ERKNet
The European Rare Kidney Disease Reference Network

INFORMATION
FOR PATIENTS

DENT'S DISEASE

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The European Rare Kidney Disease Reference Network

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WHAT IS DENT'S DISEASE?

Dent's disease is a rare congenital kidney disorder which leads to the development of kidney stones, and often also to kidney failure. Symptoms usually occur in childhood, but they can also go unnoticed until adulthood.

The main feature of the disease is the occurrence of **small proteins molecules in the urine** in combination with **hypercalciuria**, i.e., increased excretion of calcium in the urine, the formation of calcium deposits in the kidneys (**nephrocalcinosis**) and recurrent episodes of kidney stones **(nephrolithiasis**). The progressive kidney problems often lead to kidney failure in adulthood.

Less common features include **rickets**, i.e., bone deformities secondary to calcium-phosphate disorders and the **growth disturbance**.

The disease generally occurs only in men, as its inheritance is associated with the sex chromosome (see below).

The incidence of the disease, probably due to the lack of complaints in many patients and little-known nature, might be underestimated. The disease is often diagnosed too late with impaired kidney function.

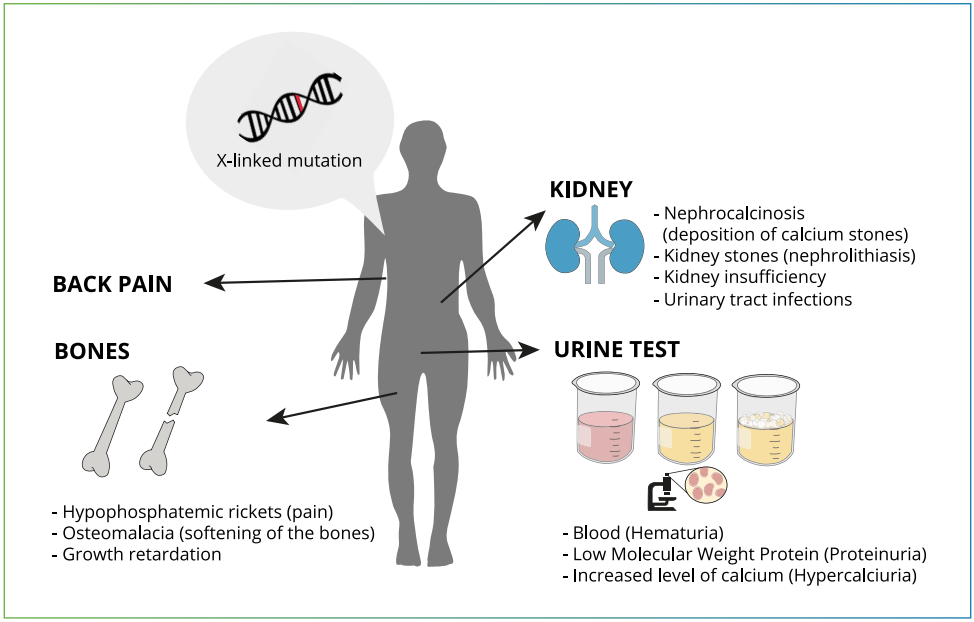


Figure 1. Short schematic characteristics of Dent's disease.

Why do I / does my child have Dent's disease?

Dent's disease is a congenital disease, i.e., genetically determined, **monogenic**, which means that its occurrence is due to the mutation of a specific single gene (in this case either the **CLCN5** or the **OCRL1** gene) and belongs to the group of diseases called tubulopathies.

Tubulopathies are diseases in which a defect affects the tubules in the kidneys (see below). Proximal and distal or mixed tubulopathies are distinguished, depending on which section of the tubules is affected.

In Dent's disease, the defect of action primarily affects the proximal tubules. In these sections of the tubules many substances which have been filtered in the glomeruli (kidney filters) are reabsorbed because the body still needs them. The CLCN5 and OCRL1 genes encode specific enzymes that are necessary for the reabsorption of low-molecular proteins and minerals such as potassium, phosphate, calcium and bicarbonate.

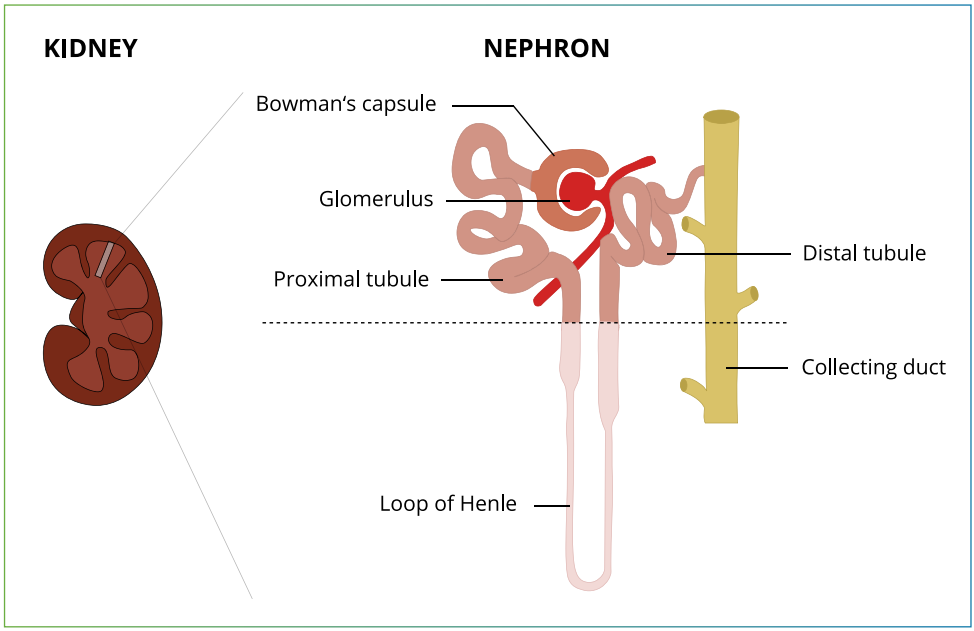
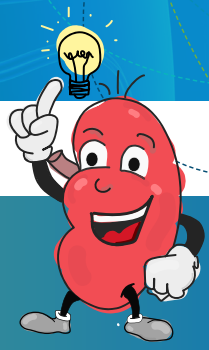


Figure 2. *Nephron structure, adopted from Infokid.org.uk*

DID YOU KNOW THAT?



