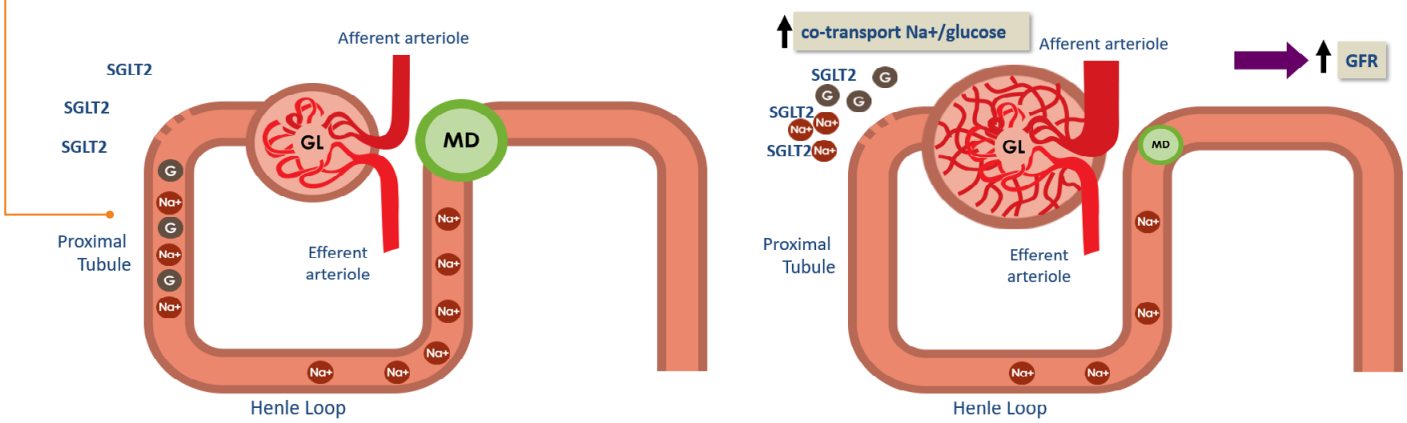
RAMB
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira
WMA

Volume 66 - 2020 - Supplement 1
ISSN 0104-4230
ISSN 1806-9282 (On-line)

Thematic Issue
Nephrology

SECTIONS



NORMAL GLOMERULAR HEMODYNAMICS (1A) AND KIDNEY DISEASE CAUSED BY DIABETES (1B).

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

SUMMARY

Thematic Issue: Nephrology

Coordenation: Renato Demarchi Foresto and José Osmar Medina Pestana

SECTIONS

ARTICLES

Novel treatment options for chronic kidney disease complications

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http://dx.doi.org/10.1590/1806-9282.66.S1.1

The worldwide prevalence of renal diseases has increased in recent years due to the concomitant growth of the prevalence of its main associated risk factors, such as hypertension, diabetes, obesity, and cardiovascular diseases[1,2]. In particular, Chronic Kidney Disease (CKD), with an estimated prevalence of around 10% worldwide[2]. In Brasil, the same trend is observed, and the number of patients with end-stage renal disease undergoing dialysis surpasses 130,000 and grows every year[3]. Prevention and early diagnosis, combined with the proper treatment of the disease, help reduce unfavorable outcomes, generate quality of life benefits, and reduce costs related to health care[4].

To meet the growing demand caused by renal diseases, there have also been many promising advances in the treatment of diseases associated with nephropathy, for example, the use of SGLT-2 inhibitors in the treatment of diabetes, with favorable results in the EMPA-REG, CANVAS, DECLARE and, more recently, CREDENCE studies regarding the progression of diabetic kidney disease, proteinuria, and cardiovascular outcomes such as mortality and hospitalization due to decompensated heart failure[5-8]. These benefits are gained through the glycosuria and natriuresis generated by inhibiting glucose reabsorption in the proximal tubule with oral hypoglycemic agents.

For the treatment of CKD anemia, there is also a new class of medications, the HIF-PH (Hypoxia Inducible Factor Prolyl Hydroxylase) inhibitors, which stimulate the endogenous production of erythropoietin. This new class of medications includes vadadustat, daprodustat, roxadustat, and molidustat. Clinical trials have demonstrated that these drugs are effective for treating CKD anemia with relatively fewer adverse events, such as a lower risk of cardiovascular events or thrombosis attributed to exogenous erythropoietin, besides the advantage of being oral medications, which provide higher patient adherence[9].

In the same way, other therapeutic advances are noteworthy, such as the new immunosuppressants for kidney transplantation, the use of rituximab for glomerulopathies, and the technological advances focused on hemodialysis. The expectation in the area is that new knowledge will be obtained regarding the understanding of the cellular regeneration, the use of stem cells, and bioengineering to develop new strategies to restore renal function[10]. Additionally, the advent of the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) genetic editing technology brings hope for the correction of genetic errors related to diseases that affect the kidneys. There are still many challenges along the way, such as the correct use of the therapy on the specific gene

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and producing hybrid animal organs for transplantation[11].

In this thematic issue, we bring a selection of reviews dedicated to the main renal diseases, such as chronic kidney disease, acute kidney injury, polycystic kidney disease, nephrotoxicity caused by medications, peritoneal dialysis, and hyperkalemia, with the latest publications in each area and also updates on the nutritional management of CKD, diabetic nephropathy and chronic kidney disease anemia.

Contribution of the authors

The authors contributed equally to the drafting and revision of this text.

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REVIEW ARTICLE

Chronic Kidney Disease

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http://dx.doi.org/10.1590/1806-9282.66.S1.3

SUMMARY

Chronic kidney disease is highly prevalent (10-13% of the population), irreversible, progressive, and associated with higher cardiovascular risk. Patients with this pathology remain asymptomatic most of the time, presenting the complications typical of renal dysfunction only in more advanced stages. Its treatment can be conservative (patients without indication for dialysis, usually those with glomerular filtration rate above 15 ml/minute) or replacement therapy (hemodialysis, peritoneal dialysis, and kidney transplantation). The objectives of the conservative treatment for chronic kidney disease are to slow down the progression of kidney dysfunction, treat complications (anemia, bone diseases, cardiovascular diseases), vaccination for hepatitis B, and preparation for kidney replacement therapy.

KEYWORDS: *Conservative Kidney Management. Chronic Kidney Disease End Stage. Renal Failure.*

DEFINITION

Chronic kidney disease (CKD) is a clinical syndrome secondary to the definitive change in function and/or structure of the kidney and is characterized by its irreversibility and slow and progressive evolution. Another important aspect is that the pathology represents a higher risk of complications and mortality, especially cardiovascular-related[1].

An adult patient is identified with CKD when they present, for a period equal to or greater than three months, glomerular filtration rate (GFR) lower than 60 ml/min/1.73 m^2, or GFR greater than 60 ml/min/1.73 m^2, but with evidence of injury of the renal structure. Some indicators of renal injury are albuminuria, changes in renal imaging, hematuria/leukocyturia, persistent hydroelectrolytic disorders, histological changes in kidney biopsy, and previous kidney transplantation [1]. Albuminuria is defined by the presence of more than 30 mg of albumin in the 24-hour urine or more than 30 mg/g of albumin in an isolated urine sample adjusted by urinary creatinine.

The main causes of CKD include diabetes, hypertension, chronic glomerulonephritis, chronic pyelonephritis, chronic use of anti-inflammatory medication, autoimmune diseases, polycystic kidney disease, Alport disease, congenital malformations, and prolonged acute renal disease.

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CLASSIFICATION

CKD is categorized into five stages, according to the GFR, and in three stages, according to the albuminuria, as shown in the tables below:[2]

TABLE 1. CKD STAGE; GFR = GLOMERULAR FILTRATION RATE.

Stages	GFR value ml/min/1.73m2	Classification
I	>90	Normal or High
II	60-89	Slightly decreased
III A	45-59	Mild to moderately decreased
III B	30-44	Moderately to severely decreased
IV	15-29	Severely decreased
V	<15	Kidney failure

TABLE 2. CATEGORIES ALBUMINURIA; A/C RATIO = ALBUMIN/CREATININE RATIO IN ISOLATED URINE SAMPLES.

Category	24-Hour Albuminuria mg/24 h	A/C Ratio Mg/g	Classification
A1	<30	<30	Normal to discrete
A2	30-300	30-300	Moderate
A3	>300	>300	Severe

Therefore, an adult patient with diabetic nephropathy, GFR estimated = 42 ml/min, and albuminuria of 200 mg/24 hours for over three months is classified as a CKD stage IIIB A2 patient.

It is worth remembering that albuminuria between 30-300 mg/g used to be called ''microalbuminúria", and greater than 300 mg/g, "macroalbuminuria". The inclusion of the degree of albuminuria in the CKD classification is justified as a way of estimating the risk of progression of renal dysfunction, as shown in the table below:

TABLE 3. RISK OF RENAL OUTCOMES ACCORDING TO THE GFR AND ALBUMINURIA; GFR: GLOMERULAR FILTRATION RATE IN ML/MIN/1.73 M².

		Albuminuria		
	GFR	<30 mg/g	30-300 mg/g	>300 mg/g
Stage 1	≥90	Low risk	Moderate risk	High risk
Stage 2	60-89	Low risk	Moderate risk	High risk
Stage 3A	45-59	Moderate risk	High risk	Very high risk
Stage 3B	30-44	High risk	Very high risk	Very high risk
Stage 4	15-29	Very high risk	Very high risk	Very high risk
Stage 5	<15	Very high risk	Very high risk	Very high risk

The staging system shown above helps physicians determine the method and intensity of monitoring that will be applied to CKD patients. A more accurate risk prediction for individual patients can be achieved by the development of risk prediction tools. In addition to the GFR and albuminuria, the cause of the kidney disease, as well as other factors (such as age, sex, race, cholesterol levels, smoking, and others), should also be considered in the prognosis estimate.

STAGING

The justification for staging asymptomatic individuals for CKD is that early detection may allow the implementation of therapeutic interventions and avoid the inappropriate exposure to nephrotoxic agents, which can slow the CKD progression to the terminal stage. Another important aspect is that the detection of CKD also identifies an important risk factor for cardiovascular disease. An additional advantage of an early diagnosis is to facilitate the adjustment of medication dose and allow better preparation for renal replacement therapy if indicated[3].

The presence of the following risk factors determines the screening for CKD in adults[4]:

- History of diabetes, hypertension, cardiovascular disease (CVD), human immunodeficiency virus (HIV) or hepatitis C virus infection, malignancy, autoimmune diseases, nephrolithiasis, or recurrent urinary tract infections.
- Family history of renal disease.

Patients selected for CKD assessment should undergo:

- Measurement of serum creatinine and GFR estimate by mathematical formulae;
- Determination of albuminuria, for which the preferred method is the measurement of the albumin/creatinine ratio in the urine of an isolated urine sample due to its ease and good correlation with the excretion in the 24-hour urine[5];
- Imaging exam, particularly an ultrasound of the kidney and urinary tract.

Some practical aspects of detecting CKD should be remembered[6]:

- The detection of CKD based on the estimated GFR is a more accurate assessment of renal function than the serum creatinine alone.
- Recent studies show that the EPI-CKD (Chronic Kidney Disease Epidemiology Collaboration) formula provides a more accurate prediction of

prognosis of renal outcomes and presents less bias that the MDRD (Chronic Kidney Disease Epidemiology Collaboration equation) formula.
- The albumin/creatinine ratio in the urine of an isolated sample is a more sensitive and specific marker of CKD than the protein/creatinine ratio.

EPIDEMIOLOGY

CKD is very prevalent in the general adult population. Data from the United States estimate a prevalence of 13.1% among adults, which has increased over time[7]. In Brasil, estimates of the prevalence of the disease are uncertain[8]. A recent study reviewed the data available in the literature and found that the prevalence varied according to the method employed in the definition of the disease; by populational criteria, 3-6 million individuals are estimated to have CKD[9]. The 2017 census by the Brazilian Society of Nephrology (BSN) reported that the total estimated number of patients on dialysis was 126,583, and the national estimates of the prevalence rates and incidence of patients under dialysis treatment per million population (pmp) was 610[10].

In addition to being highly prevalent, CKD is associated with a higher risk of cardiovascular disease, severity, and death. In fact, global data from 2013 showed that the reduction in GFR was associated with 4% of deaths worldwide, i.e., 2.2 million deaths. More than half of those deaths were due to cardiovascular causes, while 0.96 million were related to end-stage renal disease[11]. The aforementioned SBN census found a gross annual mortality rate of 19.9% on dialysis.

REFERRAL TO A NEPHROLOGIST

The referral of patients with chronic renal dysfunction to a nephrologist varies according to the characteristics of the health care system of each region, which are oftentimes not uniform, even in the same country. However, the following characteristics usually indicate the necessity of follow-up with a nephrologist[12]:

1. GFR <30 mL/min/1.73 m^2.

2. A decrease greater than or equal to 25% in the GFR.

3. Progression of the CKD with a sustained decrease in the GRF of more than 5 ml/min per year.

4. A consistent finding of significant albuminuria.

5. Persistent unexplained hematuria.

6. Secondary hyperparathyroidism, persistent metabolic acidosis, anemia due to a erythropoietin deficiency.

7. Hypertension resistant to treatment with four or more antihypertensive agents.

8. Persistent abnormalities of serum potassium.

9. Recurrent or extensive nephrolithiasis.

10. Hereditary kidney disease or unknown cause of CKD.

ROUTINE TREATMENT AND MANAGEMENT

The care of CKD patients includes:
- slowing the progression of CKD;
- treat complications related to the pathology, such as anemia, mineral and bone disorder, hydroelectrolytic disorders, metabolic acidosis, and cardiovascular disease;
- prepare the patient for renal replacement therapy (RRT);
- establish a immunization routine, especially for hepatitis B.

It is important to highlight that, in all levels of treatment, it is necessary to have a multidisciplinary team, particularly of nutrition, nursing, psychology, and social assistance.

Routine for the assessment and management of CKD progression

The evaluation of CKD progression is based on the evaluation of three aspects: decline in renal function in patients who were monitored in a longitudinal way with comparable methods; occurrence of renal failure, defined by the initiation of RRT; symptoms or complications of decrease of renal function and the development or worsening of proteinuria, particularly in diabetic nephropathy[1,2].

Data from the literature with approximately two years of follow-up of patients with CKD show that the average decrease in the glomerular filtration rate was 4-5 mL/min/year and that 85% of the patients had this average decline[13]. Therefore, we must periodically evaluate the decrease of the glomerular filtration rate (GFR), and consider a decrease greater than 5 ml/min/1.73 m^2/year[2] to be an indicator of accelerated progression. In Table 4, we suggest a frequency of monitoring; however, this scheme should be tailored according to the clinical status of the patient and the underlying renal disease.

TABLE 4. FREQUENCY OF FOLLOW-UP (NUMBER OF TIMES PER YEAR), ACCORDING TO THE GFR AND LEVEL OF ALBUMINURIA (ADAPTED FROM 3); GFR: GLOMERULAR FILTRATION RATE IN ML/MIN/1.73 M².

