COMENIUS UNIVERSITY IN BRATISLAVA
JESSENIUS FACULTY OF MEDICINE IN MARTIN

DIFFERENT TYPES OF KIDNEY DONORS

Diploma Thesis

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Rozdielne typy darcov obličiek

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LIST OF ABBREVIATIONS

ESKD – End-Stage Kidney Disease

AKI – Acute Kidney Injury

CKD – Chronic Kidney Disease

ECD – Expanded Criteria Donor

GFR – Glomerular Filtration Rate

Cr - Creatinine

A-V – Arteriovenous

CAPD - Continuous Ambulatory Peritoneal Dialysis

CCPD - Continuous Cycling Peritoneal Dialysis

TPM – Transplant Procurement Management

DCD - Donation after Cardiac Death

KPD - Kidney Paired Donation

HLA – Human Leucocyte Antigen

ABSTRACT

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Introduction: As of today, kidney transplantantation is the only definitive curative treatment for patients with kidney failure, as the remaining therapeutic options (e.g.: hemodialysis) remain with controversial results. With this in mind, this diploma thesis, which is based on a review of literature, aims at providing insight about the diferent types of kidney donors, the diseases giving rise to end-stage kidney disease and, therefore, the necessity for transplant, the marked variations in the types of donors according to different countries and the overall process of procurement and transplant, including overview of technique, complications and it's curative potential.

Method: This diploma thesis is divided in three parts. The first part focus on anatomical and physiological review of the kidney, based on anatomy and physiology books, so as to be able to provide the reader with some basic knowledge, intrinsically necessary to understand the numerous pathologies that can affect the kidney and ultimately lead to the necessity of a transplant (as the only curative modality). The second part is a review of the most common pathologies leading to kidney failure (both acute kidney injury – AKI, and chronic kidney disease – CKD). Finally, the third and last part is an overview of the existing different types of kidney donors, as wells as a basic summary of the process of procurement and transplantation technique. A basic insight about other therapeutic modalities (e.g.: hemodialysis) will also be presented.

Result and Discussion: Renal transplantation can be a blessing to those diagnosed with ESKD, and, contrary to other available therapeutic options that are offered as renal replacement therapy (the likes of hemodialysis and peritoneal dialysis), it has curative potential and can fully restore the life quality of patients with non-functional kidneys. However, not everyone is lucky enough to receive a transplant, and many die while on the waiting list. In effect, for a transplant to be performed its necessary a donor and different

kinds of kidney donors exist, with the prefered method, for most physicians, being that of living donation. Nevertheless, deceased organ donation, including brain-dead donors and donation after cardiac death, increase significantly the pool of avaiable organs for transplant, and with the advancements and development of a better procurement methodology and rise of newer immunosupressive drugs in the last decades, they have presented with excellent results following transplantation, and represent the main source for organ donation in many countries. Another factor to take in consideration is the use of expanded criteria donors, which can provide opportunity for those very low on the waiting list. Regarding the most used type of donation by a particular country and/or center, we can see that marked variations exist across the globe, reflecting different cultural, ethical, social, educational and medical values. Countries like Japan relie almost only on living donation (strongly bond by cultural values), while in the US living donation accounts for about 50% of all transplants, with deceased donors providing the remaing half. On the other hand, Spain relies mainly on deceased organ donation, a fruit of their medical legislation.

Conclusion: Despite the numerous advancements seen on the last decades that made trasplantation a great therapeutic option for patients with ESKD, still more can be done when it comes to overcoming the organ shortage and the risk of transplantation associated complications. We can recognize that many diferent sources exist for donation: Living donors, deceased donors (including ECD donors, brain-dead donors and donation after cardiac death), which implies that the problem of organ shortage and the enourmosly long waiting lists of patients (with ESKD) awaiting a transplant, can be, significantly, overcome if efforts are put in place to change the current paradigma. The Spanish model is one to be looked upon and praised, as it shows that deceased organ donors can be as effective as living donation. In other hand, much focus should also be aimed at developping newer drugs and techniques, to prevent post-transplantation complications. Finally, it's necessary, of course, to establish the value of prevention, since many disorders that give rise to kidney failure can be avoided with proper management (e.g. a good control of diabetes can delay the onset of diabetic nephropathy, the most common etiology of CKD).

Key words: Kidney, Transplant, Donors, Procurement

ABSTRACT

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Úvod: Od dnešného dňa je transplantácia pečene jedinou účinnou liečbou pre pacientov so zlyhaním pečene, nakoľko zvyšné liečebné možnosti (napr. hemodialýza) naďalej nesú kontroverzné výsledky. Vzhľadom na to, táto diplomová práca, ktorá je založená na preštudovaní odbornej literatúry, má za cieľ poskytnúť prehľad o rozličných typoch darcov obličiek; o chorobách spôsobujúcich konečnú fázu ochorenia obličiek a s tým spojenú nevyhnutnosť transplantácie; výrazné rozdiely v typoch darcov podľa jednotlivých krajín a celkový proces odberu a transplantácie, vrátane prehľadu o technike, komplikáciách a ich liečebnom potenciáli.

Metóda: Táto diplomová práca je rozdelená na tri časti. Prvá časť sa zaoberá anatomickým a fyziologickým preskúmaním obličiek, založeným na knihách o anatómii a fyziológií aby bolo možné poskytnúť čitateľovi základné vedomosti potrebné na pochopenie početných patológií, ktoré majú vplyv na obličky a ktoré nakoniec vedú k nutnosti transplantácie (ako jedinej liečebnej metóde). Druhá časť je prehľad najbežnejších patológií ktoré vedú k zlyhaniu obličiek (oboje akútne poškodenie obličiek – APO, a chronické ochorenie obličiek – CKD). Nakoniec, treťou a poslednou časťou je prehľad rozličných typov darcov obličiek, ako aj súhrn procesu odberu a transplantačnej techniky. Poskytnutý bude aj pohľad na iné terapeutické metódy (napr. hemodialýza).

Výsledky a diskusia: Transplantácia obličiek môže byť požehnaním pre tých, ktorí sú diagnostikovaní terminálnym zlyhaním obličiek a na rozdiel od iných dostupných liečebných možností, ktoré sú navrhované ako kontinuálna renálna nahradzujúca terapia (podobne ako hemodialýza peritoneálna dialýza), majú liečebný potenciál a môžu plne prinavrátiť kvalitu života pacientom s nefunkčnými obličkami. Avšak nie každý má to šťastie aby sa mu dostala transplantácia obličky a veľa ľudí umiera kým sú na čakacej listine. Na to aby sa transplantácia uskutočnila je potrebný darca a rôzne druhy darcov obličiek,

pričom najuprednostňovanejšou metódou pre väčšinu lekárov je darcovstvo orgánov od živých darcov. Darcovstvo orgánov zosnulých darcov, vrátane klinicky mŕtvych darcov a darovanie po zástave srdca, napriek tomu významne zvyšuje zásobu dostupných orgánov na transplantáciu a s pomocou pokroku a rozvoja lepšej metodológie obstarávania a vzostupu novších imunosupresívnych liekov, ktoré ukázali excelentné výsledky po transplantácií, tieto darcovstvá predstavujú hlavný zdroj darcovstva orgánov v mnohých krajinách. Ďalším faktorom, ktorý je potrebné brať do úvahy, je využitie darcov s rozšírenými kritériami, ktoré môžu poskytnúť príležitosť pre tých, ktorí sa nachádzajú v dolnej časti čakacej listiny. Čo sa týka najpoužívanejšieho typu darcovstva v konkrétnej krajine a/alebo centra, je pozorovateľné, že na celom svete existujú výrazné rozdiely, ktoré odrážajú rozličné kultúrne, etnické, sociálne, vzdelávacie a medicínske hodnoty. Krajiny ako Japonsko sa spoliehajú takmer výlučne na darcovstvo orgánov od živých darcov (silne prepojené kultúrnymi hodnotami), kým v Spojených Štátoch Amerických darcovstvo orgánov od živých darcov tvorí približne 50% zo všetkých transplantácií, pričom darcovstvo orgánov od zosnulých darcov tvorí zvyšnú polovicu. Na druhej strane Španielsko sa spolieha hlavne na darcovstvo orgánov od zosnulých darcov, čo je výsledkom ich lekárskej legislatívy.

Záver: Napriek mnohým pokrokom zaznamenaných v posledných desaťročiach, ktoré z transplantácie urobili výbornú liečebnú možnosť pre pacientov s terminálnym zlyhaním obličiek, je stále možno urobiť viac pokiaľ ide o prekonanie nedostatku orgánov a riziko komplikácií spojenými s transplantáciou. Je mnoho rôznych zdrojov darcovstva: darcovstvo orgánov od živých darcov, darcovstvo orgánov od zosnulých darcov (vrátane darcov vybraných na základe širších kritérií, klinicky mŕtvych darcov a darovaní po zástave srdca), čo znamená, že problémy ako nedostatok orgánov a enormne dlhé čakacie listiny pacientov (s terminálnym zlyhávaním obličiek) ktorí čakajú na transplantáciu, môžu byť výrazne prekonané, ak sa vyvinie úsilie na zmenu súčasnej paradigmy. Španielsky model ukazuje, že zosnulí darcovia môžu byť na darcovstvo užitoční rovnako ako žijúci darcovia, a práve preto je považovaný za chvályhodný. Na druhej strane, veľký dôraz by sa mal klásť na vývoj nových liekov a techník aby bolo možné zabrániť komplikáciám po transplantácií. Nakoniec, je samozrejme potrebné stanoviť hodnotu prevencie, keďže mnohým chorobám, ktoré majú neskôr za následok zlyhanie obličiek, môže byť zabránené použitím poriadnej starostlivosti (napr. dobrá lekárska prehliadka na cukrovku môže oddialiť nástup diabetickej nefropatie, ktorá je najčastejšou etiológiou CKD).

Kľúčové slová: Oblička, Transplantácia, Darca, Odber

PREFACE

The main topic of this thesis is a review of literature to assemble and present the knowledge about all the diferent types of kidney donors available, explaining their different characteristics. In adition to this, some focus will also be directed at explaining diferent pathologies which can give rise to kidney failure (including both acute kidney lesion and chronic kidney disease), the necessity for transplantation (as it offers the only curative possibility for people with irreversible kidney damage) will be discussed, a review of the kidney's anatomy and physiology will be presented, as well as an overview on the basics of procurement and transplantation technique (including, of course, it's therapeutic potential, post-op management and complications).

This diploma thesis was written using selective information gathered by a combination of books and journal articles from multiple scientific sources and information provided by the discussion of the various topics with my tutor and various specialists that I had the pleasure to work with.

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INTRODUCTION

The term Kidney Failure, also known as End-Stage Kidney Disease (ESKD) is, as of today, a worldwide public health problem. Both acute conditions, like acute kidney injury (AKI), and chronic pathologies, known as chronic kidney disease (CKD), can lead to irreversible damage and consequently failure of the kidneys, therefore requiring prompt adequate management.

It's estimated that in the US acute condition affects about 3 per 1,000 people a year [1], while chronic disease affects about 1 in 1,000 people, with newly developed cases of about 3 per 10,000 people each year [1] [2]. Despite the fact that a lot of resources are committed to the treatment of patients with ESKD, and the substantial improvements in the quality of the available therapeutic options, these patients still experience marked reduced quality of life, as well as significant mortality and morbidity rates.

In effect, and as of today, the only definitive curative treatment that can be offered, by physicians, to people with ESKD is kidney transplantation. Many options exist for organ donation, all with diferent advantages and disavantages as well as diferent availability, and it's important to keep in mind that, many times, the type of organ donor chosen is a reflection of the culture, population and the health care system of a given country. The topic of transplantation is a whole world by itself, including many complex processes, all that must be assessed when the need for a transplant is stablished.

1. ANATOMICAL INTRODUCTION

The Kidneys are paired bean-shaped organs which are located at the back of the abdominal cavity, one on each side of the spine, lying in the retroperitoneal space. With about 11 centimetres in lenght (right one slightly less) and weighing between 125 to 170 grams, some asymmetry is noted acording to their position, thanks to the liver's location, resulting in the right kidney being somewhat lower and smaller than it's left counterpart (which lies, aproximately, at the vertebral level T12 to L3). As the right kidney is positioned just below the diaphragm and posterior to the liver, and the left is located below the diapgragm and posterior to the spleen, it is no surprise that both move down during inhalation.

In the upper parts of each kidney are located the adrenal glands which, together with the kidneys, are surrounded by two layers of fat (perirenal and pararenal fat).