The main task of the kidneys is to remove excess water and waste products from the body by creating urine. Each kidney contains about one million nephrons on average, each consisting of a filter (glomerulus) and a tube called tubulus.

In the glomerulus primary urine is formed by filtering circulating blood. These filters are impermeable to blood cells and large proteins.

The tubuli are needed to recycle substances which have been filtered in the glomeruli but are valuable to the body such as water, electrolytes (like sodium, chloride, potassium, calcium, magnesium, phosphorus and many others), glucose, aminoacids and proteins. They also regulate the acid-base homeostasis. These processes are necessary to maintain a stable balance of body chemicals.

In an adult, the kidneys filter about 150 liter of water per day, 99% of which is reabsorbed in the tubuli, leaving about 1.5 liter of final urine. This is possible thanks to the fact that the renal tubules have a total length of **80 km**!

The tubules consist of the following segments: the proximal tubule, the Henle loop, the distal tubule, and the collecting duct. In the **proximal tubules** the bulk of reabsorption takes place.

The kidneys also produce hormones that affect the function of other organs. For example, the hormone stimulating red blood cell production. Other hormones produced by the kidneys help regulate blood pressure and control calcium metabolism.

GENETICS, OR INHERITANCE OF DENT'S DISEASE

The cause of the disease is a mutation of a single gene CLCN5 or OCRL1. Both of these genes are located on the sex chromosome X, therefore the inheritance of these mutations and disease is coupled to sex.

In a male, each body cell contains one X-chromosome and one Y-chromosome, in a female two X-chromosomes.

The inheritance of Dent's disease is **recessively linked to the X-chromosome**. This means that it usually occurs in males only, as women have two X-chromosomes, one of which can compensate for the defect of another X chromosome. The disease only manifests if a person does not have at least one healthy X-chromosome.

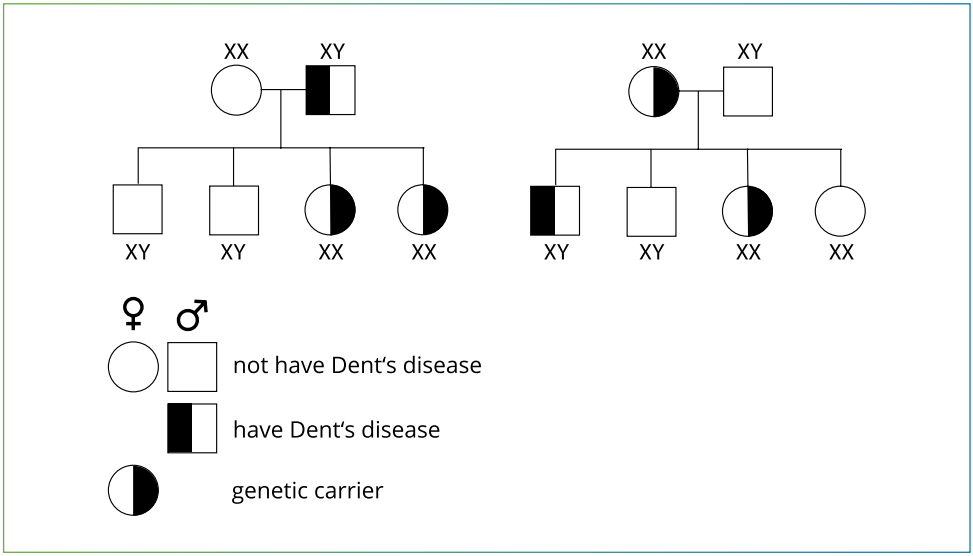


Figure 3. *Inheritance of Dent's disease is recessively linked to the X chromosome: usually only manifests in males, as males have only one X-chromosome and cannot compensate in case, they inherit a mutated CLCN5 and OCRL1 gene from their mother.*

Boys inherit the disorder from their mother as they always get the X- chromosome from their mother and the Y-chromosome from their father. If the mother is a carrier of the CLCN5 or OCRL1 mutation, there is a 50 percent chance that she will pass the mutation to her children of both sexes. Still, the girls do not get ill because they get a healthy X-chromosome from their father. The boys, however, are left with one mutated X-chromosome as they inherit the Y-chromosome from their father. A female who has an affected and a healthy X-chromosome is called a carrier of the disease because she does not have symptoms but can pass the disease to her children.

As only a single active X-chromosome is needed, one of the two is inactivated in women. This is a random event occurring in each body cell separately. Thus, women who are carriers of the disease have a mixture of mutated and unmutated cells. In some cases, women may have beneficial X inactivation in which the affected X-chromosome is silenced in most cells. These women may not develop any or only very mild symptoms of the disorder. In other cases, women may have adverse X inactivation, i.e., the intact X- chromosome is silenced in most cells. Affected women may develop various symptoms of Dent's disease.

In extremely rare cases, the mutation occurs randomly for no apparent reason, as both parents do not carry this mutation. This is called "de novo mutation" and the reason is a mutation occurring in a germ cell (egg or sperm) of one of the parents or arising in the fertilized egg itself during early embryogenesis. In this situation, the alteration manifests for the first time in this family member and all other offspring of his parents will be unaffected. Still, he will pass on the mutation to all his daughters.

