Anatomy of the Distal Convoluted Tube and Bartter & Gitelman Syndrome

In this article, you will gain a perfect overview of the distal convoluted tubule, the portion of the nephron of the kidney extending from the loop of Henle up to the collecting duct system. Furthermore, you will learn about the pathophysiology and treatment of the autosomal recessive disorders called Gitelman syndrome and Bartter syndrome for the perfect medical exam preparation.
The distal convoluted tubule is the smallest portion of the duct system (only 5 mm). It starts from macula densa. It is formed by a simple cuboidal epithelium. These cells are less active than proximal convoluted tubules with few microvilli on the apical surface. Its main function is to regulate potassium, sodium and calcium ions and in the maintenance of pH. Distal convoluted tubule cells are highly packed with mitochondria. They also have a large amount of Na+ – K+ ATPase on the basolateral membrane. These cells are impermeable to water and urea. These cells also have a prominent thiazide-sensitive sodium chloride cotransporter which is a target of many diuretic drugs.

These cells are also responsible for magnesium reabsorption by a transient receptor potential channel (TRPM6). DCT cells are also permeable to Ca via the TRPV5 channel. The basolateral surface has an ATP dependent Na+ – K+ antiporter pump. Angiotensin II and aldosterone also target DCT.

CT dysfunction causes:

- Familial Hyperkalemic Hypertension
- Gitelman syndrome
- East syndrome
- Hereditary hypomagnesemias

Functions of the Distal Convoluted Tubule

It regulates the pH. It does so by secreting protons (H+) into the filtrate and absorbing bicarbonate or by absorbing protons and secreting bicarbonates into the filtrate.

It absorbs sodium and secretes potassium. Sodium is being absorbed by hormone aldosterone. Sodium and chloride are reabsorbed by a group of kinases called WNK Kinases. There are four different kinds of kinases which are WNK1, WNK2, WNK3, and WNK4. Water and urea are not absorbed in DCT, nor it is under the regulation of aldosterone for water absorption.
It reabsorbs calcium by the action of the parathyroid hormone. Arginine vasopressin receptor 2 is also expressed on distal convoluted cells.

**Clinical Significance of the Distal Convoluted Tubule**

Thiazide diuretics mainly act on the thiazide-sensitive Na-Cl cotransporter and blocks it, thus inhibiting the reabsorption of sodium and chloride.

**Histology of the Distal Convoluted Tubule**

The distal convoluted tubules are lined with simple cuboidal epithelium which is relatively smaller than that of the proximal convoluted tubule. The lumen appears larger due to an absence of microvilli.

**Gitelman Syndrome**

Gitelman’s syndrome is an **autosomal recessive disorder caused by genetic mutations** that result in defective functioning of the thiazide-sensitive sodium chloride symporter which is located in the distal convoluted tubule of the kidney. This disorder is characterized by low levels of potassium and magnesium and decreased excretion of calcium in urine and elevated pH. This alters the electrolyte concentrations and cause leakage of extracellular fluid volume that leads to the appearance of symptoms of dehydration. It is a salt wasting disorder. The disease is similar to the metabolic abnormality caused when treated with high doses of thiazide diuretics.

**Pathophysiology of the Gitelman Syndrome**

The disease has an autosomal recessive pattern of inheritance. 80% of the individuals affected by Gitelman syndrome have **mutations in the SLC12A3 gene**. This results in loss of function of encoded thiazide-sensitive sodium chloride cotransporter. More than 180 types of different mutations in this transporter have been identified so far. When this
transporter is inactivated, the Na – K ATPase continuously acts on the basolateral membrane which creates a favorable sodium gradient across the membrane which increases the reabsorption of other divalent ions by secondary active transport. It increases the reabsorption of Na and hyperabsorption of Ca in the proximal tubules.

**Epidemiology of the Gitelman Syndrome**

Gitelman syndrome affects 1 in 40,000 people.

**Signs and symptoms of the Gitelman Syndrome**

- High blood ph
- Low levels of chloride, potassium, and magnesium
- Decreased urinary calcium excretion
- Muscle cramps or weakness
- Episodes of fainting, fatigue, and dizziness
- Vomiting or diarrhea
- Numbness
- Thirst
- Frequent urination
- Salt cravings

**More severe symptoms include**

- Seizures
- Tetany
- Paralysis
- Abnormal heart rhythm
- Prolonged QT interval
- Sudden cardiac arrest

**Diagnosis**

The diagnosis is established by blood tests, urine tests, and molecular genetic testing. Blood tests determine serum electrolyte levels, renin, and aldosterone. Urine tests determine levels of calcium, chlorides, potassium in the urine. Low urinary calcium indicates towards the disorder. Molecular genetic testing establishes the confirmation of the diagnosis and detects the specific genes responsible for the disorder.

**Treatment of the Gitelman Syndrome**

Most of the patients with Gitelman syndrome remain asymptomatic. The main aim of the treatment is to replace potassium and magnesium which are being lost. Large doses of potassium and magnesium are required to maintain the levels of these ions in the blood. Diarrhea is a common side effect of oral magnesium supplementation and that’s why it is usually given in 3 to 4 divided doses in a day for better tolerance.

