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THE KIDNEY DISEASES

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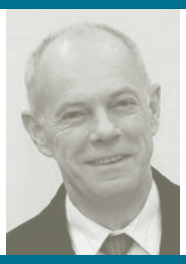


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Introduction

Kidney diseases affect approximately 10% of the world's population and this figure is expected to rise over the next decade.

The main conditions involved are diabetes, arterial hypertension, metabolic syndrome, lipid disorders or inflammatory states and obesity, which constitutes an aggravating factor (affecting 25% of dialysis patients). In addition, smoking after the age of 50 contributes to aggravating these diseases.

This publication presents some global information on kidney diseases, the definitions and basic notions, protective treatments, renal replacement therapies, disease progression information as well as proposed underwriting and claims management approaches.

The kidney – the body's filtration system

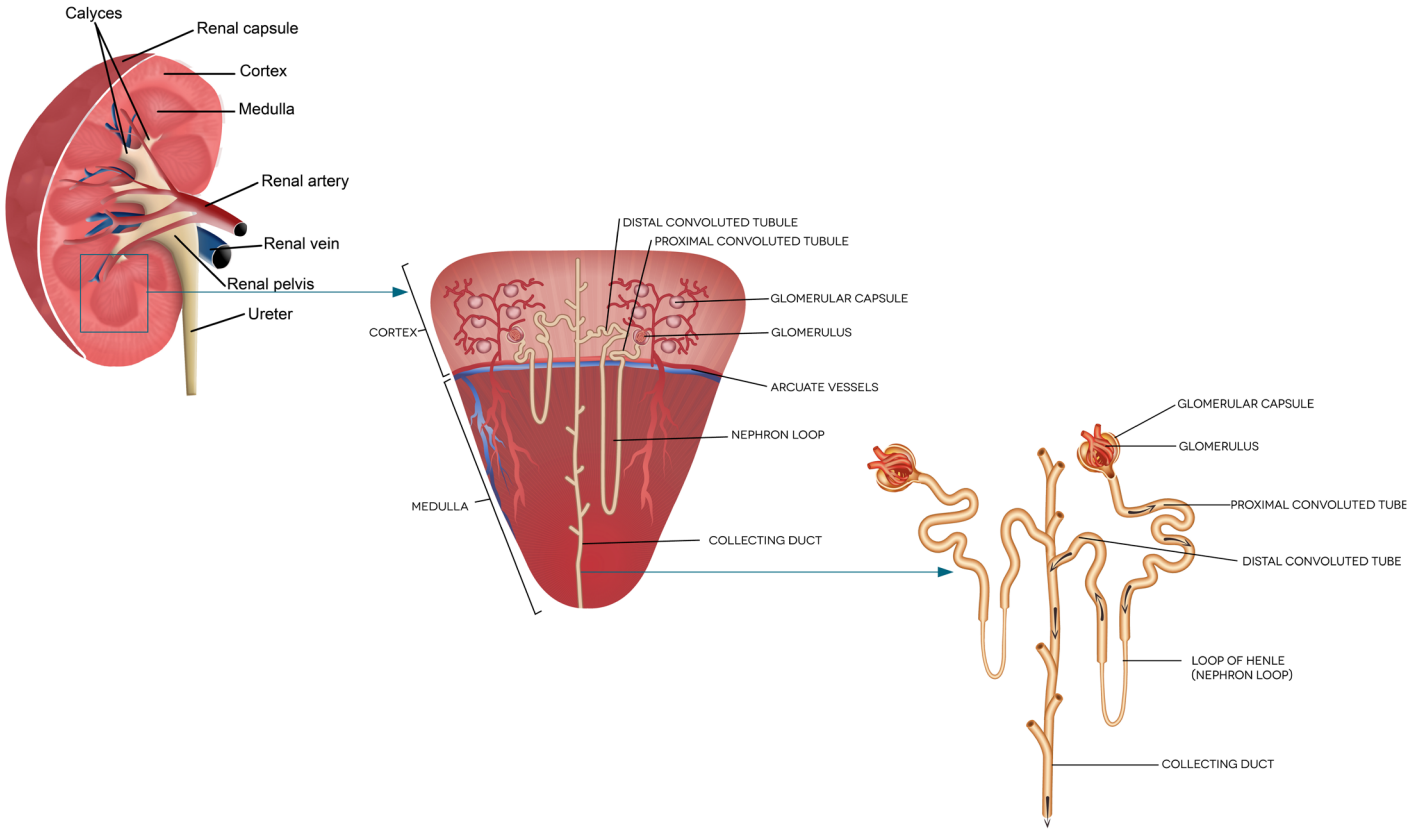
Anatomical reminders

The urinary system consists of two kidneys and two ureters that carry urine to the bladder and the urethra.