Determining the origin of the mutation (de novo vs. inherited) could be important for further family planning (risk assessment for the siblings) but also for potential kidney donation by the mother in case her son develops kidney failure.

Genetics, basic concepts

The human body is made up of millions of cells. Most cells contain a complete set of genes.

Genes are the "recipe of life" acting as a set of instructions controlling our growth and the functioning of our body. They are responsible for many of our characteristics, such as eye color or body height.

When a gene mutation occurs, the protein product may be defective, ineffective, or absent. Depending on the function of the particular protein, this may affect a single or several organ systems.

Genes are made up of a chemicals called DNA and are located inside filamentous structures called **chromosomes**.

Each person has 46 chromosomes in most cells. These are 22 pairs of autosomal chromosomes and 1 pair of sex chromosomes, i.e. X and Y. Chromosomes are inherited from parents, 23 from the mother and 23 from the father, so each person has 2 full sets of 23 chromosomes or 23 "pairs". Because chromosomes are made of genes, everyone inherits 2 copies of most genes, one copy from each parent. The situation is slightly different in the case of sex chromosomes, where in case of male gender there is one X and Y chromosome and in case of female gender two X chromosomes, respectively.

Autosomal inheritance

This type of inheritance concerns genes located on autosomal chromosomes, i.e., not related to sex.

In the case of dominant inheritance, one copy of the defective gene is enough for the symptoms of the disease to occur.

In the case of recessive inheritance, having one correct version of the gene prevents the disease from manifesting, i.e., two defective genes are necessary for manifestation.

X-linked inheritance

We talk about X-linked inheritance when the genes whose mutations cause a given disease entity are located on the X-chromosome. These diseases differ from autosomal diseases in affecting women and men in a different way. This is because both sexes have a different set of sex chromosomes: While women have two X-chromosomes, and thus two versions of each gene on the X-chromosome, men have only a single X- chromosome, i.e., only one version of a given gene. Therefore, a defective gene on the X-chromosome will lead to disease in a male, while in a female the second X-chromosome can compensate (X-linked recessive inheritance)

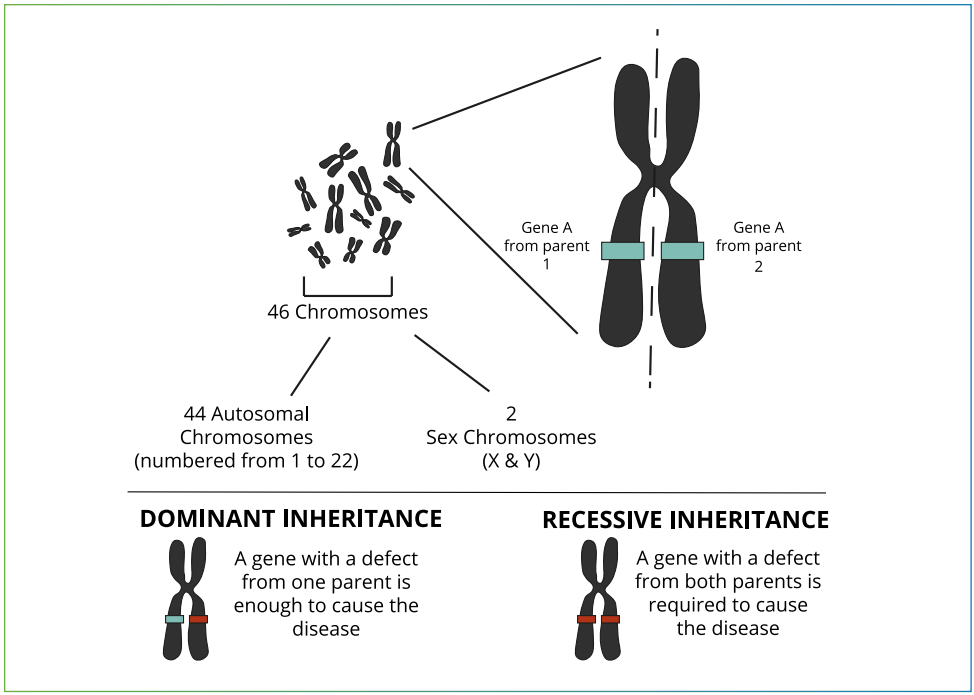


Figure 4. *Chromosome types and inheritance types*

Dent disease type 1, 2 and 3

So far, two types of disease have been identified. Both forms are inherited in an X-linked recessive manner, but the mutations involve two different genes.

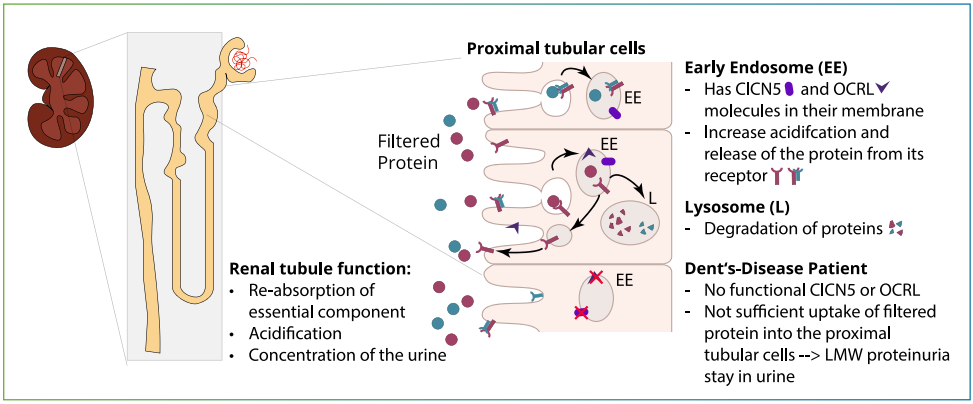


Figure 5. Role of ClCN5 and OCRL in uptake of filtered protein in the proximal tubular cells and endosomal release. Defects manifest as low molecular weight proteinuria (LMW proteinuria).