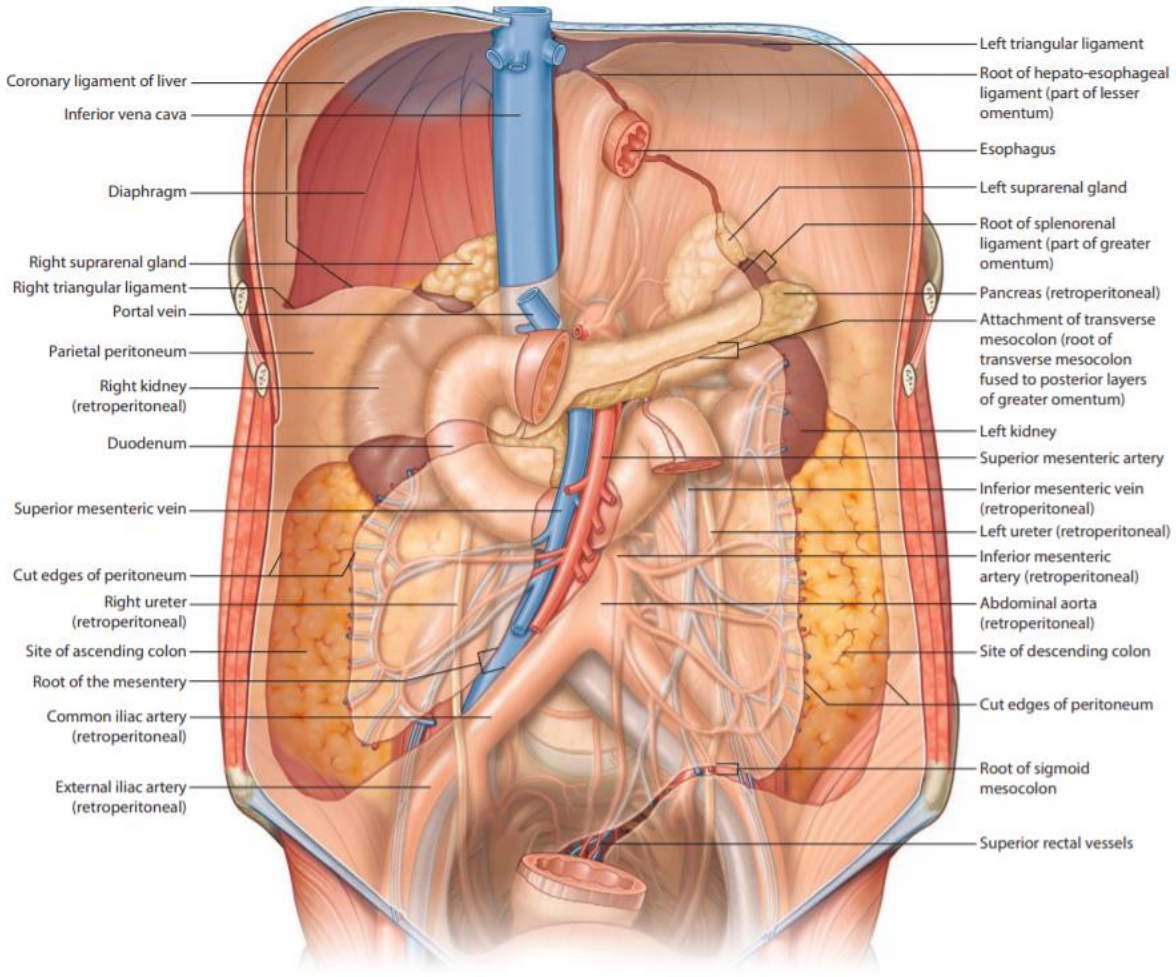

Fig. 1 - The peritoneum and the retroperitoneal position of the kidneys [21]

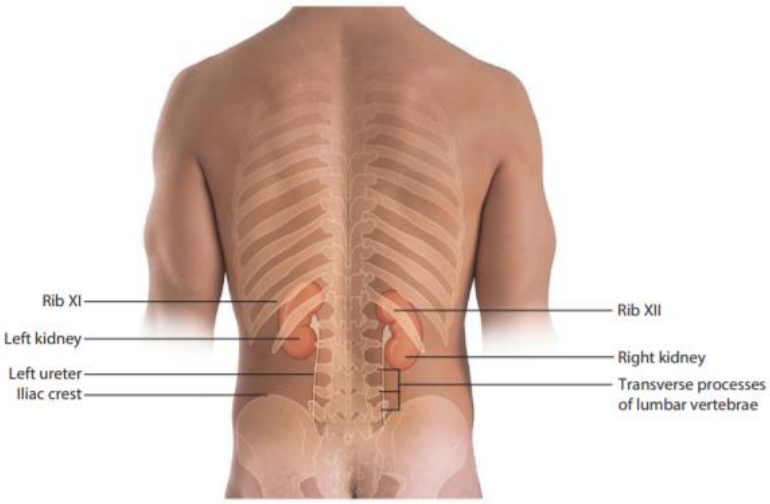

Fig. 2 - Surface projection of the kidneys and ureters (posterior view) [21]

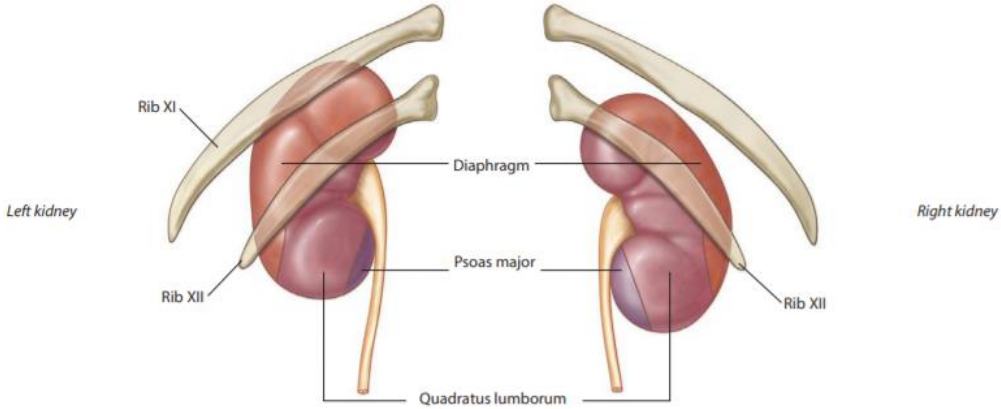

Fig. 3 - Structures related to the posterior surface of each kidney [21]

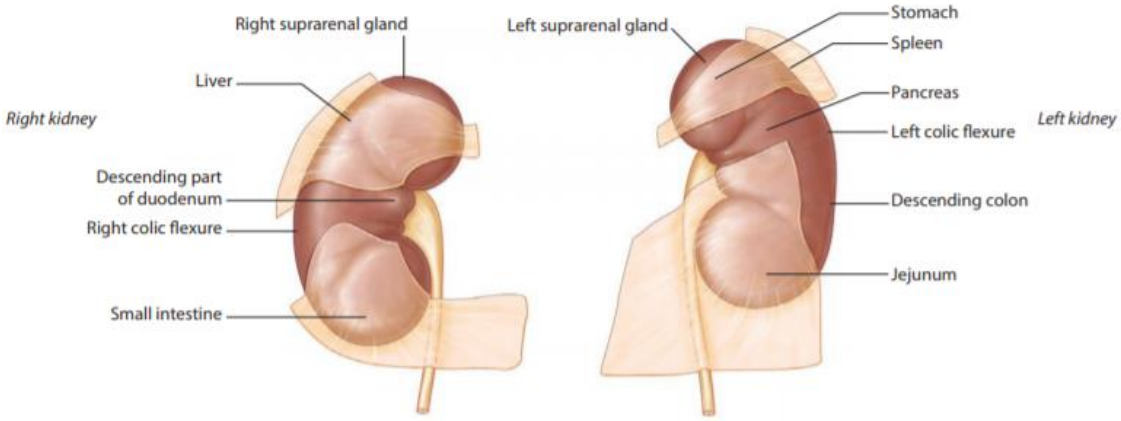

Fig. 4 - Structures related to the anterior surface of each kidney [21]

The kidneys posess a convex and concave border, and in a depression at the concave border, the so called renal hilum, the renal artery enters and the renal vein and ureter exit the kidney. Kidneys receive blood from the paired renal arteries and it exits through the also paired renal veins, as for the ureter it‘s function is to carry urine into the urinary bladder. These structures in the renal hilum are surounded by Hilar fat and lymphatic tissue. Regarding the hilar fat, it is adjacent to a cavity filled with fat, termed the renal sinus, which in turn encompasses the renal pelvis and calyces and detaches these structures from the renal medullary tissue.

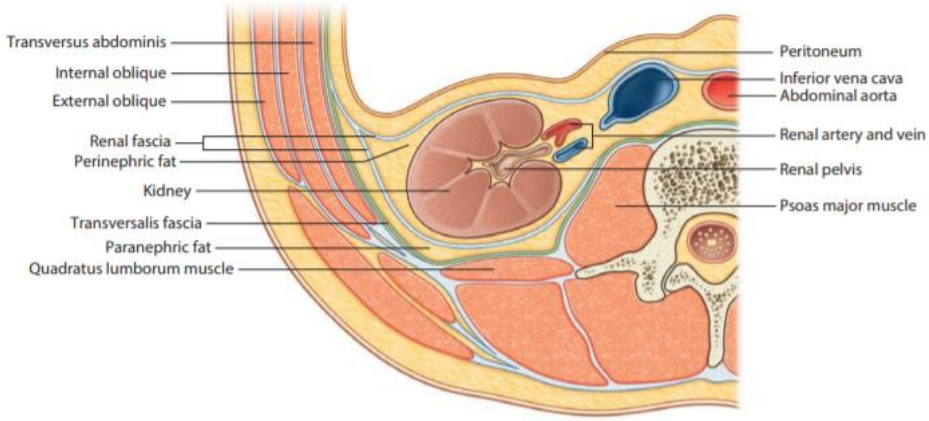

Fig. 5 - Organization of the fat and fascia surrounding the kidneys [21]

Two major structures make up the parenchyma of the kidney: the outer renal cortex and the inner renal medula. Nephrons, the so called functional and structural units of the kidney, span both structures. The parenchyma of the kidney takes the shape of about 8 to 18 renal lobes posessing a cone-shape, each being composed of a portion of the medulla, named renal pyramid, enclosed by renal cortex which shows projections (renal columns) into spaces between the renal pyramids. Each pyramid has a tip or, in other words, a papilla which empties urine into a minor calyx, which in turn drains into major calyces, subquently emptying into the renal pelvis, and this develops then into the ureter.

Regarding the nephrons, their initial filtering part is the renal corpuscle, situated in the cortex, being then followed by a renal tubule going from the cortex deeply into the medullary pyramids. An assemble of renal tubules, all draining into a single collecting duct, is termed medullary ray and is a part of the renal cortex.[1]

[1] Content based according to knowledge found on: R. L. Drake, A. W. Vogl, A. W. M. Mitchell, R. M. Tibbitts e P. E. Richardson, GRAY'S ANATOMY: THE ANATOMICAL BASIS OF CLINICAL PRACTICE, 40th ed., Philadelphia: Churchill Livingstone Elsevier, 2008.

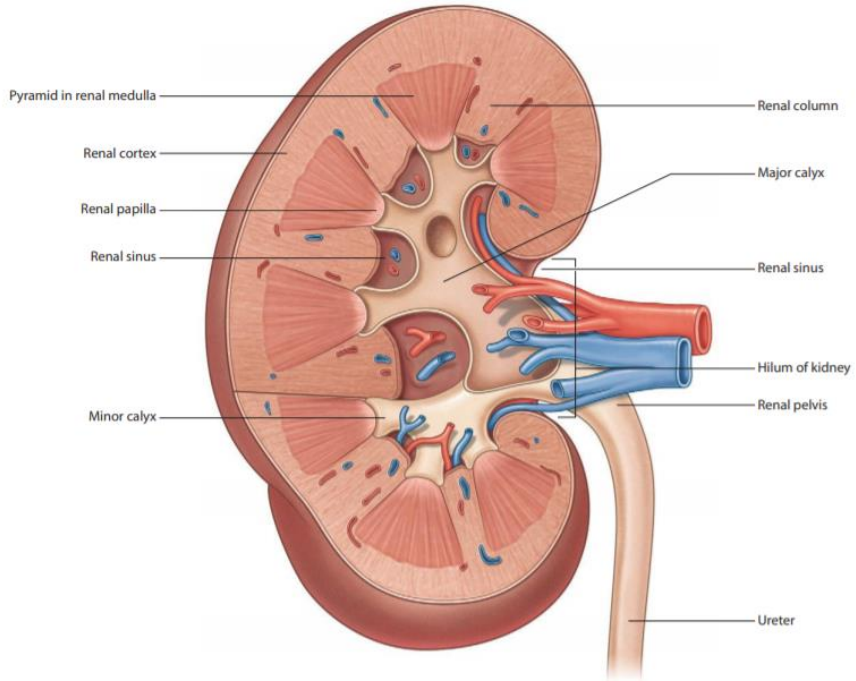

Fig. 6 - Internal structure of the right kidney [21]

1.1 Renal Circulation

Even though they are relatively small in size, the blood supply to the kidneys accounts for aproximately 20% of the whole cardiac output [3], in other words, about 1100 ml/min [4]. The renal circulation provides blood to the left and right kidneys through, respectively, the left and right renal arteries, branching directly from the abdominal aorta.

