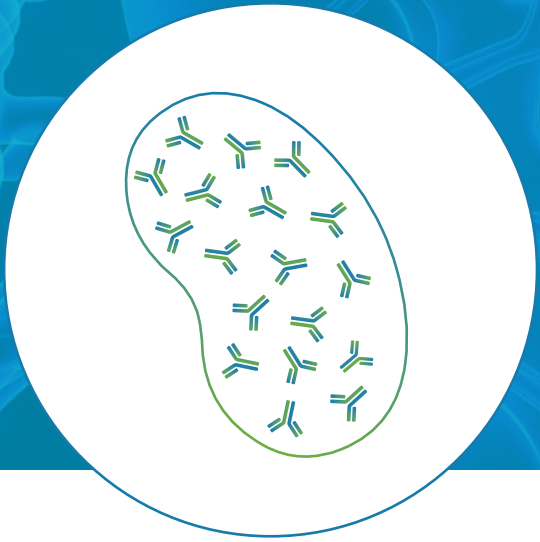
ERKNet
The European Rare Kidney Disease Reference Network

INFORMATION
FOR PATIENTS



IgA Nephropathy

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European
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When I was 18 years old, I underwent a recruitment exam for the army, and they noted tiny amounts of blood in my urine. I was then sent to a urologist, who did a cystoscopy, i.e., he looked into my urinary bladder, and he assured me that there was nothing wrong. Twenty years later, I am now self employed as a tax consultant and I went for a medical check-up after my wife kept telling me that this would be good to have at almost 40 years of age. The doctor again discovered traces of blood in my urine. I was also told that I have quite a bit of protein in the urine, that my kidney function was only half of what it should be and that my blood pressure was high. I had a kidney biopsy that showed IgA Nephropathy with quite a bit of scarring in the kidney tissue. Despite all of this, I had never felt anything! I was given blood pressure medications plus another drug that protects the kidneys (called an "SGLT-2 inhibitor"), had to stop smoking, and started to engage in regular exercise in addition to changing my diet. With this I lost 10 kg, my blood pressure is in the 110-120 mmHg systolic range and now, 3 years later, my kidney function is stable, protein in the urine is very low and I essentially enjoy an almost normal life, except that I go and see my nephrologist every 6-12 months.

MICHAEL, 45

...typically, in autumn and spring, I often have respiratory infections and have suffered from sore throat many times. Three years ago, during one of these infections, I noticed that my urine was a brownish red colour. I reported this to my mum and since then I must do regular urine dipstick tests. I almost always have blood in my urine, even when I'm not sick and even when the urine is of a normal colour. The urine test also showed the presence of protein several times. My doctor said I have to pay attention to the presence of protein, and in the case of proteinuria I should always report to him for detailed examinations. Fortunately, my blood pressure is normal. A year ago, I had tonsillectomy and since then I have not had strep throat. I do regular urine tests myself at home using strip tests. If the urine is clear, my mum must remind me to do the tests, but if it is red, I know to do the test myself. I have also had my blood tested a few times. Thankfully everything was fine, but I have to repeat these tests from time to time.

ANNA, 10

IgA Nephropathy

A year ago, I broke my arm while riding a bicycle. Because surgery was necessary, I had routine blood and urine examinations. It turned out that my kidneys are not functioning properly, that I have anaemia, hypertension, and blood and protein was found in my urine. Sometimes I had stomach pains, I generally slept more than my brothers, and I quite often had headache. My urine was never bloody, but unfortunately, I considered the foam formation on the surface of my urine to be normal.

No one in my family has kidney disease. My dad has coeliac disease and can't eat gluten-containing foods, my mum is healthy.

Soon I was in the Nephrology Department of the Children's Clinic and a kidney biopsy was performed to determine the cause of impaired kidney function and the large proteinuria. I was diagnosed with IgA Nephropathy. According to the paediatric nephrologist, because chronic as well as active changes were found in the kidneys, steroid treatment was started. I remember steroid treatment very negatively; I was unbearable to the family and was very worried that I would be fat. Fortunately, this did not happen, because I was very careful about what I eat and tried to eat only healthy foods. Treatment for hypertension caused me to stop having headaches. Apparently, the proteinuria also decreased under the influence of this treatment. Currently, I feel better overall, studies indicate that kidney function has improved, and the proteinuria has decreased, but they are still not normal. The chronic changes that have been shown in a kidney biopsy are reportedly not reversible, but the active ones that indicate inflammation, are. My further immunosupressive treatment is currently being discussed. I hope for further improvement...

ROBERT, 14

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WHAT IS IgA NEPHROPATHY?

IgA Nephropathy (IgAN), in past sometimes known as **Berger's Disease**, is an inflammatory disease of the kidney, the most common primary glomerulonephritis worldwide as well a leading cause of End-Stage Kidney Disease (ESKD).

The name comes from deposits of specific proteins in the kidney, the so-called **immunoglobulin type A1 (IgA1)**. In this case, the **IgA1** is also erroneous due to the lack of a normal sugar molecule (called galactose). This may make it more "sticky" and can lead to the formation of antibodies directed against them, such that **immune complexes form**, initiating an inflammation and progressive degenerative changes (see below). However, if a lot of IgA1 is in the blood, in particular in aggregates, i.e., "lumped together", this alone is sufficient to cause deposition in the kidney and a mild inflammation.

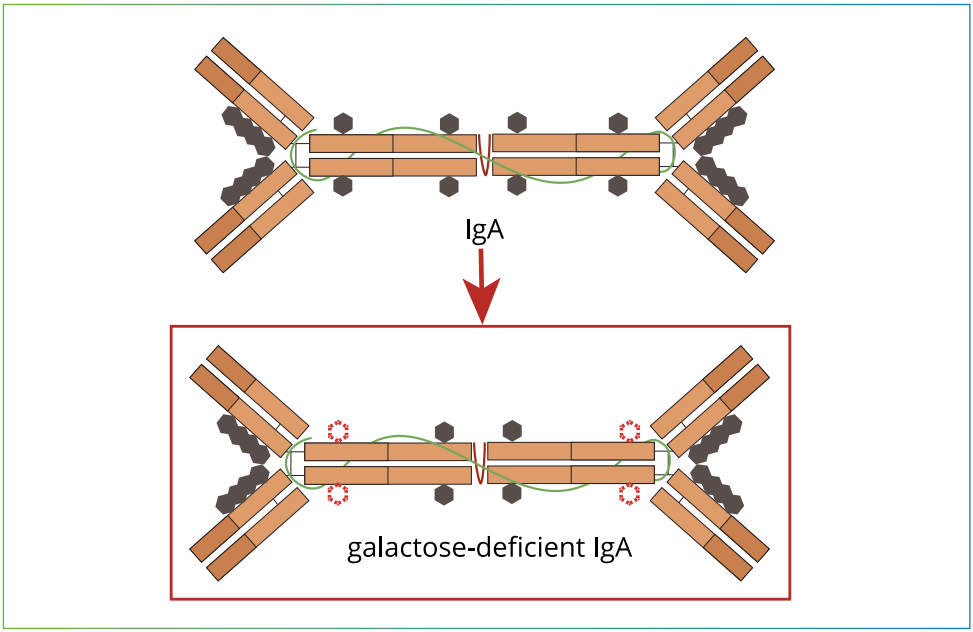


Figure 1. *In IgA nephropathy, a condition affecting the kidneys, there is a change in the IgA antibody. Normally, IgA antibody has a sugar molecule called galactose, but in this condition, galactose is missing. This leads to the presence of galactose-deficient IgA.*