Type 1

The cause of the disease is a mutation in the CLCN5 gene, which determines the function of the chloride channel CLC-5. CLC-5 plays a key role in acidification in endosomes in proximal tubular cells, which is important for the reabsorption of low molecular weight (LMW) proteins from the urine.

It is the most common type of disease and accounts for about 65% of all cases of Dent disease. There are many different mutations of this gene, and the symptoms may vary considerably even in patients sharing the same mutation.

Type 2

Type 2 occurs in approximately 10–15% of patients with Dent disease and is caused by mutations in the OCRL1 gene. This type of disease is characterized by the same renal symptoms that may occur in type 1, but in addition symptoms such as mild **intellectual disability**, changes in the eyes in form of mild **cataracts** (a clouding of the normally clear lens), also short stature can be observed.

The OCRL gene encodes a protein involved in intracellular transport in proximal tubules cells but is also involved in many other processes in the body. Some types of mutations in the OCRL gene cause Dent disease type 2, while others cause a much more severe disease called Lowe syndrome (see below).

Type 3

It concerns the remaining patients with features of Dent's disease (25-35%) in whom none of the above mutations could be demonstrated. It is likely that other, yet unidentified genes cause this disease.

SYMPTOMS

Dent's disease should be suspected when the following features are present:

1. **Male gender**
2. **High level of low molecular weight proteins in the urine**
3. **Excess calcium in the urine**
4. **The presence of one of the following characteristics:**
   - **Calcification of the kidneys**
   - **Kidney stones**
   - **Blood in the urine**
   - **Low levels of phosphate in the blood serum**
   - **Decreased kidney function**
   - **Evidence of X-linked recessive inheritance**

Figure 6. *Characteristic symptoms of Dent's disease.*

Dent's disease was first described by Charles Enrique Dent and M. Friedman in 1964, when they reported two unrelated British boys with rickets and renal tubular damage characterized by hypercalciuria, hyperphosphaturia, proteinuria, and aminoaciduria (aminoaciduria – see the term also in glossary - abnormally high amounts of amino acids in urine). The name of the disease was given 30 years later, when the nephrologist Oliver Wrong more fully described the disease and chose to name the disease after his mentor.

The disease almost exclusively occurs in men, and symptoms may appear from early childhood.

The severity of Dent's disease can vary greatly, even among affected family members. Affected individuals may not have all the symptoms discussed below. In each specific case, the occurring abnormalities, their treatment as well as the general prognosis should be assessed individually.

There are accidental diagnoses of the disease in the asymptomatic phase possible, but most often it takes place secondarily to the diagnosed advanced chronic kidney disease of unknown etiology at the age of 30-50 years.

Women carrying Dent's disease mutations may have mild small-molecule proteinuria and hypercalciuria, but kidney stones and kidney failure are rare.

Low molecular weight proteinuria (LMW proteinuria)

Usually it is more than 5-fold increased excretion of beta 2-microglobulin in the urine!

Patients with Dent's disease have elevated levels of protein in the urine, which is the only constant laboratory symptom of the disease.

The type of proteinuria observed in Dent's disease is known as low molecular weight proteinuria (LMW proteinuria). LMW proteins are small proteins which are filtered by the kidneys but reabsorbed in the proximal tubules so that they are usually undetectable in the urine of healthy subjects. Measurement of LMW proteins requires specific tests and the can be missed in routine urine tests. Examples for LMW proteins used for diagnostics are beta-2 microglobulin, alpha-1 microglobulin and retinol-binding protein.

The presence of a LMW protein in the urine indicates impaired function of the proximal tubule. In Dent's disease, the urine concentration of beta-2 microglobulin is at least five times higher than the upper limit of normal.

For the quantitative assessment of low-molecular proteinuria, you can perform a 24-hour collection of urine or assess the ratio of beta 2-microglobulin (as an example of a LMW protein) to creatinine in a random urine portion.

As the presence of proteins in the urine is a common symptom of disorders of the glomerulus rather than the tubulus, this can be misleading and physicians may initially mistake Dent's disease for a form of glomerulonephritis (inflammation of the glomerulus) or a nephrotic syndrome (massive leakage of proteins through glomerular filters). A more detailed analysis of the urine will reveal that LMW proteins constitute the majority of proteins in the urine of patients with Dent's disease.

Hypercalciuria – increased excretion of calcium in the urine

Hypercalciuria, like LMW proteinuria, can only be detected by laboratory tests. When looking at the urine it is usually unremarkable, although hypercalciuria may be accompanied by hematuria - the presence of blood in the urine.

The cause of hypercalciuria in Dent's disease is not fully understood yet. A potential mechanism is failure to reabsorb parathyroid hormone, a low-molecular protein which acts on calcium excretion. Also, the loss of a protein binding vitamin D could be involved.

Another mechanism might be increased calcium-release from bone resorption due to metabolic acidosis, another feature of Dent disease.

To assess the excretion of calcium in the urine, a 24h- urine collection is recommended. If this is not possible, for example if the child is still wearing diapers, the ratio of calcium to creatinine concentration in a portion of urine can be determined, although this it is less accurate.

Kidney calcifications (nephrocalcinosis) or kidney stones (nephrolithiasis)

Increased calcium concentration in the urine leads to crystallization and the formation of calcifications in the kidney tissue (nephrocalcinosis) as well as the formation of kidney stones (nephrolithiasis).

Kidney calcifications and kidney stones can be visualized by ultrasound. Sometimes the first symptom suggestive of kidney stones is blood in the urine – which can sometimes only be seen by urine microscopy ("microscopic hematuria").