In turn, each of the renal arteries will branch into segmental arteries, further subdiving and giving rise to the interlobar ateries which penetrate into the renal capsule and reach through the renal columns. It's these arteries which then provide blood to the arcuate arteries running across the border of the cortex and the medulla. Finally, arcuarte arteries will supply interlobular arteries that lead into the afferent arterioles to supply the glomeruli and it is at this point that filtration occurs.

After this process, blood will be passed through a small network of venules that ultimately converge into interlobular veins. The veins will then follow a similar patter as the arteriole distribution: Interlobular veins supply arcuate veins, then back to the interlobar veins which join to produce the exiting renal vein.

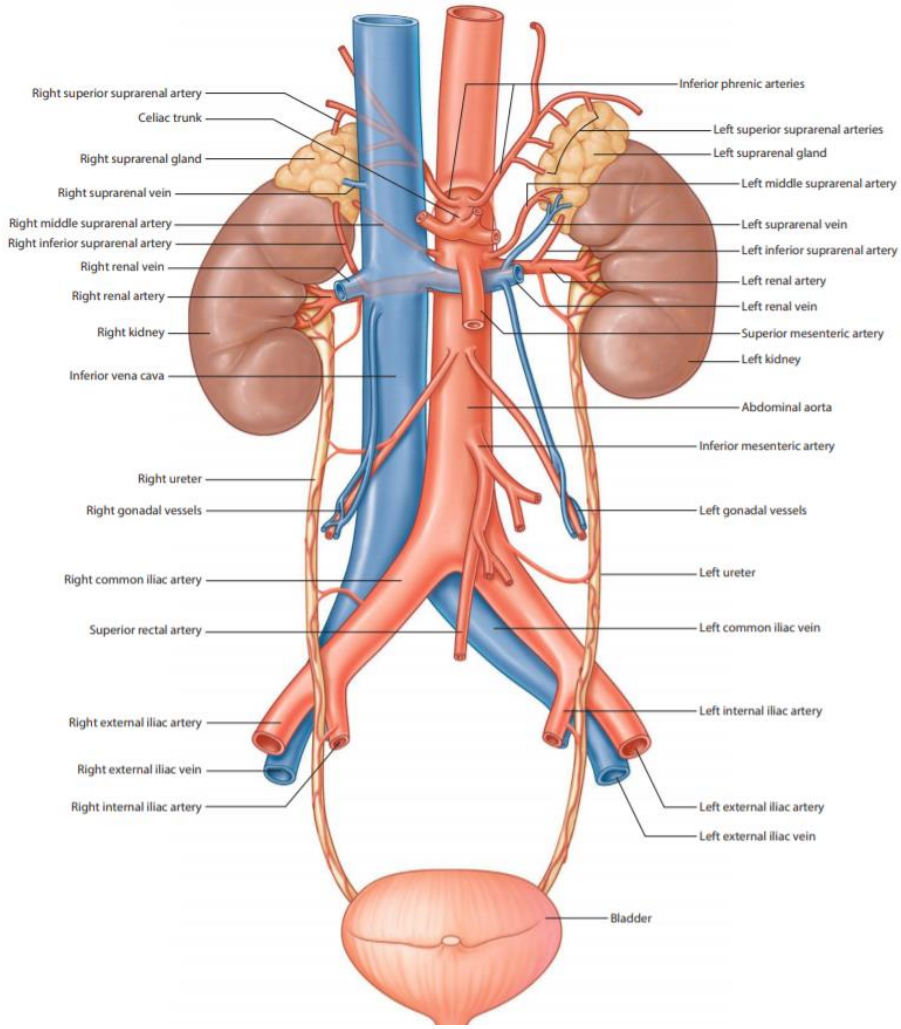

Fig. 7 - Vasculature relating to kidneys, suprarenal glands, and ureters [21]

2. PHYSIOLOGY OF THE KIDNEY

It's understood that the kidneys are organs of paramount value as they execute a variety of bodily functions of extreme importance which, if severely depressed or completly unfunctional, lead to a state incompatible with life.

The most well know renal action is that of urine production, with excretion of body waste materials that are either ingested or result from metabolism. However, another function that is also of vital significance is the control of volume and electrolyte composition of the body fluids, as the balance of water and most body's electrolytes is manteined largely by the kidneys.

These important renal functions are performed by the process of plasma filtration and removal of substances from the filtrate at variable rates, intrinsically dependent on the body's needs. Eventually, the unwanted substances obtained from the filtrate are excreted into the urine, while substances that are still needed are returned back to the blood.
A summarized list of the numerous homeostatic functions performed by the kidneys is expressed bellow [4]:

- Excretion of metabolic waste products and foreign
- chemicals
- Regulation of water and electrolyte balances
- Regulation of body fluid osmolality and electrolyte
- concentrations
- Regulation of arterial pressure
- Regulation of acid-base balance
- Regulation of erythrocyte production
- Secretion, metabolism, and excretion of hormones
- Gluconeogenesis

2.1 NEPHRON

For correct understanding of the renal functions, it's necessary to explain the term nephron, which is is the microscopic structural and functional unit of the kidney.
This small units contain the glomerulus (encased by the bowman's capsule) which is a cluster of branching and anastomosing glomerular capillaries with high hydrostatic pressure (aproximatelly 60 mmHg), and a long tubule. It is through the glomerulus that large amounts of fluid are filtered from the blood, being then converted into urine by the tubule on the way to the kidney's pelvis.
A healthy human kidney contains, aproximately, from 800,000 to 1,000,000 nephrons [4], each being able to form urine. Despite this great number, the kidneys are not able to regenerate new nephrons. In effect, the number of functional nephrons can decrease as the result of renal injury or through the normal process of aging. After humans reach the age 40 years, the amount of avaiable functioning nephrons will gradually decrease at a rate of aproximately 10 percent every 10 years [4]. So, taking this in consideration, people at an age of 80 years will have 40 percent fewer functioning nephrons that they had when they were

half this age. Despite this significant lost of nephrons, this is not a life threatning situation due to adaptive changes in the remaining nephrons which grants them the ability to excrete the proper amounts of water, electrolytes, and waste products. In order to properly perform it's abilities, the kidneys require adequate blood supply.

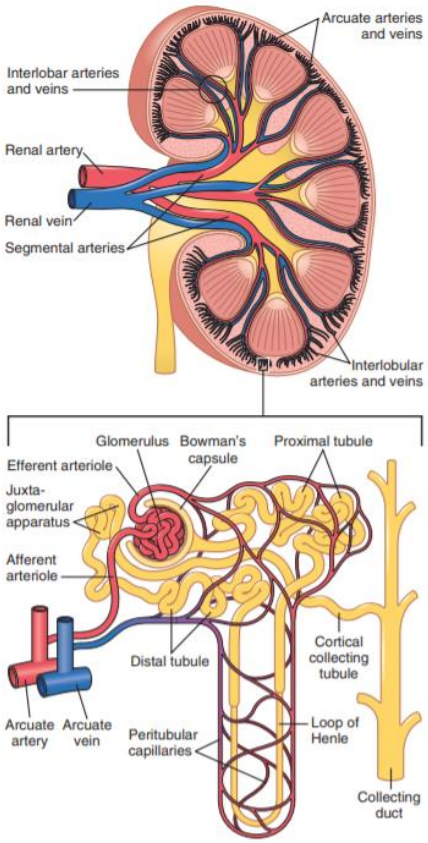

Fig. 8 - Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the microcirculation of each nephron [4]

2.2 Renal Mechanisms

To be able to perform the majority of its functions, the kidneys depend on three critical processes: Filtration, reasorption and secretion. The sum of this abilities is termed renal clearence or renal excretion, expressed by:

Urinary excretion rate = Filtration rate – Reabsorption rate + Secretion rate [4]

As was previously stated, the mechanism of filtration is accomplished by the nephrons. Continuing with this line of thought, cells, proteins and other large molecules are filtred from

blood coming to the glomerulus by a process of ultrafiltration, producing an ultrafiltrate (that resembles plasma but has negligible plasma proteins) that enters the bowman's space. This process is driven by Starling forces. Eventually, the untrafiltrate is passed through the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule, and a series of collecting ducts, therefore forming urine.

As for reabsorption, it is a process carried out in the tubule where solutes and water are removed from the tubular fluid and transported back into the blood. It can be thought as a two-step process which starts with the active or passive removal of substances from the tubule fluid into the renal interstitium, followed by the transport of said substances from the interstitium all the way into the bloodstream. Again, the driving forces of this transport process are the Starling forces, diffusion and active transport.

Also of note is to mention that situations exist in which reabsorption is indirect, as in the case of bicarbonate (HCO3-) which does not have a transporter, so the reabsorption relies on a series of reactions in the tubule lumen and tubular epithelium.

2.3 Hormone Secretion

The kidneys are involved in the production and secretion of a couple of hormones with a variety of functions:

- Erythropoietin, important for the regulation of red blood cell production in the bone marrow.
- Renin, a key component of the renin–angiotensin–aldosterone system.
- Secretion of the active form of vitamin D, termed calcitriol, and prostaglandins.

2.4 Gluconeogenesis

In human beings, glucose production can be accomplished in the kidneys from lactate, glycerol and glutamine, and the overall weight of the kidney's role in producing glucose is about half ot the total gluconeogenesis during fasting. Similar to other hormones, gluconeogenesis is regulated by the actions of insulin, catecholamines and other hormones [5]. Renal glucose production happens in the renal cortex as the renal medulla is not able of gluconeogenesis owing this due to absence of the enzymes required for the task.

2.5. Extracellular Homeostasis

Substance	Comments	Proximal tubule	Loop of Henle	Distal tubule	Collecting duct
Glucose	Failure of propper renal absorption of glucose cause it to appear in the urine and is termed glycosuria.	reabsorption (almost 100%) via sodium-glucose transport proteins (apical) and GLUT (basolateral).	–	–	–
Oligopeptides, proteins, and amino acids	All are reabsorbed almost entirerly.	reabsorption	–	–	–
Urea	Regulation of osmolality.	reabsorption (50%) via passive transport	secretion	–	reabsorption in medullary collecting ducts
Sodium	Uses Na-H antiport, Na-glucose symport, sodium ion channels (minor)	reabsorption (65%, isosmotic)	reabsorption (25%, thick ascending, Na-K-2Cl symporter)	reabsorption (5%, sodium-chloride symporter)	reabsorption (5%, principal cells), stimulated by aldosterone via ENaC
Chloride	Frequently follows sodium. Active (transcellular) and passive (paracellular)	reabsorption	reabsorption (thin ascending, thick ascending, Na-K-2Cl symporter)	reabsorption (sodium-chloride symporter)	–
Water	Uses aquaporin water channels.	absorbed osmotically along with solutes	reabsorption (descending)	–	reabsorption (regulated by ADH, via arginine vasopressin receptor 2)
Bicarbonate	Maintenance of acid-base balance.	reabsorption (80–90%)	reabsorption (thick ascending)	–	reabsorption

Protons	Uses vacuolar H+ATPase	–	–	–	secretion (intercalated cells)
Potassium	Variable. Depending on dietary needs.	reabsorption (65%)	reabsorption (20%, thick ascending, Na-K-2Cl symporter)	–	secretion (common, via Na+/K+-ATPase, increased by aldosterone), or reabsorption (rare, hydrogen potassium ATPase)
Calcium	Uses calcium ATPase, sodium-calcium exchanger	reabsorption	reabsorption (thick ascending) via passive transport	reabsorption in response to PTH and ↑ reabsorption with Thiazide Diuretics.	–
Magnesium	Calcium and magnesium compete, and an excess of one can lead to excretion of the other.	reabsorption	reabsorption (thick ascending)	reabsorption	–
Phosphate	Excreted as titratable acid.	reabsorption (85%) via sodium/phosphate cotransporter. Inhibited by parathyroid hormone.	–	–	–
Carboxylate		reabsorption (100%) via carboxylate transporters.	–	–	–

Table 1 – Summary of the substances absorved and/or secreted by the kidneys, responsible for mantaining their balance throughout the body [4]**.**

2.6 Clearence methods to quantify renal function

A particularly useful way of quantifying renal function or, in other words, the effectiveness of the kidneys in excreting a variety of substances, can be acomplished by measuring the rates at which individual substances are removed from the plasma. Therefore, the term renal clearence of a given substance can be defined as the volume of plasma that is entirerly cleared of the substance by the kidneys per unit of time [4].