The kidney acts as a filter, by removing the waste products transported by the blood, which are then eliminated via the urine. It also maintains a constant internal environment regarding the quantity of water and mineral salts in the body.

The nephron is the functional unit of the kidney. It consists of two parts: the glomerulus or corpuscle, which contains a large number of capillaries, and the renal tubule. The latter is made up of the proximal convoluted tubule, the Henle loop and the distal convoluted tubule.

Anatomy of the kidney



Physiology

Each kidney contains about a million nephrons, which maintain a constant internal environment and enable filtration to take place. One to 1.5 litres of urine are produced every 24 hours.

The kidney's primary role is filtration, an exocrine function, which allows the concentrations of several substances, such as ions, proteins or uric acid to be maintained within physiological norms.

The kidney's second function is an endocrine function, consisting of producing hormones such as erythropoietin, calcitriol, and renin that enter the blood stream. The renin-angiotensin-aldosterone hormonal system located in the kidney plays a prominent role in regulating blood pressure.

Erythropoietin (EPO) is a hormone secreted by the kidney. It stimulates the production of red blood cells in the bone marrow. EPO deficiency leads to anaemia. Finally, the kidney secretes active vitamin D. In the event of serious kidney failure, the drop in the production of vitamin D impairs the calcium metabolism, which can have serious consequences (hyperparathyroidism). The kidney, therefore, plays regulatory role as well.

Renal function is measured by the blood creatinine level (creatininaemia). Normally, creatinine is transported by the blood, then filtered by the kidneys and eliminated in the urine. An elevated creatinine level signifies impaired kidney function.

The glomerular filtration rate (GFR) is based on calculating the rate of filtration, i.e. the volume of plasma completely cleared of creatinine per unit of time. A test is conducted on a blood sample, and three parameters are involved: age, sex and weight of the person. Normal values vary from 80 to 110 µmol/L in males and from 60 to 90 µmol/L in females. Creatinine clearance is reduced in the event of kidney failure, and the reduction in the rate is correlated with the severity of the kidney failure.

Creatinine clearance, estimated by the Cockcroft-Gault equation, reflects correct renal function
The glomerular filtration rate is calculated as follows:
GFR (mL/min/1,73m²) = [(140-age) x weight/creatinine (in µmol/L)] x k
k = 1.23 for males, 1.04 for females
Normal GFR being 120 mL ± 20 mL/min/1.73 m²

Definition and basic notions

The creatinine level varies with muscle mass and gender. To diagnose chronic kidney disease in adults, the renal function is assessed based on creatininaemia, by estimating the glomerular filtration rate (GFR).

Chronic kidney disease (CKD) is defined by an irreversible reduction in the GFR and more precisely by the existence of a GFR below 60 mL/min/1.73 m^2 for more than three months.

MARKERS

Several markers of kidney function that can be used to assess the progression of CKD. The one generally used is creatininaemia. Blood urea is another, but it is not very precise as it depends on protein metabolism. Its normal value is from 4 to 7 mmol/L.

The most reliable marker remains the glomerular filtration rate. Two reference equations are used to calculate it: the MDRD (Modification of Diet in Renal Disease) and the CKD-EPI (Chronic Kidney Disease - Epidemiology Collaboration).

At the same time, the urine is tested for the presence of markers of kidney impairment: albumin (proteinuria), red blood cells (haematuria), white blood cells (leukocyturia):

- Proteinuria is an independent marker of kidney disease. It can coexist with normal renal function. Classically, a 24-hour urine protein quantification will be done, but the protein-to-creatinine (P/C) ratio can be measured from a simple sample. Microalbuminuria (presence of albumin) constitutes the main marker of kidney disease in type 1 diabetics. It is also a cardiovascular risk factor.
- Haematuria is defined by the presence of red blood cells (RBC) in the urine above a threshold of 10 RBC, 10/mm^3 or 10^4/mL,
- Leukocyturia exists if leukocytes > 10/mm^3 or 10^4/mL.