Kidney stones can also cause other symptoms like painful urination (dysuria), a desire to urinate frequently, abdominal pain (renal colic), obstruction of urine flow or repeated urinary tract infections.

Hematuria (usually microhaematuria)

Hematuria occurs very often in patients with Dent's disease and is a consequence of nephrolithiasis / nephrocalcinosis. In exceptional cases, hematuria can also be a sign of damaged kidney filters (glomerulonephritis).

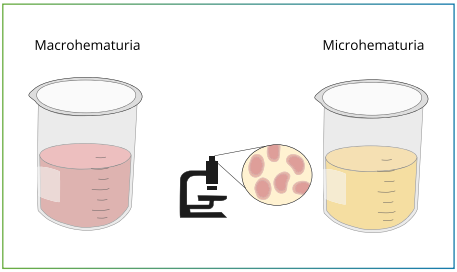


Figure 7. *The presence of blood in the urine: visible - macrohematuria and diagnosed only by microscopic examination – microhematuria.*

Fanconi syndrome and low serum phosphate levels

Impaired reabsorption of low molecular weight proteins in the proximal renal tubules often coexists with defective absorption of other substances like phosphate, potassium, amino acids or bicarbonates.

Depending on the number of substances affected this is called an incomplete or complete renal Fanconi syndrome.

Complete Fanconi syndrome (De Toni–Debré–Fanconi syndrome – a defect affecting all functions of the proximal tubules, causing loss of amino acids, glucose, phosphates, uric acid, citrate, small molecular weight proteins, magnesium, potassium, calcium, bicarbonate and water.

Incomplete Fanconi syndrome refers to the loss of only some of the above-mentioned components. In most patients with Dent's disease not all the functions of the proximal tubule are affected.

Ongoing urinary losses lead to decreased blood concentrations of the affected substances: phosphate losses lead to **hypophosphataemia**, potassium losses to **hypokalemia**, bicarbonate losses kidney tubular **acidosis**. The loss of aminoacids does not have any metabolic consequences. As phosphate is required for bone formation, hypophosphatemia can cause **rickets** or **osteomalacia** (see in glossary), which (unlike other forms of rickets) do not respond to high doses of vitamin D. Bone damage is aggravated by the renal tubular acidosis, which causes bone resorption. Ultimately, growth may be impaired and patients may develop bone deformities. Hypokalemia may cause to muscle weakness and impair water absorption leading to increased urine production (**polyuria**) and thirst (**polydipsia**) potentially causing dehydration.

Chronic kidney disease and kidney failure

The progression of the disease can cause chronic kidney disease (CKD) with a progressive decrease in kidney function.

Symptoms associated with very advanced chronic kidney disease include loss of appetite, unintentional weight loss, fatigue, and anemia.

In some cases, sometimes as early as 30-50 years of age, affected persons may develop kidney failure and require dialysis or a kidney transplantation.

Other symptoms

1. Some people with Dent's disease may also develop bone diseases such as **bone softening (osteomalacia)** and **hypophosphataemic rickets**, a condition caused by impaired phosphate transport and altered vitamin D metabolism in the kidneys.

2. In children with Dent's disease, the growth rate may be slower than normal, often resulting in **mild short stature**. Children may also experience bone pain and difficulty walking. Due to bone abnormalities, both children and adults may have an increased risk of bone fractures.

3. Some people with Dent's disease are deficient in vitamin A, which can lead to **impaired night vision and dry eyes (xerophthalmia)**.

   Vitamin A deficiency in this case is caused by the loss in the urine of a low-molecular protein binding retinol. Symptoms can be corrected by appropriate vitamin A supplementation.

4 Some people with Dent's disease type 2 may have other additional symptoms, including **mild intellectual disability, decreased muscle tone**, and **associated delayed motoric development**, as well as the **clouding of the eye lenses (cataracts)**, which usually does not impair vision.

DIAGNOSIS

Low molecular weight proteinuria in combination with hypercalciuria or nephrocalcinosis or kidney stones in a boy/a male may be the only symptoms of the disease and should prompt further diagnostics.

The clinical diagnosis of Dent's disease is based on the identification of characteristic symptoms (see **Figures 1 and 6**), the assessment of a detailed patient and family history, a thorough clinical assessment and various specialized tests.

However, due to the diverse nature of the symptoms of the disease, Dent 's disease should also be considered in **males** who have:

- symptoms of glomerular disease (steroid-resistant nephrotic syndrome)
- kidneys tubular dysfunction/Fanconi syndrome
- idiopathic nephrolithiasis
- unspecified chronic kidney disease

Molecular genetic tests can detect mutations in two genes that are known to cause Dent disease but are not always necessary if a clinical diagnosis can be made (for example, low molecular weight proteinuria and hypercalciuria in men). On the other hand, molecular testing is recommended to differentiate this condition from other genetic causes of nephrocalcinosis and chronic kidney disease. It should be kept in mind that no mutation in the two Dent's disease genes is found in about one third of males with the typical picture of Dent's disease.

Kidney biopsies (taking a small specimen of kidney tissue for microscopic evaluation) are often performed in patients with unexplained kidney disease and significant proteinuria and hematuria, so that some patients with Dent's disease undergo a kidney biopsy before the diagnosis has been made. The biopsy results are non-specific and demonstrate glomerular sclerosis (FSGS) (see in glossary), interstitial fibrosis (scarring) and nephrocalcinosis.

Kidney biopsy is not necessary to diagnose Dent's disease and may even be misleading.