Even though it's not possible for a single volume of plasma to be cleared of a substance completely, this method gives a very useful contribution when it comes to quantifying the renal excretory function. The following example provides a good way to ilustrate this clearence principle: *„If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter and if 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is"cleared" of the substance. Thus, clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit of time"* [4].

Term	Equation	Units
Clearance rate	$C_s = \frac{U_s \times \dot{V}}{P_s}$	ml/min
Glomerular filtration rate	$GFR = \frac{U_{inulin} \times \dot{V}}{P_{inulin}}$	
Clearance ratio	$\text{Clearance ratio} = \frac{C_s}{C_{inulin}}$	None
Effective renal plasma flow	$ERPF = C_{PAH} = \frac{U_{PAH} \times \dot{V}}{P_{PAH}}$	ml/min
Renal plasma flow	$RPF = \frac{C_{PAH}}{E_{PAH}} = \frac{(U_{PAH} \times \dot{V}/P_{PAH})}{(P_{PAH} - V_{PAH})/P_{PAH}} = \frac{U_{PAH} \times \dot{V}}{P_{PAH} - V_{PAH}}$	ml/min
Renal blood flow	$RBF = \frac{RPF}{1 - \text{Hematocrit}}$	ml/min
Excretion rate	$\text{Excretion rate} = U_s \times \dot{V}$	mg/min, mmol/min, or mEq/min
Reabsorption rate	$\text{Reabsorption rate} = \text{Filtered load} - \text{Excretion rate} = (GFR \times P_s) - (\dot{U}_s \times V)$	mg/min, mmol/min, or mEq/min
Secretion rate	$\text{Secretion rate} = \text{Excretion rate} - \text{Filtered load}$	mg/min, mmol/min, or mEq/min

C_s, clearance rate of substance "s"; E_{PAH}, PAH extraction ratio; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; P, plasma concentration; PAH, para-aminohippuric acid; P_{PAH}, renal arterial PAH concentration; RBF, renal blood flow; RPF, renal plasma flow; S, a substance; U, urine concentration; $\dot{V}$, urine flow rate; V_{PAH}, renal venous PAH concentration.

Table 2 – Use of Clearance to Quantify Kidney Function [4].

3. RENAL PATHOLOGY

3.1 Renal failure

End-stage kidney disease (ESKD), also known by the term „renal failure“ can be defined as failure of renal excretory function resulting from depression of the glomerular filtration rate (GFR) [6]. It’s important to mention that this is accompanied, to a variable extent, by failure of erythropoietin production, vitamin D hydroxylation, control of acid–base balance and regulation of salt and water balance and blood pressure. The terminal clinical manifestation of kidney failure is the so-called uremic syndrome, characterized by an increased serum level of protein and amino-acid metabolism end-products like urea and creatinine.

Two main types of kidney failure are recognized: Acute kidney failure and chronic kidney failure, however, in recent times, two new terms have been developed (replacing the previous nomenculature) that better describe the conditions to which they refer. In effect, what was previous know as acute kidney failure was renamed acute kidney injury (AKI), while it’s chronic counterpart is now mentioned as chronic kidney disease. Of vital significance is the ability to differentiate CKD from AKI, because the latter can be reversible, in some situations. The distinction between both AKI and CKD, or even a third case which manifests as acute-on-chronic renal failure, is, many times, not readily apparent in a patient presenting with uremia, but one important diagnostic clue that provides help in differentiating CKD from AKI is a the rate of rise in serum creatinine: Gradual and over several months or years for CKD, in contrast to the sudden increase during the time span of several days to weeks seen in AKI.

3.2 Acute Kidney Injury

In all cases of patients presenting with AKI, creatinine and urea build up in the blood over several days, with subsquent development of fluid and electrolyte disorders. The most critically serious of these disbalances are hyperkalemia and fluid overload (possibly responsible for causing pulmonary edema). Hyperphophatemia arises due to phosphate retention, while hypocalcemia is believed to result from the impaired kidney no longer being able to produce calcitriol and also because hyperphosphatemia causes Ca phosphate precipitation in the tissues. Hydrogen ions cannot be excreted, therefore resulting in acidosis.

With significant uremia, coagulation may be impaired, and possibility exists for pericarditis to arise. Regarding the urinary output, it varies with the type and cause of AKI [7].
To aid in the overall assessment of the severity of a person's acute kidney injury the „*Acute Dialysis Quality Initiative group*" proposed the „*RIFLE criteria*" [8],characterized by three levels of renal dysfunction (R, I, F) and two outcome measures (L, E). These criteria indicate an increasing degree of renal damage and have a predictive value for mortality, utilizing either increases in serum levels of creatinine or decreases in urinary output.

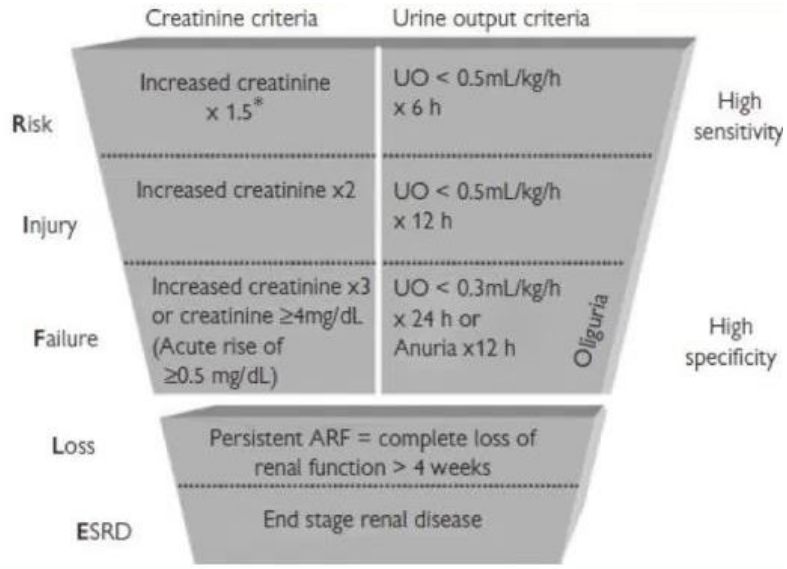

Fig. 9 - The Rifle Criteria [23]

For a better undestanding of the etiology of AKI, the causes are usually divided into 3 main groups: prerenal, renal or postrenal. However, it's necessary to keep in mind than more than one category may be present in an individual patient.

- **Prerenal Uremia**: Prerenal conditions acount for about 50 to 80% cases of AKI but do not cause permanent renal damage (and hence are potentially reversible) unless hypoperfusion is severe enough to cause tubular ischemia. In prerenal uremia, there is impaired perfusion of the kidneys with blood. It can result from an absolute fluid loss where there is decrease in the total amount of fluid in the body due to hypovolemia (hemorrhage, severe burnings, vomiting or diarrhea). Can also be due to a relative fluid loss, in this case the total amount of fluid in the body stays the same, but part of the fluid from the blood vessels moves to the tissues (distributive

shock) reducing the total blood volume (the best example is congestive heart failure). Finally, another cause of prerenal uremia is vascular disease limiting renal blood flow (stenosis in the renal artery or an embolus, blocking the blood flow in these vessels). [9]

- **Renal Uremia**: Renal causes of AKI involve intrinsic renal disease or damage. This type is responsible for about 10 to 40% of cases. Typically, the intrarenal causes of AKI are the result of damage in the tubules, glomerulus and the interstitium, so in the etiologic list can be included the following: glomerulonephritis, acute tubular necrosis, and acute interstitial nephritis. In the case of acute tubular necrosis, it can arise due to ischemia or due to nephrotoxins like some antibiotics (aminoglycosides), heavy metals (lead), myoglobin (from rhabdomyolysis), radiocontrast die and uric acid. Glomerular disease may be inflammatory (glomerulonephritis) or the result of vascular damage from ischemia or vasculitis. Finally, for the interstitial damage, a good example, and one of the most common is acute interstitial inflammation (nephritis), usually involving an immunologic or allergic phenomenon. [9]

- **Postrenal Uremia**: As for the etiology of postrenal uremia, what is involved is some kind of obstruction of the urinary track that can happen at any point from the calyces to the external urethral orifice. The resulting decreased flow can develop from something compressing the ureter as BPH or an intraabdominal tumor and can also result from blockage inside the ureter as is seen in the case of kidney stones, for example. The obstruction subsquently leads to fluid accumulation proximal to the obstruction creating high pressures in the renal tubules. In normal conditions, the filtration is acomplished from a high pressure arterial system (glomeruli) against a low-pressure system in the tubules, however because of obstruction, this pressure increases in the kidney tubules and less filtration will be made since it will try to filtrate against a high-pressure place. As a consequence, the GFR will decrease, oliguria will be present as less urine will be produced and azotemia will result. [9]

3.3 Chronic Kidney Disease

CKD is more prevalent in the elderly population and implies a long-standing, and usually progressive, impairment in renal function. In most of the cases, no effective means exist to be able to reverse the primary disease process. However, some exceptions exist, and include correction of urinary tract obstruction, immunosuppressive therapy for systemic vasculitis and Goodpasture's syndrome, treatment of accelerated hypertension, and correction of critical narrowing of renal arteries causing renal impairment [9].

CKD may be the end-result from any cause of renal dysfunction of enough magnitude. The most common cause, worldwide, of CKD is diabetic nephropathy, followed by hypertensive nephroangiosclerosis and various primary and secondary glomerulopathies. Metabolic syndrome, in which hypertension and type 2 diabetes coexist, is a large and growing cause of renal damage.

A rough categorization of CKD is that of a diminuished renal reserve, renal insufficiency or renal failure (ESKD). All patients that present with a GFR <60 ml/min/1.73 m2 for 3 months are classified as having chronic kidney disease, independently of the presence or absence of damage to the kidneys [10].

According to the GFR, CKD can be classified into different stages which form the KDIGO classification. [11]

CKD Classification and Staging

Green: Low risk (LR)
Yellow: Moderate risk (MR)
Orange: High risk (HR)
Red: Very high risk (VHR)

Kidney function stage GFR (ml/min/1.73m²) Description and range				Kidney damage stage Urine albumin/creatinine ratio Description and range		
				A1	A2	A3
				Normal to mild increase <30mg/g	Moderate increase 30-300 mg/g	Severe increase >300mg/g
	G1	Normal or high	≥90	LR	MR	HR
	G2	Mild decrease	60-89	LR	MR	HR
	G3a	Mild to moderate decrease	45-59	MR	HR	VHR
	G3b	Moderate to severe decrease	30-44	HR	VHR	VHR
	G4	Severe decrease	15-29	VHR	VHR	VHR
	G5	Kidney failure	<15	VHR	VHR	VHR

Fig. 10 - The KDIGO Classification [24]

As for the pathophysiology involved in CKD, initially, as renal tissue loses function, there are only some minor abnormalities because of renal adaptation causing the remaining tissue to increase its performance. In the case of loss of 75% of renal tissue, it will result in the fall of GFR to only 50% of normal. Decreased renal function will, of course, interfer with the kidneys' ability to maintain fluid and electrolyte homeostasis. The renal capacity to concentrate urine declines early and is accompanied by a decrease in ability to excrete phosphate (causing hyperphosphatemia), acid (leading to acidosis), and K (resulting in hyperkalemia).

When renal failure is advanced (GFR $\leq$ 10 mL/min/1.73 m2), the ability to dilute urine is lost, thus urine osmolality is closely related to that of plasma, and urinary volume does not respond readily to variations in water intake. Plasma concentrations of creatinine and urea begin to rise, since their filtration and excretion in the glomeruli is impaired, causing azotemia.

