Chronic Kidney Disease (CKD) — Pathophysiology and Diagnosis

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Kidneys are central metabolic organs in our body. They regulate our water and electrolyte balance amongst other things, and are responsible for the removal of potentially toxic substances and medications. Shockingly, many of today’s widespread diseases can lead to damaged kidneys and an impairment of their function. Chronic renal failure is a systemic disease with massive effects on the whole organism. It is not always easy to understand all of the various facets of the disease. This article should make the mechanisms and processes easier to understand, and will explain them in more detail.

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 the endocrine renal function. This presents as pathologically disturbed excretory and incretionary renal function. This damage has to have been exhibited for longer than three months.
Epidemiology and Etiology of Chronic Kidney Disease

Causes and Distribution of Chronic Kidney Disease

The incidence of chronic renal failure is in the region of 10 cases per 100,000 people. In the industrialized nations alone, tens of thousands of people are dependent on dialysis. This relatively high quantity is linked to the widespread contributory causes of chronic kidney failure in these nations.

The most common cause by a significant margin is diabetic nephropathy (Kimmelstiel-Wilson syndrome, diabetic glomerulosclerosis). This class alone represents 30 - 40% of all patients. Around a further 20% of patients suffer from hypertensive nephropathy.

Glomerulonephritis is responsible for almost 15% of cases and primarily tends to affect younger people. In addition to those are polycystic kidney disease (around 10%) and tubulointerstitial nephritis (around 10%). 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 which end with terminal kidney damage. During this timescale, there is modulation and adaptation in the still functional glomeruli, which serves to keep the kidney function normal 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 an increased permeability and proteinuria. Increased protein concentrations in the proximal tube system are therefore regarded as direct nephrotoxins and can further impair kidney function.

To understand the treatments and therapies, it is important to consider renal physiology and pathophysiology. Fundamentally, one has to consider four pillars of chronic renal failure:

1. **Reduction in Excretory Function**

Breakdown of excretory function is the consequence of an accumulation of endogenous and extraneous substances. In particular, this leads to changes in pharmacokinetics and an increase in the concentration of various medications. The following mechanisms lie at the root of this.

The remaining glomeruli are confronted by a surplus of waste products, which leads 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 in renal failure. Following that, there is no further possible increase in excretion so this results in an accumulation in waste substances.

2. **Reduction in Incretory Renal Function**

The kidney is integrated in the regulation of many important hormonal cycles so chronic renal failure also has endocrinal consequences:

Through a shortage of erythropoietin, there is a reduction in erythrocyte synthesis which leads to renal anemia; even uremia itself leads to a reduction of functional erythrocytes due to hemolysis or hemorrhages.

Vitamin D production is impaired. At the same time, phosphate excretion is reduced. Secondary hyperparathyroidism and the associated renal osteopathy (“high turnover osteopathy”) develop as a result of hyperphosphatemia and, parallel to this, other pathomechanisms lead to a disruption in bone metabolism: osteomalacia due to a disruption of mineralization and adynamic bone disease due to a reduction in bone cell activity that occurs in dialysis patients in particular.

3. **Over-hydration and the Disruption of Electrolyte Balance**

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

Hypertension, pulmonary edema and peripheral edema are results of over-hydration. Water and salt excretion are thereby inextricably linked. Diuretics can be of use to aid water and salt excretion where critical glomerular damage is present. Early loss of salts is to be reckoned with in primary tubulointerstitial diseases as a result of the disturbance in the resorption process, which could actually be made worse by treatment with diuretics!
Thus, as the glomeruli adapt themselves to compensate, the tubular transport mechanisms also adapt in order to prevent hyperkalemia through increased potassium secretion. **Hyperkalemia** only develops as a result of hyper-stimulation of the resorption capacity. As many patients have often been treated with calcium sparing diuretics due to previous conditions, it is vital to refer to their medication history and adapt the treatment accordingly.