Among these markers, proteinuria and haematuria are signs of glomerular disease, whilst leukocyturia tends to indicate tubular dysfunction. A simple test with a urine reagent strip indicates which part of the kidney is damaged and gives an idea of the aetiology of the kidney disease.

AT-RISK POPULATIONS

Numerous populations are at risk. They include hypertensive subjects, diabetics, obese, over-60s, people subject to urinary infections and recurringlithiasis or those with a congenital nephron deficit.

Individuals exposed to nephrotoxic substances (lead, lithium, non-steroidal anti-inflammatory drugs, etc.) or with a family history of kidney disease, subjects with an autoimmune disease (such as lupus), a congenital or acquired immunodeficiency syndrome or people who have been exposed to repeated systemic infections as well as smokers are among the populations to be monitored.

The international KDIGO 2012 (Kidney Disease Improving Global Outcomes) guidelines recommend regular monitoring of creatininaemia in at-risk patients as well as estimation of the GFR to check for kidney failure. It should be noted that there are some kidney diseases where there is no kidney failure, which are easily detectable on a urine reagent strip.

RECOMMENDED TREATMENT

For about 20 years, there has been a standard prescription for each of the stages of kidney disease. In stage 1, 85% of patients suffer from arterial hypertension (cardiovascular risk factors) and the treatment includes ACE inhibitors (angiotensin converting enzyme inhibitors) and ARBs (angiotensin II receptor blockers). The treatment is identical in stage 2, as renal failure is minimal. In stage 3, it is necessary to treat the phosphocalcic metabolism disorders and to vaccinate against hepatitis B. Stage 4 requires treatment for anaemia, acidosis and hyperkalaemia. Haemodialysis or peritoneal dialysis and even transplantation start to be necessary in the end stage.

THE 5 STAGES OF CHRONIC KIDNEY DISEASE (CKD)
1: CKD with normal renal function (GFR≥ 90 mL/min/1.73 m^2)
2: Mild CKD (GFR: 60-89 mL/min/1.73 m^2)
3: Moderate CKD (GFR: 30-59 mL/min/1.73 m^2)
4: Severe CKD (GFR: 15-29 mL/min/1.73 m^2)
5: End-stage renal disease (ESRD) (GFR < 15 mL/min/1.73 m^2)

From CKD to ESRD

CAUSES

End-stage renal disease (ESRD) is the final stage in chronic kidney disease when the kidney is no longer capable of eliminating toxins and potassium.