In early stages these changes are minimal, but in advanced stages, their levels quickly increase and are frequently associated with systemic manifestations. Despite many common assumptions, urea and creatinine are not major contributors to the uremic symptoms as they are merely markers for many other substances (some not yet well defined) that are the root of the symptoms experienced by people with CKD.

In face of a diminishing GFR, Na and water balance are surprisingly well maintained by increased fractional excretion of Na and a physiological normal response to thirst. With this in consideration, the plasma Na concentration is typically normal, and hypervolemia is not commonly seen unless the dietary intake of Na or water is very restricted or excessive. As for substances whose secretion is regulated mainly through distal nephron secretion (like potassium), adaptation usually maintains plasma levels at physiological or near physiological values until renal failure is advanced.

Abnormalities of Ca, phosphate, parathyroid hormone, vitamin D metabolism, and renal osteodystrophy can occur. Hypocalcemia is contributed, in a good part, by the decreased renal production of calcitriol, which in turn may lead to secondary hyperparathyroidism, while hyperphosphatemia results from decreased renal excretion of phosphate. Moderate acidosis (plasma HCO3 content 15 to 20 mmol/L) and anemia are characteristic. The anemia of CKD is classified as normochromic normocytic, frequently due to deficient erythropoietin production caused by a reduction of functional renal mass. Other causes that may be involved include deficiencies of iron, folate, and vitamin B12. [1]

4. THERAPEUTIC OPTIONS FOR PATIENTS WITH END-STAGE KIDNEY DISEASE

Before the advances in modern medicine and the rise of newer therapeutic methods, the therapeutic options for patients presenting with ESKD were significantly limited and offered little beneficits, management and improvement. In effect, before the 70's decade in the 20th century, only a relatively minor portion of patients received dialysis due to the existence of only a few dialysis-able facilities. Extensive medical screening to assess their eligibility for ongoing therapy and treatment was proposed only to a handfull of patients who had renal failure as the predominant clinical management issue.

At this times, kidney transplantation and all that it involves was in its infancy, in other words, it was in the early stages of development as a viable curative option. Therefore, the diagnosis of renal failure was mainstreamly accepted as a death sentence, often a slowly progressive and painfull one.

In the following decades, the avaiability for management of patients with ESKD dramatically increased throughout the developed world, while in the developing world such services are still at fault in comparison, exemplified by these countries high rates of mortality of people diagnosed with ESKD. [12]

However, even though significnt medical and technical advances were made, patients with renal failure that are treated with dialysis often remain with severely compromised lifestyle and disabilities. With this in consideration, constitutional symptoms of fatigue and malaise persist despite better management of anemia with erythropoietin. Progressive cardiovascular disease, peripheral and autonomic neuropathy, bone diseases and sexual dysfunction are common findings even in those patients deemed well treated and managed with adequate dialysis. This shouldn't come as a surprise, since even the most effecient dialysis regimens and modalities only provide, at most, 15% of the small-solute removal of two normally functioning kidneys. As for the removal of larger and higher-molecular-weight solutes, this value is even smaller. [12]

In view of this, the therapeutic option with the best outcome and the only modality which offers a curative potential and restoring of a healthy and productive life for patients with ESKD, is that of kidney transplantation. Despite all of this, it's not an „utopian" or perfect option, many things have to be taken in consideration when talking about the benefits and disavantages of kidney transplantation, and it remains a controversial topic worldide. [12]

4.1 Hemodialysis

The prevailing method, worldwide, for management of patients with ESKD is hemodialysis. This therapeutic procedure involves the removal of solutes across a semipermeable membrane within a dialyzer, or artificial kidney, from blood circulated through an extracorporeal circuit. This process of blood purification achieves the removal of waste products like urea and creatinine when the kidneys cannot function properly anymore. As for the fluid retained during the interval between procedures, it is removed by regulation of the hydrostatic pressure across the membrane of the dialyzer. Nowadays, the vast majority of the hemodialysis machines can control fluid removal, or ultrafiltration, using volumetric systems precisely controled by electronic microcircuits to ensure accurate and predictable results [12].

Hemodialysis is the first-line treatment when it comes to renal replacement therapy for patients who need dialysis acutely, and, of course, for those requiring it as maintenance therapy, as in the case of ESKD. Overall, it provides rapid clearance of solutes [13].

This therapeutic option can be performed either in a medical facility designed specifically for this goal, or in the patient's own home. In the case of the first option, the procedure usually ranges in lenght from 2.5 to 5 hours and it is performed typically 3 times during the span of a week. In other hand, patients that are highly motivated and posess a suitable living environment and a willing assistant (for example, a spouse) can have hemodialysis performed at home, therefore releasing the patient from the burden of having to visit a dialysis center and to adhere to a strict treatment schedule [12].

The need for dialysis and the various parameters that it involves are decided, usually, by the nephrologist that is taking care of the patient. These parameters include the frequency (the number of treatments performed each week), the length of each individual treatment, and the blood and dialysis solution flow rates, as well as the size of the dialyzer.

This therapeutic option is, for the most part, well tolerated, even though the process of ultrafiltration can result in hypotension, nausea and muscle cramps. For those patients of higher age and/or with established cardiovascular disease, they may be less tolerant to the procedure. Of additional concern is the need for intermittent heparanization (to prevent clotting in the extracorporeal blood circuit), as well as the common occurance of vascular acess failure due to repeated cannulation procedures. In the immediate period afte the treatment, the symptoms of malaise and fatigue may arise, owing it's apearence due to the

intermittent nature of hemodialysis which results in rapid changes in extracellular fluid volume, blood solute concentrations and plasma osmolality.

In view of this reality, attempts have been made to increase the frequency and, therefore, the overall solute and fluid removal abilities of hemodialysis, and under current studies are the approaches of 5 to 6 times a week treatments, increasing the time of each treatment and using nocturnal dialysis.

During this procedure, urea clearences of 180 to 200ml, per minute, are achieved, however, the clearence of middle and higher-molecular-weight toxins remains only a small fraction of the value achieved for small substances, despite the favorable water permeability of synthetic membranes, Even though the minute-by-minute removal of small solutes acomplished during dialysis can even exceed what is normally provided by the physiological kidney function, the intermittent nature of the procedure undermines the overall efficiency of this option for renal replacement therapy. In effect, even for those patients receiving 12 to 15 hours of hemodialysis a week, the accomplished solute clearence is only around 10% of what is physiologically adequate [12].

The process of hemodialysis requires an avaiable acess to the patient's circulation in order to provide continuous blood flow to the extracorporeal dialysis circuit. In the case of an ongoing hemodialysis regimen, some diferent options are available, particularly the autologous arteriovenous(A-V) fistula and the A-V grafts. In terms of long-term patency, it is greater in the case of autologous A-V fistula which also carries low incidence rates of thrombosis and infection. In contrast, A-V grafts, which are frequently applied in elderly people and in diabetic patients whose native blood vessels may be inadequate for the creation of a functional A-V fistula, the complication rates are significantly higher, with thrombosis being a recurrent concern. When talking about urgent situations, a temporary venous catheter can be used to establish vascular acess so that hemodialysis may be started immediatly.

As it can be logically concluded, despite the advancements made in regards to this type of procedure, it's efficiency is not remotely comparable to that of a normal functioning kidney, and many complications may arise, both acute as well as long-term. As it was previously stated, due to the rapid shift in fluid and solutes, a common constelation of symptoms may arise and includes hypotension, nausea, muscle cramps, fatigue and headaches. In light of this, their severity is, of course, proportional to the amount and speed of fluid removal.

4.2 Peritoneal dialysis

As therapeutical alternative to hemodialysis, peritoneal dialysis is a type of dialysis that utilizes the patient's peritoneum as a viable membrane through which fluid and dissolved substances exchanged with the blood. In effect, this procedure exploits the fluid and solute transport characteristic abilities inherent to the peritoneum as an endogenous dialysis membrane. The goal is the same as in hemodialysis, and is that of renal replacement: removal of excess fluid and toxins and correction of electrolyte disbalances.

The choice between diferent modalities of dialysis is controversial, with different proven benifits and adverse effects for all of the offered therapies, so it shouldn't come as a surprise that marked variations regarding their use is seen across different nations. So, while in many countries peritoneal dialysis is more popular, in the US it accounts for only 10% of the management option for patients with ESKD. [12]

The process of peritoneal dialysis is accomplished by the means of infusing a specified volume of peritoneal fluid (frequently in the range between 1500 and 3000ml) into the abdominal cavity by gravitity-induced flow, enabling said fluid to remain in the abdomen for a defined period, after which it is drained and discarded. During the time period the fluid is in the abdomen, both solute removal and ultrafiltration are accomplished. Acess to the peritoneal cavity is made by surgically inserting a silastic catheter (named Tenckhodd catheter) through the abdominal wall.

The removal of solutes happens according to a concentration gradient from the extracellular fluid into the peritoneal dialysate, and the peritoneal membrane acts as a functional semipermeable dialysis membrane. As for the ultrafiltration, it is achieved by osmotic water movement from the extracellular fluid compartment into hypertonic peritoneal dialysate that has a high concentration of dextrose [14].

If comparison is made with hemodialysis, the efficiency of small solutes removal is relatively low for peritoneal dialysis. However, when talking about the clearence of higher-molecular-weight solutes, the efficiency is, somewhat, improved.

Two ways of providing peritoneal dialysis are recognized: Continuous ambulatory peritoneal dialysis (CAPD) and continuous cycling peritoneal dialysis (CCPD). In the case of CCPD, its performed during the night, lasting over 8 to 10 hours, using the assistance of a automated cycling device to regulate and monitor the dialysate flow in and out of the abdominal cavity. As for CAPD, it is executed 24 hours a day, 7 days a week, using manual exchanges of peritoneal dialysate 4 or 5 times a day.

As it is expected, some advantages are present when choosing peritoneal dialysis over hemodialysis, and this includes the ability to mantain relatively constant blood levels of urea, nitrogen, creatinine, sodium and portassium. Also, since it is a type of self-care, this procedure promotes patient independence.

In other hand, peritoneal dialysis also carries severall risks, and the major complication of this procedure is bacterial peritonitis. The frequency of arising varies significantly among pacients and among treatment centers, but an overall average can be made of about one episode per patient per year. Not only is bacterial peritonitis an acute threat, in the long-term it can also lead to deletorious effects, like scarring of the peritoneal cavity and loss of peritoneum, therefore decressing its effect as a viable dialysis membrane and compromising the sucess of peritoneal dialysis [12].

With all things considered, despite some few exceptions, hemodialysis has no greatly improved medical advantage over peritoneal dialysis, as both methods effectively manage the consequence of uremia.

	Advantages	**Disadvantages**
Hemodialysis	Short treatment time. Highly efficient for small solute removal. Socialization occurs in the dialysis center (important for older and single patients).	Need for heparin. Need for vascular acess. Hypotension with fluid removal. Poor blod pressure control. Need to follow diet and treatment schedule.
Peritoneal dialysis	Steady-state chemistries. Higher hematocrit. Better blood pressure control. Dialysate source of nutrition. Intraperitoneal insulin administration. Self-care form of theraphy. Highly efficient for large solute removal. Liberalization of diet.	Peritonitis. Obesity. Hypertriglyceridemia. Malnutrition. Hernia formation. Back pain.

Table 3 - Comparisson between hemodialysis and peritoneal dialysis. A summary of their advantages and disadvantages. [12]

4.3 Transplantation

The therapeutic modality of transplantation is characterized by the organ transplant of a kidney, from some donor, into a patient (recipient) who has been diagnozed with ESKD. Transplantation is a complex process, involving many medical and surgical characteristics, but one with the ability to frankly restore the quality of life of patient with non-viable renal function.

A variety of different types of kidney donors exist, and they can be broadly classified as deceased-donor (previously termed cadaveric donor), or living-donor transplantion. Further subdivisions exist and will be presented and discussed.

Wide variation in the rates of renal transplantation exists among patient groups. In effect, the transplantation rates are lower in patients with more advanced age, since they represent a high-risk group. In other hand, variations are also seen across the plantet, with different countries having extremly different statistics. The rates are lower in developing countries (for example in Africa), with a big factor of contribution being the limited acess to deceased organ donors.