- Since the kidney damage occurs because of alterations in the immune system, **IgAN is considered an immune-mediated disease**.
- **IgAN can occur at any age, both in adults and young children**. In children, the diagnosis of the disease is often made in its active phase, when the start of an appropriate treatment can significantly reduce the further progression of the disease and even reverse the changes in the kidney. In adults, the disease is often detected in its chronic phase, when permanent changes have already established in the kidney.
- **The disease is often detected accidentally**. Proteinuria (protein in the urine) and/or haematuria (blood in the urine) are found during routine check-ups. Frequently, the first manifestation consists of recurrent visible haematuria during infectious episodes, but this gets less and less as patients get older. In adults, IgAN is sometimes diagnosed only in a very advanced stage because of the onset of symptoms of kidney failure (oedema, hypertension, possibly even signs of uraemia, i.e., end stage kidney failure).
- Even if most of affected children have a **mild course of the disease**, up to 30-40% of them may already present **advanced chronic lesions that require specialised treatment** at the time of diagnosis. However, in some patients (about 30%) **IgAN can spontaneously disappear**, in particular in early stages of the disease.
- **In some 30-50% of paediatric and adult cases, IgAN is known to be at risk of progression if not properly treated**. The choice of the therapeutic approach varies according to the individual condition and risk of progression to end-stage kidney disease (ESKD). In the vast majority of the patients, where IgAN causes progressive loss of kidney function, this is a very slow process and it often takes 20, 30 or more years until end stage kidney failure develops and some form of kidney replacement therapy (i.e., dialysis, transplantation) is necessary.
- **All patients with IgAN require regular check-ups**, especially urine tests, blood tests and monitoring of blood pressure. Hospitalisation may be necessary, especially at the time of diagnosis, e.g., when a kidney biopsy is performed, or when there is a significant clinical impairment.

Please note:
Some useful vocabularies are explained in the text, additional vocabularies are listed and explained at the end.

WHAT IS THE GLOMERULUS? WHAT GLOMERULONEPHRITIS MEANS?

To put it simply, the human urinary system consists of 2 kidneys, the ureters departing from them, the bladder to which the ureters supply urine and the urethra, from which urine is excreted from the body.

The kidneys are a pair of bean-shaped organs on either side of the spine.

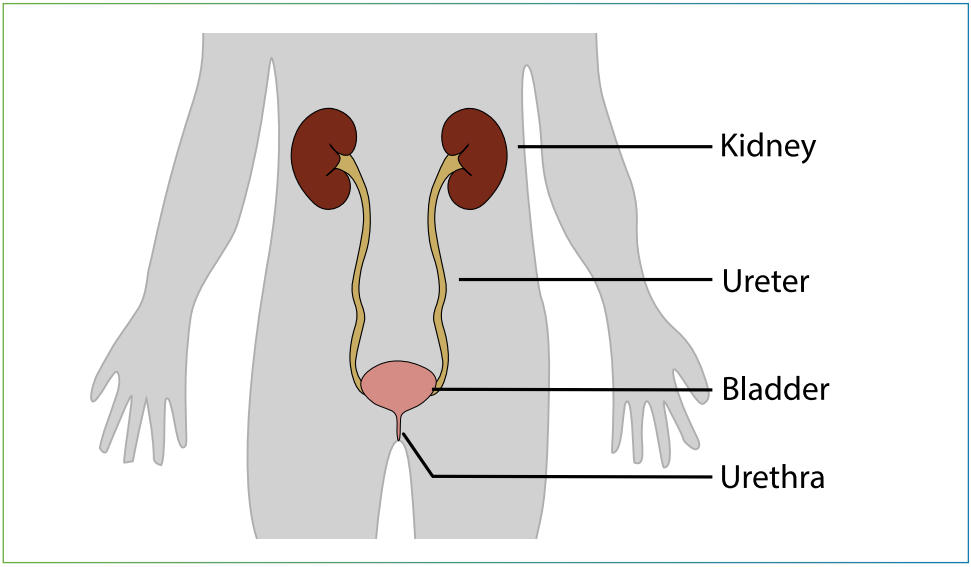


Figure 2. *Schematic illustration of the urinary system.*

Each kidney consists of about one million functional units, called nephrons. The number of nephrons is individual determined and depending on many factors. For the kidney to function properly, it is necessary to keep at least 30% of the nephrons in operation to work well.

The **nephron** is made of two essential parts: the **glomerulus** and the **tubule**.

The **glomerulus** is a network of tiny blood vessels, where, on the principle of filtration, primary urine is formed (primary urine consists of blood deprived of proteins and blood cells).

The primary urine is processed flowing through the **tubule**.

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, amino acids and proteins. They also regulate the acid-base homeostasis. These processes are necessary to maintain a stable balance of body chemicals.

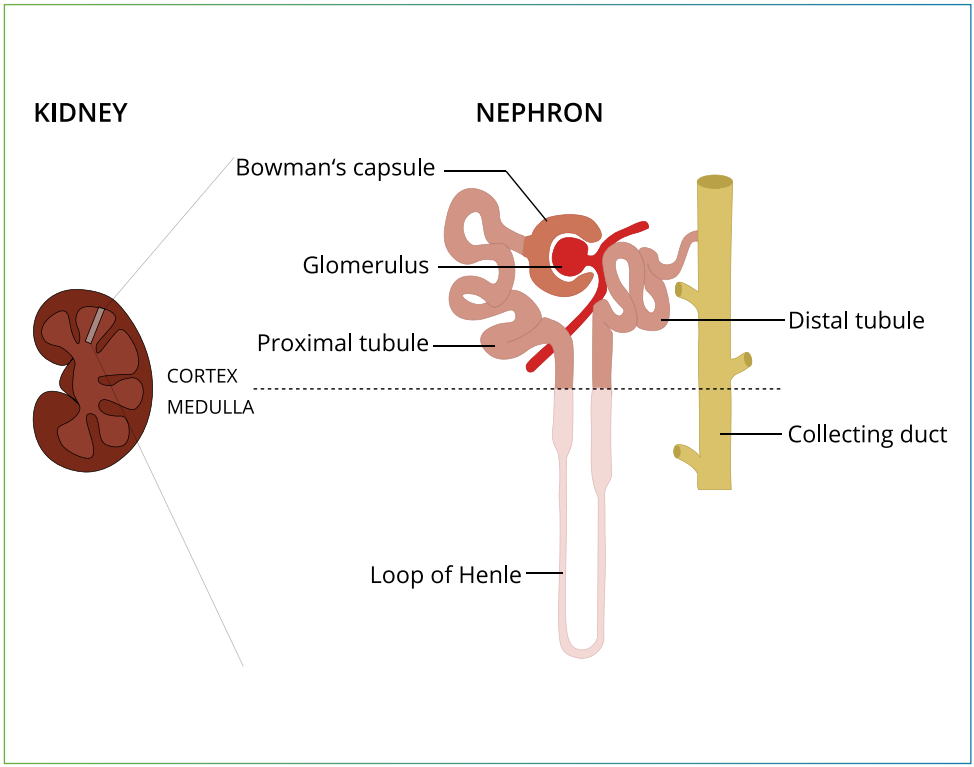


Figure 3. *The nephron as functional unit of the kidney.*

The glomerulus in more detail

The glomeruli are the most prominent histological structural units of the kidney.