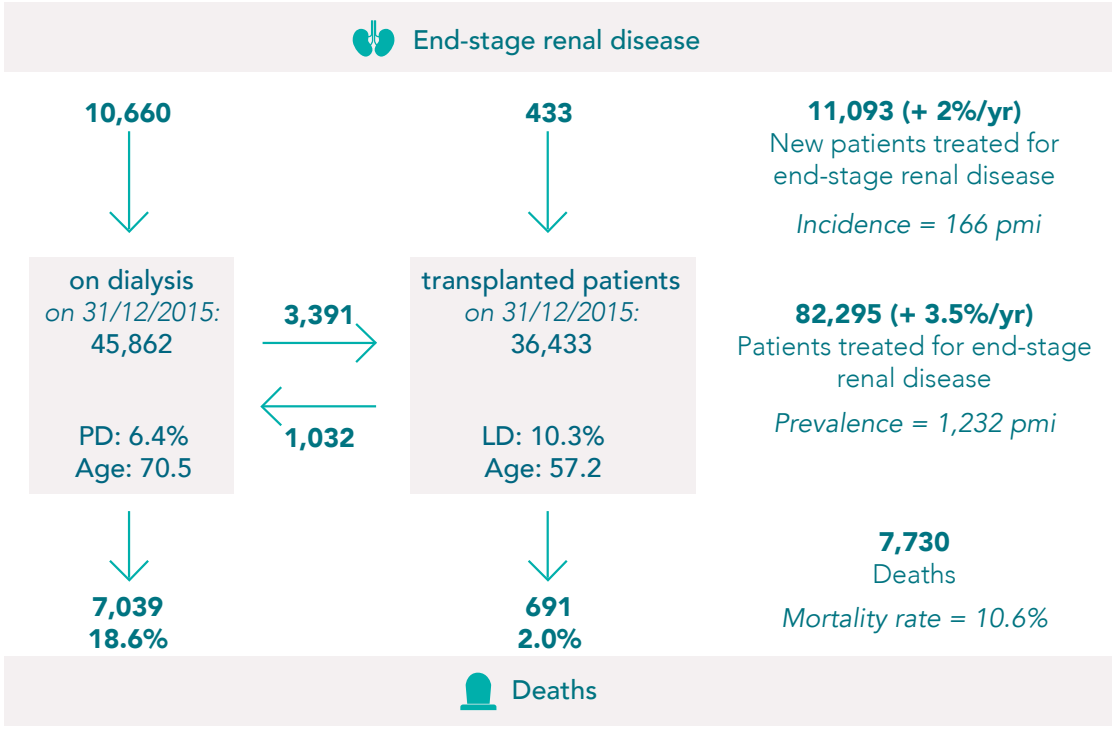
Daily urine elimination (diuresis) is now doing a poor job, leading to fluid and sodium overload as well as hyperkalaemia (excess potassium in the blood), which can lead to cardiac arrest. Hydro-sodium overload can lead to arterial hypertension and the failure to make enough EPO can cause anaemia.

The main causes of ESRD are vascular nephropathy, due to poorly controlled arterial hypertension, diabetic nephropathy, and glomerular diseases (such as Berger's disease, the most common condition, also known as IgA nephropathy). In addition, there are cases where the causes are unknown. The indolent nature of the disease often means that it is diagnosed late, when it has already reached the end stage. These four main causes are common to all the G20 countries.

In Japan, for example, the number 1 cause of CKD is Berger's disease. In the United States, it is diabetic nephropathy. The incidence of ESRD is higher in men than in women.

Dialysis is initiated when the person reaches the ESRD stage. It is a replacement therapy. The patient may also be offered a kidney transplant. Dialysis and transplantation are successive therapies and can be offered alternately to the same patient.

FRENCH EPIDEMIOLOGICAL DATA ON ESRD IN 2015



PD - peritoneal dialysis | LD - living donor | pmi - per million inhabitants

Source: Register report of R.E.I.N. (Réseau Epidemiologique et Information en Néphrologie 2015)

CONSEQUENCES

When the kidneys are no longer working, many other organs are also impacted and the consequences are numerous.

The cardiovascular consequences:

Arterial hypertension (AHT) (85% of cases) is both a cause and a consequence of kidney disease: the more the kidney is impaired, the more severe the AHT. Atherosclerosis is accelerated due to the cardiovascular risk factors (AHT, dyslipidaemia, glucose intolerance), medial calcific sclerosis and hyperhomocysteinaemia. Hypertrophic cardiomyopathy (left ventricular hypertrophy (LVH)) and ischaemic cardiomyopathy are also common.

Furthermore, when the kidney stops working, it eliminates phosphates less effectively. Hyperphosphataemia accompanied by hypercalcaemia lead to the formation of crystals of calcium phosphate in the blood, which will be deposited on the walls of the blood vessels, leading to calcification of the arteries. This is medial calcific sclerosis, which plays an important role in cardiovascular morbidity and mortality.

Metabolic acidosis is the third complication of CKD. The kidney no longer eliminates H+ ions and, this type of acidosis aggravates bone lesions. It also causes an increase in muscle catabolism with hyperkalaemia. It can lead to hyponatraemia and ventricular rhythm disorders, such as ventricular fibrillation with a risk of cardiac arrest.

The metabolic consequences:

These are very diverse: protein-energy undernutrition, hyperuricaemia, dyslipidaemia, glucose intolerance and impotence, amenorrhaea and low fertility.