		Albuminuria		
	GFR	<30 mg/g	30-300 mg/g	>300 mg/g
Stage 1	≥90	1 if CKD	1	2
Stage 2	60-89	1 if CKD	1	2
Stage 3A	45-59	1	2	3
Stage 3B	30-44	2	3	3
Stage 4	15-29	3	3	4 or more
Stage 5	<15	4 or more	4 or more	4 or more

In general, the strategies used to reduce the progression of CKD are:

- use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with proteinuria above 500 mg/24 hours;
- reach target blood pressure below 130x80 mmHg;
- reach levels of glycated hemoglobin lower than 7% for diabetic patients;
- protein restriction indicated and managed by a nutritionist;
- correction of metabolic acidosis;
- stimulation for smoking cessation.

In addition, it is essential to assess the presence of factors of exacerbation of CKD, such as volume depletion, use of nephrotoxic substances, such as iodinated contrast, antibiotics, non-steroidal anti-inflammatory drugs, and obstruction of the urinary tract.

Routine for the evaluation of anemia in CKD

Anemia is a frequent complication in individuals with CKD[14], and the erythropoietin deficiency is its most common factor, together with iron, folic acid, and vitamin B12 deficiency. Therefore, it is part of the routine treatment of CKD patients to investigate the presence of anemia and indicate and follow-up its treatment.

For patients without anemia, the hemoglobin concentration should be requested when clinically indicated or according to the suggestion presented in Table 5[14].

For patients with anemia, defined by hemoglobin lower than 13 g/dl for men and 12 for women[14], hemoglobin concentration tests should be requested when clinically indicated or every three months for patients in stages III to V of CKD.

For patients under treatment for anemia with iron replacement and/or using erythropoiesis-stimulating agents, the hemoglobin and iron control must be done at every patient consultation or at least every three months.

Routine for the evaluation of mineral and bone disorder in CKD

Mineral and bone disorder in CKD is defined as a set of changes in the mineral metabolism of CKD patients, including renal osteodystrophy, a histological manifestation of the disease.

To diagnose mineral and bone disorder in CKD, it is necessary to determine the serum levels of calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone (PTH), in addition to venous blood gas. These examinations should be performed in all CKD patients with GFR below 60 ml/min/1.73 m². The frequency of the exams must be based on the stage and risk of progression of CKD, as suggested in Table 5[15].

Another aspect that could be part of the routine treatment is the assessment of vitamin D deficiency since its incidence is high in CKD under conservative treatment[16] and is associated with the progression of hyperparathyroidism, lower bone mineral density, and risk of fractures[17,18]. In addition, vitamin D deficiency has been associated with changes in the immune response, insulin resistance, changes in vascular function, and cardiomyopathy[19].

Routine for the evaluation of metabolic acidosis and electrolytic changes in CKD

Metabolic acidosis occurs in most CKD patients when the glomerular filtration rate is less than 30 ml/min[20]. It is usually mild to moderate, with bicarbonate ranging between 12 and 22 mEq/L.

The benefits of correcting metabolic acidosis have been described in the literature. In fact, Brito-Ashurst and col.[21] evaluated 134 patients with CKD (creatinine clearance of 15 to 30 ml/min/1.73 m²) and serum bicarbonate between 16 and 20 mmol/L and found that the supplementation with bicarbonate slowed progression to the final stages of CKD, as well as improving the nutritional status of patients.

The determination of bicarbonate should be routinely done according to the stage of CKD, and the target level of bicarbonate must be greater than or equal to 22 mEq/L; alkaline salts should be used to achieve this target.

The main electrolyte disorder in CKD patients under conservative treatment is hyperkalemia.

The measurement of potassium levels should be done at every patient consultation, and, when hyperkalemia is detected, it is important to assess errors in diet, medications that can lead to hyperkalemia, the presence of metabolic acidosis, and question the use or dose increase of potassium-sparing diuretics.

Routine for the evaluation of cardiovascular disease in CKD

Cardiovascular disease (CVD) is the main cause of morbidity and mortality among the population with CKD[22]. Based on data from the literature, all patients with CKD should be considered at high risk for CVD, evaluated based on "traditional" and "non-traditional" (related to uremia) risk factors for CVD, and treated for the reduction of modifiable cardiovascular risk factors[23].

The following can be established as routine identification of CVD in these patients: yearly electrocardiogram and echocardiogram, and non-invasive tests, such as myocardial scintigraphy or stress echocardiography for patients who are symptomatic or have changes in segmental motility, with three or more traditional risk factors, or with a history of peripheral vascular insufficiency and cerebral vascular accident. In the presence of clinical symptoms and positive results in invasive or non-invasive exams, it is recommended to refer the patient to a specialized cardiac assessment.

In addition to identifying CVD, it is important to establish strategies to reduce risk factors, such as control of hypertension and diabetes, dyslipidemia assessment, smoking cessation, stimulation of physical exercises, treatment of anemia, and reduction of proteinuria levels.

Routine for hepatitis B immunization in CKD

According to the 2012 dialysis census by the SBN, the prevalence of hepatitis B in patients undergoing hemodialysis in Brasil is 1%. The correct application of a vaccination scheme is one of the main factors responsible for the reduction in the incidence of this infection in dialysis. It is worth pointing out that the response to vaccination in this population varies from 40% to 60%, and that the maintenance of the antibodies titer is not sustained. It is important to establish a routine vaccination for non-immune patients. One of the proposed schemes carried out in basic health units is to make four applications with a double dose (4 ml) of Engedrix B© on the deltoid muscle in months 0, 1, 2, and 6. After 30 days of the end of the scheme, the AntiHbs are monitored - if lower than 10 miu/ml, a booster dose is recommended with a double dose (4 ml) of Engedrix B©; the maximum booster doses allowed are three.

Routine to prepare for renal replacement therapy

The decision to start dialysis in a CKD patient involves considering subjective and objectives parameters by the physician and patient. There are no absolute laboratory values that indicate a requirement to begin dialysis. The following are considered when deciding to initiate RRT: aspects of quality of life, psychological aspects associated with the anxiety of undergoing complex therapy, the perception of the nephrologist on the health state of the patient, the decline of renal function, and the risks associated with renal replacement therapy.

In the follow-up of CDK patients that present a progressive decrease of renal function and in those with GFR less than 20 ml/min, it is essential to address the types of RRT, along with their Indications, advantages, and disadvantages. Once the patient has opted for a particular type of RRT and provided there are no medical contraindications, it is necessary to initiate the appropriate preparations, especially the manufacturing of the arteriovenous fistula for hemodialysis, peritoneal dialysis training, implantation of the Tenckhoff catheter, serology for hepatitis B, C, and HIV. If the patient is interested and meets the clinical conditions, they can also be forwarded to outpatient clinics specialized in pre-renal transplantation evaluation.

As soon as the patient presents very reduced GFR and/or compatible symptoms, such as nausea, vomiting, drowsiness, weight loss, hiccups, among others, we must request RRT to the competent organs of the Single Health System or through complementary medical services. It is important to emphasize that if these symptoms are accentuated or if there are changes in laboratory findings that indicate high risk, the patient must be referred to the urgent start of RRT.

In Table 5, we suggest a model of test grouping according to the risk of progression of CKD.

TABLE 5. ROUTINE OF EXAMS ACCORDING TO THE RISK OF PROGRESSION OF CKD.

Department	Low	Moderate	High	Very high
Renal function				
GFR	Every consultation	Every consultation	Every consultation	Every consultation
Urine 1	Yearly	Every six months	Every six months	Every six months
Proteinuria	Yearly	Every six months	Every six months	Every six months
Anemia				
Complete blood count	Yearly	Every six months	Every consultation	Every consultation
Iron	-	Every six months	Quarterly #	Quarterly #
Transferrin	-	Every six months	Quarterly #	Quarterly #
Ferritin	-	Every six months	Quarterly #	Quarterly #
Bone disease				
Ionized calcium	Yearly	Every six months	Quarterly	Every consultation
Phosphorus	Yearly	Every six months	Quarterly	Every consultation
PTH	-	Yearly	Every six months	Quarterly #
Metabolism				
Cholesterol	Yearly	CV Risk*	CV Risk*	CV Risk*
Triglycerides	Yearly	CV Risk*	CV Risk*	CV Risk*
Uric acid	Yearly	Every six months	Every six months	Every six months
Venous blood gas	-	Yearly	Quarterly	Every consultation
Glycemia	Yearly	If diabetes	Quarterly	Every consultation
Hb1Ac	-	If diabetes	Quarterly	Quarterly
TGO, TGP; CPK	Consultation[&]	Consultation[&]	Consultation[&]	Consultation[&]
Nutrition				
Urea clearance	-	Every six months	Quarterly	Bimonthly
Urine Sodium	Yearly	Every six months	Every six months	Every six months
Potassium	Yearly	Every consultation	Every consultation	Every consultation
Viral profile				
HbsAg	-	Yearly	Yearly	Dialysis**
Anti-HbsAg	-	Yearly	Yearly	Dialysis**
Anti-Hbc	-	Yearly	Yearly	Dialysis**
Anti-HIV	-			Dialysis**
Anti-HCV	-			Dialysis**
Others				
Echocardiogram	Yearly	Yearly	Yearly	Yearly

GFR = estimated glomerular filtration rate or by 24-hour urine creatinine clearance; # if treatment; * according to the cardiovascular risk; ** at the moment of referral to dialysis; [&] if under treatment with statins or fibrates.

CONCLUSION

Chronic renal disease has an important impact on the morbidity and mortality of patients. The organization of the conservative treatment is crucial to slow the progression of kidney dysfunction, as well as to lessen the occurrence of complications, with a positive impact on the prognosis of the affected population. Another important aspect is the preparation for renal replacement treatment, which greatly facilitates the adaptation of patients to the chosen therapy.

PALAVRAS-CHAVE: *Doença renal crônica. Doença renal crônica estágio final. Tratamento conservador.*

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REVIEW ARTICLE

Fabry disease: genetics, pathology, and treatment

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http://dx.doi.org/10.1590/1806-9282.66.S1.10

SUMMARY

Fabry disease (FD) is a recessive monogenic inheritance disease linked to chromosome X, secondary to mutations in the GLA gene. Its prevalence is estimated between 1:8,454 and 1:117,000 among males and is probably underdiagnosed. Mutations in the GLA gene lead to the progressive accumulation of globotriaosylceramide (Gb3). Gb3 accumulates in lysosomes of different types of cells of the heart, kidneys, skin, eyes, central nervous system, and gastrointestinal system, and may lead to different clinical scenarios. The onset of symptoms occurs during childhood, with acroparesthesia, heat intolerance, and gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and neuropathic pain. Subsequently, symptoms related to progressive impairment appear, such as angiokeratomas, cornea verticillata, left ventricular hypertrophy, myocardial fibrosis, proteinuria, and renal insufficiency. The latter being the main cause of death in FD. The gold standard for diagnosis is the genetic analysis in search of mutation, in addition to family history. In homozygous patients, the enzyme activity can also be used. Once the diagnosis is confirmed, the patient and their family should receive genetic counseling. The treatment, in turn, currently focuses mainly on replacing the enzyme that is absent or deficient by means of enzyme replacement therapy, with the purpose of avoiding or removing deposits of Gb3. Chaperones can also be used for the treatment of some cases. It is considered that the specific treatment should be initiated as soon as a diagnosis is obtained, which can change the prognosis of the disease.

KEYWORDS: *alpha-Galactosidase. Fabry Disease. Renal Insufficiency Chronic. Proteinuria. Enzyme Replacement Therapy.*

INTRODUCTION

Fabry disease (DF) is an inborn error of metabolism that causes partial or total inability of catabolizing lipids. It is caused by mutations in the gene that codifies the lysosomal enzyme α-galactosidase A (α-GAL), leading to the progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3). Gb3 accumulates in lysosomes of different types of cells and can affect the heart, kidneys, skin, eyes, central nervous system, and gastrointestinal system. It has a progressive nature and may lead to organ failure[1-4].

The process of lysosomal involvement is likely to begin as early as in the fetal stage; however, the first symptoms usually appear after 3 years, or before in males, since it is an inheritance linked to the chromosome X. The manifestation of the disease in heterozygous women can vary from asymptomatic to a condition as serious as in males[1-4].

In 1898, the first reports of the disease were made by two dermatologists, William Anderson and Johannes Fabry, who described patients with "angiokeratoma corporis diffusum" in independent studies.

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However, it was only in 1947, after the finding of abnormal vacuoles in the blood vessels of two patients who died of kidney failure, that the condition was classified as a deposit disease. In 1967, the relationship between the deficiency of the α-GAL enzyme and the etiology of the disease was established [5-8].

EPIDEMIOLOGY

The estimated prevalence of FD varies from 1:8,454 to 1:117,000 in males, and it has been described in various ethnic groups, with no predilection identified to date[2,9,10)]. It should be noted that recent studies in newborns found a high incidence, ranging from 1:3,100 in newborns in Italy to 1:1,550 in newborns of Taiwan. Therefore, it is likely that the disease had been underdiagnosed[11.12].

There are reports of FD prevalence of 0.019% and 0.017% in in dialysis record programs in Europe and in the United States, respectively[13]. In Brasil, few studies have assessed the prevalence of FD in the dialysis population. In studies carried out between 2007 and 2008 in a small number of patients, the prevalence ranged from 0.36% to 0.57%[14-16]. In a more recent study, conducted in Bahia with 2,583 male patients on hemodialysis, the prevalence rate of FD was 0.12%[17].

GENETIC

FD is a monogenic, recessive inheritance disorder linked to the X chromosome, secondary to a mutation in the GLA gene. This gene is responsible for encoding the α-GAL enzyme and is located on the long arm of the X chromosome at the Xq22 position. Most cases are hereditary, and cases of *new* mutations are rare[1,18,19]. Over 900 different mutations have been described as the cause of the disease[20].

α-GAL has approximately 429 amino acids and is responsible for breaking Gb3 into galactose and lactosylceramide in the lysosomes. Therefore, in patients with FD, GB3 is accumulated in different tissues. It has a predilection for the vascular endothelium and smooth muscle cells of the cardiovascular system and for kidney podocytes, which explains the predominance of clinical manifestations affecting these organs[21-24].

The gene that encodes α-GAL has approximately 12 kb and seven exons. FD can be caused by several types of molecular mutations in this gene: missense (57%), nonsense 11%), partial deletions 6%), insertion (6%), and defects in the processing of RNA, which lead to abhorrent splicings (6%). The correlation between genotype and phenotype is complex, since the same mutation may determine different clinical manifestations. This could be attributed both to environmental factors and the blood group. Patients of blood groups AB or B may have more severe disease presentations since they have an additional accumulation of glycosphingolipids in the membrane of erythrocytes of blood group B[25].

CLINICAL FINDINGS

Patients with FD can present a spectrum of clinical manifestations, ranging from classic FD in males, to the asymptomatic disease in females, with several variants between these two extremes. The clinical signs and symptoms are subtle at first, which can hinder or delay the diagnosis, especially if there is no family history[1,26,27].

The classical presentation of FD is the more severe phenotype and occurs predominantly in men, with activity absent or minimal residual activity of the α-GAL enzyme. The onset of symptoms occurs during childhood or adolescence, with acroparesthesia, heat intolerance, and gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain. Between the third and fourth decades of life, the symptoms related to the progressive systemic impairment appear, i.e., changes in cardiac, renal, and cerebral function[1,3,4,26,27].

The cutaneous involvement is characterized by the presence of angiokeratomas, small telangiectasias, usually in the buttocks and thigh region. The impairment of the nervous system, in addition to the acroparesthesias, is characterized by hypohidrosis and cerebrovascular accidents. Ocular alterations are secondary to the Gb3 deposits in the cornea, causing an opacity called cornea verticillata[1,3,4,26,27].