When it comes to survival, data shows that the mean average of 1-year survival for all types of living-donor grafts is about 95%, while in many individual centers it is greater than 90% for all match grades of deceased donor transplants. [12]

The requirements for renal transplantation differ from program to program and from nation to nation. Limits can be placed on age and the overall health status. Frequent exclusion criteria include a significant cardiovascular disease, incurable terminal infectious diseases and cancer. History of mental illness and/or on-going abuse issues of significant magnitute are also marked possible reasons for exclusion. Also, up until recently HIV was considered to be an absolute contraindication for eligibility for transplantation, since it was feared that imumunosupressing someone (always indicated after transplantation to prevent rejection) who already has a depleted immune system due to HIV infection would result in worsening of the patient’s state and contribute to mortality. Despite some data suggesting that immunosuppressive drugs and antiretrovirals may work synergistically to help both HIV viral loads/CD4 cell counts and prevent active rejection, it remains a controversial issue.

Not less important, transplant candidates are typically screened to assess their compliance towards future management with medication and lifestle modifications, all of which are essential for the survival of the transplanted organ.

4.4 Initiation of end-stage kidney disease therapy

The indications for starting with renal replacement therapy are manyfold. A vast majority of patients with progressive renal failure tend to develop symptoms of ESKD and require treatment when the GFR decreases to levels below 15ml per minute, or when their serum creatinine value rises to more than 10mg/dl. In other hand, a good amount of patients, specially those with diabetes, can present with symptoms at lower serum creatinine levels and higher values of GFR.

If the decision is made to start with either hemodialysis or peritoneal dialysis, the respective dialysis access should be achieved sufficiently early in the time scale, in order that the treatment can be initiated when required, instead of urgent or emergency needs. A good example to ilustrate this is the fact that a permanent vascular acess for hemodialysis needs from 4 to 8 weeks to properly mature, so it's placement should be accomplished early on to avoid relying on temporary venous catheters.

Overall, the decision to initiate dialysis is a clinical one, and should take in consideration both the assesment of uremic symptoms, as well as laboratory results: Plasma levels of creatinine, urea nitrogen and selected electrolytes. With the iniciation of some type of dialysis, patients with ESKD can be spared of a good amount of suffering and risk that accompanies this condition.

When it comes to life quality after the initiation of therapy, it varies according to the different types of procedures. A large amount of data seem to imply that the quality of life of patients with peritoneal dialysis exceeds that of patients receiving hemodialysis in a dialysis dacility. This can be explained in the light of the burden that hemodialysis has on a patient due to strict regimens, which are necessary for optimal results. If we talk about home hemodialysis, then we see a reported increase in patient's life quality. Many factors (including patient's motivation and overall health status at the start of treatment) influence the satisfaction and efficiency of each method, therefore making it extremely difficult to properly assess each modality alone.

Patients who have undergone kidney transplantation report a significant better quality of life than those undergoing dialysis of any kind. In fact, what we can see, in patients who have received a viable transplant, is marked improvement in life satisfaction, physical and emotional well-being, and ability to return to work and not being restricted to the harsh regimens inherent to the dialysis therapeutic options.

5. KIDNEY DONORS

In order for a transplant to be possible, its necessary the existance of an organ donor, and even though much attention is devoted, and well, to post-transplantation management of a patient, an adequate identification and preparation of both living and deceased donors is a critical contribution to the sucess of the transplantation.

As it was previously stated, sources of donors can be, in rough terms, divided into two main types: Living donors and deceased donors. As of today, each account for about half of all the kidney transplantations made in the US. [6]

As it can be easily infered, marked variations exist worldwide regarding the rates of use of different kidney donors, these variations being a reflection of many medical, societal and cultural values pertaining to a given society. Another factors of contribution to these diferences seen wordwide are the availability of deceased organ donors relative to patients awaiting for transplatantion, the national deceased donor legislation, the attitude of the physician towards living donation and the degree of government oversight.

A good contrast can be expressed in the example of the US and Spain. In effect, in the iberian country, everyone is considered a donor unless stated otherwise (either by a legal paper signed during their natural life or due to family's wishes refusing transplantation), therefore increasing substantially the pool of deceased donors. In addition to this, Spain also posesses very well functioning and organized TPM departments allowing for quick identification and procurement of deceased donors. Opposite to this is the example of the US, where for a person to be considered a donor, after they are declared legally dead, it is required for said person to sign a legal form in life, therefore declaring himself/herself a donor. Overall, what we can see is that in the spanish model, most kidney transplantations are derived from deceased donors (living donors account for less than 5%), whereas in the US they account for only aproximatelly 53%, with living donation providing the remaining half. [6]

In effect, living donation is the prefered donation modality for a vast majority of transplantation centers, but this shouldn't discard the value of other types of donors. In fact, deceased organ donation should maximized not only when talking about kidney transplantation but also for other solid organs where living transplantation is not an option. In conclusion, by raising efforts to increase deceased organ donation, it can have the beneficial effect of decreasing the burden on living organ donation and increasing the chance for a patient (who doesn't have the option of a living donor) to receive a transplant. [6]

5.1 Deceased Kidney Donors

In the group of deceased organ donors, we can recognize the following subdivisions:

- Brain-dead Donors
- Donation after Cardiac Death (DCD)

The diagnosis of death remains a controversial topic worldwide. In a traditional sense, in the lay, legal and medical communities death is characterized by an irreversible cessation of both cardiac and respiratory function. However, in the last decades a new term gained acceptance in the medical community and is of extreme importance, particularly in the chapter of organ transplantation. This term brain death emerged in the 60's decade in the last century, and arose as a response to the ability to resuscitate individuals and mechanically mantain cardiac and respiratory function. Therefore, we can talk about brain death and cardiac death as two separate entities. Is is worth saying that these are not perfect terms and many times they can overlap and be a source of confusion and distress.
In either case, prompt identification of all possible organ donors is critically imporant to maximize organ donation and transplantation. In effect, most deceased organ donors have suffered irreversible/nonsurvivable brain injury, traumatic or otherwise, and are, at first, rushed to the emergency department and then transfered to the intensive care unit. To ensure that every potential organ donation opportunity is realized, it is necessary vigillant surveillance for potential organ donors on the part of the emergency and critical care staff. [12]

5.1.1 Brain-dead Donors

The vast majority of deceased organ donors present with brain injury and a low glasgow coma scale score at the time of their arrival to the hospital. In effect, a propper diagnosis of brain death is required and considered essential to the organ donation process.
For the diagnosis of brain death there exist a well documented criteria and requires irrefutable evidence. Overall, it includes a known cause of brain injury, irreversibility and absence of cerebral and brainstem function (including apnea). This diagnosis should be made by a physician who is not part of the transplant team and is, of course, impartial and free of conflict of interests.

Evidence in the form of some exams is particularly helpful for the diagnosis of brain death and it may include electroencephalography, conventional angiography, radionuclide angiography, magnetic ressonance angiography, computed tomographic angiography and transcranial doppler ultrasound. The indications to perform said examinations include conditions that can mimic the state of brain death, like drug intoxication, chronic CO2 retention and so on. In addition to this, this examination are mandated in the presence of inconclusive apnea testing, normal neuroimaging or inability to perform a clinical examination.

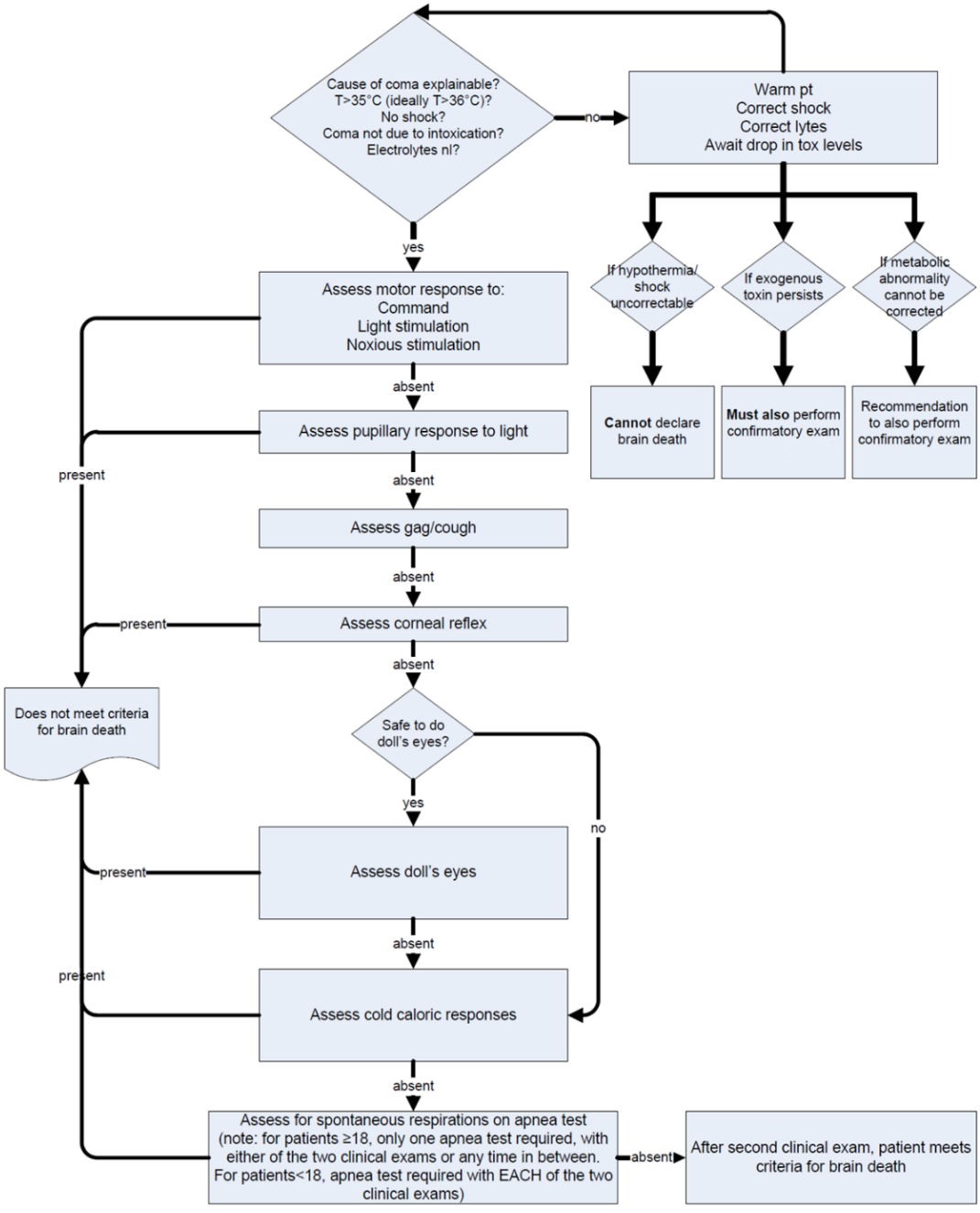

Fig. 11 – Clinical examination for diagnosis of Brain death [25]

Despite the fact that brain-dead donors are considered to be dead, it’s important to take note that the donor's heart continues to beat, therefore being able to function as a pump and maintain the circulation. This fact opens the possibility for surgeons to start the operation while the organs are still being perfused. During the operation, the aorta will be cannulated, after which the donor's blood will be replaced by an ice-cold storage solution. Because of the temperature of the solution, and also due to great amounts of cold NaCl-solution that are poured over the organs to achieve a rapid cooling, the heart will then have cessation of it‘s pumping ability. [12]

5.1.2 Donation after Cardiac Death

In the past, the term non-heart beating donor was widely used. Today, the term donation after cardiac death is the most accepted term since it allows for a better differentiation from brain death. Before the acceptance of the critteria for brain death, all deceased organ donors were recovered from patients with cardiac arrest. However, due to the acceptance of brain death criteria and the development of multiorgan recovery, the use of DCD organs has decreased substantially, mainly due to the risks involved with the ischemic damage that haunts this potential donors. Nevertheless, the verified worldwide organ shortage has made a good argument in favor of modifying this policy.

DCD donors are divided into four groups, commonly known as the four Maastrich categories of DCD donors. Categories I and II, also known as uncontrolled donors, are pulseless and asystolic depite adequate, but ultimately failed, attempts at ressuscitation. Types III and IV are refered to as controlled, and present as comatose, irreversibly brain damaged and respirator dependant, but not brain-dead by definition.

As a summary, we can define DCD donors as patients who do not meet the brain-dead established criteria, however, since the chance of recovery is unlikely (or nearly impossible), have decided, either through a living will or due to family wishes, to have support withdrawn, therefore ending their life.