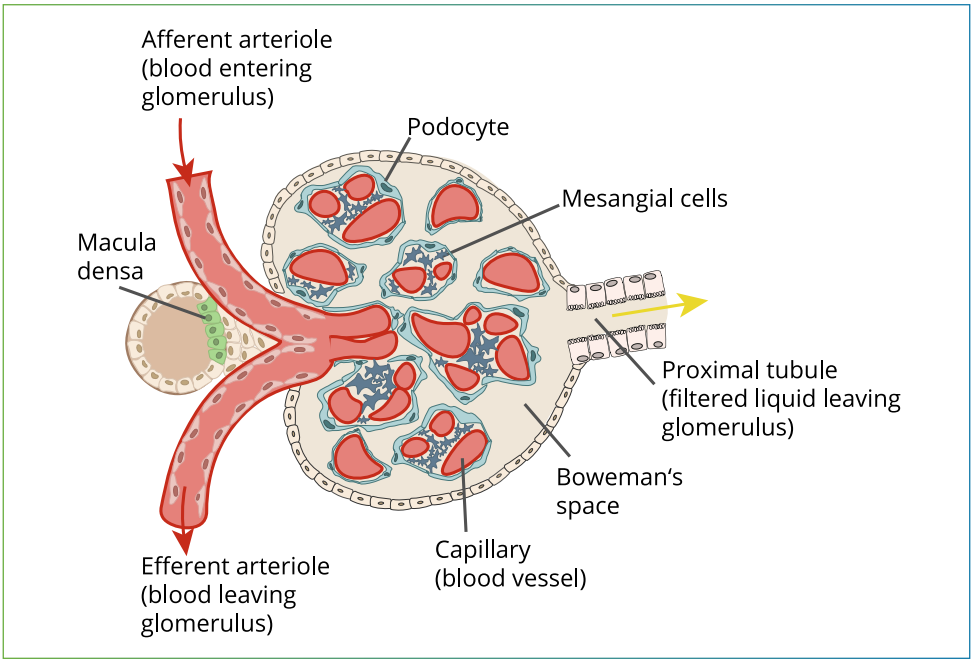


Figure 4. *The glomerulus as a filtration unit.*

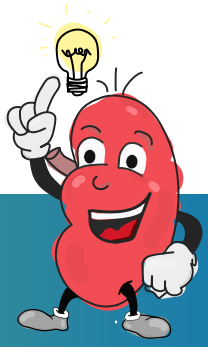
The incoming arterial vessel (**afferent arteriole**) brings blood containing toxins into the glomeruli. There, the vessels branch into a bundle of thin capillaries. The vessels are surrounded by a capsule (Bowman's capsule). The capillaries of the glomerulus reunite to form a vessel that leads a way (**efferent ateriole**) that returns the filtered blood to the body.

The capillary vessels and specialized cells called **podocytes** that surround the capillaries are responsible for the filtration of the blood.

The capillaries of the glomerulus are held in place by a central stalk, called the mesangium. It consists of the **mesangial cells** and an extracellular matrix.

The primary urine is formed in the so-called capsular space (also: **Bowman's space**). This liquid of this capsular space flows into the kidney tubule.

DID YOU KNOW?



Each day, about 150 litres of blood are filtered by the kidneys and filtrate is transported into the tubules. Of this fluid (primary urine), 99% is returned to the body. Therefore, healthy kidneys produce only 1.5 litres per day!

Glomerulonephritis (GN) is an inflammation of the glomeruli. It can damage the structures of the kidney to varying degrees. The basis of inflammation may be a primary abnormality of the immune system (immune-mediated disease), secondary to other diseases (infections, drugs, systemic diseases, cancer) or other abnormalities such as the deposition of proteins that cause inflammation in the filter.

WHAT IS THE CAUSE OF THE DISEASE?

IgA Nephropathy is an immune-mediated inflammatory disease of the glomeruli. The exact cause of the disease has not been fully determined.

Extensive research in recent years has found that several mechanisms underlie the disease. It is presumed that the development of the disease occurs due to a combination of environmental factors and the presence of genetic predisposition.

The name IgAN comes from the presence in the kidney of specific proteins, the so-called immunoglobulin type A1, in the form of immune complexes, which cause an inflammation and progressive degenerative changes in the kidneys.

The immune system is composed of special cells, proteins, tissues and organs. It is responsible for the body's immunity, i.e., the body's ability to protect itself against any dangerous substances and infectious germs. The intrusion of harmful microorganisms into the body activates the immune system response, thanks to which the rapid elimination of these harmful microorganisms is possible. Unfortunately, like any other system or organ, the immune system can be affected by various diseases. Its function is then weakened/completely blocked, or on the contrary, overly active where and when it should not be, as in autoimmune diseases.

IgA Nephropathy

Immunoglobulins are the most important proteins of the specific immune response. Their task is to protect the body against the threat of microorganisms. They are also called "antibodies" and are found both in the blood and in tissues. The antibodies are Y-shaped and consist of two pairs of protein chains – the light chain and the heavy chain. Based on differences in the structure of heavy chains, several classes (types) of antibodies are distinguished: IgA, IgD, IgE, IgM, IgG.

Immunoglobulins type A (IgA) are the subgroup of antibodies mainly secreted by mucous membranes, e.g., intestines, respiratory tract, and salivary glands. They provide local immunity and protect mucous membranes against microorganisms and allergens. Two IgA types are distinguished, IgA1 and IgA2 molecules.

Complement system consists of several proteins. They play an important role in the immune system, the defence against pathogens immune cells migration and cells disruption. Unfortunately, this part of the immune system can also be dysregulated and thus become active against the body's own substances, which is, among others, the case of IgAN.

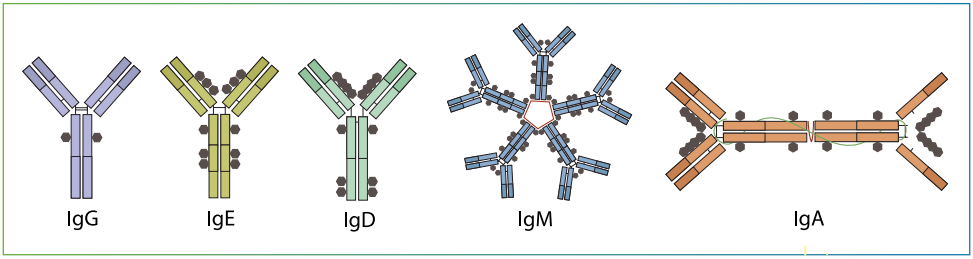
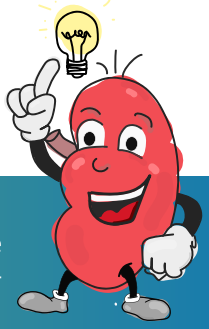


Figure 5. *The different types of immunoglobulins.*

DID YOU KNOW?