Cardiac alterations increase with age, which possible left ventricular hypertrophy, fibrosis of the myocardium, valve regurgitation mainly mitral), arrhythmias, and even coronary disease. The mild phenotype of FD is characterized primarily by cardiac alterations and is compatible with residual activity of about 5-10% of the α-GAL enzyme[1,3,4,26,27].

The presentation in women is highly variable, ranging from asymptomatic patients to scenarios very similar to classic FD. Ocular lesions are com-

mon, and cornea verticillata may be the only sign in asymptomatic women[1,3,4,26,27].

Kidney failure is the main cause of death. The most prevalent change is proteinuria, which occurs in 80% of men left untreated in the fourth decade of life. In addition, patients can develop end-stage kidney disease ESKD)[1,3,4,26,27].

Renal involvement usually starts with microalbuminuria, followed by proteinuria in the second or third decades of life. Its progression is similar to diabetic nephropathy and contributes to the progression of chronic kidney disease. When patients are left untreated, it evolves to ESKD, usually between the fourth and the fifth decade of life. In general, the severity of the renal condition correlates with the residual enzyme activity[1,28-30)]. In a previous study, when enzyme activity was lower than 1%, renal disease was diagnosed at age 22 and, when the activity was between 1% and 12%, at age 47[30].

The study by Brandon et al. allowed a better understanding of the renal involvement; however, it is important to emphasize that in it, no patient survived beyond 60 years. A total of 82.5% of the patients developed proteinuria, and 22% developed chronic kidney disease. The onset of proteinuria was, on average, at around 34 years of age. Nephrotic proteinuria occurred only in 18% of patients, but nephrotic syndrome was not a common finding. In addition, urinary protein electrophoresis showed that proteinuria was of glomerular origin albuminuria ≥50%), regardless of the degree of proteinuria[2.30].

Another highlight of this study was establishing that, in FD patients with renal involvement, the average time of progression to ESKD was four years. That is a very rapid progression, with an estimated annual decrease in glomerular filtration rate of approximately 12.2 ml/min. Even when compared to other causes of chronic kidney disease, such as diabetes and hypertension, this rate of decline is very high[30].

FD may cause Gb3 deposits in the tubules, particularly in the distal tubules, causing distal renal tubular acidosis and isosthenuria. However, there are also reports of the involvement of the proximal convoluted tubule, causing Fanconi syndrome[1.28].

Due to this broad renal involvement, many patients develop ESKD, requiring renal replacement therapy. Considering that renal transplantation is the best therapy, it can and should be performed in these patients, since it increases their survival. Although there is a deposit of Gb3 in the transplanted kidney, patients do not develop graft dysfunction. The deposits appear to be insufficient to cause impairment of renal function. Recent studies have demonstrated that renal transplantation normalizes only the urinary levels of α-GAL, not the plasma levels. Thus, renal transplantation has no effect on the progression of non-renal manifestations of FD[30.31].

RENAL PATHOLOGY

The accumulation of Gb3 occurs in virtually all types of kidney cells: endothelial, tubular, mesangial, and podocytes, with a predilection for the latter. Therefore, FD can cause tubular, vascular, and glomerular disorders[1.30].

The definitive diagnosis of renal involvement due to FD is made by renal biopsy. It is an important tool in the diagnosis and, according to some, the evaluation of treatment efficacy. The Gb3 deposits are found both in the vascular and glomerular compartments, as well as in the interstitial-tubule. These deposits are correlated with the severity of the morphological and functional renal changes[2,29,30].

Using optical microscopy, it is possible to observe vacuolizations in the cytoplasm of cells, especially of podocytes Figures 1a and 1b), with subsequent impairment of mesangial and endothelial cells. With the progression of the disease, there may be an increase in the mesangial matrix associated with glomerular sclerosis, in addition to interstitial fibrosis and tubular atrophy. Using immunofluorescence, deposits of immune complexes are generally not found[29.30].

Whereas using electronic microscopy, deposits of Gb3 strongly stained with blue are found inside the cells Figure 1c). The deposits inside the lysosomes are electron-dense structures intercalated with electron-lucid lamellas, forming “myelin figures” or “zebra bodies” Figure 1d). The cell with most deposits is the podocyte. The deposits of Gb3 affect the structure of its cytoskeleton, promoting erasure of pedicels, and, thus, altering its permeability and leading to the loss of proteins[29.30].

Diagnosis and biomarkers

The diagnosis of FD usually takes some time, especially in the pediatric population, since the symptoms are often nonspecific, and the disease is not widely known. In addition, renal and cardiac dysfunction appear only in more advanced stages of the

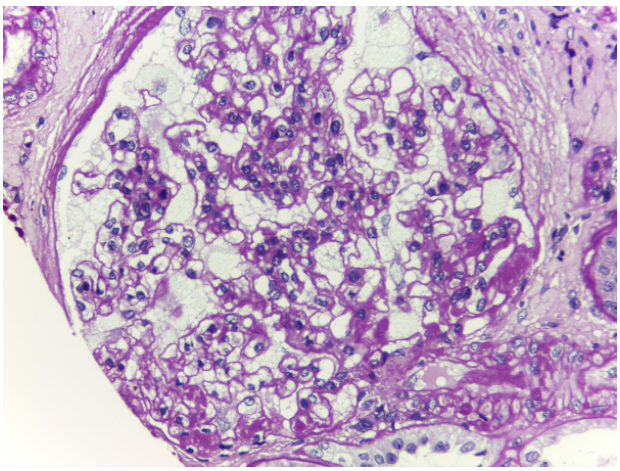

FIGURE 1A - Optical microscopy showing podocyte vacuolization SBP – (400x).

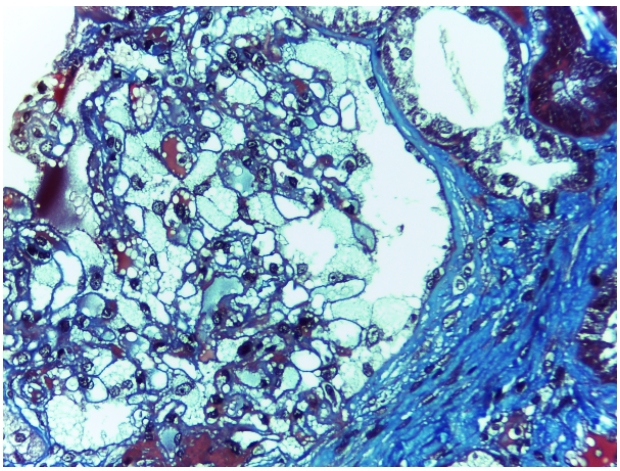

FIGURE 1B- Optical microscopy showing vacuolated podocytes Masson's trichrome – (400x).

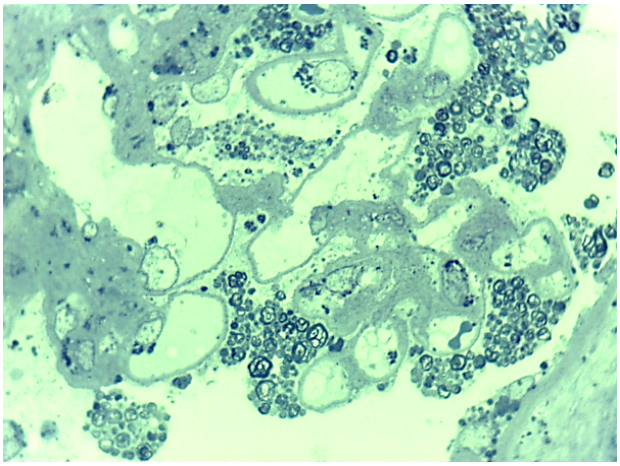

FIGURE 1C - Optical microscopy with semi-thin planes showing corpuscles of inclusion in podocytes, endothelial, and mesangial cells Toluidine Blue – (1,000x).

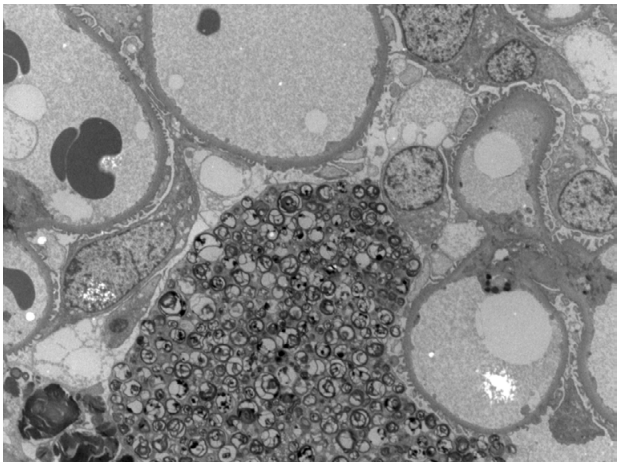

FIGURE 1D - Electronic microscopy showing lamellar inclusions in a podocyte, endothelial cell, and visceral epithelium (3,000x).

disease. Recent data suggest delays of up to 15 years in the diagnosis[1].

Genetic investigation and family history are crucial for the diagnosis. In the absence of such information, the suspected diagnosis is based on clinical information, such as the presence of angiokeratomas or opacity of the cornea. The finding of cornea verticillata has increasingly contributed to the diagnosis, as it can be observed since childhood and even in patients with normal enzyme dosage of α-GAL[1,32-35].

The images can be used to document areas of ischemia or cerebral vasculopathy. An echocardiogram is useful in the search for hypertrophy of the left ventricle, and an electrocardiogram can be used to evaluate arrhythmias. However, if the clinical examination raises suspicion of FD, the biochemical examination and genetic confirmation are required[1,32-35].

In homozygotes, the enzyme activity can be used for diagnosis. The levels of α-GAL usually are low, and a finding of activity <15% constitutes a diagnostic of the disease. However, in female patients and in some variants in males, it is common to have false-negative results[1,32-35].

Another form of diagnosis uses the dosage of Gb3 in urine and blood. If high values are found, these are suggestive of the disease. Some women test normal for enzyme activity, but have high levels of Gb3 in urine, with that it is possible to distinguish a patient who has the condition from one who does not[1,32-35].

However, the genetic analysis in search of mutations in the α-GAL gene is the gold standard test to confirm the diagnosis of FD in both sexes. The sequencing of the coding region of the gene can detect a mutation that causes the disease in more than 97% of the patients. However, this analysis has a high cost, which hinders its widespread use[1,32-35].

Therefore, a new biomarker was sought to assist in the diagnosis and monitoring of the therapy. The answer found was to measure the product of Gb3 degradation, the globotriaosylsphingosine (lysoGb3). In a prospective study with 124 patients, the levels of lysoGb3 were correlated to the clinical condition, type of mutation, as well as to changes in imaging examinations, proving to be a reliable predictor of the disease. In another study, a high level of lysoGb3 was found even in women with the normal activity of α-GAL who, subsequently, had a clinically significant presentation of the disease, thus showing advantages in relation to the direct measurement of GB3. In addition, it was demonstrated that the levels of lysoGb3 decrease with enzyme replacement therapy (ERT). Thus, lysoGb3 has been accepted as a more accurate marker of disease activity. However, long-term data still need to be analyzed[36.37].

The prenatal diagnosis is also possible, since the accumulation of Gb3 starts early, still in intrauterine life. When there is a XY fetus, it is possible to demonstrate low α-GAL activity through a biopsy of the chorionic villi or amniotic cell cultures[1,32-35].

Biopsies of different tissues of FD patients can also suggest the disease. Using optical microscopy, the presence of cytoplasmic vacuoles containing the lipids can be seen. Using electronic microscopy, lysosomal inclusions are seen, with the lamellar configuration. When these findings are not conclusive, immunoelectron microscopy can be used to search for anti-Gb3 antibodies[1,32-35].

Genetic counseling

Once the FD diagnosis is confirmed, the patient and their family should receive genetic counseling. Family screening is useful to identify additional cases. In addition, counseling is essential to inform about the risk of offspring inheriting the disease. All daughters of a homozygote father will inherit the disease since they will inherit the X from the father who has the mutation; none of the sons will inherit the disease, since they will receive only the Y chromosome from the father. Half of the children of a woman who carries the mutation will be affected, given that she has one normal X and one X with the mutation[32.38].

Treatment and prospects

The treatment of FD patients focuses mainly on replacing the enzyme that is absent or deficient by means of ERT, with the purpose of avoiding or removing deposits of Gb3. The ERT currently used is based on the discovery that cells can incorporate an enzyme from the extracellular medium and use it in its normal metabolism[1,39-41].

In addition, patients should receive specific treatment for the organs affected to control symptoms. Some important measures include: nephroprotection with the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) to control proteinuria; pain control with the use of analgesics and opiates, avoiding the use of anti-inflammatory agents; and control of blood pressure, with a preference for the use of ACEI or ARB. Prophylaxis with anticoagulants and antiplatelet agents can also be considered in patients with a history of ischemia. Another very important factor is to instruct the change of habits and lifestyle, including cessation of smoking, reduction of sodium intake, and practice of physical activity[1.39].

In general, it is considered that all male patients affected by the classical presentation of FD should receive ERT. It should be started as soon as the diagnosis is made, regardless of whether or not there are clinical manifestations since the deposit of Gb3 starts as early as in intrauterine life. Women and patients with atypical presentations should receive ERT if there is a clinical manifestation. It is also important to stress that even patients who are already undergoing dialysis should be treated since ERT can reduce cardiovascular and neurological complications[1,39,40].

Two formulations of recombinant human α-GAL have been developed: algasidase alfa and algasidase beta. Both proteins appear to be equally effective and are administered intravenously every 15 days. There are no studies with a definitive recommendation for the duration of therapy, but it is believed that it is necessary for the entire life of the patient, since the amount of the enzyme in the plasma is rapidly depleted. The treatment is expensive. In 2005, for example, the estimated retail cost for the therapy with the first formulation for a year was US$ 160,000 in Europe and $206,000 in the United States. The tolerance to ERT is normally good, except for mild or moderate reactions associated with the infusion[1,39,40].

Clinical studies have found a decrease in the frequency of pain episodes, cardiac mass, and Gb3 deposits in the skin and kidneys, with even improvement of renal function in some patients. There is also evidence that ERT improves sudoresis and gastroin-

testinal symptoms. However, there are still no studies that prove the decrease in mortality. In addition, the formation of antibodies against the enzyme is described, which reduces its effectiveness in the long term[1,39,40].

There are other therapies under study. One of them included chaperones and would be useful to patients that have unstable variants of the mutant α-GAL. These variants are retained in the endoplasmic reticulum due to its defects but still maintain residual enzymatic activity. Small synthetic molecules that act as a chaperone are used to recover residual α-GAL, transporting it to the lysosomes and, thus, increasing its activity[1,41,42].

The drug already produced with this purpose is the migalastat, which is administered orally, thereby avoiding the need for fortnightly infusions. However, it can only be used in 30-50% of patients with FD that have specific mutations. A first randomized clinical trial on migalastat showed an effect comparable to that of ERT on renal function and cardiac outcomes. Another study analyzed the combination of this chaperone with ERT and showed promising results, with an increase from 1.2 to 5.1 times in enzymatic activity in comparison to ERT alone. Further studies are still needed to confirm these findings and evaluate long-term results[43].