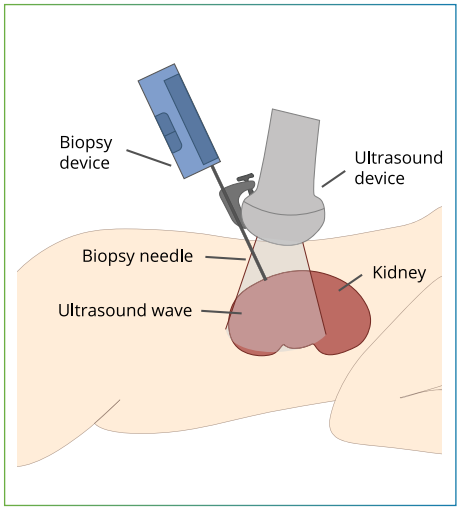


Figure 8. *Kidney biopsy, a procedure which is usually not necessary for the assessment and diagnosis of Dent's disease.*

Can Dent's disease be confused with another disease?

There are several rare genetic disorders characterized by the formation of stones in the kidneys or urinary tract in childhood similar to those observed in Dent's disease.

Such disorders include primary hyperoxaluria, familial hypercalciuria -hypomagnesaemia-nephrocalcinosis (Michelis-Castrillo syndrome), adenine phosphoribosyltransferase (APRT) deficiency and cystinuria.

Primary hyperoxaluria (PH) is a group of rare genetic metabolic disorders that are characterized by the accumulation of a substance known as oxalate in the kidneys and other organ systems of the body. Affected individuals lack an enzyme that normally prevents the accumulation of oxalate.

Familial hypercalciuria - hypomagnesaemia-nephrocalcinosis (Michelis-Castrillo syndrome, FHHNC) is a rare genetic disease inherited in an autosomal recessive manner, presenting with urinary loss of magnesium and calcium. The cardinal features of the disease are hypomagnesemia, hypercalciuria and nephrocalcinosis and patients present clinically with polyuria/polydipsia and vitamin D-resistant rickets. FHHNC results from mutations in the CLDN16 or CLDN19 genes. CLDN16 and CLDN19 encode the tight-junction proteins claudin-16 and claudin-19, respectively, which are expressed in the thick ascending limb of Henle's loop and form an essential complex for the paracellular reabsorption of magnesium and calcium.

These patients do not have hypokalaemia or salt wasting. Patients with mutations in CLDN19 also present severe ocular abnormalities such as myopia, nystagmus and macular colobamata.

Adenine phosphoribosyltransferase (APRT) deficiency is characterized by excessive production and renal excretion of 2,8-dihydroxyadenine (DHA), which leads to kidney stone formation and crystal-induced kidney damage (i.e., DHA crystal nephropathy) causing episodes of acute kidney failure and progressive chronic kidney disease.

Cystinuria is an inherited autosomal recessive disease characterized by high concentrations of the amino acid cystine in the urine, leading to the formation of cystine stones in the kidneys and urinary tract.

A variety of hereditary disorders are characterized by Fanconi syndrome and therefore should also be considered in the differentiation of Dent's disease. Examples include genetic disorders such as cystinosis, hereditary fructose intolerance, galactosemia, tyrosinemia, Wilson's disease, and various glycogen storage diseases.

Renal Fanconi syndrome can also be acquired during life as a side effect of certain drugs (e.g., **valproate, deferasirox, cisplastin, ifosfamide**) or be secondary to certain kidney diseases, cancers such as multiple myeloma, Sjögren's syndrome or hyperparathyroidism. In children, exposure to heavy metals can also cause Fanconi syndrome.

Lowe's syndrome, is a rare genetic disorder characterized by vision problems, including clouding of the eye lenses (cataracts) that are present at birth, kidney problems that usually develop in the first year of life, and brain abnormalities associated with intellectual disability. The specific symptoms and severity of the disorder can vary greatly from person to person. Lowe syndrome is inherited as an X-linked trait. Lowe syndrome is caused by mutations in the same gene (OCRL1) that causes Dent's disease type 2. The disorder is fully expressed only in men.

If proteinuria is the presenting symptom, Dent's disease can easily be confused with diseases affecting the glomerulus (glomerulonephritis and nephrotic syndrome). These diseases are often treated with corticosteroids, which of course do not help because Dent's disease isn't an inflammation of the kidneys but a genetic disease. The fact, that glucorticosteroids don't help may lead the physician to classify Dent's disease as a **"steroid-resistant nephrotic syndrome"** before the correct diagnosis is made. It could be especially be misleading as a renal biopsy is done and demonstrates focal glomerular sclerosis.

TREATMENT

Who will be involved in my/my child's treatment?

Treatment of Dent's disease should be guided by a nephrologist and is usually aimed at reducing symptoms by taking medications that inhibit the formation of kidney stones as well as taking supplements that correct electrolyte and metabolic disorders. Treatment may require the coordinated cooperation of a team of specialist doctors: pediatricians, nephrologists, and urologists, dieticians, and other health professionals.

Treatment consists of:

- Minimizing the deposition of calcium deposits (prophylactic treatment, preventing the formation of stones, the so-called metaphylaxis)
- Removal of stones from the urinary tract (symptomatic treatment)
- Treatment of the effects of the disease, including the correction of electrolyte disturbances, as well as the effects of progressive chronic kidney failure

A. Prophylactic measures / Prevention of kidney stone formation

1. Adequate hydration > 3 liters / m² of body surface area.

- Adequate, in this case greater than average fluid intake is an important intervention that reduces the deposition of calcium deposits in the kidneys. It is believed that the lack of adequate hydration reduces the effectiveness of the other preventive methods.
- To estimate the daily fluid requirement, body surface area (BSA) can be calculated using calculators available online or using the formula:

  BSA=√(Body weight (kg) x height (cm)/ 3600).

- Don't forget that in situations such as diarrhea, fever, vomiting or being in a hot climate, the need for fluids increases.
- Therefore, increased fluid loss or diminished intake should prompt immediate medical attention to prevent sudden progression of the disease. In these cases, extra fluid supplementation may even be needed intravenously if the oral route proves impossible. Patients, caregivers and teachers need to be aware of this.
- It may be particularly important to have a document with this information especially during the holiday season, during travel, especially when the child is away from home without parents or close guardians.