The consequences on the bones:

Phosphocalcic metabolism disorders also come high on the list of consequences: CKD causes production of active vitamin D to stop and therefore hypocalcaemia results. The parathyroid glands then secrete parathyroid hormone (PTH), and this secondary hyperparathyroidism leads to osteitis fibrosa cystica. Renal osteodystrophy (alteration of bone morphology) is the sum of osteomalacia due to vitamin D deficiency and osteitis fibrosa cystica secondary to hypercalcaemia.

Haematological consequences:

The main disorder is non-regenerative normocytic normochromic anaemia due to erythropoietin deficiency and disorders of primary haemostasis.

Further symptoms:

In stage 5, further symptoms can belatedly appear. These include nausea, vomiting or gastritis, extremely painful nocturnal cramps, itching, uraemic peripheral neuropathy, sleep disorders, uraemic pericarditis and undernutrition.

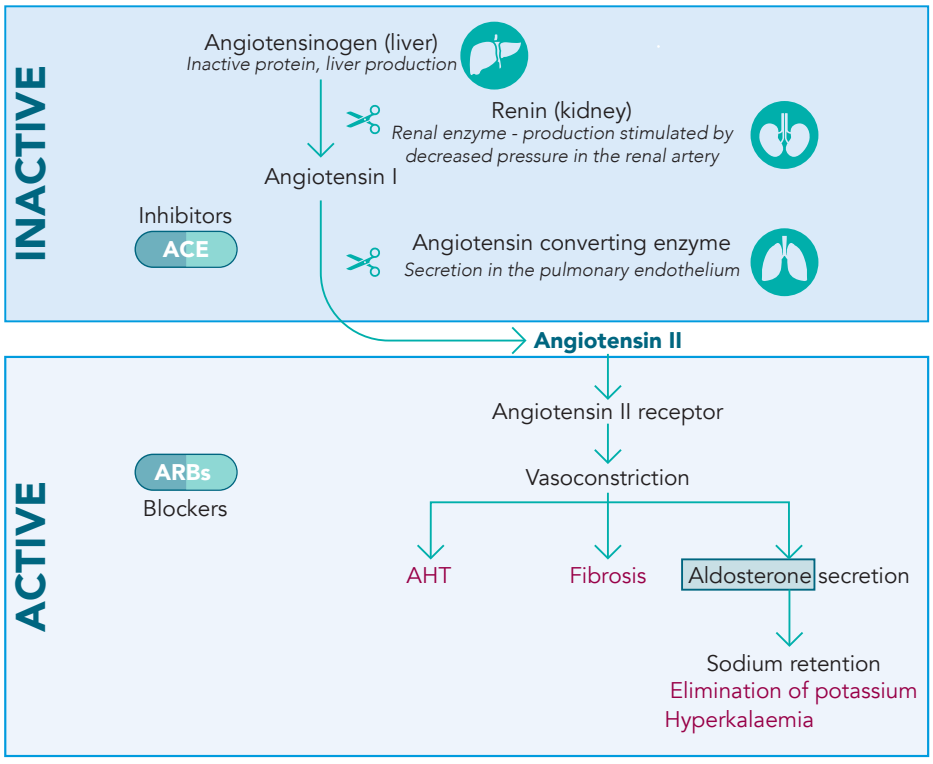
> “When the kidneys are no longer working, many other organs are also impacted.”

NEPHROPROTECTIVE DRUGS

Preventive measures include keeping proteinuria below 0.5 g/day, monitoring arterial blood pressure (arterial blood pressure below 130/80 mm Hg if the albuminuria is above 30 mg/day and arterial blood pressure below 140/90 in other cases), prescription of ACE inhibitors or ARBs, sodium intake of less than 6 g/day or moderate protein restriction (1g/kg/day).

Patients are also advised to watch their weight, stop smoking, avoid nephrotoxic substances such as NSAIDs (non-steroidal anti-inflammatory drugs), control their diabetes and engage in regular physical exercise.

ENZYMATIC CASCADE:
THE FUNCTIONING OF THE ENZYMES IN THE KIDNEY AND NEPHROPROTECTION



Angiotensinogen is secreted by the liver. When it enters the kidney, the renin converts it into angiotensin I, then the angiotensin converting enzyme converts it into angiotensin II. The latter fixes onto the angiotensin II receptor, which is the most powerful of the vasoconstrictors, leading to arterial hypertension, fibrosis and secretion of aldosterone by the adrenal glands (causing the body to retain sodium and eliminate potassium).