Another option would be the use of reversible competitive inhibitors of α-GAL. These, from the inside of the cells, would determine an increase in the enzyme activity. In addition, these substances seem to accelerate the transportation, maturation, and stability of the mutant enzyme. Again, these would only be useful in patients with residual enzymatic activity[1,42].

Finally, FD seems to be a disease suitable for gene therapy. This technique aims to add a normal gene of α-GAL to the DNA of the patient, which would then start producing a normal enzyme. Thus, definitive treatment for the disease is proposed. This therapy is promising but is still under the testing of experimental models[1,44].

CONCLUSION

FD is a lysosomal storage disorder that generates a systemic and severe condition, with onset in childhood, and that should be promptly diagnosed since there is an effective treatment. Delays in diagnosis certainly contribute to high morbidity and mortality due to this disease, which should be more well known by health professionals. It stands out, finally, the extreme importance of genetic counseling in this type of disease. Future possibilities include the early diagnosis and perhaps even cure by means of gene therapy.

Acknowledgments

We would like to thank the illustrious professor dr. Luiz Antônio Ribeiro Moura for the contribution by providing the figures.

Contribution of the authors

Thaíza Passaglia Bernardes - Drafting of the text.
Renato Demarchi Foresto; Gianna Mastroianni Kirsztajn - Drafting and revision of the text.

PALAVRAS-CHAVE: α-*galactosidase A. Doença de Fabry. Doença renal crônica. Proteinúria. Terapia de reposição enzimática.*

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REVIEW ARTICLE

SGLT-2 inhibitors in diabetes: a focus on renoprotection

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http://dx.doi.org/10.1590/1806-9282.66.S1.17

SUMMARY

Type 2 diabetes mellitus is an important public health problem, with a significant impact on cardiovascular morbidity and mortality and an important risk factor for chronic kidney disease. Various hypoglycemic therapies have proved to be beneficial to clinical outcomes, while others have failed to provide an improvement in cardiovascular and renal failure, only reducing blood glucose levels.

Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors, represented by the empagliflozin, dapagliflozin, and canagliflozin, have been showing satisfactory and strong results in several clinical trials, especially regarding the reduction of cardiovascular mortality, reduction of hospitalization due to heart failure, reduction of albuminuria, and long-term maintenance of the glomerular filtration rate. The benefit from SGLT2 inhibitors stems from its main mechanism of action, which occurs in the proximal tubule of the nephron, causing glycosuria, and a consequent increase in natriuresis. This leads to increased sodium intake by the juxtaglomerular apparatus, activating the tubule glomerular-feedback and, finally, reducing intraglomerular hypertension, a frequent physiopathological condition in kidney disease caused by diabetes. In addition, this class of medication presents an appropriate safety profile, and its most frequently reported complication is an increase in the incidence of genital infections.

Thus, these hypoglycemic agents gained space in practical recommendations for the management of type 2 diabetes mellitus and should be part of the initial therapeutic approach to provide, in addition to glycemic control, cardiovascular outcomes, and the renoprotection in the long term.

INTRODUCTION

Type 2 diabetes mellitus is considered an important public health problem that is aggravated by a context of a populational aging, sedentary lifestyle, and accumulation of body fat. In 2014, the estimated prevalence of the disease was 422 million, 8.5% of the world population, which is twice the number from the beginning of the 1980s. In addition, 1.5 million deaths recorded in 2012 were attributed to diabetes, 43% of which were individuals aged less than 70 years. In the long term, the disease is an important risk factor for retinopathy, cardio-cerebrovascular disease, and kidney disease[1].

Chronic kidney disease (CKD) has worldwide prevalence estimated at 10%, with a predilection for individuals over 60 years old[2], a condition with complex and multifactorial physiopathology, in addition to a systemic impact in several organs and apparatus. Hospitalization, risk of death, and cardiovascu-

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lar events are increased in CKD, especially with the progression of the disease to stages of glomerular filtration rate lower than 45 ml/min per 1.73 m^2 [3].

Diabetes mellitus has a relevant impact on cardiovascular morbidity and mortality, especially when associated with renal disease[4]. In Brasil, the magnitude of the problem is visible in the statistics of end-stage kidney disease: 30% of patients on a permanent dialysis program have diabetes as the etiology, which is the second main cause for end-stage kidney disease requiring renal replacement therapy[5].

The treatment of this metabolic disorder is represented by an extensive list of drugs of different pharmacodynamics, whose main goal is to optimize glycemic control. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, a class of oral hypoglycemic agents that have recently become popular, have an insulin-independent effect. Their main mechanism of action is to inhibit SGLT2 in the proximal portion of the nephron, with consequent glycosuria and natriuretic effect and attenuation of glomerular hyperfiltration, improvement of blood pressure levels, and weight reduction. Thus, this class of medication has been a surprise in several trials due to their broad renal and cardiovascular benefits[6].

Next, we review this class of medication, bringing the major clinical outcomes described in the literature, with a focus on renoprotection.

THE KIDNEY AND THE GLUCOSE METABOLISM

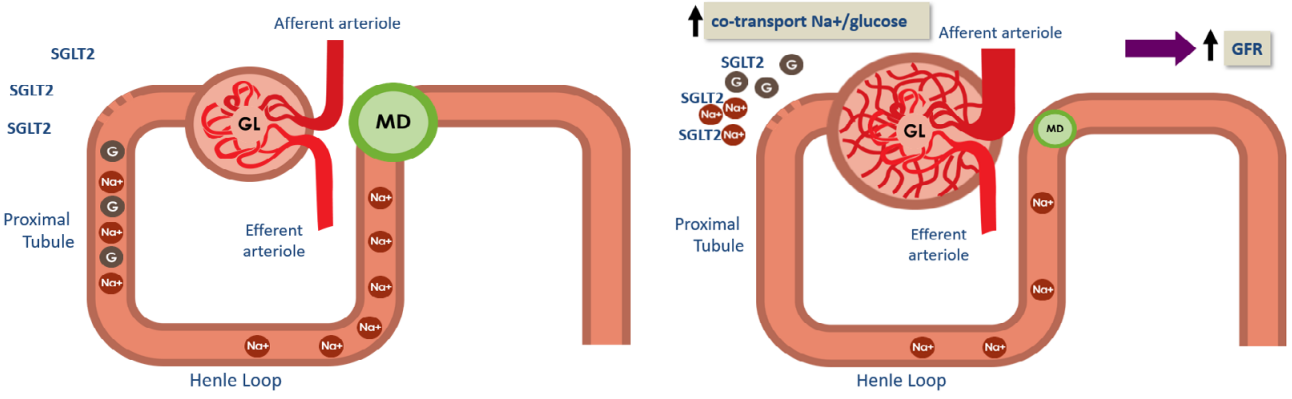
Approximately 80% of endogenous glucose is of hepatic origin, while 20% is renal. In the kidney, the production occurs mainly in cortical cells by adrenergic stimulation, while the glucose consumption occurs significantly in the renal medulla. With a normal glomerular filtration rate (180 liters per day) and glycemia around 100 mg/dL, 180 g of glucose is filtered daily, with total reabsorption in the proximal tubule level[7]. This balance occurs by the SGLT2 action in the S1 segment of the proximal tubule, with 80% to 90% participation in the glucose reabsorption, while SGLT1 has minimum participation of 10-20% in the segments S2 and S3. The function of SGLT 1 and 2 depends on the Na^+-K^+-ATPase pump of the basolateral membrane: the sodium (Na) output from the pump reduces intracellular Na, causing the sodium from the tubular to enter the cell with the glucose; this finally reaches the interstitium at the basolateral membrane through the glucose transporter (GLUT)[8]. A glucose value of 180 mg/dL is considered to be the limit for renal reabsorption capacity; anything above that will cause glycosuria[9].

RENAL INVOLVEMENT IN DIABETES MELLITUS

Kidney disease caused by diabetes is characterized by structural and functional alterations, whose manifestations include albuminuria and decreased glomerular filtration rate[10]. The initial pathophysiological events stages that lead to CKD progression are divided into early (hemodynamic and metabolic) and late (cell and tissue remodeling)[11].

In a scenario of hyperglycemia, tubular glucose reabsorptive capacity (Tmg) increases with greater glucose reabsorption and, therefore, sodium. Thus, a lower concentration of sodium chloride reaches the macula densa and, through tubule-glomerular feed-

FIGURE 1. NORMAL GLOMERULAR HEMODYNAMICS (1A) AND KIDNEY DISEASE CAUSED BY DIABETES (1B).



back, resembling a situation of renal hypoperfusion, the renin-angiotensin-aldosterone system (RAAS) is activated with efferent arteriolar vasoconstriction and afferent arteriolar vasodilation, generating increased intraglomerular and GFR pressure; over time, this hemodynamic mechanism results in injury of the glomeruli[12] (Figure 1). The consequences of diabetes mellitus, such as exacerbated production of growth factors and the aforementioned changes in glomerular hemodynamics, lead to hyperfiltration and glomerular hypertension, renal hypertrophy, and changes in the glomerular structure, with clinical manifestation typical of kidney disease caused by diabetes: albuminuria and hypertension.

SGLT2 INHIBITION AS A THERAPEUTIC TARGET IN DIABETES MELLITUS AND IN NEPHROPROTECTION

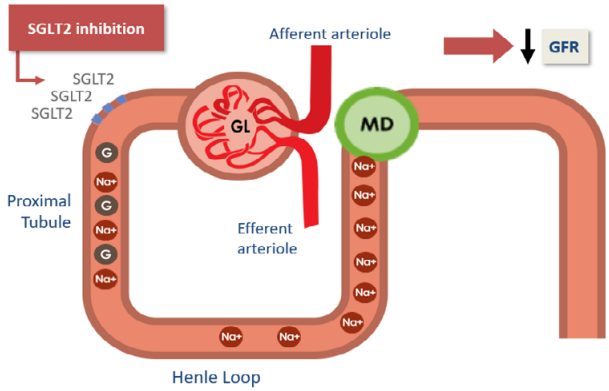
Although this is a current issue that has been frequently discussed in recent years, the renal SGLT inhibition was originated in the 1980s, still in experimental studies. On that occasion, it was found that the administration of Phlorizin, a non-selective SGLT inhibitor, reduced hyperglycemia in rats, in addition to improving insulin resistance; however, there was reduced bioavailability, in addition to gastrointestinal effects that hindered its application in clinical studies[13]. This class of drugs has evolved and, currently, there are three main representatives of selective SGLT2 inhibitors: empagliflozin, dapagliflozin, and canagliflozin.

The glycosuria action of this class of medication is due to three mechanisms of action: the reduction of Tmg; reduction of glycosuria threshold; increase in the linear transition between reabsorption and renal excretion of glucose as the Tmg is reached[9]. When examined experimentally, the increase of glucose in urine occurred both in diabetic and normoglycemic patients, and the reduction of the glucose threshold appears to be the most significant pharmacological mechanism[14].

The lower glucose reabsorption at the proximal tubule increases the availability of sodium and chloride that reaches the distal portions of the nephron, especially the macula densa. Thus, the greater intake of sodium chloride by this structure leads to the local release of adenosine and, consequently, of intracellular calcium, generating afferent arteriolar vasoconstriction[15,16]. This results in a reduction of glomerular hyperfiltration and, consequently, of intraglomerular hypertension, attenuating albuminuria, which are primary pathophysiological components in the development of kidney disease caused by diabetes, which explains the medication benefits beyond the blood glucose reduction[17] (Figure 2).

In addition to the beneficial hemodynamic action, other effects also seem to contribute positively regarding the renal condition in diabetes mellitus; however, in a smaller proportion. The inhibition of SGLT2 reduces renal energy requirements, thus reducing renal hypoxia[18]. There is also an antioxidant, antifibrotic, and anti-inflammatory action due to the reduction of glycosylation products and the expression of inflammatory molecules[19]. Therefore, it is essential to stress the idea that the renal benefit from the SGLT2 action comes mostly from the glomerular hemodynamic effect to the detriment of the glucosuric effect alone, and, supposedly, hypoglycemic - which can vary from 0.4% to 1.1% of the glycated hemoglobin, in addition to reducing body weight[20].

FIGURE 2. GLOMERULAR HEMODYNAMIC EFFECT AS A RESULT OF SGLT2 INHIBITION.



RELEVANT CLINICAL STUDIES ON BENEFITS AND SECURITY

To date, three large clinical trials have studied the cardiovascular and renal benefits of SGLT2 inhibitors, namely: EMPA-REG Outcome (empagliflozin), CANVAS (canagliflozin), and DECLARE-TIMI 58 (dapagliflozin)[21-23]. More recently, CREDENCE assessed in a primary way the renal outcomes with the use of canagliflozin[24]; we have detailed such evidence, and the data are summarized in Table 1.

EMPA-REG Outcome was a clinical trial, double-blind, that randomized 7,028 patients with type

2 diabetes mellitus and established cardiovascular disease in 42 countries, who were divided into three groups: placebo, 10 mg, and 25 mg of empagliflozin, with a three-year follow-up. The medication was added to the standard therapy (metformin and other hypoglycemic agents, as indicated by the clinical context of each patient). In the empagliflozin group, for both doses used, there was a significant reduction of cardiovascular mortality, a 32% reduction of general mortality, in addition to a 35% reduction of hospitalization due to heart failure. However, for acute myocardial infarction (AMI) and fatal and non-fatal stroke, there were no statistically significant differences[21]. Subsequently, the population studied in the EMPA-REG Outcome was studied specifically for renal outcomes, i.e., progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy (RRT), and death due to kidney failure[25]. It is worth noting that most individuals (approximately 75%) had an estimated glomerular filtration rate (EGFR) above 60 ml/min/1.73 m², and 40% had an albuminuria/creatinine ratio (UACR) above 30 mg/g (population with incipient kidney disease, which limited more robust evaluations of the renal outcomes). Other than that, there were positive results in the aspects analyzed, and it was inferred that the patients in the group treated with empagliflozin had a reduction in the progression of the chronic kidney disease and lower incidence of clinically significant renal events. It was noted that, in both dose groups treated with the SGLT2 inhibitor, there was a decrease of up to 4 ml/min/1.73 m² in the first four weeks of treatment, which remained stable and without progression, unlike in the placebo group, in which there was a progressive decrease of eGFR during the period studied. This decrease in the first month of treatment is justified by the intraglomerular hemodynamic alteration, by the glomerular-tubule feedback mechanism with afferent arteriolar vasoconstriction, as previously explained. In regard to the safety of the treatment, the only significant finding was genital infection. The risk of worsening of renal function, dehydration, and fracture did not differ between the groups studied[25].

The CANVAS, a randomized, multicenter clinical trial that included 10,142 patients in two study designs (Canvas and Canvas-R), had as its primary outcome to analyze cardiovascular mortality, non-fatal AMI, and non-fatal stroke. The trial included patients with type 2 diabetes mellitus and established cardiovascular disease or with the presence of two risk factors for cardiovascular disease. In Canvas, there was randomization into three groups: canagliflozin 100 mg, canagliflozin 300 mg, and placebo, while in Canvas-R, there were two groups: canagliflozin 100 mg (with an optional increase to 300 mg during follow-up) and placebo. Following the trends of analyzes for empagliflozin, the Canvas showed a reduction in cardiovascular mortality and hospitalization due to heart failure, with no significant impact on stroke and non-fatal AMI. When analyzed from the nephrological point of view, the average eGFR, from basic characteristics in all groups, was 76 ml/min/1.73 m², and 30% of individuals presented some degree of UACR (7% above 300 mg/g). In patients treated with the canagliflozin, there was a reduction in the progression of albuminuria, need for RRT, eGFR in 40%, or renal death. The noteworthy significant adverse effects were an increase in the incidence of genital infections, greater osmotic diuresis, and reduced blood volume in the canaglifozin groups[22]. Other adverse effects, which previously had not been noticed, were a higher incidence of fractures and amputations in patients treated with the canagliflozin. Regarding the risk of amputation, no precise physiopathological explanation was found for it; it is possibly associated with episodes of dehydration and consequent hemoconcentration in individuals with previous peripheral arterial vascular involvement. A prior retrospective analysis also noted that risk as an effect of the SGLT2 inhibitor class, warning about the need for caution in susceptible patients, and monitoring for security in the long term[26].