Please note:

- Always have with you a document with the diagnosis of your disease (emergency passport).
- The daily fluid intake should exceed 2.5-3 Liters/m² of body surface area.
- Make sure you always have plenty of fluids at your disposal.
- Always take water with you when you are visiting new places.
- Drink even if you are not thirsty - in regular intervals throughout the day.
- Schedule frequent visits to the toilet.
- You can set reminders on your mobile phone to remember to drink water, you can also use special apps to record how much water you drink.
- Remember to always have water filled bottles everywhere in your apartment, car, backpack or your bag.

2. Diet.

Limited intake of table salt reduces the amount of calcium excreted in the urine and thus reduces the risk of kidney stone formation.

3. Drug treatment.

Potassium and phosphate supplementation

As Dent's disease is characterized by tubular losses of important minerals such as potassium these need to be supplemented to keep the blood concentrations in the normal range.

In patients with low phosphate levels (hypophosphatamia) and rickets, phosphate supplements are prescribed. Phosphate supplementation can reduce hypercalciuria, even in the absence of hypophosphatemia.

Drugs which reduce calcium crystallization (in combination with fluid intake) can further reduce the risk of stone forming.

The best results are achieved when the drugs are taken at regular intervals during the day.

Potassium citrate forms soluble complexes with calcium in the urine, thereby reducing the availability of calcium for crystal formation.

Citrate is metabolized to bicarbonate in the liver and leads to more alkaline blood and urine (higher pH of blood and urine). Under these conditions, less citrate is reabsorbed in the renal tubule and this more is excreted in the urine. Citrate binds calcium and reduces the availability of calcium for stone formation.

The dosage of alkaline citrates is individually adjusted based on the result of the urine test pH, which can be tested using pH indicator paper.

Target pH values are between 6.2 and 7.4.

Chronic treatment with citrate may delay the progression of kidney disease and even prevent the formation of stones.

Thiazide diuretics are often prescribed in Dent's disease to reduce hypercalciuria. Still, their use is limited by side effects like hypovolemia (decreased body fluids, water loss) and hypokalemia (decreased serum potassium levels). Therefore, this treatment needs to be monitored closely by the treating nephrologist and extra caution is advised in case of decreased fluid intake or increased fluid losses.

ACE-inhibitors are prescribed by some nephrologists in an attempt to lower proteinuria. These drugs lower the filtration pressure in the glomeruli and thus the amount of proteins crossing the glomerular filters. This treatment is controversial as the problem in Dent's disease is decreased uptake of proteins in the tubulus and not increased filtration in the glomeruli. Until now, no trials have been performed to test if ACE-inhibitor are beneficial in Dent's disease.

B. Symptomatic Treatment of Nephrolithiasis

Extracorporeal lithotripsy is a non-invasive procedure that uses ultrasonic shock waves to break stones in the urinary tract and kidneys. Its use is restricted to smaller stones and often requires general anesthesia in children.

Ureteroscopic laser lithotripsy is a minimally invasive method for removing stones from the urinary tract by accessing the kidney via the ureter and crushing the stones directly using laser. Under general anesthesia an endoscope is inserted into the bladder via the urethra. The ureter is canulated and the stone is visualized. Depending on the size of the stone, the fragments will be small enough to pass spontaneously or can be taken out using the endoscope.

C. Treatment of Chronic Kidney Failure

Even nowadays, Dent's disease is often only diagnosed when kidney function is already impaired significantly. In these cases, treatment of chronic kidney failure and its complications is required.

To **maintain kidney function for as long as possible**, it is important to pay special attention to factors which can be detrimental to kidney function.

For this reason, it is recommended:

1. To avoid drugs which can damage the kidneys, such as nonsteroidal anti-inflammatory drugs ("NSAID") – such as Ibuprofen, Naproxen, etc. which are available without prescription in many drug stores. There are number of other drugs which should be avoided – your treating physician will be aware of this.

2. Avoidance or very careful use of contrast dyes for radiological examinations such as computed tomography (CT scan).

3. Always, regardless of the kind of another medical conditions, alert your doctor about the diagnosis of Dent's disease, so that he/she can adjust the treatment or schedule extra controls if needed.

In end-stage kidney failure, when the kidneys are unable to excrete sufficient metabolic waste products to keep the body alive, dialysis is started, or a **kidney transplantation** performed.

Dialysis is a procedure in which the basic functions of the kidneys, i.e. removal of water and metabolic waste products are taken over by a machine. There are two types of dialysis: hemodialysis and peritoneal dialysis.

In hemodialysis, the blood is pumped through a filter where it is cleaned, and excess fluid is removed. This method is usually performed in the hospital, e.g. 4 times a week for several hours.

Peritoneal dialysis involves repeated administration and removal of dialysis fluid into/out of the abdominal cavity by a catheter. This method can be performed at home using a special machine, usually during the night while the patient sleeps.

D. Further Prospects for the Treatment of Dent's Disease

So far, no causal treatment for Dent's disease has been developed, yet. Also, due to the diversity of symptoms that occur there is no standard treatment. Due to the rarity of Dent's diseases, there is a lack of clinical trials in a large group of patients to prove the effectiveness of medications like citrate or thiazides. Still, experiments in animal models of Dent's disease have yielded important insights.

Gene therapy research for the treatment of Dent's disease is ongoing. Experimental data show that the defective function of the CLC5 protein mutated in Dent's type 1 disease might be saved by so-called small-molecule treatment.

E. Emergencies

Patients with Dent's disease run a high risk of dehydration and emergencies like febrile, diarrhea/vomiting may require treatment and fluid therapy in hospital setting. It is also important to closely monitor electrolytes.

If patients have kidney stones, this might lead to obstruction of the urinary tract requiring urgent urological interventions to prevent deterioration of kidney function.