Drugs are used to stop this cascade: ACE inhibitors (angiotensin converting enzyme inhibitors), which block the angiotensin converting enzyme and prevent the change to angiotension II, and ARBs (angiotensin II receptor blockers). These drugs protect the kidneys by preventing the cascade, even in the absence of hypertension.

Kidney disease treatments

In the end stage of CKD progression, a replacement therapy is necessary to compensate for the kidney failure: dialysis (haemodialysis or peritoneal dialysis) and kidney transplant.

DIALYSIS

Dialysis is a method of filtering the blood to eliminate the toxic waste products and excess water that accumulate in the body.

This is an extracorporeal circuit: the blood taken from the patient is then returned via an arteriovenous (AV) fistula. The dialysis fluid, a liquid devoid of uraemic toxins, through semi-permeable membranes will enable the exchanges between the blood and the dialysis fluid, facilitating the extraction of the uraemic toxins and providing the blood with the missing elements.

In haemodialysis, the blood is filtered through an artificial membrane. This technique requires easy access to the blood via a vascular access. Indeed, the blood flow in the superficial veins is insufficient to allow haemodialysis. The surgeon therefore has to create an AV fistula, which consists of connecting a vein to a nearby artery so that part of the arterial blood is diverted into the vein.

Haemodialysis is done three times a week (12 hours a week), sometimes more, either at home or in a dialysis centre. Approximately 85% of dialysis patients undergo this treatment despite the high cost.

PERITONEAL DIALYSIS

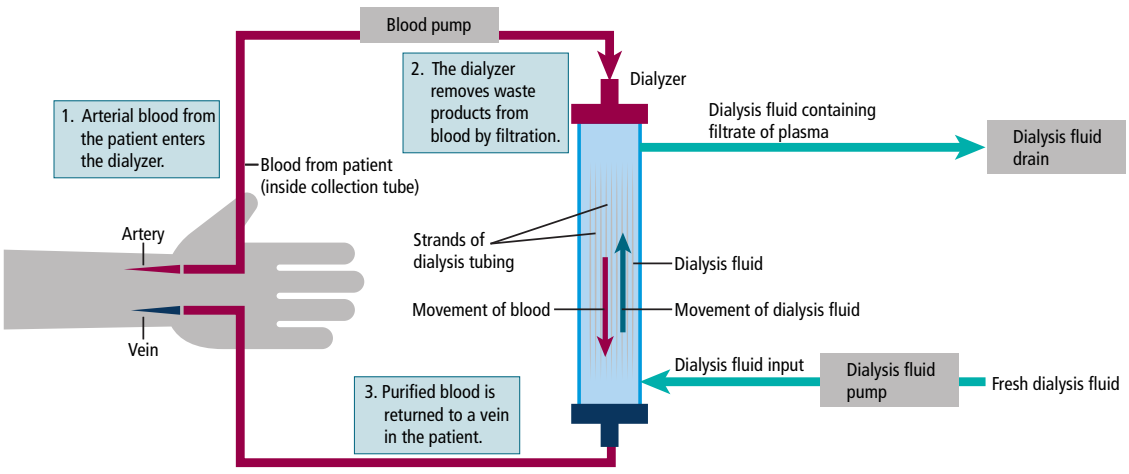
Peritoneal dialysis is an extrarenal procedure either performed by the patient or by an assisting person. It uses the peritoneum as a filter membrane and requires the creation of a peritoneal access by introducing a catheter into the peritoneal cavity. Once in place, this catheter is used to infuse a dialysis solution contained in sterile plastic bags that fit onto the infusion tube into the peritoneal cavity. The exchanges between the dialysis solution and the blood eliminate the waste products and excess water.

Peritoneal dialysis is done daily and can be done manually, with several bag changes over the course of the day (three times a day), or it can be automated with a cycler during the night. This procedure requires a permanent peritoneal dialysis catheter, which involves a high risk of infection.

This technique is used by less than 15% of dialysis patients.