Another randomized, multicenter clinical trial, the DECLARE-TIMI 58, aimed to evaluate the clinical outcomes of dapagliflozin. In it, 17,160 patients with type 2 diabetes and established cardiovascular disease or high cardiovascular risk were studied by an average period of four years. Two groups were analyzed: a treatment group, which received 10 mg of dapagliflozin, and a placebo group. Similar to previous trials, there was a benefit in the treatment group, with a reduction in cardiovascular mortality and hospitalization due to heart failure, but with no significance in the reduction of stroke and non-fatal AMI. There was also no reduction in the incidence of major cardiovascular effects, which is a possible explanation for the exclusion of patients with eGFR below 60 ml/min/1.73 m² (a group known to be of higher cardiovascular risk), which differs from pre-

TABLE 1. OUTCOMES OF THE MAIN CLINICAL STUDIES INVOLVING SGLT2 INHIBITORS

Study	Design	Study population	Participants	Comparison	Duration	Primary outcome	Results of cardiovascular outcomes	Renal characteristics	Renal outcomes analyzed	Results of renal outcomes
Empa-REG (21,25)	RCT Double-blind	T2DM with CVD	7,028	1:1:1 Empagliflozin 10 mg Empagliflozin 25 mg Placebo	3.1 years	MACE (CV death, non-fatal AMI, non-fatal Stroke)	Primary outcome: HR 0.86, 95% CI 0.74 to 0.99; CV death: HR 0.62, 95% CI 0.49 to 0.77; Mortality due to all causes: HR 0.68, 95% CI 0.57 to 0.82; Hospitalization due to HF: HR 0.65, 95% CI 0.50 to 0.85; Stroke: HR 1.18, 95% CI 0.89 to 1.56.	Mean age 63 years eGFR: 74 ml/min/1.73 m^2 % of patients with eGFR <60 ml/min/1.73 m^2): 26% UACR > 300 mg/g: 11.1% eGFR <30: exclusion	Progression to macroalbuminuria Doubling of the SCr Start of RRT Death due to renal causes.	Renal outcome: HR 0.61, 95% CI 0.53 to 0.70 Double SCr And eGFR< 45 mL/ Min/1.73 m^2: HR 0.56, 95% CI 0.39 to 0.79 Start RRT: HR 0.45, 95% CI 0.21 to 0.97 UACR evolution: HR 0.62, 95% CI 0.54 to 0.72
Canvas (24)	RCT Double-blind	T2DM with high CV risk	10,142	1:1:1 Canagliflozin 100 mg Canagliflozin 300 mg Placebo	188 weeks	CV death, non-fatal AMI, non-fatal Stroke	Primary outcome: HR 0.86, 95% CI 0.75 to 0.97; General mortality: HR 0.87, 95% CI 0.74 to 1.01; Hospitalization due to HF: HR 0.67, 95% CI 0.52 to 0.87; Stroke: HR 0.87, 95% CI 0.67 to 1.09	Average age: 63 years eGFR: 76.5 mL/ min/1.73 m^2 eGFR <60 mL/ min/1.73 m^2: 20% Macroalbuminuria: 7.6% eGFR <30: exclusion	40% reduction in eGFR Need of RRT Death due to renal cause	Renal outcome HR 0.60, 95% CI 0.47 to 0.77 Double the SCr: HR 0.50, 95% CI 0.30 to 0.84 ESKD: HR 0.77, 95% CI 0.30 to 1.97 Ad hoc: Double SCr End-stage CKD or death due to renal cause: HR 0.53, 95% CI 0.33 to 0.84
Declare-Timi 58 (23)	RCT Double-blind	T2DM with risk factors or established CVD	17,160	1:1 Dapagliflozin 10 mg Placebo	4.2 years	CV death, MACE, hospitalization due to HF	MACE: HR 0.93, 95% CI 0.84 to 1.03; CV death or hospitalization due to HF: HR 0.83, 95% CI 0.73 to 0.95; Cardiovascular death: HR 0.98, 95% CI 0.82 to 1.17; General mortality: HR 0.98, 95% CI 0.82 to 1.17; Hospitalization due to HF: HR 0.73, 95% CI 0.61 to 0.88;	Average age: 64 years eGFR <60: exclusion	Decrease of >40% of eGFR to <60 ml/ min/1.73 m^2 ESKD Death due to renal cause	Renal outcome: HR 0.76, 95% CI 0.67-0.87 Ad hoc: >40% decrease of eGFR to <60 mL/ min/1.73 m^2 ESKD or death due to renal cause: HR 0.53, 95% CI 0.43-0.66
Credence (24)	RCT Double-blind	T2DM eGFR <90 ml/min/1.73 m^2 UACR: 300–5,000 mg/g	4,401	1:1 Canagliflozin 100 mg Placebo	2.6 years	ESKD Double SCr Death due to renal or CV cause	CV death or hospitalization due to HF: HR 0.69, 95% CI 0.57 to 0.83 CV death, AMI, or Stroke: HR 0.80, 95% CI 0.67 to 0.95	Average age 63 years eGFR~ 56 ml/min/1.73 m^2 UACR~ 930 mg/g	ESKD Double SCr Death due to renal or cardiovascular cause	Double SCr HR 0.60, 95% 0.48 to 0.76 ESKD: HR 0.68, 95% 0.54 to 0.86 CV death: HR 0.78, CI 95% 0.61 to 1.00

RCT: Randomized clinical trial; T2DM: Type 2 Diabetes Mellitus; CV: Cardiovascular; CVD: Cardiovascular disease; MACE: Major Adverse Cardiovascular Events; AMI: Acute myocardial infarction; HR: Hazard ratio; CI: Confidence interval, HF: Heart failure, eGFR: Estimated glomerular filtration rate; UACR: Urine Albumin-to-Creatinine Ratio, SCr: Serum creatinine; RRT: Renal replacement therapy; CKD: Chronic kidney disease; ESKD: End-Stage Kidney Diseasee.

vious clinical studies. Despite this, when the renal outcomes were analyzed, there was a reduction in the incidence of end-stage kidney disease, a decrease greater than 40% in the eGFR, and death due to kidney failure. Basal levels and progression of albuminuria were not included in the analysis. Genital infection and diabetic ketoacidosis were adverse effects described as significant in the group treated with dapagliflozin[23].

In these three large clinical trials, we note that, in relation to renal outcomes, individuals with no or little albuminuria were selected, as well as with normal or slightly reduced eGFR, which makes it difficult to make more complex analyses since this population has a low risk for progression of kidney disease. In this context, the CREDENCE study randomized 4,401 patients into a placebo group or a treatment group with 100 mg of canagliflozin, with a follow-up of 2.6 years. Patients needed to meet the following inclusion criteria: type 2 diabetes with eGFR from 30 to 90 ml/min/1.73 m², UACR of 300 to 5,000 mg/g, and have an optimal and stable dose of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker. Thus, the randomized groups included patients with an average of eGFR of 56 ml/min/1.73 m² and UACR of 930 mg/g. There was a reduction of 30% in the primary outcomes analyzed: end-stage kidney disease, doubling of serum creatinine, renal and cardiovascular mortality. For specific renal outcomes, the reduction was 34%. In the analysis of subgroups, 59% of the patients presented eGFR between 60 and 30 ml/min/1.73 m², a percentage that presented significant outcomes (the subgroup of 45 to 60 ml/min/1.73 m² had a 53% reduction in specific renal risk). It should be emphasized that such improvements were independent of the reduction in glycated hemoglobin. The subgroups with UACR greater than 1,000 mg/g and lower than 1,000 mg/g were also studied, with positive results in patients with a higher degree of proteinuria. In contrast with the CANVAS results, there was no difference in the incidence of amputations and fractures between the groups analyzed; there was an active investigation of signs of lesions on patient's feet during protocol visits and, in case of suspicion of worsening of the peripheral arterial disease, the treatment could be interrupted[24].

In order to strengthen the evidence for the population with more advanced chronic kidney disease, the DAPA-CKD (Clinical trials: NCT03036150) is being conducted and will include patients with eGFR between 25 and 75 ml/min/1.73 m² or UACR between 200 and 5,000 mg/g, with completion expected by November 2020 and the purpose of assessing the renal benefits of dapagliflozin in patients with chronic kidney disease, whether or not diabetic[27]. Another promising clinical trial is the Empa-Kidney (Clinical trials: NCT03594110), which will include patients with eGFR from 20 to 45 ml/min/1.73 m² and 45 to 90 ml/min/1.73 m² and UACR greater than 200 mg/g; diabetic patients, or with established cardiovascular disease and eGFR >60 ml/min/1.73 m² will be excluded. The primary goals are to evaluate the progression of kidney disease and cardiovascular death, and the study is expected to be completed by 2022[28].

In smaller proportions, the SGLT2 inhibitors, in particular, empagliflozin, were also studied in another scenario of chronic kidney disease: post-transplant diabetes mellitus. In a small, non-randomized study, empagliflozin proved to be safe in these individuals, with a low risk of serious adverse effects. It had a low impact on the reduction of blood glucose levels, but significant weight reduction; there was not enough power to assess graft survival. This study emphasizes the safety of the medication and maintains the subject open to larger trials to expand results for the population of solid organ transplantation, in particular to kidney transplantation recipients[29].

In relation to the safety profile of SGLT2 inhibitors, in general, they are well tolerated, safe medications, whose main significant adverse effect described were fungal genital infections (vulvovaginitis and balanoposthitis). Volume depletion, amputations, and fractures (these last two seen only with canagliflozin), although a controversial impact in trials, are described and deserve attention by the prescribing physician. Diabetic ketoacidosis, in particular, the euglycemic subtype, is classically associated with users of this medication who have type 1 diabetes mellitus - which actually hinders its use in this profile of patients. However, this was also observed in type 2 diabetic patients, so attention should be paid when the individual under treatment presents metabolic acidosis of unknown etiology[30]. Urinary tract infections were initially a cause for concern; however, subsequent strong analysis of the therapy did not correlate it with a higher incidence of urinary tract infections of any severity[31]. As more studies are awaited to better understand the extent of benefits, the safety assessment of

SGLT2 inhibitors will continue to be discussed, especially in the population of greater risk, that is, that with impaired renal function. After consideration, without a doubt, the benefits of SGLT2 inhibition outweigh the risks; however, good clinical practice must be based on patient safety first, and the monitoring of adverse reactions should be thorough and continuous.

PRACTICAL RECOMMENDATIONS FOR THE USE OF THE SGLT2 INHIBITORS IN CLINICAL PRACTICE

The recommendation for initial treatment, according to the American Diabetes Association (ADA), is still metformin combined with changes in lifestyle. The cost-benefit relationship of the medication, allied to cardiovascular and metabolic benefits, justifies this as the first choice in the therapeutic line[32]. As adjuvant pharmacological therapy, the ADA recommends associating, in individuals with established cardiovascular disease, a SGLT2 inhibitor or glucagon-like peptide 1 (GLP-1) agonist. The GLP-1 agonists, represented mainly by exenatide, liraglutide, and semaglutide, belong to the group of incretin mimetics, intestinal hormones which potentiate the secretion of insulin, optimizing blood glucose levels, in addition to having cardio and renoprotective pleiotropic effects, although its clinical outcomes are less impactful[33]. In patients with risk of or established heart failure, there is a preference for the SGLT2 inhibitor, in view of the evidence above. If poor glycemic values persist, it is recommended that another hypoglycemic medication is added[34]. One alternative is the class of dipeptidyl peptidase 4 (DPP4) inhibitors, which have a different mechanism of action than the glycosuric drugs; the inhibition of this enzyme leads to the stabilization of GLP1, which justifies the glucose reduction effect. The impacts on cardiovascular and renal outcomes were controversial. However, recently, benefits in the short-term improvement of glycated hemoglobin and albuminuria were observed when used concomitantly to SGLT2 inhibitors, with good tolerability and security profile[35].

Regarding the use of SGLT2 inhibitors in patients with reduced renal function, the recommendation is to use empagliflozin and canagliflozin when the eGFR is greater than 30 ml/min/1.73 m²; dapagliflozin should be used when the eGFR is of at least 60 ml/min/1.73 m². For the subpopulation with advanced CKD, when the other studies are completed, we will have answers regarding their efficacy and safety.

CONCLUSION

SGLT2 inhibitors are likely the greatest pharmacological advancement in nephrology since RAAS blockers; they are agents capable of reducing renal cardiovascular, a great foundation for oral hypoglycemic therapy[36]. With well-established clinical outcomes, they are already part of the therapeutic armamentarium against type 2 diabetes mellitus. Although limited for use in the Brazilian population, primarily due to its cost, its prescription should be instigated, and the cost-benefit relationship presented to the patient. Future publications are promising for the non-diabetic population, with even greater hopes of renal survival in patients with CKD.

Contribution of the authors

Diego Ennes Gonzalez, Renato Demarchi Foresto, and Artur Beltrame Ribeiro contributed substantially to the planning, drafting, and revision of this paper.

There is no conflict of interest in the present study.

There was no external funding.

PALAVRAS-CHAVE: *Diabetes mellitus. Insuficiência renal crônica. Hipoglicemiantes. Inibidores do transportador 2 de sódio-glicose.*

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REVIEW ARTICLE

Acute kidney injury in cancer patients

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http://dx.doi.org/10.1590/1806-9282.66.S1.25

SUMMARY

The increasing prevalence of neoplasias is associated with new clinical challenges, one of which is acute kidney injury (AKI). In addition to possibly constituting a clinical emergency, kidney failure significantly interferes with the choice and continuation of antineoplastic therapy, with prognostic implications in cancer patients. Some types of neoplasia are more susceptible to AKI, such as multiple myeloma and renal carcinoma. In cancer patients, AKI can be divided into pre-renal, renal (intrinsic), and post-renal. Conventional platinum-based chemotherapy and new targeted therapy agents against cancer are examples of drugs that cause an intrinsic renal lesion in this group of patients. This topic is of great importance to the daily practice of nephrologists and even constitutes a subspecialty in the field, the onco-nephrology.

KEYWORDS: *Acute Kidney Injury. Neoplasia. Malignant tumor. Chemotherapy.*

INTRODUCTION

With the epidemiological transition of recent decades, cancer has become the object of several clinical studies that resulted in more options for the diagnosis and treatment of the disease. Thus, there was an increase in the survival of patients, and handling complications of the disease and treatment adverse effects also became more common[1].