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

4. Toxic Organ Damage as a Result of Retention of Urinary Excreted Metabolites
Toxic organ damage is summarized by the umbrella term **uremic syndrome**. The rise in urinary excreted metabolites in the blood is also called **azotemia**. These metabolites include: urea, creatinine, beta-2 microglobulin, parathyroid hormone and many more. Uremic syndrome (uremia) principally describes a systemic disruption of all organ functions; crucially, the circulatory system, the central nervous system, blood and membranes are affected.

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 and **elevated cardiovascular risk**. This leads to **media calcification** caused by calcium phosphate and to **intima calcification** through inflammatory factors and cholesterol plaques. Alongside hypertension, **edemas** and **pulmonary congestion** are common.

**Impairments of the central nervous system** are indicated by a reduction in vigilance. This can be anything 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 pains 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, it leads to **oliguria** or anuria, dyspnea, vomiting, uremic encephalopathy with a severe reduction in vigilance, as well as the patient being more **susceptible to bleeding**.

**Diagnosis of Chronic Kidney Disease**

**Detection of Chronic Kidney Disease**

Diagnosis is primarily based upon 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, CT and MRI scans) can provide helpful supporting information. In the case of doubt, a renal biopsy can be requested.

Above all, clinical laboratory testing of the GFR (glomerular filtration rate) serves to determine the National Kidney Foundation disease stage:

<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>
</tr>
</tbody>
</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. Progression of the disease has to be hindered! There are various conservative strategies to choose from which will be explained here.

The underlying renal disease has to be consequently treated and a reduction in risk factors and nephrotoxic substances such as NSAIDs, nicotine, aminoglycosides and X-Ray contrast medium is necessary.

Water and electrolyte balance has to be monitored and compensated for. The simplest way to notice water retention is by regular weighing of the patient. If the water balance is normal, a fluid intake of around 2 liters per day is recommended. A good 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, there may possibly be a resistance to diuretics present which can be overcome by sequential nephron blockade. For this, loop diuretics are combined with thiazide. The resultant loss of electrolytes must be closely monitored and replaced.

Symptoms of hyperkalemia have to be looked for and reacted to. 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 is a blood pressure of 130 / 80 mmHg. If significant **proteinuria** of > 1 g / 24 h is present, a target blood pressure of 125 / 75 mmHg 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 simply undertaking combined antihypertensive therapy, during which ACE inhibitors or angiotensin receptor blockers should be avoided due to their nephroprotective properties.

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

**Renal anemia** can be improved by subscribing synthetic **erythropoietin**. Depending on the blood parameters, iron supplements can also be necessary; in particular, if dialysis is already taking place and there is blood loss, as this is often accompanied by an iron deficiency.

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

**UV-phototherapy** is the principle option for alleviating 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 are a range of different extra or intracorporeal dialysis treatments available.
The treatment of choice for terminal renal failure is **kidney transplant**. Kidney transplant is still far preferable to long-term dialysis, despite the operative procedure and immunosuppressive therapy necessary.

**Review Questions**

Answers can be found below the references.

1. **Chronic renal failure is accompanied by anemia. Which of these is the least likely pathophysiological cause for anemia?**
   
   A. Reduced production of erythropoietin.
   B. Hemorrhage
   C. Hemolysis
   D. Toxic effects of uremia
   E. Functional hypersplenism

2. **You are preparing for a visit from the senior physician and want to impress. You know that your senior physician likes to use various scoring systems. Your next patient has chronic renal failure and you are trying to remember what parameter is relevant to diagnose the disease stages in renal failure. Is it...**
   
   A. ...Urine volume
   B. ...Urea concentration
   C. ...Glomerular filtration rate
   D. ...Specific gravity of urine
3. The patient from question 2 has distinct cardiovascular risk factors. You have completed comprehensive diagnostic tests and want to prevent the progression of chronic renal failure. Which of these treatment plans would be the best option?

A. Correction of hypertension is only measured by target blood pressure values.
B. Correction of hypertension should be treated with calcium antagonists and nitrates in particular.
C. As renal failure progresses, you can expect a decreased demand for insulin.
D. If the patient is diabetic, it is essential that they are treated with metformin.
E. In the case of over-hydration, it is normally sufficient to prescribe a thiazide diuretic irrespective of the level of disruption to the kidney function.

References


Correct answers: 1E, 2C, 3C

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