If the loss is severe than these ions can also be given by intravenous route. If the oral supplementation is not enough for the patient then aldosterone antagonists such as spironolactone or eplerenone can be given. Epithelial sodium channel blockers such as amiloride can also be given to decrease urinary wasting of potassium. Monitoring of hypotension is equally important in Gitelman Syndrome with the therapeutic
Bartter Syndrome

Bartter syndrome is an **autosomal recessive disorder** that is characterized by hypokalemia, hypochloremia, metabolic alkalosis and hyperreninemia with normal blood pressure. There is an excess loss of sodium, chloride, and potassium in the urine. Bartter syndrome is classified into three main clinical variants:

- Neonatal or antenatal Bartter syndrome
- Classic Bartter syndrome
- Gitelman syndrome

Numerous underlying mutations have been found to cause the disease but the following are the main causes leading to salt losing tubulopathy:

**Classic Bartter syndrome**
- Involves thick ascending limb of the loop of Henle or the distal convoluted tubule dysfunction leading to hypokalemia.
- Mutations in the CLCNKB gene
- Mutation in the calcium-sensing receptor has been linked to a milder form of classic Bartter syndrome

**Gitelman syndrome**
- Mutations in the NCCT gene

**Neonatal or antenatal Bartter syndrome**
- More severe
- Mutations in the NKCC2 and ROMK genes

**Neonatal or antenatal Bartter syndrome with a sensorineural deafness**
- Most severe form of the disease
- Involves both loop of Henle and distal convoluted tubule
- Caused by defects in the chloride channel genes CLCNKB and CLCNKA or their beta subunit

More recently a disorder has been identified which is associated with **mutations in MAGED 2 gene on X chromosome** that encodes for melanoma associated antigen D2. This is required for fetal renal salt reabsorption, amniotic fluid homeostasis, and maintenance of pregnancy. The defective gene was associated with polyhydramnios with prematurity and severe form of antenatal Bartter syndrome.

**Pathophysiology of the Bartter Syndrome**

Bartter syndrome is a **salt wasting disease**. Due to mutations, the kidneys are unable to reabsorb chloride in the thick ascending loop of Henle or distal convoluted tubule depending on the mutation. Chloride is transported by passive absorption in the proximal tubule but in the thick ascending limb and distal convoluted tubule, it is actively transported. As chloride is not being absorbed it leads to failure of absorption of sodium as well leading to wastage of sodium and chloride from the body.

The renin-angiotensin aldosterone system is also activated with volume depletion. Angiotensin II is vasoconstrictive in action which prevents from **hypotension** by increasing sodium reabsorption. It directly increases proximal renal tubular reabsorption with a counter-regulatory decrease in potassium. High levels of aldosterone also promote potassium and hydrogen ion loss in exchange for sodium. These all events promote hypokalemia and metabolic alkalosis.
Patients with Bartter syndrome also have hypercalciuria. Calcium ions are reabsorbed through paracellular tight junctions. Dysfunctional thick ascending limb transporters prevent reabsorption of calcium. Hypercalciuria may be one of the reasons of nephrocalcinosis in these patients. Sensorineural deafness is associated with type IV Bartter syndrome which is due to defects in the barttin subunit of CIC-Ka and CIC-Kb channels. Mutations in only CIC-Kb channels does not lead to sensorineural deafness as in type III Bartter syndrome.

**Etiology of the Bartter Syndrome**

Both familial and sporadic forms of Gitelman syndrome exist. If these are inherited, these syndromes are passed on as autosomal recessive disease.

**Epidemiology of the Bartter Syndrome**

Bartter syndrome is a rare disease and its occurrence varies among different countries. In Costa Rica, the prevalence was 1.2 cases per 100,000 live births and in Kuwait, the prevalence was 1.7 cases per 100,000 persons. In Sweden, the frequency was 1.2 cases per million.

**Prognosis of the Bartter Syndrome**

As the disease is inherited as autosomal recessive, it’s not curable. The disease severity depends of the degree of dysfunction of the receptors. With treatment, the patients live a good life and achieve developmental goals. If the disease is left untreated, mortality and morbidity can happen.

**Types the Bartter Syndrome**

Bartter syndrome is characterized by 5 different subtypes depending on the gene involved and the transporter being affected.

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Mutated gene</th>
<th>Defect</th>
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<tbody>
<tr>
<td>Neonatal Bartter’s syndrome</td>
<td>1</td>
<td>SLC12A2</td>
<td>Na-K-2Cl symporter</td>
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<td>Neonatal Bartter’s syndrome</td>
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<td>ROMK</td>
<td>Thick ascending limb</td>
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<td></td>
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<td>BSND</td>
<td>Chloride channel accessory subunit</td>
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<td>Bartter´s syndrome with hypocalcemia</td>
<td>5</td>
<td>CaSR</td>
<td>Activating mutation of calcium sensing receptor</td>
</tr>
</tbody>
</table>

**Signs and symptoms of the Bartter Syndrome**

- Neonatal Bartter syndrome presents with polyhydramnios (excessive amount of amniotic fluid) and delivery before term as a history in their mothers.
- Polyuria
- Polydipsia
- Hypercalciuria
- Nephrocalcinosis
- Kidney stones
• Vomiting
• Growth retardation
• Craving for salt
• Constipation
• Muscle weakness
• Fatigue
• Muscular cramps
• Developmental delay

**Diagnosis of the Bartter Syndrome**

• Hypokalemia
• Metabolic alkalosis
• Low levels of serum magnesium and calcium
• Elevated renin and aldosterone levels

**Treatment of the Bartter Syndrome**

• Replacement of sodium and potassium
• Spironolactone (to reduce potassium loss)
• Nonsteroidal anti-inflammatory drugs
• Angiotensin-converting enzyme inhibitors

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**Complications of the Bartter Syndrome**

• Cardiac arrhythmias and sudden cardiac death which results from electrolyte imbalances
• Failure to thrive
• Developmental delay
• Decrease in bone mineral density

**References**


MedEd at Loyola mech/cases/case24/kidney.htm

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Notes