The association between cancer and kidney disease has been known for a long time[2,3]. The kidney toxicity of antineoplastic drugs, renal lesions in multiple myelomas (MM), malignant obstructive uropathy, and oncologic emergencies, such as tumor lysis syndrome (TLS), are examples of renal diseases that affect cancer patients[4]. Acute kidney injury (AKI) increases the risk of toxic effects of chemotherapy (CT), compromises the continuation of treatment, and limits the participation of patients in studies with new drugs.

EPIDEMIOLOGY

Among hospitalized patients, AKI is a common complication. Among those with cancer, the incidence reaches up to 12% of cases, and, often, the AKI develops within the first 48 hours of admission[5,6]. A Danish study with 37,257 cancer patients had 17.5% of AKI incidence, per the definitions of the Rifle classification (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease)[7]. In an environment of intensive therapy in cancer

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hospitals, the incidence increases to approximately up to 50%[4].

CANCERS WITH A HIGHER RISK OF AKI

The risk of AKI is greater in hematological neoplasias, especially in MM and neoplasms of the urinary tract, with emphasis on renal and bladder carcinomas[4,7,8]. In cases of renal carcinoma treated with radical nephrectomy, 34% presented AKI, that this procedure was also a predictor of the development of chronic kidney disease (CKD)[9]. Among other hematological neoplasias, in a cohort of 537 patients with acute myeloid leukemia (AML) and high-grade myelodysplastic syndrome, 36% developed AKI[10].

Risk factors

In addition to certain types of cancer being more prone to renal injury, there are factors that increase that risk, among them: age (>65 years), female gender, chronic kidney disease, diabetes, hypertension, renal artery stenosis, advanced-stage cancer, hypoalbuminemia, hyponatremia, leukopenia, absolute (vomiting, diarrhea) or relative (congestive heart failure, cirrhosis or nephrotic syndrome) hypovolemia, use of contrast agents, chemotherapy, antibiotics, mechanical ventilation, vasoactive drugs, use of oral drugs - diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-II-converting enzyme inhibitors II (ACEI) or angiotensin II receptor blockers (ARB)[6,8,10-12].

Evaluation of renal function in cancer patients

Equations that estimate the glomerular filtration rate (GFR) as those of the MDRD (*Modification of Diet in Renal Disease*) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) studies use as reference the iothalamate clearance and are currently the bedside methods available that offer the best accuracy and convenience for the evaluation of renal function. The Cockcroft Gault (CG) equation, since it is based on the creatinine clearance, may underestimate the glomerular filtration rate in elderly and malnourished patients, common characteristics among cancer patients. However, it is still used because it was the method chosen by the FDA (Food and Drug Administration) in 1998 as the standard for dose correction in patients with kidney failure and cancer[13].

Cancer patients often present alterations in the GFR that are not detected by the physician. In a multicenter study with 4,684 patients, the use of creatinine alone underestimated the diagnosis of CKD, since 60% of patients with GFR estimated at <90 ml/min/1.73 m² had creatinine values within the limits of normality[14]. Therefore, the search for more accurate biomarkers is the target of research. That is the case of cystatin C, produced in constant concentrations by all nucleated cells and freely filtered at the glomerulus, is not relevantly influenced by the nutritional state and muscle mass, which makes its use promising, although there have been contradictory preliminary studies estimating the GFR in cancer patients[15].

Regarding the definition of renal injury in these patients, most clinical studies published used the 2004 Rifle criteria. In 2012, the Kdigo (Kidney Disease Improve Global Outcomes) classification established a new system for defining and classifying acute kidney injury (Table 1). For the calculation, it is necessary to know the value of the baseline creatinine, which is the value reviewed from the last 7 to 365 days prior to hospital admis-

TABLE 1. CRITERIA FOR ACUTE KIDNEY INJURY

		RIFLE* 2004	AKIN 2007		KDIGO 2012
Criteria Stages	Diuresis (Same criteria in all three classifications)	GFR (Estimated decrease)	Creatinine clearance		
1	<0.5 ml/kg/h in 6h	>25%	**Risk:** ≥1.5xCr(s)	≥1.5x or increase ≥0.3 mg/dl	≥1.5x or increase ≥0.3mg/dl
2	<0.5 ml/kg/h in 12h	>50%	**Injury:** ≥2x Cr(s)	≥2x	≥2x
3	<0.3 ml/kg/h in 24h or anuria for 12h	>75%	**Failure:** ≥3x Cr(s)	≥3x or ≥4 mg/dl + increase of ≥0.5 mg/dl or TRS	≥3x or increased to values ≥ 4mg/dl** or RRT
Time	In hours	In the last 7 days		in 48h	≥1.5x in up to 7 days ≥0.3 mg/dl in 48h

*The Rifle Classification also has the following stages: Loss: loss of function for >4 weeks. ESRD - need of RRT for >3 months. ** Provided there is an increase ≥0.3 mg/dl in 48h or ≥1.5x in up to 7 days

sion; or the lowest value recorded during hospitalization. When the baseline value is unknown, the calculation of the creatinine value corresponds to the GFR estimated by a MDRD of 75 ml/min/1.73 m². However, in patients with previous CKD, this type of calculation may overestimate the incidence of AKI and its severity[16].

New biomarkers of acute kidney injury are under study, among which those related to inflammation are especially noteworthy, such as neutrophil gelatinase-associated lipocalin (NGAL) and those involved in cell cycle, like the tissue inhibitors of metalloproteinases (TIMP-2) and the IGF binding proteins (IGFBP-7), which require further studies involving cancer patients[17].

CAUSES OF AKI IN CANCER PATIENTS

In a cohort study, the most frequent causes of AKI were ischemia/shock, sepsis, contrast/nephrotoxins, obstruction, post-nephrectomy (renal carcinoma), and TLS[18]. In another study with hematological cancer patients, 68.5% presented AKI, and the main causes were hypoperfusion, TLS, acute tubular necrosis, and nephrotoxic agents[19]. In addition to the etiologies that are common among the general population (sepsis, NSAIDs, antibiotics, and contrast), cancer patients have a higher incidence of injuries due to antineoplastic drugs, post-renal injuries (genitourinary tumors), paraneoplastic syndromes, and TLS after chemotherapy.

In a systematic approach, we can separate the AKI etiologies associated with pre-renal, renal (intrinsic), and post-renal cancer, as is already done in the general population (Tables 2, 3, and 4).

Pre-renal

It is the most common cause of acute kidney injury in this group. The low oral intake, vomiting, and diarrhea after chemotherapy are responsible for most of the cases[20]. Fluid loss can also occur due to diabetes insipidus (DI) (nephrogenic - due to hypercalcemia, chemotherapic, post-renal - or central due to brain injury), third spacing, formation of cavitary effusion, and insensible losses (febrile neutropenia).

Post-renal

Cases of post-renal lesions are more common in cancer patients than in the general population[21]. The tumors were most frequently involved are those of the urinary tract, such as of the prostate and bladder, and those the adjacent systems, such as gynecological and gastrointestinal, and previous local therapeutic interventions such as surgery and radiotherapy increase the risk. This lesion may become irreversible; thus, prompt intervention is necessary. Before definitive surgery, maneuvers to decompress the urinary tract can be used, with ureteral catheters or nephrostomy. The decision on the use of decompression can be based on the presence of clinical parameters that compromise survival, such as hypoalbuminemia, degree of hydronephrosis, and metastatic events[22]. After reducing the obstruction, the tubular cells can be insensitive to vasopressin (nephrogenic DI), with possible polyuria and loss of electrolytes. Thus, it is of fundamental importance to control the hydroelectrolytic balance[23].

Although infrequent, anuria, flank pain, and a palpable mass are the clinical triad of post-renal AKI. Other possible signs are hematuria, abdominal distension, vesical dysfunction, and urinary tract infection. Urinary sediment is usually harmless and may contain red blood cells, crystals (uric acid), and cylinders (light chains). In addition to DI, hyperchloremic acidosis with hyperkalemia is suggestive of type IV

TABLE 2. CAUSES OF PRE-RENAL LESION IN CANCER

Absolute hypovolemia
Low food intake, vomiting, diarrhea - Gastrointestinal effects of chemotherapy - Obstructive abdomen (primary tumors or distant metastasis, adherence due to surgery/previous radiotherapy) - Injuries of the gastrointestinal mucosa of graft-versus-host disease Polyuria - Diabetes insipidus Insensible Losses - Sepsis/febrile neutropenia Others - Losses due to ostomies and drains
Relative hypovolemia
Vasodilation/hypotension. - Sepsis - Veno-occlusive disease/ Hepatorenal syndrome - Iatrogenic (antihypertensives) Renal vasoconstriction - Drugs (NSAIDS, calcineurin inhibitors) Decreased cardiac output - Heart failure due to coronary disease or cardiotoxic drugs Third Spacing - Metastases implants and cavitary effusion - Hypoalbuminemia/ nephrotic syndrome
Vascular compression
- Intra-abdominal hypertension/ abdominal compartment syndrome

renal tubular acidosis[12]. The definitive diagnosis of post-renal AKI is confirmed by radiological examination. Kidney ultrasonography (USG) is an excellent tool for the rapid detection of hydronephrosis/hydroureter. Occasionally, the findings may be negative, if the obstruction is of short duration or when there is renal entrapment due to cancer/retroperitoneal fibrosis. Computed tomography or magnetic resonance imaging are examinations that give more details on the obstruction, guiding the appropriate treatment.

In addition to tumors that compress the urinary tract, intraluminal causes should also be remembered, such as intratubular cylinders (light chain myeloma) and ureterolithiasis (Table 3).

TABLE 3. CAUSES OF POST-RENAL LESIONS

Intraluminal obstruction
Intratubulares crystals - TLS (uric acid, calcium phosphate, xanthine) - Drugs (Methotrexate) Intratubular cylinders *(light chains)* Ureterolithiasis *(hyperuricemia, hypercalcemia)* Urinary bladder clot *(bladder cancer, hemorrhagic cystitis)*
Extraluminal obstruction
Primary tumors of the urinary tract *(Bladder, Prostate)* Gynecological tumors *(uterus, ovary)* Metastases/ adenomegaly compressive of the urinary tract Retroperitoneal fibrosis

Renal (intrinsic)

Acute tubular necrosis due to sepsis and nephrotoxic agents such as antibiotics and contrast are important intrinsic etiologies in this group of patients. However, other causes specific of cancer patients should be remembered, among them nephrotoxicity caused by chemotherapy, TLS, renal injury related to MM, and renal carcinoma (post-nephrectomy).

TABLE 4. INTRINSIC RENAL INJURY

Sepsis Nephrotoxic drugs - Chemotherapy drugs, targeted therapy against cancer, immunotherapy - Bisphosphonates - Antibiotics, antivirals Contrast Ischemia/ pre-renal progression Tumor lysis syndrome Paraproteinemias Infections (pyelonephritis, viral infection - BK and Adenovirus) Renal carcinoma (post-nephrectomy) Tumor infiltration (lymphoma and leukemia) Glomerulopathies - Membranous, thrombotic microangiopathies, amyloidosis and others Endogenous nephrotoxins - Hyperuricosuria, hemoglobinuria, and myoglobinuria

Antineoplastic drugs

Table 5 shows the classes of drugs most frequently involved with nephrotoxicity in daily practice.

Platinum-based drugs are the most frequently involved in cases of nephrotoxicity. The class prototype is the cis-diamminedichloroplatinum (II) (CDDP) or cisplatin. This drug is commonly used in tumors of the lung, head and neck, bladder, testicles, and ovary[24]. Acute kidney injury occurs in approximately one-third of the patients. The drug affects several renal compartments and presents clinical manifestations, from renal injury to thrombotic microangiopathy and tubulopathies, with various electrolyte disturbances during its course, among them hypomagnesemia, proximal tubulopathy, and nephrogenic DI[25]. Renal injury can be prevented by adjusting the dose and maintaining adequate hydration; some studies showed benefits with the use of amifostine (free radical binder) and with a magnesium infusion during preparation for CT[26,27]. Analog substances, such as carboplatin and oxaliplatin, seem to be less nephrotoxic.

The ifosfamide is an alkylating agent used in the treatment of sarcomas, lymphomas, and testicle tumors. It is also associated with increased tubular injury and can manifest in the form of Fanconi Syndrome and even nephrogenic DI. The drug metabolite, chloroacetaldehyde, is the great responsible for the injury. In cyclophosphamide, another drug of the same class, this compound is formed in smaller quantities, and acrolein is produced, whose main side effect is hemorrhagic cystitis. The Mesna synthetic compound binds to and prevents cystitis[24].

The evolution of research in therapeutic tools to fight cancer has led to the emergence of drugs that act more directly on the tumor and have a lower effect against other cells. Among these are the target agents against cancer. The vascular endothelial growth factor (VEGF) and its receptor (VEGFR) and tyrosine kinase inhibitors - who act against the VEGFR and also against the platelet-derived growth factor receptor (PDGFR) - are some of the examples of targets of this new class of drugs, which ends up acting in the tumoral angiogenesis. The VEGF and its receptor are also present in podocytes, the endothelium, mesangium, and kidney tubular cells[28]. Thus, the glomerular lesions most frequently observed are endotheliosis, focal and segmental glomerulosclerosis, and thrombotic microangiopathy. Thus, patients who use these drugs commonly develop hypertension (which is actually a marker

TABLE 5. EXAMPLES OF ANTINEOPLASTIC DRUGS RELATED TO RENAL LESION

Antineoplastic drugs	Examples
Conventional chemotherapy agents	
Platinum-based Alkylating Antimetabolites	Cisplatin, carboplatin, oxaliplatin Ifosfamide, cyclophosphamide Methotrexate, gemcitabine
Targeted therapy	
Anti-VEGF antibodies Tyrosine kinase inhibitors EGFR inhibitors Checkpoint inhibitors - Anti-PD1 antibodies - Anti-CTL-4 antibodies mTOR	Bevacizumab, Aflibercept Sunitinib, Pazopanib, Sorafenib, Imatinib Cetuximab, Panitumumab Pembrolizumab, Nivolumab Ipilimumab Everolimus, Temsirolimus
Others IL2, IFN, Bisphosphonates, Denosumab	

of adequate antitumor response) and mild proteinuria. They can also develop nephrotic syndrome, AKI, and thrombotic microangiopathy, which should be monitored. Proteinuria should be treated with ACEI/ARB, and hypertension with the same drugs or dihydropyridine calcium channel blockers, such as nifedipine. Acute kidney injury with thrombotic microangiopathy is an indication to suspend the antineoplastic drug[28,29].

CONCLUSION

In addition to the etiologies briefly explored in this review, it is worth stressing the importance of acute kidney injury related to the transplantation of hematopoietic cells and renal carcinoma. The emergence of the onco-nephrology subspecialty caters to the need to integrate the treatment of patients with cancer and renal dysfunction. Interaction with other specialties is mandatory: oncology, hematology, urology, clinical pharmacy, a multi-professional team, and others.

Contribution of the authors:

Bruno Nogueira César[1], literature review, drafting of the paper. Marcelino de Souza Durão Júnior[1,2], literature review, drafting, and review of the article.

RESUMO

A crescente prevalência de neoplasias se associa a novos desafios clínicos, sendo a lesão renal aguda (LRA) um deles. Além de ser possível emergência clínica, a insuficiência renal interfere significativamente na escolha e continuação da terapia antineoplásica, tendo implicações prognósticas no paciente com câncer. Alguns tipos de neoplasias são mais suscetíveis a LRA, como o mieloma múltiplo e o carcinoma renal. Nos pacientes oncológicos, a LRA pode ser dividida em pré-renal, renal (intrínseca) e pós-renal. A quimioterapia convencional com platinas e os novos agentes de terapia-alvo contra o câncer são exemplos de drogas que causam lesão renal intrínseca nesse grupo de pacientes. Este tema é de grande importância atual para a prática diária do nefrologista, tornando-se inclusive subespecialidade na área, a onconefrologia.