In 1919, Jules Bordet (a Belgian microbiologist at the Pasteur Institute in Brussels) was awarded the Nobel Prize in Medicine for his discovery of the bacteria-destructive bacteriolytic properties of serum. He observed that the breakdown of certain bacteria occurs under the influence components of the serum which later could be described as complement system.

Pathophysiology

IgAN is caused by the accumulation of altered immunoglobulins type A1 (IgA1) that lack the normal sugar/galactose particles. This galactose deficient IgA1 may be more "sticky" than normal IgA1 and often comes in pairs, triplets or even aggregates in the blood in IgAN. This in itself may be enough to cause deposition and inflammation in in glomeruli, as illustrated by many animal strains with IgA overproduction, that develop an IgAN-like disease. In addition, galactose-deficient IgA is considered "foreign", and so the body produces antibodies directed against defective IgA (anti- IgA autoantibodies). These antibodies bind to the altered IgA1 proteins forming immune complexes, which accumulate in the glomeruli – more precisely, in the mesangium (please see Figure 6).

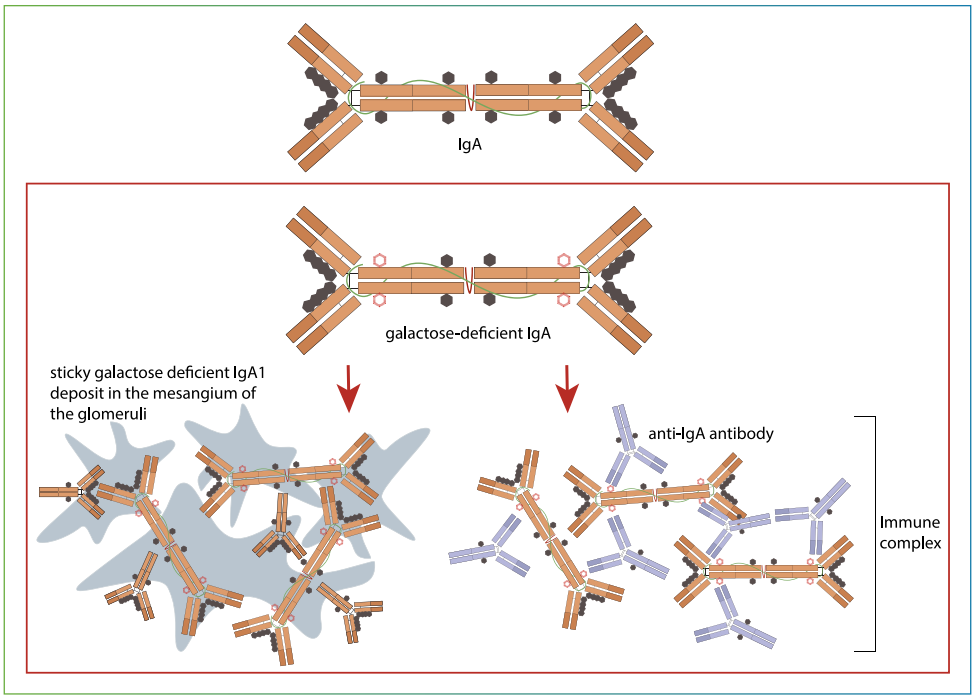


Figure 6. *In patients with IgAN, this galactose deficient IgA1 can be more 'sticky' than normal IgA1, often appearing in pairs, triplets or even aggregates in the blood. As a result, the body produces antibodies against the defective IgA and immune complexes are formed.*

Infections of the upper respiratory tract (mouth, nose, throat, and larynx) or gastrointestinal tract result in increased production of IgA, including defective IgA, which in turn may aggregate and it may increase the formation of autoantibodies resulting in IgA-IgA and IgA-IgG immune complexes which deposit in the mesangium. This explains why infectious episodes can worsen the symptoms of IgAN.

Furthermore, there is some evidence to show that immune complexes, due to the defective structure of IgA1, cannot be degraded/metabolized in the liver, where normally the IgA1 molecule would be broken down and excreted. This further promotes the accumulation in the circulation and deposition in the glomeruli.

Immune complexes deposition provokes activation of the complement system and a variable inflammatory reaction. As a result, the damage of filtration barrier (glomeruli) leads the abnormal leak of blood and protein in the urine.

To sum up, the chain of events that lead to the development of the disease are:

1. **Production and accumulation of improperly built IgA1.**

   People with IgAN have elevated levels of IgA in their blood, which contains lower quantities of the special sugar, galactose, than normal.

   It is likely that this is caused by multiple factors: genetic predisposition, bacterial infections, hyperreactivity of intestinal lymphoid tissue, in some cases acute or chronic inflammatory bowel disease or celiac disease.

2. **Production of IgG autoantibodies against Gd-IgA1.**

   The presence of galactose deficient IgA1 (Gd-IgA1) and their penetration into the circulation stimulates the development of IgG autoantibodies against Gd-IgA1 themselves.

3. **Formation of immune complexes.**

   The presence of immune complexes composed of galactose-deficient IgA itself and/or IgA-IgG complexes promotes their binding to receptors and deposition of in the glomeruli/ mesangium.

4. **Deposition of deposits in the glomeruli. Activation of the complement system and inflammatory reactions. Degenerative changes in the kidneys.**

   The deposits stimulate an inflammatory response and activation of the complement system, followed by mesangial cell division and an overproduction of matrix. Activation of the complement system can intensify the inflammatory response and the remodelling of the structure of the glomerulus.