It is less costly than haemodialysis and enables patients to stay in their own homes. However, there are many contraindications: obesity, a history of abdominal surgery, insalubrious or cramped living conditions, anuric patient, undernutrition and so on. It is effective for a maximum of five years.

Haemodialysis



Source: Solution Physidia Human

TRANSPLANT

A kidney transplant is a surgical procedure consisting of replacing the failed kidney with a healthy one taken from a donor. The new kidney can be grafted without removing the diseased kidney or kidneys.

When it is possible, a kidney transplant is the treatment of choice for ESRD as the transplanted kidney usually provides all the renal functions. This method improves the patient's life expectancy and quality of life, gives them more freedom and the possibility of leading a normal life.

In women, fertility is restored within weeks of the transplant.

Transplantation can be envisaged after dialysis and even before if the creatinine clearance is already below 20 mL/min/1.73 m² and the clinical situation requires it.

There are some post-transplantation complications:

- Graft rejection, which can affect up to 15% of patients.
- Surgical complications.
- Complications linked to the toxicity of immunosuppressive drugs.
- Recurrence of the nephropathy that caused the CKD.
- It is possible for cardiovascular or infectious complications and subsequent occurrence of cancers.

COMPARATIVE SURVIVAL RATES FOR DIALYSIS AND TRANSPLANTATION

Patients' life expectancy is highly dependent on their renal replacement therapy. Thus, a patient undergoing a transplant at the age of 30 has an average life expectancy of 41 more years, compared to 23 years for a dialysed patient of the same age.

Likewise, patients who have received a kidney transplant have a much lower mortality rate overall than patients on dialysis. Thus, between the ages of 60 – 69, 132 patients per 1,000 on dialysis died in 2012, compared to 27 for 1,000 patients of the same age with a functional transplanted kidney.

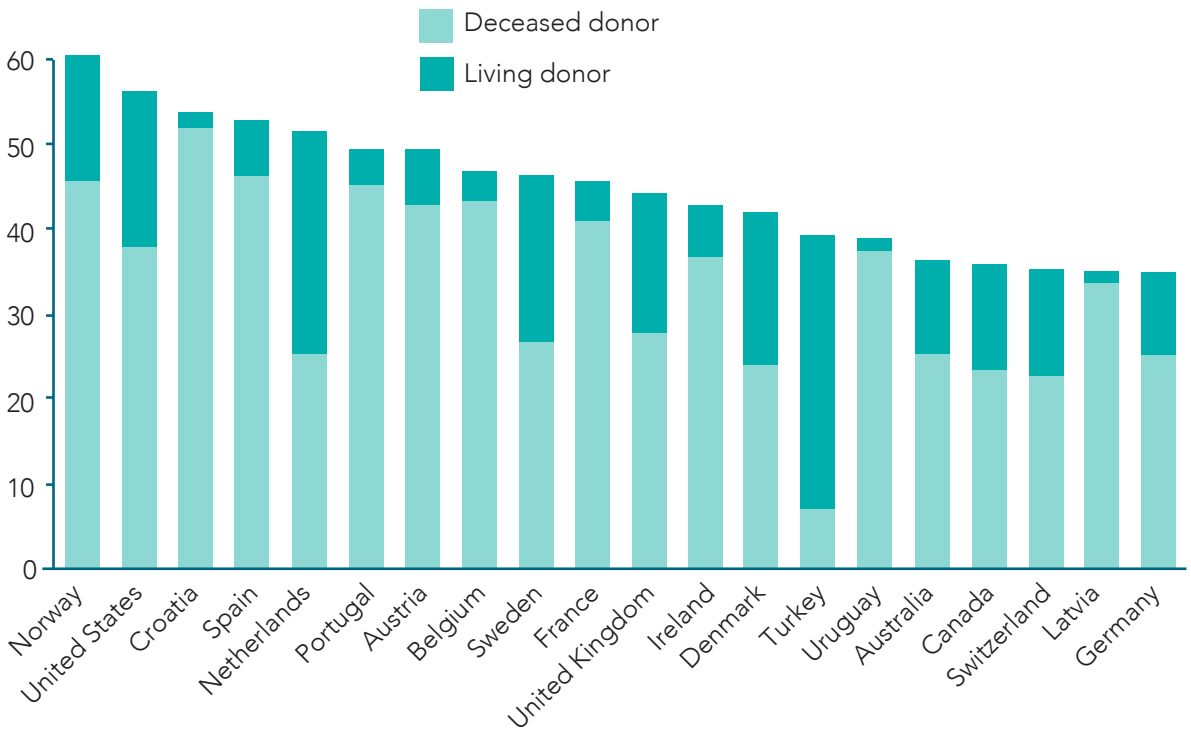
Transplant facts

In 2014, almost 120,000 transplants of complete organs were performed in the world. Almost 80,000 of these transplants concerned kidneys (source: statistica.com).