PALAVRAS-CHAVE: *Lesão renal aguda. Neoplasia. Tumor maligno. Quimioterapia.*

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REVIEW ARTICLE

Hyperkalemia in chronic kidney disease

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http://dx.doi.org/10.1590/1806-9282.66.S1.31

SUMMARY

Hyperkalemia is a frequent finding in patients with chronic kidney disease (CKD). This increase in serum potassium levels is associated with decreased renal ion excretion, as well as the use of medications to reduce the progression of CKD or to control associated diseases such as diabetes mellitus and heart failure. Hyperkalemia increases the risk of cardiac arrhythmia episodes and sudden death. Thus, the control of potassium elevation is essential for reducing the mortality rate in this population. Initially, the management of hyperkalemia includes orientation of low potassium diets and monitoring of patients' adherence to this procedure. It is also important to know the medications in use and the presence of comorbidities to guide dose reduction or even temporary withdrawal of any of the potassium retention-related drugs. And finally, the use of potassium binders is indicated in both acute episodes and chronic hyperkalemia.

Keywords: Chronic renal disease. Hyperkalemia. Renin-angiotensin-aldosterone system inhibitors. Calcium polystyrene sulfonate. Partomer. Sodium zirconium cyclosilicate.

INTRODUCTION

Potassium is the ion most present in body fluids, and approximately 98% of its concentration is intracellular. The main physiological functions of the ion are to adjust the cellular metabolism, such as the protein and glycogen synthesis, and the basic acid balance. In addition, the difference in potassium concentration intra and extracellular creates a transmembrane potential that is responsible for neuromuscular function[1]. The serum level of potassium is maintained by the daily excretion of a quantity close to that ingested, approximately 100 mEq/day. The elimination of the ion occurs through the skin, gastrointestinal tract, and kidneys. Normally, the potassium excretion through sweat is approximately 5 mEq/day, in stool between 5 to 10 mEq/day, and in urine around 92 mEq/day. The main mechanism by which the kidney maintains the homeostasis of potassium is by secreting the ion through the distal convoluted tubule and the proximal collecting duct[1,2].

Hyperkalemia is one of the most important metabolic complications because it can cause electrophysiological disorders with severe clinical repercussions that may lead to death[3,4]. This electrolytic change is defined as the elevation in the serum level of potassium above the range of normality. The mechanisms that lead to hyperkalemia typically involve a combination of factors, such as the increase in the intake of foods rich in potassium, disorderly distribution between the intra and extracellular compartments, and abnormalities in potassium excretion. Chronic kidney disease (CKD) is the most common predisposing condition for an increased level of potassium[4,5].

The incidence of hyperkalemia varies between 2-35% of CKD patients, depending on the rate of glomerular filtration rate (GFR) of the population studied, the potassium level considered high by researchers in different studies, the use of inhibitors of the renin-angiotensin-aldosterone system (RAAS) and of

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potassium-sparing diuretics, in addition to the presence of comorbidities, such as diabetes and heart failure[6]. Studies have shown that patients with CKD associated with diabetes mellitus and/or heart failure have a greater risk of developing this metabolic alteration. A decrease in the renal excretion of potassium in combination with one or more exacerbating factors, such as hyperglycemia, insulin deficiency, hyporeninemic hypoaldosteronism, and the use of inhibitors of the RAAS, may induce recurrent episodes of hyperkalemia[7,8].

A high level of this ion has been associated with increased mortality in the general population and in CKD patients, in its different stages, which highlights the importance of maintaining the serum levels of potassium in the normal range[7-9]. This review summarizes the mechanisms that lead to hyperkalemia, its clinical consequences and treatments, with a focus on CKD patients.

MECHANISMS OF HYPERKALEMIA IN CKD

With the progression of CKD, potassium excretion is decreased, and, in this condition, the intake of foods rich in potassium contributes significantly to the difficulty of maintaining the ion in the normal range. Metabolic acidosis, commonly found in this population, causes the ion to exit the intracellular space to the extracellular, leading to an increase of serum potassium. In renal-transplant patients, acidosis, as well as the use of calcineurin inhibitors, are associated with the occurrence of hyperkalemia[10].

Some comorbidities, often found in CKD patients, may lead to increased serum levels of the ion. Acute kidney injury results in a rapid decrease in GFR and tubular flow and, usually, is accompanied by a hypercatabolic state, tissue injury, and high levels of potassium (for example, secondary to bleeding). In addition, the acute elevation of the ion can also occur after a blood transfusion. These conditions contribute to the elevation of the serum level of potassium, which may present a risk to the patient's life and is one of the most common indications for emergency dialysis treatment[10]. Diabetes mellitus and cardiovascular disease are two of the most common comorbidities in CKD patients, and both are related to the development of hyperkalemia through different mechanisms. Insulin deficiency and hypertonicity caused by hyperglycemia in patients with diabetes contribute to the reduction of potassium transport to the intracellular space. In addition, diabetes mellitus is associated with hyponatremia hypoaldosteronism and the resulting inability to regulate the tubular secretion of potassium[4,10].

Cardiovascular diseases, such as hypertension, acute myocardial infarction, left ventricular hypertrophy, and congestive heart failure, require drugs that can lead to hyperkalemia. These drugs, such as cardiac glycosides, contribute to the increase of serum potassium due to inhibition of the Na+/K+ ATPase pump, which exchanges intracellular sodium for extracellular potassium. Heparin has also been associated with hyperkalemia, and its mechanism involves a decrease in the production of aldosterone. The most relevant drugs associated with the increase of potassium are the β2-adrenergic receptors blockers and the RAAS inhibitors, which prevent the production of renin and reduce the capacity of redistribution of potassium in the intracellular space[10]. Among the population without CKD, the incidence of hyperkalemia associated with the use of these drugs is highly variable, depending on the design of the study and the serum level of potassium considered high[11]. The increase of potassium ion has serious outcomes, such as arrhythmia, death, and discontinuation of drugs related to its elevation, which could lead to the worsening of the disease[11,12]. A recent retrospective study demonstrated that patients with serum potassium level >6.0 mmol/L had higher rates of hospitalization and death in comparison with individuals with serum potassium ≤5 mmol/L. In addition, it demonstrated that the development of hyperkalemia was related to the use of RAAS inhibitors and the patients' initial GFR[12].

In clinical practice, RAAS inhibitors are widely used in the treatment of CKD patients due to its cardiac and renal protective effect. In a recent review and meta-analysis, the use of RAAS inhibitors showed a kidney-protective effect in CKD patients with proteinuria; this is the first class of anti-hypertensive drugs for patients with this profile. However, the authors pointed out the risk of hyperkalemia[13]. Several clinical studies have shown the association of RAAS inhibitors with increased levels of potassium in CKD patients. In an observational study, the use of this class of medication was associated with an increase of 41% in the occurrence of hyperkalemia. Furthermore, the authors showed that individuals with CKD had a higher risk of increased potassium compared with patients with no renal injury[14]. The Renaal study followed patients with diabetic kidney disease in who used Losartan or a placebo. In this clinical trial, the

group of individuals who used the Losartan had a greater risk of increased serum potassium than the placebo group[15]. In another study, patients who used the irbesartan had an incidence of 18.6% of hyperkalemia, while among patients who used the placebo, it was only 6%[16]. Like in the general population without CKD, hyperkalemia is associated with a higher incidence of cardiovascular events and death in patients with renal injury[17]. It is worth noting that previous studies have demonstrated that the dual blockade with ACEI and ARB increased the incidence of hyperkalemia episodes, in addition to the occurrence of acute kidney injury[18,19]. Due to the risk of increased serum levels of potassium and, consequently, the unfavorable outcomes related to this event, the reduction or suspension of RAAS inhibitors is a common practice[20]. However, this practice can also cause undesirable events for patients. Epstein et al. demonstrated that patients who received a smaller dose or whose use of RAAS inhibitors was suspended after the occurrence of hyperkalemia presented a greater number of adverse events related to the progression of CKD, beginning of dialysis treatment, cardiovascular events, or death when compared to patients who maintained the maximum tolerated dose of these medications[21]. The balance between the risk of hyperkalemia and cardiac-renal protection that this class of medication presents makes it necessary to evaluate other therapeutic options to control the level of potassium.

CLINICAL CONSEQUENCES

Hyperkalemia can be classified according to the level of serum potassium into: mild (5.5-6.0 mmol/L), moderate (6.0-6.5 mmol/L), and severe (>6.5 mmol/L). Often, the clinical manifestations present as muscle weakness, paresthesia, paralysis, nausea, dyspnea, hypotension, cardiac arrhythmia, or cardiac arrest. One study showed that a serum potassium level >6.0 mmol/L was associated with an increase of 30 times in the risk of mortality in one day; however, a level >5.0 mmol/L was associated with long-term adverse events[22]. Thomsen et al. demonstrated that CKD patients who were not on dialysis and presented an episode of hyperkalemia during the study period had a higher risk of hospitalization due to ventricular arrhythmia, cardiac arrest, or other cardiac events[8]. Electrocardiographic changes that can be observed are the peaked T waves, prolonged PR interval, shorter QT interval, wider QRS complex, absence of P wave, ventricular fibrillation, or ventricular tachycardia. Additional laboratory tests are suggested, such as measurements of glucose, sodium, blood gas, renin, aldosterone, and cortisol, in addition to an electrocardiogram to assist in the choice of the best therapeutic option[22].

TREATMENT

The management of hyperkalemia is divided into treatment for acute events and chronic control of serum potassium.

The treatment for acute elevations of potassium aims to antagonize the action of the ion in the cellular membrane and increase the potassium intake to the intracellular space. These measures provide a temporary reduction or removal of serum potassium. For that end, the therapeutic options are calcium gluconate, insulin, sodium bicarbonate, b-adrenergic antagonists, diuretics, and/or initiation or intensification of dialysis[22]. The focus of this review is not to provide a detailed description of the treatment for acute hyperkalemia.

In the treatment of non-severe hyperkalemia, for patients with CKD, dietary guidance should be carried out by a team of nutritionists to identify and replace foods rich in potassium and improve adherence to the dietary plan. It is worth mentioning that in patients with CKD, the inadequate restriction of vegetable, fruit, and liquid intake can cause or aggravate intestinal constipation, which results in increased intestinal absorption of potassium[6,23].

Drugs associated with increased serum levels of potassium, such as beta-blockers, mineralocorticoids receptor antagonists, calcineurin, nonsteroidal anti-inflammatories, trimethoprim, and heparin should be adjusted or replaced in the occurrence of this complication[10]. Special attention should be taken regarding RAAS inhibitors. As described above, these classes of drugs have a fundamental role in cardiac-renal protection, and their suspension should take into account the benefits of their use and the unfavorable outcomes that may occur after their suspension or reduction[21].

Some patients, after the initial measures, still maintain a high level of potassium. For these, it is indicated to associate pharmacological approaches, such as the use of sodium bicarbonate and the introduction or increase of diuretics. The sodium bicarbonate dose varies between 3-5 grams per day and is indicated only in patients with metabolic acidosis. It

is worth noting that this measure is poorly tolerated in patients with CKD patients in advanced stages due to the risk of increased blood pressure and fluid retention[23]. The prescription of diuretics should be made with caution and strict control to prevent hypovolemia, hypotension, decreased GFR, and, consequently, the recurrence of hyperkalemia[24]. In addition, exchange resins can be used (calcium polystyrene sulfonate; sodium polystyrene sulfonate; patiromer; sodium zirconium cyclosilicate).

Sodium polystyrene sulfonate is a resin that exchanges sodium for potassium, calcium, and ammonia and acts on the distal portion of the colon. The administration is via oral or rectal route, through laxatives and enemas, respectively. Clinical trials show that this resin is effective in the treatment of mild hyperkalemia in patients with CDK in the early stages. Doses between 60-80 grams lead to the fall of potassium serum levels by 0.9-1.7 mmol/L; however, it takes a long time for the medication to act. In addition to this delay of the therapeutic effect, the medication has frequent side effects, such as gastrointestinal intolerance, hypocalcemia, and magnesium deficiency. Also, to a lesser incidence, intestinal necrosis can occur. A recent study showed that patients with CKD and GFR <30 mL/min who used sodium polystyrene sulfonate had a higher risk of gastrointestinal events, including digestive bleeding. Thus, the use of this medication in CKD patients is questionable due to its uncertain efficacy, delayed effect, and the restricted use to mild hyperkalemia[25].

Calcium polystyrene sulfonate is another resin that exchanges calcium for potassium. It also acts in the intestine and is administered via the oral route. The drug information leaflet makes reference to a rectal use by diluting it in sorbitol or methylcellulose. Its main side effect is constipation, but there have also been reported occurrences of hypercalcemia and hypercalciuria[25]. A Korean group followed 247 patients with GFR of 3015 ± mL/min/1.73 m^2, for a period of 5-6 months and found a reduction in serum potassium levels (≥ 0.3 mmol/L) in more than 70% of the participants who used the medication in a dose of 2.5-15 grams a day[26]. Wang et al. evaluated 58 patients on hemodialysis who presented hyperkalemia (³5.5 mmol/L) for three weeks. In 61% of patients who used calcium polystyrene sulfonate, there was a decrease in the serum level of potassium (<5.5 mmol/L)[27].

Similar to calcium polystyrene sulfonate, patiromer is a resin that acts in the colon, exchanging potassium for calcium. It is a new medication for the treatment of chronic hyperkalemia in CKD patients, and studies have demonstrated a good response to treatment. Like other ion exchange resins, the main side effect described is constipation. In addition to that, there have also been reports of mild hypomagnesemia[5]. The Amethyst-DN study evaluated 306 diabetic patients with CKD in stages 3 and 4, who used RAAS inhibitors for 52 weeks. The patients were stratified into mild and moderate hyperkalemia according to the serum level of potassium at the beginning of the study. The dose ranged from 4.2 to 16.8 grams twice a day, according to the initial potassium level. In the group classified as mild, the reduction of the serum level of potassium ranged between 0.35-0.55 mEq/L. In patients of the moderate group, the reduction was 0.87-0.92 mEq/L. The reduction in both groups was dose-dependent. In this study, they found a rate of 9.2% of worsening of CKD among patients treated with the medication. The authors cannot say whether this adverse event was secondary to the effect of drugs, an inherent progression of CKD, or due to the increased doses of the RAAS inhibiting drugs used in the treatment group[28]. Another large study evaluated patients with CKD, GFR between 15-60 mL/min/1.73 m^2, serum levels of potassium between 5.1-6.6 mmol/L, and who were taking stable doses of all medications, including RAAS inhibitors and diuretics. All patients used patiromer for four weeks, with doses ranging between 4.2-8.4 grams twice a day, according to the initial potassium level. After this stage, the patients were divided into two groups, placebo and medication, for 8 more weeks of follow-up. In the patiromer group, there was a reduction in serum levels of potassium and an increased number of patients who were able to continue the use of RAAS inhibitors during the study period. In the placebo group, 60% of individuals had at least one episode of hyperkalemia during the second stage of the study[29]. A small study with patients on hemodialysis demonstrated that the use of patiromer decreased serum levels of potassium and phosphorus and increased potassium in the stool. The reported that no adverse effect was observed during the study period[30].