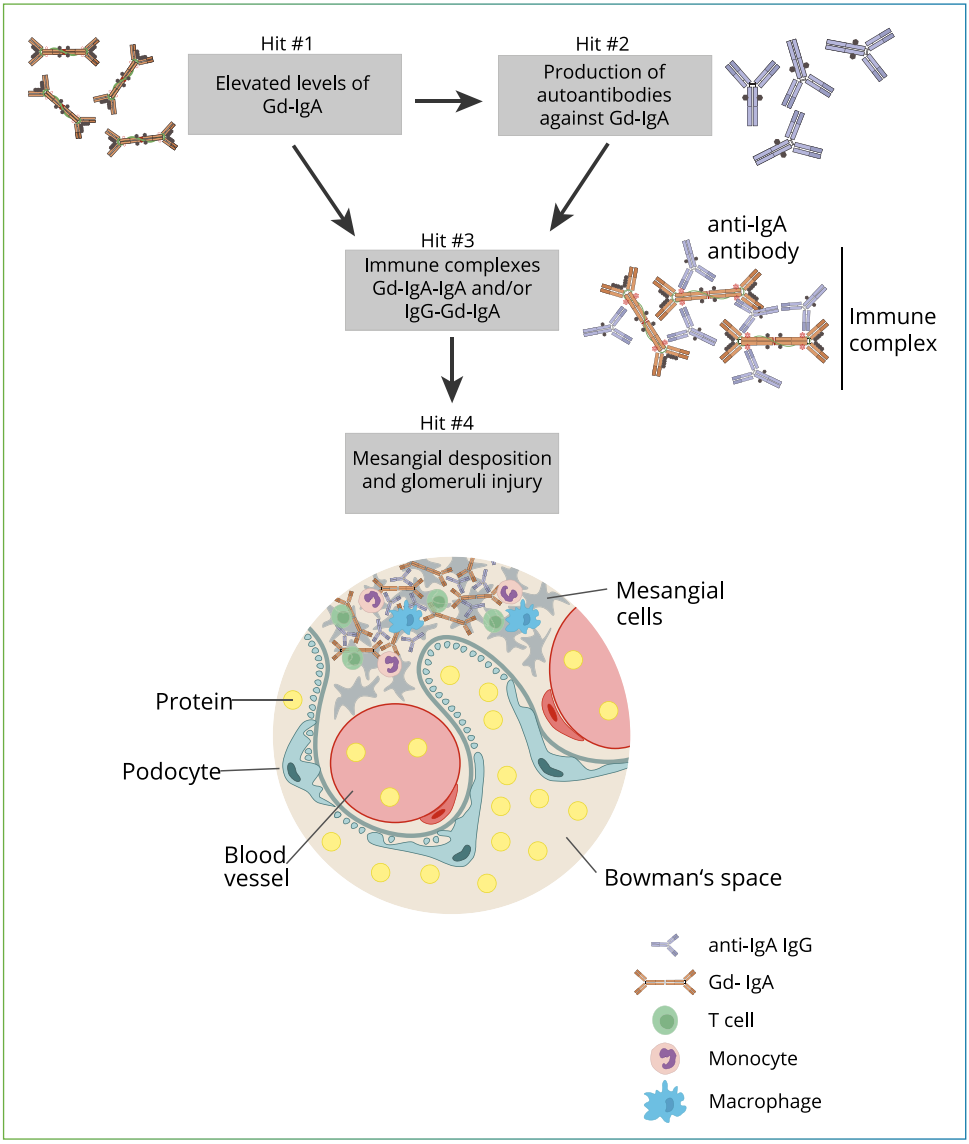


Figure 7. *The multi-hit hypothesis for the emergence of the IgA nephropathy.*

WHAT IS THE RISK OF DEVELOPING THE DISEASE?

IgAN is one of the most common "idiopathic" (**idiopathic** means that these are diseases whose exact cause cannot be proven or is not identified) glomerulonephritis in the world. It is estimated that IgA Nephropathy accounts for as much as 15-40% of all primary glomerulopathies.

IgAN occurs most frequently in patients of Asian descent, less commonly in white patients and only rarely in patients of African descent which clearly points at the importance of genetics in the development of the disease.

The disease affects people of all ages, although it is most often diagnosed in people under 30 years of age, particularly in older children and adolescents, more often in male and white individuals in patients of European descent, but with no gender predilection in patients of Asian descent.

The disease is more often diagnosed among individuals with coeliac disease (gluten intolerance) or the coexistence of other immune-mediated diseases (inflammatory bowel disease, asthma, psoriasis).

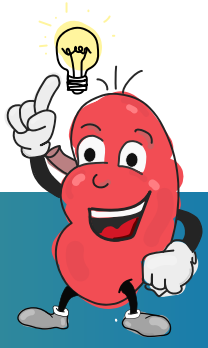
In some families, there seems to be a predisposition to the development of the disease, but the disease is not caused by a specific or single gene, like cystic fibrosis or haemophilia. It seems that in addition to the genetic predisposition, the action of additional factors is necessary to trigger the disease.

Some genes involved in bowel inflammatory diseases or genes responsible for proper immune response against pathogens seem to be associated with a higher incidence/predisposition of IgAN.

IgAN can be secondary to other diseases, e.g. systemic diseases, including:

1. Ankylosing spondylitis (AS)
2. Rheumatoid arthritis
3. Reiter's syndrome
4. Coeliac disease
5. Inflammatory bowel disease
6. Alcoholic liver disease
7. Sarcoidosis
8. Psoriasis
9. Hepatitis B or C.

IgAN may also be a part of a systemic disease, called IgA vasculitis (in the past called "Schönlein-Henoch vasculitis"), where patients exhibit a skin rash, IgAN, joint pain (arthritis) and/or belly pain (arising from an inflamed bowel).



DID YOU KNOW?

IgA vasculitis (IgAV), previously **Schoenlein-Henoch purpura**, is an inflammatory disease of small blood vessels associated with the deposition of IgA antibodies. Immune complexes can be observed in the vessels of many different organs, such as the skin, lungs, as well as the kidneys. Much scientific evidence points to a link between IgAV and IgAN. A common ethology of both diseases is very likely, although the prognosis is different, with better outcomes for IgAV.

SYMPTOMS

The course of the disease can vary widely among affected individuals.

IgAN is almost always painless. Due to the overlooked and non-specific symptoms, the diagnosis is often made accidentally, when the presence of blood and / or proteins is detected in the urine during routine check-ups. The urine abnormalities associated with IgAN are:

Macrohaematuria – the presence of visible amounts of blood cells in the urine. Urine may have a brown tint. Macrohematuria means more serious damage to the glomeruli.

Microhaematuria – the presence in the urine of red blood cells (erythrocytes). The abnormality is not visible without microscopic analysis - the colour of the urine does not change. Isolated hematuria indicates less kidney damage.

Proteinuria – the presence of proteins in the urine. Usually, proteinuria does not give any symptoms and only in extreme cases a characteristic foamy urine may appear.

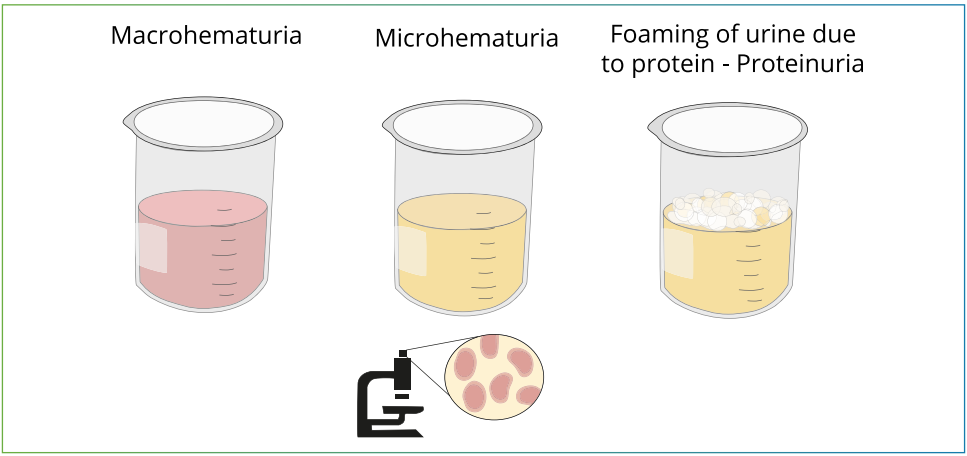


Figure 8. *The presence of blood in the urine: visible – macrohematuria, diagnosed only by microscopic examination – microhematuria. Proteinuria may be suspected if the urine is foamy, frothy or bubbly.*

Patients or their parents may also notice symptoms such as:

- **Elevated blood pressure (hypertension)**, which initially is mild but in late stages of the disease can become severe enough to cause headache, changes in vision or even heart and brain problems
- **Oedema**, i.e. swelling of the hands, feet, abdomen or face
- More frequent urination at night (**nycturia**)
- **Nausea, vomiting**
- **Muscle spasms** at night

During the course of the disease, the presence of recurrent macrohematuria during an upper respiratory tract infection is very characteristic, but mostly limited to children and young adults. It becomes very rare in older adults.