The replacement kidney can be taken from a brain-dead person: this a deceased donor transplant. The conditions of such transplants vary around the world. In Japan, for example, brain death is not recognized. In other countries, such as France, individuals are presumed to be donors unless they have made it known that they do not wish to donate their organs: this is the principle of presumed consent. Since 2017, only refusals actually recorded in the register are recognized. In 2015, 84% of kidney transplants were from brain-dead donors.

Generally, requesters are registered on the national waiting list. Organs are allocated based on different criteria: age, medical urgency, HLA ("human leukocyte antigen") tissue compatibility between donor and recipient, immunological characteristics of the recipient, time on the waiting list, length of time on dialysis, etc.

International comparison of kidney transplant rates from living or deceased donors



Source: Ch. Hiesse / Néphrologie & Thérapeutiques, Volume 9, Issue 6, November 2013

Progression of kidney conditions

Not all kidney diseases progress at the same rate.

The rate of progression is estimated with the annual decline rate, calculated by subtracting the GFR of year N from the GFR of year N+1.

Three situations are possible:

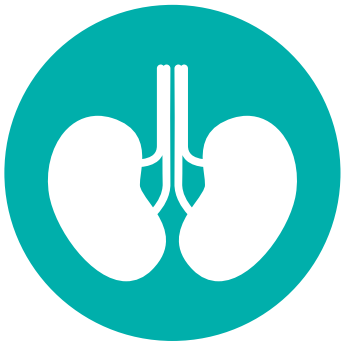
- stability (change of less than 1 mL/min/1.73 m^2/year)
- "moderate" decline (change between 1 and 5 mL/min/1.73 m^2/year),
- "rapid" decline (change greater than 5 mL/min/1.73 m^2/year).

A progression of less than 2 mL/min/1,73m^2/year will concern conditions such as lithium-induced nephropathy, chronic interstitial nephropathy, lupus or most cases of Berger's disease.

Conversely, a progression of over 10 mL/min/1,73m^2/year can be a sign of poorly controlled diabetic nephropathy with proteinuria over 4 g/day, of primary focal and segmental hyalinosis in adults or of renal amyloidosis.

The rate of progression will also vary from one patient to another for the same condition. So, in the case of Berger's disease (IgA nephropathy), progression is extremely heterogeneous and dialysis can be necessary before the age of 35. However, progression is generally very slow and lasts about 25 years. Certain factors influence prognosis: poorly controlled AHT, very high levels of proteinuria and renal histological data.

Finally, certain people (particularly women) born prematurely or with a very low birth weight, have a smaller than average number of nephrons and therefore a lower GFR. Nevertheless, their kidneys work well and do not progress to ESRD.



Approach to underwriting and claims

APPLICATION

Age at end of contract

Loan term

Creatininaemia, clearance

So-called replacement therapies

- Haemodialysis/Dialysis
- Transplant: living or brain dead donor
- On waiting list

Existence of proteinuria

Kidney function status

- Stable/Progressive
- Stage of disease
- Arterial blood pressure

CLAIMS

Obtain the date of diagnosis

Identify treatments

Monitor progression

Expert assessment of disability rate

Conclusion

Chronic kidney disease is an indolent disease which often goes unnoticed in its initial stages. It is commonly discovered on the occasion of tests done for a different condition or when monitoring a person with risk factors. Diagnosis often comes belatedly, in the end stage.

Regular kidney functions tests, measuring urea, creatinine and GFR in particular, enable an early diagnosis that allows for an adequate treatment, although CKD cannot be cured other than by a transplant.

Underwriting and claims need to take into account the specific situation of the patient.

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