In this case, all therapeutic modalities are discontinued (e.g. mechanical ventilation is turned off). Finally, after a time of death has been declared, the patient is transfered quickly to the operating room, where the organs can be extracted and used for transplantation. A storage solution is then flushed through the organs. Because blood is no longer being circulated, the

risk for coagulation is high, therefore it must be prevented with the use of large amounts of anti-coagulation agents (heparin).
Similar to brain death, the decision to „shut off the machines“ is not easy and controversial, so several ethical and procedural guidelines must be followed strictly and the team responsible for the organ recovery should not be active participants in the patient's care in any way until after death has been pronounced.
DCD is associated with increased risk of delayed graft rejection. However, the long-term graft survival is very similar to that experienced by people who were recipients of brain-dead organ donors.
Despite the decline in use of DCD donors, it is estimated that if DCD donor protocols were maximized, the supply of deceased organ donors would increase exponentially. [12]

5.1.3 Expanded Criteria Donors

In terms of renal transplants, an expanded criteria donor is characterized as a kidney recovered from a deceased donor that is, either, older than 60 years old, or is aged between 50 to 59 years old with two additional risk factors, which includes a history oh hypertension, death occuring as a result from some kind of cerebrovascular accident, or a raised terminal serum creatinine (> 1.5 mg/dl). [12]
According to the most recent data, kidneys obtained from an ECD have, statistically, an increased risk (of about 70%) of graft failure within 2 years (independently of the age of the recipient), compared with standard criteria kidneys. The meaning of this, is explained as following: Considering that a standard kidney has a 2-year graft survival of 88%, the estimated value of survival, at 2 years, for an ECD is of 80%. [12]
As of today, we see a worlwide problem when it comes to transplantation: Organ shortage. In effect, because of excessivly long waiting times, changing donor demographics and an ever raising disbalance between organ supply and demand, ECDs have gained more approval in the medical community (despite remaining a controversial issue) and are becoming more commonly offered to many patients with ESKD.
This new approach towards ECD comes as a response of the transplant communiy to combat the crisis in organ supply, therefore changing the thresholds for what is accepted as a risk factor and maximizing and utilizing organs from all possible sources.

Nevertheless, the decision to offer an ECD kidney as a viable transplant to any given patient with ESKD is a complex topic, since much research seem to imply that the donated kidneys possess an increased rate of primary nonfunction, delayed graft function, rejection, and an increased vulnerability to preservation injury, drug toxicity, and the effects of posttransplant hypertension.

Also, ECD kidneys have some further disadvantages, as they are more resource-intensive and costly. Finally, the „life-span" of an ECD kidney is believed to be significantly shorter, as it's half-life is estimated to be in the range of 6 to 8 years compared to that of standard donors with about 10 to 12 years.

Taking all of this in consideration, ECD kidneys are offered as an option to patients who have been informed and know about all the risks associated with these type of donation and understand that the possibility of failure is higher, and still choose to accept them.

Despite all of the disadvantages of ECD, they can be seen as a blessing for patients very low on the waiting list and, when facing such a crisis as is that of organ shortage, it is impossible, in today's conditions, to hope that all patients can receive perfect transplants.

Advantages	**Disadvantages**
Annual mortality rate in dialysis patients exceeds 20%	70% increased risk for graft failure vs SCD kidneys
Quickly growing transplant waiting lists and, subsequently, increasingly longer waiting times	17% primary graft non-function vs SCD kidneys
Survival advantage of ECD kidney transplant recipients over dialysis patients remaining on transplant waiting list	38% of ECD kidneys were discarded vs 9% for all other kidneys
	Increased treatment cost and resource use
	Mortality in perioperative period greater in ECD kidney recipients
	Higher DGF rates, more acute rejection episodes and decreased long-term graft function in ECD vs SCD kidneys

Table 4 - A summary of their advantages and disadvantages of the use of ECD's, a very controversial topic in the world of transplantation [26]

5.1.4 Surgical Technique of Deceased Organ Donor Recovery

Independently of the organs to be removed, the principles of organ extraction surgery are similar. A wide surgical exposure is required, and each organ to be recovered is dissected with an intact vasculature. In order to prevent damage to the vasculature, and to avoid the risk of delayed graft function due to vasospasm, it is not performed dissection into the renal hilum. Cannulas are put in place for „in situ“ cooling and when aortic cross-clampling is made, flush and cooling begin. The method for kidney extraction is called dissection „*En Block*“ and it means the kidneys are removed together with the aorta and the vena cava [12]. If multiple organs are to be extracted, then the prefered sequence of events is that of heart or lungs at first, followed by liver or pancreas, and finally the kidneys. During the time required for removal of the other organs, the kidneys are protected from ischemic damage by the cold flush and surface cooling.

An important part for the sucess of the procedure is that of warm ischemia time, and it reffers to the time period between circulatory arrest and initiation of cold storage. When it comes to the kidney, it may survive and still function up until 60 minutes of warm ischemia, however, delayed function or nunfunction have been reported to significantly increase after 20 minutes [12].

5.2 Living Kidney Donors

Living donor kidney transplantation involves the extraction of a kidney from a healthy individual, and this type of procedure has come a long way, developing immensly since the first sucesseful identical twin donor transplantation in 1954. Overall, the significant advances observed in immunosupressive therapy, the development of more refined surgical techniques and increase in public awareness and altruism have greatly increased the sucess of this type of donation. Living kidney donors can be further classified into related or non-related, according to the blood bonds between the donor and the recipient.

In effect, today it is safe to consider that almost all biologically related and unrelated, medically and psychosocial adequate individuals can be potential donors. This has led to an increase in living organ donation, and it manifests in the rates of its use, for example, in the US, during the time period between 1996 and 2006, the number of living donor kidney

transplantations almost doubled, and now accounts for almost half of all renal transplantations [12].

Another very important factor of contribution to the increased rates of living donation is the statistically comprovated facts of superior patient and graft survival rates achieved, contrasting with that of deceased organ donation.

Of course wide variations are observed througout the globe regarding the rates of use of living donation, ranging from less than 5% in countries like Spain, to being, in the vast majority of cases, the exclusive source of donors in Japan, where very strong cultural values (and legal barriers) portray deceased organ donors in a not such a colourful light. [12]

These marked differences have to be analyzed in the context of a given country's own religious, social and cultural values, as well as the medical policies and governmental laws which guide the population. In addition to this, the variations can also be explained in the light of the availability of deceased organ donors in regard to the number of patients on the waiting list for transplants. [12]

A problematic concern, particularly in the developing world, is that of illegal organ trade, where people, either intentionally or forced, sell their organs to be used for people with necessity for a transplant, often very low on the waiting list. Many of these donors, living in great poverty, are exploited by profit-motivated agents who, without any consideration, decide to take advantage of the donor's desperate need to survive or pay for such basic requirements such as food, medical care and housing. [12]

When refering to transplants perfomed in this illegal manner, it is important to realized that the donors often don't receive sufficient after-operation care resulting in high mortality rates. The risks for the recipient are also manyfold, and it is common the situation in which the donated kidney is not functionally viable, and the risk of infections (HIV) transmitted from donor to recipient is also greatly increased. Also, it is worth mentioning the price of a kidney, in the black market, can ascend to very high values, in the range of hundreds of thousand euros [15].

It has been estimated, by the World Health Organization, that up to 10% of all transplants, worlwide, are accomplished in an illegal manner, and efforts and have been made to ban this type of practise. In effect, the Declaration of Istanbul on Organ Trafficking and Transplant Tourism was designed to finish the exploitation of living donors while encouraging healthy and legal transplantion procedures. [12]

6. PROCUREMENT AND TRANSPLANT

The procedure of organ procurement, formerly known as organ harvesting, involves the whole process of donor identification, selection and the surgical techqnique that removes organs or tissues for organ transplantation. In the algorythm of organ procurement, the following steps are involved [16]:

- Detection and identification of potential donors
- Facilitating the diagnosis of brain death
- Management of donor, organ and tissue viability studies
- Family interview
- Organizing the extraction and distribution of organs and tissues

The first step is critically important to realize the donation potential and ensure that no disease is transmitted from the organ's donor to the pacient who will receive the transplant, termed the recipient.

The presence of a transplant procurement management (TPM) specialist is also important to oversee possible donors who remain in a state of brain death or cardiorespiratory arrest, lending aid and making the necessary resources available so that a brain death diagnosis may be achieved.

In addition to this, the TPM specialist should be an active participant in all donor management aspects, with a special emphasis on organ and tissue suitability studies so that decisions can be made regarding organ and tissue transplantation viability.

In regards to family interview, the family has to be informed about the donation and, when necessary, family authorisation and consent have to be adquired,

Finally, the TPM has in its list of duties the organization of multiorgan and tissue extraction and coordination of the necessary and existing resources for extraction (operating room, anaesthesia, surgical teams, etc.).

Over the years many improvements have been made to the whole process of procurement, with special merit being the development of transplant coordination teams, specialized departments and worldwide organizations, responsible for regulating all the aspects necessary for organ donation.

In light of this, a new „vital cycle“ has been developed and it is the cornerstone of procurement. This „philosophy“ allows an organ-donating society, which has a transplant coordination system available , to receive the benefit of transplants. This cycle is dependant on the attitude of the society involved which, of course, is a mirror of it’s culture, religion, economic and educational factors.

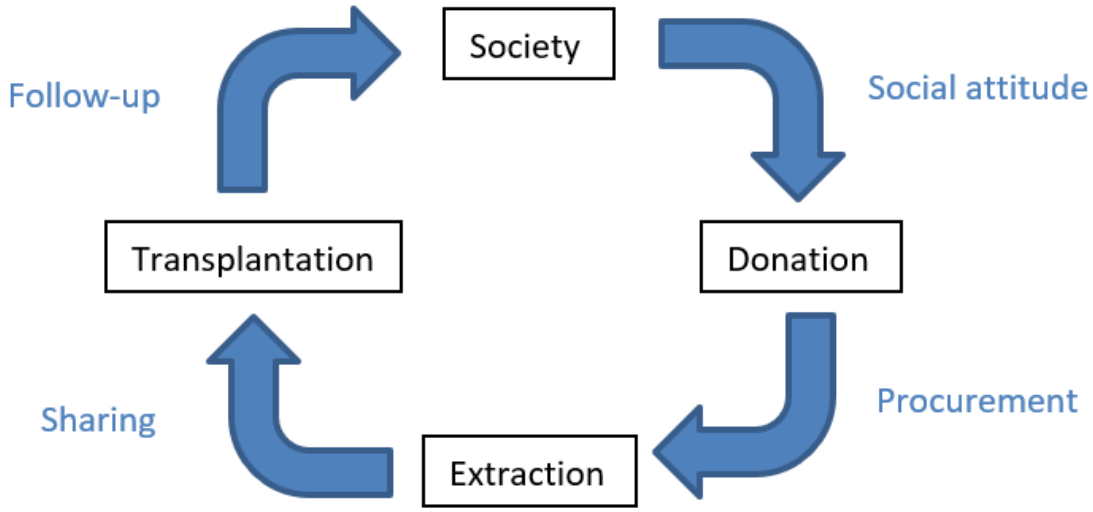

Fig. 12 – The new vital cycle: Donation and Transplantation process [16]

The procurement process will, of course, be different when talking about different types of donors. In addition to this, many countries have certain laws that can limit the pool of potential organ donors, like for example requiring the donor to be legally dead for consideration of organ transplantation.

Overall, organs cannot be viable procured if the heart has stopped beating for a prolonged period of time. Continuing with this line of thought, donation after brain death is the typically prefered option since organs continue receiving blood from the donor’s heart until minutes before being extracted from the body and placed on ice.

In other hand, donation after cardiac death involves a restricted timeline with surgeons taking the donor’s organs within minutes of cessation of respiration and other forms of life support for patients who still posess some form of brain activity. To illustrate a situation like this, a good example would be that of a patient being withdrawn from life support according to his family’s whishes.

When talking about multiple-organ procurement, coordination between teams working on different organs is frequently necessary.

When organ procurement has finished, the organs are, most frequently, rushed to the location of the recipient for transplantation, or, in other hand, can be preserved for later study. Overall, research shows that the faster an organ is transplanted into the recipient, the potential for a better outcome increases. Important to mention is the term „cold ischemia time“, and it denotes the time period when the organ is being transported while being stored in an icy cold solution to help preserve it. Different organs possess different values of cold ischemia time, with the heart and lungs posessing the lowest at less than 6 hours, liver from 6 to 10 hours, and the kidneys having a larger period of about 24 hours [17].