Even in case of severe kidney disease and impaired kidney function, the symptoms can be inconspicuous, especially when the disease develops slowly, and the patient adapts to the changes. It is only over time, at the disease's advanced stages, that symptoms of kidney failure may appear, or otherwise when sudden drop of kidney function occurs, and the body has no time to adapt.

How is chronic kidney failure manifested?

The kidney failure is diagnosed by blood tests through detection of decrease in the so-called glomerular filtration rate (GFR) and increase of creatinine level (waste product). Kidneys have many functions: the clearance of wastes and extra fluid, the regulation of acid-base and electrolytes balance, and furthermore, the production of important substances, like erythropoietin (see below) and vitamin D. The progressive loss of kidney function may manifest with different symptoms related to the decline of the different kidney duties:

Swelling or water retention. If too little urine is excreted, fluid is accumulated in the tissues – swelling of the lower legs at first or swelling of the face is visible especially after night rest.

Hypertension, i.e., high blood pressure, occurs secondary to an increase in vascular resistance as well as water retention in the body. Elevated blood pressure, in turn, has a negative effect on kidney function and this vicious circle usually requires drugs to avoid it.

In other words, high blood pressure can be both a cause and a consequence of chronic kidney disease. Blood pressure that is too high damages the tiny blood vessels in the kidneys, leading destruction of kidney tissue.

Furthermore, persistent hypertension stresses the heart and damages the blood vessel wall, followed by atherosclerosis.

Symptoms suggestive of hypertension include headaches, visual disturbances and others.

General symptoms: usually only appear when the GFR falls way below 20-30 ml/min (normal GFR is 80-120 ml/min) and include fatigue, nausea, decreased appetite, general deterioration of clinical condition, increased susceptibility to infections.

Other symptoms of advanced kidney failure (i.e., GFR below 20-30 ml/min) may include:

Anaemia, because of the decreased kidney production of EPO (Erythropoietin) which stimulates the bone marrow to form new blood. Symptoms of anaemia are fatigue, a decrease in physical form and exercise tolerance, pallor of the skin, susceptibility to infections.

Bone demineralization is the result of reduced vitamin D synthesis, increased urinary phosphate excretion, and secondary dysregulation of mineral bone metabolism. It can lead to fractures, bone deformities and growth disorders.

Impaired growth, low growth results from bone demineralization but also loss of appetite and characteristic tissues resistance to growth hormone.

DIAGNOSIS

While clinical symptoms and blood tests may be suspicious of IgAN, a certain diagnosis can only made by kidney biopsy.

Indications for kidney biopsy in children and adults with suspicion of IgAN include impaired renal function and/or persistent high proteinuria.

Kidney biopsy

A kidney biopsy is a procedure consisting of removing a tiny piece of kidney tissue through a special needle for microscopic analysis. It is an invasive test, but it is essential in diagnosing this kidney disease and in seeing how severe the kidney damage is. The examination is carried out under local anaesthesia or under short general anaesthesia in children. In the case of a biopsy of native kidney (not transplanted), the patient lies on their stomach and a thin biopsy needle is inserted from behind under the control of ultrasound. The tissue is then examined in microscopy in a laboratory.

A kidney biopsy makes it possible to observe changes in the structure of the organ, as well as to locate the presence of IgA immunoglobulins. The result of the kidney biopsy along with laboratory parameters, such as the amount of proteinuria and the degree of impairment of renal function, helps to assess the individual risk of disease progression and decide the appropriate treatment approach.

Complications of the procedure are rare. However, they can include bleeding, pain, and development of an abnormal connection between two blood vessels (a fistula).

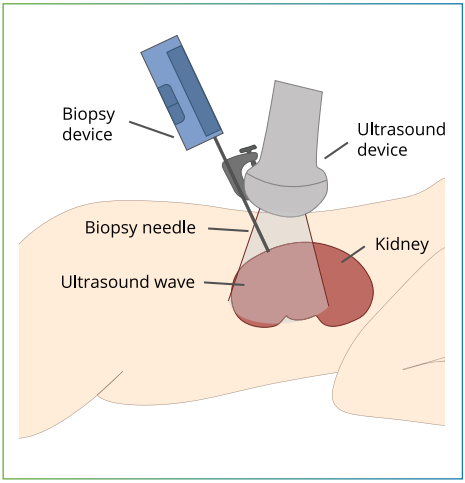


Figure 9. *Kidney biopsy, a procedure in which a sample of tissue from the kidney is taken and sent to a laboratory for testing. Short anaesthesia is administered so that the patient is asleep during the biopsy to prevent movement and discomfort. This is usually done in a hospital.*

TREATMENT

The choice of the therapeutic approach varies according to the individual's condition and in particular the estimated risk of progression to end-stage kidney disease (ESKD). A proper early diagnosis may give the opportunity for early treatment and for the improvement of the prognosis. It is still unknown why 30-60% of children and adults with IgAN will never experience a decrease in kidney function during life, while about 10% of them will develop symptoms of chronic kidney failure within 10 years from the diagnostic kidney biopsy, or within 20 years additional 20-30% of patients.

1. Lifestyle changes

Essential at any stage of the disease are changes in lifestyle, consisting of:

- Increasing regular physical activity focusing on endurance sports (while avoiding high intensity sports such as lifting heavy weights)
- Weight control for reduction/prevention of obesity
- Healthy diet and correction of possible lipid disorders
- Stopping smoking (smoking increases the risk of dialysis 5-10-fold!)
- Low salt intake
- Avoidance of using so-called non-steroid antiphlogistic drugs as pain killers, e.g. diclofenac, ibuprofen, indomethacine (aspirin, paracetamol and opiates are safe as far as the kidneys are concerned).
- There is no need to maintain a high fluid intake and about 1.5 liters of daily fluid is enough unless patients have either kidney stones or repeated bladder infections in addition to the IgAN.

All these measures greatly improve the prognosis and decrease the risk of progression to kidney failure in IgAN.