F. Preoperative Care and Surgery

Inform the surgeon / anesthesiologist about the diagnosis "Dent's disease".

Preoperative assessment of renal function and blood electrolytes (in particular potassium) should be performed in all patients with Dent's disease.

If possible, contact the (pediatrics) nephrologist caring for you/your child before surgery or other medical interventions to discuss special requirements/needs or restrictions for you/your child.

G. Psychological Care

The unpredictable course and the risk of a sudden deterioration of kidney function form a high psychological burden – both for the affected patients and their families. Most patients, including their parents, require psychological support.

PROGNOSIS

What will be the long-term results of treatment?

Based on previous observations of patients with Dent's disease, kidneys stop working between the age of 30 – 50 years in 30-80% of men with Dent's disease.

Due to the rarity of the disease, there is a lack of data assessing the impact of early diagnosis on further prognosis.

It seems, however, that timely interventions decrease the development of kidney calcification and stone forming which might slow down the progression of kidney failure.

SUPPORTIVE CARE

How and where can I get more help?

In many countries there are Dent's disease patient support groups. Dent's disease is a rare disease and not understood completely. The exchange of information and experiences can be very helpful for patients and their families. Patient support groups and foundations organize meetings, lectures as well as holiday camps.

Please find the links to the Dent's disease patient group on the ERKNet patient website:

If you have any other questions or need for support, do not hesitate to ask your general practitioner, paediatric nephrologist, or nephrologist.

GLOSSARY

ACE-inhibitors - a class of drugs reducing the filtration pressure in the kidneys and are the mainstay of the treatment of glomerular diseases.

Aminoaciduria - abnormally high amounts of amino acids in urine.

Creatinine - a metabolic product circulating in blood, which is filtered by the kidneys and excreted in the urine. Creatinine is not harmful but is used as an indicator of the function of the kidneys: The higher the blood concentration of creatinine, the worse the kidney function.

Chronic kidney disease (CKD) - progressive and irreversible kidney damage that can lead to kidney failure within months or years. As kidneys cannot regenerate, there is no treatment to reverse chronic kidney disease, but there are treatments that slow the progression of the disease if implemented in time.

Dialysis - method to remove metabolic waste products and excess fluid from the blood. There are two main types of dialysis: hemodialysis and peritoneal dialysis. In the case of hemodialysis, blood is pumped through a filter using a machine. Peritoneal dialysis involves repeated administration and removal of dialysis fluid into/out of the abdomen which also cleans the blood.

End stage kidney disease (ESKD) - the most severe form of kidney disease when the kidneys have stopped working (may still produce urine which is of very poor quality, however). This means that kidney replacement therapy (dialysis or kidney transplantation) is needed.

Fanconi syndrome - a set of symptoms caused by a defect in the first part of the nephron (proximal tubule), causing a disturbance in the resorption of amino acids (aminoaciduria), glucose, phosphate, uric acid, citrate, small proteins, magnesium, potassium, calcium, bicarbonate and water.

Focal segmental glomerulosclerosis (FSGS) - a condition in which scar tissue develops in the kidney filters (glomeruli) and can lead to kidney failure. FSGS usually manifests with large amounts of protein in the urine.

Gene - the genetic unit containing the instruction ("recipe") how to produce each protein in the body.

Glomeruli – the little filters in the kidney at the start of each nephron. Each kidney holds between 250,000 and 1 million glomeruli.

(GFR) glomerular filtration rate – describes the rate at which the kidneys filter waste products from the blood. GFR is normally higher than 90 ml/min/1.73 m^2, a lower value indicates impaired kidney function. A value below 30 ml/min/1.73 m^2 corresponds to severe kidney failure, at about 10 ml/min/1.73 m^2 renal replacement therapy is necessary.

Kidney transplantation – surgery putting a healthy kidney into a person whose kidney have stopped working (end-stage kidney disease).

Lowe syndrome – oculo-cerebro-renal syndrome, caused by mutations in the same gene (OCRL1) that causes Dent's disease type 2. It is also inherited X-linked recessive and only affects males.

Macrohematuria – the visible presence of the blood in the urine.

Microhematuria – the presence of a small amount of red blood cells (erythrocytes) in the urine. The color of urine is normal, the erythrocytes are only visible by microscopic examination.

Nephrocalcinosis - the occurrence of numerous punctate calcifications in the kidney tissue reflecting calcium crystal deposition., These changes are readily visible by ultrasound. Nephrocalcinosis may predispose to the development of kidney stones.

Nephron - is the basic functional and structural unit of the kidney, it consists of two parts: the renal filter (glomerulus) and the tubule where reabsorption takes place.

Nephrotic syndrome – a condition where kidney filters leak excessive amounts of proteins leading to low proteins in the blood and retention of fluid in the body often resulting in visible swollen eyes and legs.

Osteomalacia - the softening of the bones caused by impaired bone metabolism primarily due to inadequate supply of phosphate, calcium, and vitamin D. Can also be caused by increased calcium release from the bones.

Polydipsia - excessive drinking. This can be a symptom of a number of diseases causing water losses and resulting in excessive thirst.

Polyuria - abnormally large urine production (e.g., more than 3 liter per day in adults).

Renal tubule - part of the nephron, where the primary urine from the glomerulus is modified by resorption and secretion of molecules. In the tubules about 150 liters of primary urine is modified resulting in about 1.5 liters of urine excreted in the bladder. The tubule consists of several sections: proximal tubule, Henle loop, distal tubule, and collecting duct.

Rickets - bone deformities caused by disorders of calcium-phosphate metabolism.

Tubulopathies - rare kidney diseases in which renal tubular function is impaired while the glomeruli are functioning normally.

Urolithiasis (nephrolithiasis) - formation of stones in the urinary tract (in the kidney).

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Funded by the European Union