However, regarding kidney transplants, as the cold ischemia time increases, the risk of delayed function of the kidney also increases. Because of this, sometimes the necessity arises for the recipient to require temporary dialysis until the transplanted kidney returns to proper levels of function [12].

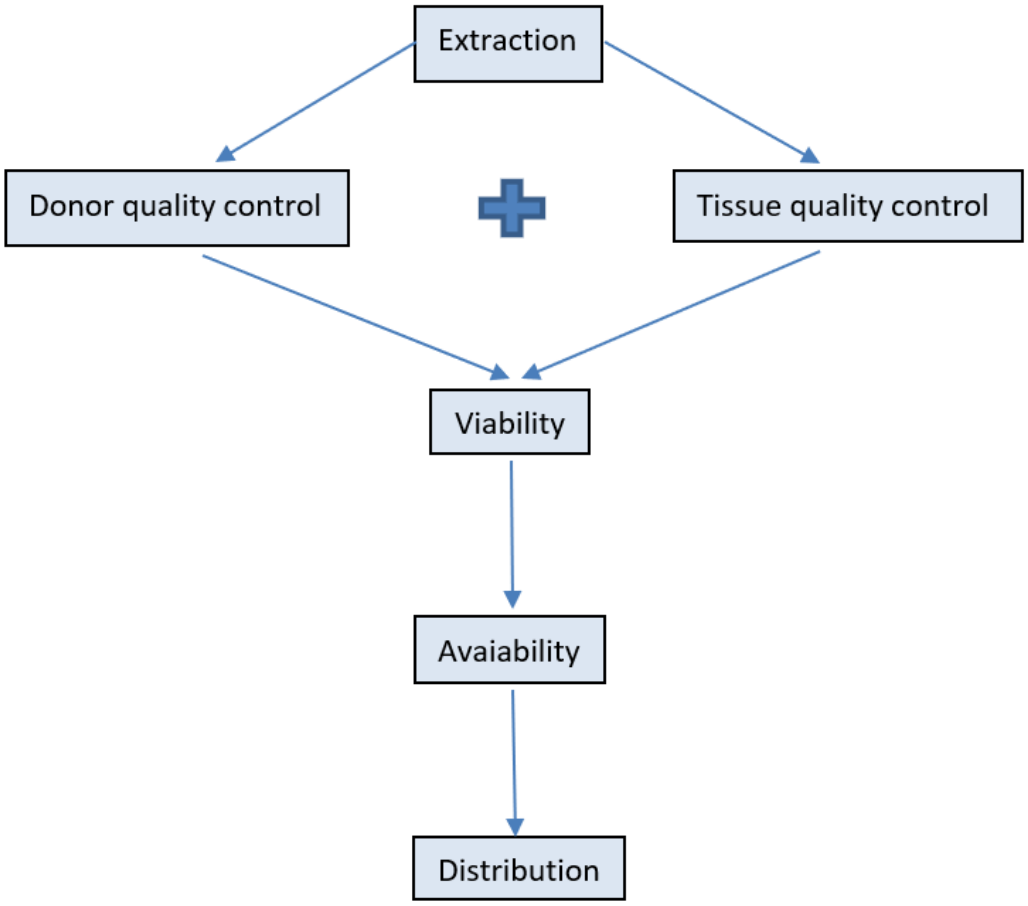

Fig. 13 – Procurement algorithm following organ extraction [16]

6.1 Compatibility

A very important step belonging to procurement is that of donor and recipient compatibility. Generally speaking, it is required for the donor and repicient to belong to the same ABO blood group and be crossmatch (HLA-human leukocyte antigen) compatible.
This is done as a crucial effort to reduce the risk of developing rejection thanks to an incompatible transplantation. Therefore, if a potential donor is incompatible with the recipient, then transplantation will not occur/be advised.
When talking about living donation, it's important to mention the term „kidney paired donation" (KPD), which involves patients with incompatible donors (for example, a family member willing to donate a kidney) to swap donors ir order to receive a better match, in other words, a compatible kidney. This poses as a great opportunity to provide better matches for recipients, in the process reducing the risk or organ rejection and lowering lifetime mortality [18].

6.2 Kidney Viability Criteria

Both absolute and relative contraindications exist that can exclude someone from being a donor. The absolute criteria for exclusion, regarding potential kidney donors, is as following [16]:

- HIV or risk group
- Multi-organ failure/Sepsis
- Malignant Tumour diseases
- Chronic renal insufficiency

In addition to this, the list of relative contraindications that can possibly prevent someone from being a kidney donor includes the risks expressed bellow [16]:

- Age
  Arterial Hypertension
- Diabetes
- Acute Renal Failure
- Prolonged warm ischemia

- Glomerulonephritis and other nephropathies in normal renal function phase
- Hepatitis B and C infection

6.3 Renal Transplantation Procedure

During extraction, kidneys are removed accompanied by their respective renal artery and renal vein, as well as the donor's ureter. Eventually, they are transplanted into the recipient's body.

In the vast majority of cases, the patient's existing kidneys are not removed, even though they are barely or completly non-functional. The reason for this is that research has shown increased rates of surgical morbidity when removing the recipient's kidneys. In effect, the donor's kidney is frequently inserted in a location different from the orginal kidney's placement. The most common location is the iliac fossa, and a different blood supply is required.

The renal artery belonging to the donor's kidney, is usually connected to the external iliac artery in the recipient. As for the renal vein, it is typically connected to the external ilica vein in the recipient. When this process his finished, blood is allowed to flow into the kidney again. Also, and has a final step, the donor's ureter is anastomosed with the recipient bladder. The transplant surgery usually takes about 3 hours. [12]

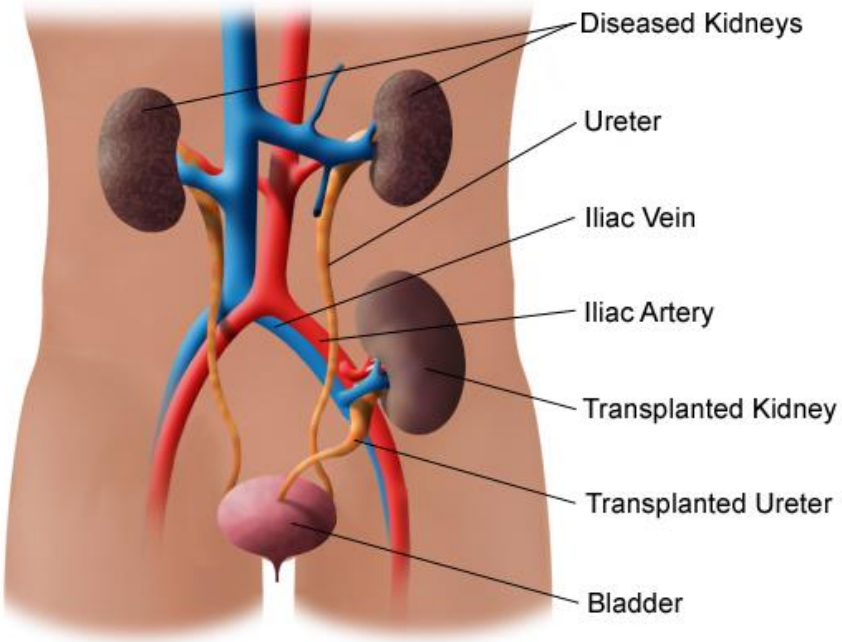

Fig. 14 Renal transplantation – Donor's kidney position [27]

6.4 Life after renal transplantation: Management and Complications

After the transplant operation, some days need to pass untill the new kidneys can return to normally functioning levels. For living donor kidneys, it is usually required 3 to 4 days, contrasting with 7-15 days required for deceased donor kidneys. Post-operatively the kidneys are periodically evaluated by ultrasound, so that physiological changes (often accompanying transplant rejection) can be assessed.

Accompaning the new organ, many lifestyle modifications are imposed to the recipient, in order to improve the transplanted organ survival and to ensure restoration of life quality. This encompasses medical therapy, frequent follow-ups, diet and lifestyle changes.

To prevent the risk of the recipient‘s immune system to reject the donor‘s kidney, immunosupressant drugs are prescribed and they must be taken for the rest of the recipient’s life. There are a variety of immunosupressant drugs, with the most common medication regimen being a mixture of tacrolimus, mucophenolate and corticosteroids, commonly prednisolone. In addition to the mentioned drugs, some recipientes may, instead, be administered cyclosporin, sirolimus or azhathioprine. [12]

As for diet, the recipients of kidney transplants are discouraged from consuming products known to interact with transplant medications, particularly tacrolimus, cyclosporin and sirolimys. Common foods to be avoided are grapefruit, pomegranate and green tea products. Smoking and alchool intake is discoraged as much as can be possibly expressed.

Complications of renal transplantation can be better described according to their division in the following categories: Pathological or surgical complications. When refering about the former, it includes rejection, infection, and cardiovascular events, while surgical complications involve vascular and urological complications, lymphocele, wound infection, and herniation.

The most common graft-endangering complications are mainly of vascular etiology. In effect, vascular complications account for 3%–15% of all cases [19]. They are manifested mainly by thrombosis or stenosis of the renal artery or vein. In addition, other rarer complications include aneurysms formation, arteriovenous fistulas or hematomas.

According to reports from the United Network of Organ Sharing (UNOS), graft survival at two years is 90%, nevertheless, in 5-year surveillance studies it was reported that 30% of patients have lost the graft or died with a functioning kidney [19].

In the majority of cases of early graft failure (defined as happening in the first 6 months), the causes are acute rejection, technical problems, and a nonviable kidney. In the case of

chronic failure, it is caused by death because of a non-kidney-related problem with a functional graft and chronic kidney disease. In addition to this, about 4.8% of post-transplantation patients have returned to dialysis [20].

When it comes to rejection, we recognize 3 types, according to the time period and also histological differences: Hyperacute, acute and chronic. Hyperacute rejection of the renal graft happens within hours of the transplant (nephrectomy is indicated). In the case of acute rejection, it occurs within the first 6 months after transplantation. As for chronic rejection, it develops more than 1 year after transplantation and is a major cause of graft loss.

A summary of the list of complications that can arise after kidney transplantation, both in the short as well as in the long-term, is expressed bellow, and it is necessary to keep in mind that the risk of complications is greatly influenced by the patient's age and health condition before transplantation [12]:

- **Transplant rejection** (hyperacute, acute or chronic).
- **Post-operative complications**: Bleeding, infection, vascular stenosis and vascular thrombosis, urinary complications, lymphocele.
- **Infections** and **sepsis** due to the immunosuppressant drugs that are necessary to reduce the risk of rejection.
- **Post-transplant lymphoproliferative disorder** (lymphoma arising due to the immune suppressants).
- **Imbalances in electrolytes** (e.g.: calcium and phosphate)
- **Proteinuria.**
- **Hypertension.**
- **Cardiovascular disease**
- **Liver disease**

CONCLUSION

Transplantation is, as of today, one of the established treatments of irreversible kidney disease with the best outcome, owing this to its curative potential. Improvements in surgical techniques and more sophisticated, potent immunosuppressive drugs have resulted in remarkable advances in survival of patients and renal grafts.

Of course, the type of donor influences greatly the outcome, and of paramount importane is that of compatibility. While a living donor can come across as being the best option when it comes to long-term graft survival and reduced risk of rejection, some countries, particularly the example of Spain, have proven, through their excellent transplantation procurement policies and organ donation legislation, that deceased donors can, in fact, present with practically simillar outcomes and very well satisfy the needs of their patients.

For those less fortunate, in other words, in a low place in the waiting list, the use of an expanded criteria donor can provide a good fighting chance for someone that, most probably, would die while waiting for a suitable transplant.

Regarding the most used type of donation by a particular country and/or center, we can see that marked variations exist across the globe, reflecting different cultural, ethical, social, educational and medical values. In effect, this can be ilustrated by the following facts: In the US, both living donation and deceased organ donors supply each about half of all transplantations, while in Spain deceased donation accounts for more than 95% of all renal transplants.

Even though many sources exist for donation, organ shortage continues to be a worldwide problem, and many people still die on the waiting list while hoping for a transplant. There is much potential to overcome this fact: Exploring the diferent sources of organ donors available and not relying only on one source. In addition to this, many complications can arise following a transplant, with particular interest being that of rejection. The rise of newer and more effective immunosupressant drugs and better post-op management has greatly improved both graft and patient survival in the last decades.

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