2. Renin-angiotensin-aldosterone system inhibitors

In both adult and paediatric patients at risk for progressive kidney disease, **renin-angiotensin-aldosterone system inhibitors**, i.e. ACEi (angiotensin converting enzyme inhibitors) or ARBs (angiotensin receptor blockers) constitute the basis of therapy, since these drugs have reduce arterial blood pressure, and, by lowering the blood pressure in the glomerulus of the kidneys, reduce protein loss in the urine and slow down scarring of the kidneys. This treatment usually begins at the time of diagnosis and is calibrated on the severity of proteinuria and the occurrence of hypertension.

3. SGLT2-inhibitors

A new class of drugs to protects the kidneys, which like ACEi and ARBs have very little side effects, are so-called SGLT2-inhibitors. These drugs, e.g., dapagliflozine and empagliflozine, block glucose uptake in the nephron such that the urine suddenly contains a lot of sugar and this "relief from work" apparently protects the kidney function. For children the therapy with SGLT1-Inhibitors is not yet authorised nor has it been investigated in clinical trials, so its use still needs to be confirmed in this population.

4. Immunosuppression

Studies have shown that the changes in kidney biopsy as well as the clinical course of IgAN detected in children differ from those that occur in adult patients. In children the disease is more often mild, characterised by recurrent episodes of haematuria, and rarely associated with impaired kidney function. In the kidney biopsy active over chronic changes predominate. For this reason, in children, unlike adults, there may be a greater chance of regression of changes with appropriate immunosuppressive therapy, thus reducing/stopping the disease progression. An immunosuppressive therapy that has shown better benefit and provide kidney protection in children with IgAN is the steroid therapy (corticosteroids). **The steroids are usually administered over several months (four-six months); other immunosuppressive drugs are only used in most severe cases.**

In adults with high risk IgAN, in particular in in patients of white European descent, the use of steroids is controversial with some studies showing benefits for the kidneys and other studies, showing no benefits and just side effects up to fatal infections. Thus, in adults, the start of immunosuppression should be critically discussed with the treating nephrologist.

As immunosuppressive drugs, steroids suppress the immune system and therefore have an anti-inflammatory effect. However, they have important side effects on glucose metabolism, growth, the nervous and cardiovascular systems. Based on current findings, the use of corticosteroids is carried out after careful consideration of the risks and steroid therapy is discouraged if patients are

obese, have diabetes, infections, psychiatric disease, stomach ulcers or other concomitant conditions. The same critical discussion is necessary when considering other immunosuppressive drugs.

In recent years, research has identified an steroid molecule, named **budesonide**, that, if taken in an encapsulated form (so-called "targeted release budesonide"), mostly acts locally on the immune system of the gut. Only about 10% of the drug is absorbed and enters the body and thus, there are fewer systemic side effects. This drug reduces proteinuria and stabilises kidney function in adult patients with IgAN and is currently being licensed for use in adults with IgAN in Europe. Its use needs to be confirmed in controlled clinical trials in children.

5. Blockade of complement activation

There are promising, yet still ongoing **trials testing drugs that block the complement system or reduce IgA- and IgG-production in adult patients with IgAN.**

6. Gluten-free diet

In terms of other effective and well-tolerated approaches that can improve symptoms and delay the progression of the disease, the value of particular diets, e.g., a gluten-free diet in the treatment of IgAN, is **uncertain,** unless there is an underlying bowel disease such as coeliac disease that causes secondary IgAN.

7. Others

Treatment with vitamin E, fish oil, drugs that inhibit platelet aggregation and anticoagulants, statins, herbs, or performing prophylactic removal of palatine tonsils **are not currently recommended** due to the lack of evidence of efficacy.

Experts recommend giving all patients a chance to participate in new clinical trials, especially patients at high risk of progression.

PROGNOSIS

What will happen to me / my child in the future?

The course of the disease and the prognosis must be assessed individually, considering concomitant risk factors, the results of laboratory tests, kidney biopsy, clinical parameters and response to treatment. Talk to your attending physician and discuss your condition.

In general, periodic clinical check-ups are indicated throughout the whole life:

- blood pressure assessment
- laboratory tests to assess kidney function, the amount and the course of proteinuria / haematuria
- anthropometric measurements, height, body weight, calculation of body mass index

The frequency of tests depends on the abnormalities found as well as the stage of development. These checks will be carried out more frequently during periods of intense growth, i.e., early childhood or adolescence, or in case of identified problems.

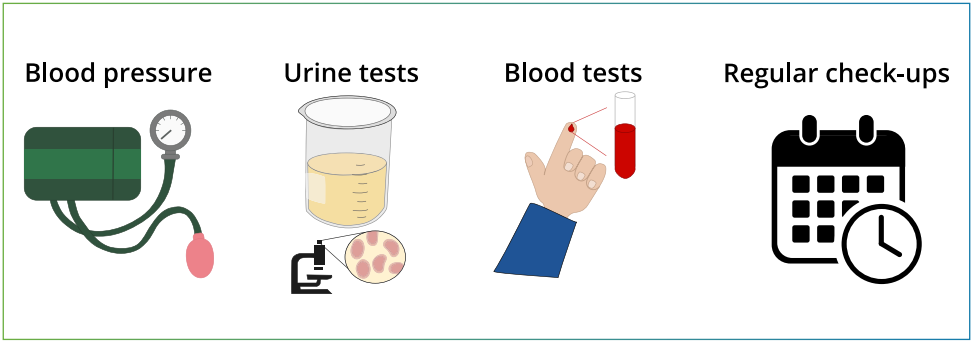


Figure 10. *People with IgAN should have regular clinical check-ups throughout their lives.*

Will I / my child get any improvement? Can my child recover?

IgAN that comes to medical attention is usually a chronic and progressive disease. This means that it does not go away, and in some patients, it may worsen over time. However, there is also evidence that very mild cases of IgAN exist, that are never recognised and never cause clinical problems in particular kidney failure. Also, with optimal therapy, IgAN may become "quiescent" and kidney functions stabilizes or sometimes the disease completely disappears.

In case of appearance of proteinuria, deterioration in general condition, increase in blood pressure or onset of other symptoms, be sure to contact your doctor.

Even if the course of the disease is mild, regular assessment of kidney function, urine composition and clinical symptoms is mandatory throughout life.

Are there any restrictions on my / my child's daily life?

The lifes of children/adults with IgA nephropathy should not be fundamentally different from the lifes of children/adults without the condition. Children should continue their education at school or in kindergarten, they can play with other children and take active participation in extracurricular activities, including sports. It is especially recommended to adopt a healthy lifestyle to minimise additional risk factors that may damage the kidneys. This includes **physical activity, weight control (preventing obesity), healthy diet, limiting salt intake and avoiding drugs that have a potentially nephrotoxic effect.**

Since exacerbations of the disease usually occur in connection with infections, special care should be taken to ensure that all possible **preventive vaccinations** are carried out in accordance with recommendations of experts. In case of immunosuppressive therapy, talk to your doctor to adequate plan the vaccination schedule.

RECOMENDATIONS

What can you do for your kidneys yourself? How to live with the disease? How to improve the prognosis?

