for this and a reduction in dietary phosphates is also recommended (eg, avoiding nuts, offal, egg yolk, and certain sausage meats.) Cinacalcet increases the sensitivity of the parathyroid to calcium and leads to reduced excretion of the parathyroid hormone. An uncontrollable hyperparathyroidism, accompanied by increasing osteopenia and extraosseous calcifications, can indicate the need for a parathyroidectomy.

Ultraviolet phototherapy is the principal treatment for uremic pruritus.

If it is not possible to stop or slow the progress of renal failure via conservative therapies, then renal replacement therapy is essential. There is a range of different extra or intracorporeal dialysis treatments available.
The treatment of choice for terminal renal failure is kidney transplant. Kidney transplant is far preferable to long-term dialysis, despite the operative procedure and immunosuppressive therapy necessary.

References


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