A healthy lifestyle may significantly reduce and delay the progression of the disease or halt it all together.

Inhibiting the progression of the disease or postponing the need to start dialysis is a goal worth fighting for.

1. Do not be in the denial about the disease, but rather learn how to live with your diagnosis. Expand your knowledge, do not hesitate to ask questions. Talk to your doctor, find out what to do to maintain good kidney function, how to control blood pressure and how to avoid factors harmful to the kidneys.
2. Do not underestimate the timing of check-ups and, when necessary, take your medication regularly. If you have trouble taking your medication regularly, you should talk to your doctor about it. Together, you can think about how to integrate the intake into your daily chores and daily routine. Regular reminders using the alarm clock function on your mobile phone can be very helpful.

3. Check your blood pressure regularly. If you detect values higher than recommended, contact your doctor.
4. Check your urine regularly with a strip test. Determine the frequency of testing with your doctor. You should especially do it in case of malaise or in case of sudden abnormal appearance of urine.
5. Take care to consume the right amount of fluids and avoid states of dehydration. The average amount of fluid we should normally take in is about 1.5-2 liters per day. The demand for water in the body is influenced by age, health, kidney function, body weight, temperature, or physical activity. Follow the advice of your doctor who will tell you about the best amount for you.
6. Avoid drugs that damage the kidneys – so-called nephrotoxic drugs, which include, among others, the quite commonly used non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen or naproxen). Drugs of this type should be used as directed, in the lowest doses and the shortest time possible. It is important to seek advice from your nephrologist on which medicines should be strictly avoided or when to adjust the doses of medicines to the degree of kidney function.
7. Regulate your salt intake (sodium chloride). Excessive salt intake causes water retention in the body, increases the blood pressure and the amount of protein contained in the urine, accelerating the progression of kidney failure. The recommended daily dose of salt for adults is 6 g, approximately one teaspoon. Meanwhile, it is quite common to consume an average of 8 g of sodium chloride per day, most of which comes from industrially processed products (fast food, frozen products). Limit the consumption of products of this type.
8. Get regular exercise focusing on endurance sports like walking, jogging, rowing, cycling or swimming. Lack of exercise and lack of physical activity promotes insulin resistance and obesity, which also lead to the development of hypertension. High intensity sports, in particular body building, should be avoided.
9. Control your weight to not reach obesity. Obesity further burdens the work of the kidneys and heart and accelerates the progression of the disease
10. Take care to get regular hours of sleep.
11. Do not smoke. Smoking, both active and passive, increases the blood pressure and is a huge risk factor for the progression of atherosclerosis which impairs the blood supply to the kidneys. Smoking is also a causal factor in the development of lung, kidney and urinary tract cancers (e.g. bladder cancer).

12. No matter how busy you are, remember to empty your bladder regularly. Urine retention promotes the development and multiplication of bacteria in the urinary tract, which can further cause kidney problems.
13. Make sure you have all your vaccinations, including the annual flu jab. Many people with IgAN experience a worsening of the disease during infections. Please discuss the current recommendations for COVID-19 vaccination with your nephrologist.
14. Be informed and actively involved. Ask your doctor about currently available treatment options and specialised referral nephrologists/ medical centres that may offer new clinical trials.
15. Take into consideration your potential constraints, but do not give up on the goals set for yourself. Try not to give in to negative thoughts and plan how best to deal with the disease. This will allow you to accept kidney disease and consider it part of your life. Do not hide the disease. If you don't feel well or if you're not coping well with the disease, talk to your doctor about it. Sometimes an open conversation helps you put things in perspective. Also, do not hesitate to seek psychological help.

Recommendations during pregnancy

ACE Inhibitors and ARBs should not be used in women of childbearing age unless there is good contraception, and they are strongly contraindicated during pregnancy. Exposure of babies to these drugs has been associated with a number of serious malformations, impaired kidney function, low birth weight, growth retardation, and premature delivery.

IgAN disease itself is not a contraindication to getting pregnant/planning a family, but during pregnancy regular tests of kidney function, blood pressure measurements and urine tests should be performed. The existence of the disease should be immediately reported to the doctor who cares for the pregnancy.

What is the risk that my offspring will also develop the disease?

It is extremely rare that the disease affects more than one family member. Some genes may predispose to the onset of the disease, but an important role is played by the coexistence of many other trigger factors. The disease is not inherited like cystic fibrosis or eye colour. However, it may be wise to measure blood pressure once and to do a urine dipstick test for blood and protein in siblings or children if the disease is diagnosed in you.

SUPPORTIVE CARE

If you need support or have any questions about illness, the disease course, or long-term outcomes, please do not hesitate to talk to your GP, nephrologist or paediatric nephrologist.

In many clinics it is also possible to get psychological support. If your child/you can't cope with the disease, ask your doctor about the possibility of getting such help.

In many countries, there are support groups for patients with IgAN. The exchange of information and own experiences can be very helpful for many patients and their families.

Please find on our ERKNet patients' website the link to the proved patients organisations:

GLOSSARY

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

Albumin is a type of protein that is found in your blood. Normally, albumin should not pass into your urine, and when it does, it's indicative of kidney damage.

Albuminuria, this simply means having albumin in the urine.

CKD (chronic kidney disease) is a 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.

Creatinine is a normal body waste product derived from muscles. Measurement of its level in the blood is used to assess the kidney function. Most estimations of the GFR are based on the blood creatinine level. The higher the blood concentration of creatinine, the worse the kidney function. In addition to kidney function, the blood level depends on muscle mass and will, for example, increase if you gain a lot of muscle or eat huge amounts of muscle such as huge steaks.

Cystatin C is a protein, and the measurement of its level is used to assess the kidney function (blood test). It is produced by all cells containing a nucleus. It is freely filtered through the glomeruli, and then undergoes reabsorption and complete decomposition. Its level in the

blood correlates with the glomerular filtration rate. Since its concentration is slightly dependent on age, weight, height and muscle mass, the measurement of cystatin C concentration is effectively used to assess the glomerular filtration rate, using appropriate formulas.

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

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

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 m2, 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 kidney replacement therapy is necessary.

Kidney transplantation means the surgery putting a healthy kidney into a person whose kidney has stopped working (end-stage renal disease).

Macrohaematuria is a visible presence of the blood in the urine.

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

Nephron is a 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 is 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.

Renoprotection means the measures taken to prevent damage to the kidney from any cause.

SGLT-2 inhibitors, also called gliflozins or flozins, are a class of medications that modulate sodium-glucose transport proteins in the kidney. SGLT2 inhibitors are especially used in the treatment of type II diabetes mellitus (T2DM), but apart from blood sugar control, have been shown to provide significant cardiovascular benefit, have been posited to exhibit protective effects on the heart, liver, kidneys, antihyperlipidemic, anti-atherosclerotic, anti-obesity, antineoplastic effects in in vitro, preclinical, and clinical studies and those effects have been attributed to a variety of its pharmacodynamic actions such as natriuresis, deactivation of renin-angiotensin-aldosterone system, alterations in energy homeostasis, glycosuria, lipolysis, anti-inflammatory, and antioxidative action.

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