Sodium zirconium cyclosilicate is a non-absorbable compound of zirconium silicate that acts as a selective exchanger of potassium and sodium for ammonia and hydrogen in the gastrointestinal tract, thus increasing the stool excretion of potassium. The recommended initial dose is 10 grams, three times a

day. Normokalemia is achieved in a period of 24-48 hours, and it is recommended that the dose is reduced to maintain an optimal serum level of potassium[25]. A stage 3 study included 753 patients who had potassium levels between 5.0-6.5 mmol/L and divided them into placebo and medication groups. After 48 hours, there was a decrease in the level of potassium in the group that used sodium zirconium cyclosilicate, and the decrease rate was dose-dependent. In the maintenance stage, the potassium level remained within the range of normality in patients from the medication group. Diarrhea was the most common complication reported by the authors[31]. Kosiborod et al. evaluated patients with CKD, heart failure, and diabetes who presented hyperkalemia. The authors demonstrated that zirconium cyclosilicate was effective both in the rapid reduction, with an average time of two hours to decrease the level of potassium, and in the maintenance of normokalemia for up to four weeks in patients with various degrees of hyperkalemia. Normokalemia was achieved in 84% of patients after 24 hours, and in 98% after 48 hours of the onset of treatment[32]. In the recent Dialize study, the use of sodium zirconium cyclosilicate in patients undergoing hemodialysis treatment was able to maintain the serum level of potassium between 4.0-5.0 mmol/L in the period between dialysis, with few records of adverse events[33].

Finally, in patients with pre-dialysis CKD, hyperkalemia resistant to pharmacological approaches have an indication to start renal replacement therapy[6,22]. For patients undergoing dialysis and with potassium levels constantly high, the use of dialysate with a low concentration (0 or 1 mmol/L) of potassium is controversial since there have been reports of arrhythmia and sudden death after hemodialysis sessions with these concentrations. Studies suggest that these events could be related to the rapid fall in the extracellular concentration of the ion[22,34]. It is worth mentioning that these studies are all observational, and there have been no formal clinical trials. Possible solutions to this problem include prolonging the duration of the dialysis session, increasing the frequency of dialysis sessions, using new modalities of hemodialysis and/or potassium-binding resins[22,34]. Another obstacle to the control of hyperkalemia in CKD patients undergoing dialysis is the fluctuations in the serum level of potassium. These fluctuations may not be detected, since, usually, serum potassium is measured monthly, which would lead to the use of dialysate at an inadequate concentration of potassium in the dialysis infusion[34].

CONCLUSION

Hyperkalemia is a metabolic complication often found in CKD patients and associated with severe outcomes. The rise of serum potassium is mainly related to the decrease in GFR and medications used to slow the progression of CKD and control associated diseases. The treatment of hyperkalemia includes dietary counseling and control, reduction or temporary suspension of medications, as well as the control of blood glucose levels in diabetic patients. In addition, sodium bicarbonate, diuretics, and potassium-binding resins can be used. Calcium polystyrene sulfonate is the only resin used in Brasil, and it has shown to be effective in the reduction of potassium, but it is poorly tolerated. Recent studies on resins not yet available in Brasil, i.e., patiromer and sodium zirconium cyclosilicate, show promising results for reducing serum potassium in CDK patients in all its stages.

RESUMO

A hiperpotassemia é um achado frequente em pacientes com doença renal crônica (DRC). Esta elevação do nível sérico de potássio está associada à diminuição da excreção renal do íon, assim como ao uso de medicações para retardar a progressão da DRC ou para controlar doenças associadas, como diabetes mellitus e insuficiência cardíaca. A hiperpotassemia aumenta o risco de episódios de arritmia cardíaca e morte súbita. Assim, o controle da elevação de potássio é essencial para a diminuição da taxa de mortalidade nessa população. O manejo da hiperpotassemia inclui, inicialmente, orientação de dietas com baixo teor de potássio e acompanhamento da aderência dos pacientes a esse procedimento. Também é importante conhecer as medicações em uso e a presença de comorbidades, a fim de orientar a redução de doses ou até mesmo a suspensão temporária de alguma das drogas relacionadas à retenção de potássio. E, finalmente, o uso de quelantes de potássio é indicado tanto em episódios agudos como nos casos de hiperpotassemia crônica.

PALAVRAS-CHAVE: *Doença renal crônica. Hiperpotassemia. Inibidores do sistema renina-angiotensina-aldosterona. Poliestireno sulfonato de cálcio. Patiromer. Ciclossilicato de zircônio sódico.*

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REVIEW ARTICLE

Peritoneal Dialysis

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http://dx.doi.org/10.1590/1806-9282.66.S1.37

SUMMARY

Peritoneal dialysis (PD) is a renal replacement therapy based on infusing a sterile solution into the peritoneal cavity through a catheter and provides for the removal of solutes and water using the peritoneal membrane as the exchange surface. This solution, which is in close contact with the capillaries in the peritoneum, allows diffusion solute transport and osmotic ultrafiltration water loss since it is hyperosmolar to plasma due to the addition of osmotic agents (most commonly glucose). Infusion and drainage of the solution into the peritoneal cavity can be performed in two ways: manually (continuous ambulatory PD), in which the patient usually goes through four solution changes throughout the day, or machine-assisted PD (automated PD), in which dialysis is performed with the aid of a cycling machine that allows changes to be made overnight while the patient is sleeping. Prescription and follow-up of PD involve characterizing the type of peritoneal transport and assessing the offered dialysis dose (solute clearance) as well as diagnosing and treating possible method-related complications (infectious and non-infectious).

KEYWORDS: *Peritoneal Dialysis. Renal Replacement Therapy. End Stage Renal Disease. Chronic Kidney Failure.*

INTRODUCTION

Individuals with stage V or terminal chronic kidney disease, which means those with a glomerular filtration rate <15 mL/min/1.73 m², will need some therapy to replace renal function[1]. This therapy can include kidney transplantation or one of the available dialysis modalities: hemodialysis (HD) or peritoneal dialysis (PD). Both forms of dialysis promote renal replacement by withdrawing solutes and water, restoring the electrolyte balance and correcting acidosis. However, unlike HD, which is based on blood passing through an extracorporeal circuit through a vascular access, PD involves the exchange of solutes and water between blood in the peritoneal capillaries and the instilled solution in the peritoneal cavity (dialysate) through a catheter, using the peritoneal membrane as the dialysing surface[2]. This dialysis solution is packaged in clear flexible plastic bags, and the patient or caregiver is trained by specialized nursing staff to connect these bags to the catheter through the sterile technique in their home or another appropriate environment (for example, their workplace).

One of the greatest advantages of PD is its portability, because as the treatment is provided by the patient or caregiver, there is greater freedom to travel and greater independence from medical and nursing staff compared to HD. Moreover, as it is a continuous therapy, PD constantly removes solutes and water, allowing for a less restrictive diet. Since it is a milder method, PD also provides greater preservation of residual renal function[3]. However, PD should be carried out daily, and the patient or caregiver is fully responsible for compliance with the prescription and paying

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attention to their technique to prevent infectious complications. Also, potential metabolic complications as well as structural changes in the peritoneal membrane can occur over time, which may compromise the effectiveness of the method, as will be seen later.

Absolute contraindications to PD are uncorrectable surgical conditions (e.g., extensive hernias, diaphragmatic hernias, or bladder exstrophy), loss of peritoneal function or multiple peritoneal adhesions and physical or mental inability to perform the method. Relative contraindications are the presence of abdominal vascular prostheses for less than four months, the presence of recent ventriculoperitoneal shunts, frequent episodes of diverticulitis, inflammatory or ischemic intestinal disease and morbid obesity[4].

The peritoneum is a serous membrane with a surface of approximately 1 to 2 m^2 in adults and has two leaflets, the visceral and the parietal. The structure of the peritoneal membrane is composed of a monolayer of mesothelial cells, the interstitium, peritoneal capillaries and visceral lymphatics[5]. The number of perfused capillaries determines the effective peritoneal surface area, which means the functional area available for exchanging between blood and the dialysate[2]. Capillaries represent the largest barrier to the transport of solutes and water. This transport can be explained by the three pore model: ultra-pores, small pores and large pores. The endothelial cells of peritoneal capillaries are permeable to water through ultrapores (<0.5 nm radius). These transcellular pores are represented by endothelial cell membrane proteins called aquaporins. Small solutes and water are transported through intercellular slits called small pores (4 nm radius). In smaller numbers, large pores (12 to 15 nm radius) are sparsely distributed and responsible for the passive transport of macromolecules, such as albumin. Approximately 40% of ultrafiltration is believed to occur via solute-free transcellular pathways (aquaporins), and small pores are responsible for the transport of small solutes by diffusion and/or convection[6].

Solute movement occurs as a result of both diffusional and convective transport, while fluid removal occurs through the osmotic gradient created by the addition of osmotic agents to the dialysis solution. Solute diffusion primarily occurs by a concentration gradient, with solutes such as urea, creatinine and potassium moving from the plasma toward the dialysate, while other solutes, such as bicarbonate, usually move in the opposite direction.

Standard PD solutions contain high concentrations of glucose as an osmotic agent. This plasma hyperosmolar dialysate induces fluid removal from plasma, a process called ultrafiltration. The higher the ultrafiltration, the greater the convective transport of solutes. The volume of ultrafiltration depends on the glucose concentration in the dialysis solution used, the period of permanence of the fluid in the peritoneal cavity and the individual characteristics of each patient's peritoneal membrane, which we discuss below. With longer permanence periods, transperitoneal absorption of glucose leads to a decreased concentration of glucose in the dialysate, decreasing the osmotic gradient.

There is still a small amount of absorption of liquids, approximately 1 mL/min, and solutes through the lymphatic path.

PERITONEAL ACCESS

To perform PD, it is necessary to implant a catheter in the abdominal wall that will allow bidirectional flow of the dialysis solution. The catheter is a flexible silicone tube with multiple pores on its distal (intra-abdominal) portion, and it should ideally be positioned freely in the pelvic area. The most commonly used catheter is the Tenckhoff catheter, which has a straight configuration. The Tenckhoff catheter is laterally externalized through a hole called an exit point, and it has two Dacron cuffs. One of the cuffs is subcutaneous and 1 to 2 cm from the exit-site on the skin (external cuff), and the other cuff is near the peritoneum[2].

Between catheter implantation and the beginning of dialysis therapy, it is advisable to wait at least two weeks[7], a period called break-in, to prevent leakage of the pericatheter dialysate. In some cases, patients may require initiation of dialysis therapy immediately after catheter implantation; in these situations, only small volume exchanges are made, preferably in the supine position[2].

TYPES OF PD TREATMENT AND SOLUTIONS

Chronic PD can be prescribed as follows:

Continuous Ambulatory Peritoneal Dialysis (CAPD): In this method, the peritoneal cavity is always filled with the dialysis solution (usually 2 L of solution), and this fluid is changed four times a day at 4–8 hour intervals (there may be variations, with infusions of 2–2.5 L and 3–5 changes per day in adults, according

to the needs of each patient). This change is performed manually and occurs due to gravity through a system consisting of two bags connected by a Y-piece to the catheter. This two-bag system consists of an empty floor-standing bag to drain the solution from the peritoneal cavity (toxin saturated solution) and a fresh-solution bag that hangs on a stand at a height above catheter level to be infused immediately after draining the saturated solution (Figure 1). When connecting the system to the catheter, the patient first drains the solution that was left in the cavity for a few hours and then infuses the new solution. After this infusion, the patient disconnects the system and disposes it and is then free to perform activities until the next change.

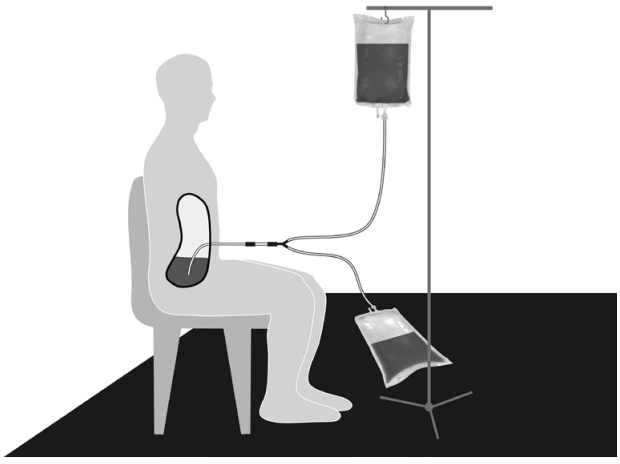
Automated Peritoneal Dialysis (APD): Three to six changes are performed by an automatic cycler overnight while the patient is sleeping. APD can be of the following types:

Intermittent Night Peritoneal Dialysis: In this method, the patient makes the changes at night with the cycler, and the peritoneal cavity remains without dialysis fluid during the day. This method is generally indicated for patients who have residual renal function.

Continuous Cycling Peritoneal Dialysis: In addition to making the changes at night with the cycler, the patient maintains the dialysis solution within the peritoneal cavity during the day and may or may not perform manual changes during the day. This modality is performed by patients who do not have residual renal function[8].

PD solutions come in 2 and 2.5 L plastic bags for use in CAPD and in 6 L bags for APD. The usual composition of the dialysis solution may vary according to the concentrations of glucose (1.5%, 2.5% and 4.25%) and calcium (2.5 and 3.5 mEq/L) and have a standard formulation for most suppliers (sodium 132 mEq/L, chlorine 95 to 102 mEq/L and lactate 35 to 40 mEq/L). The pH of the dialysis solution is low (5.5) to avoid glucose caramelization during heat sterilization. This low pH is generally well tolerated, but some patients may experience pain during infusion. This symptom is attributed to the low pH and hyperosmolarity of the solution. Typically, the solutions contain magnesium levels of 0.5 or 0.25 mM.

FIGURE 1. SCHEME OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD).



Glucose, which is used as an osmotic agent, has the advantage of being known, being relatively safe and inexpensive and being a source of calories, but also predisposes individuals to hyperglycaemia, dyslipidaemia, obesity and peritoneum damage in the long-term, either directly or through the products of glucose degradation. Another available osmotic agent is icodextrin, which is a high molecular weight glucose polymer.

Icodextrin is an iso-osmolar solution and induces ultrafiltration through its oncotic effect. As icodextrin is absorbed into the plasma through the lymphatic vessels, its absorption is much slower than that of glucose, and its associated oncotic effect and ultrafiltration are also more continuous than those of glucose[9]. Thus, icodextrin maintains the ultrafiltration capacity for several hours, and its main indications are the nocturnal permanence of CAPD and the daytime permanence of APD. Icodextrin is metabolised to maltose, maltotriose and other polysaccharides. As maltose can interfere with capillary blood glucose readings, leading to falsely elevated results, blood glucose monitoring in patients using icodextrin should be performed by specific devices (monitor and reagent strips)[10]. The icodextrin solution is available in Brasil.

ADEQUACY IN PERITONEAL DIALYSIS

The Guidelines of the International Society of Peritoneal Dialysis (ISPD) suggest that the adequacy of PD should be interpreted considering not only the adequate clearance of small solutes but should also include a clinical analysis that assesses quality of life, laboratory tests, nutritional aspects and appetite, volume status with adequate ultrafiltration to avoid volume overload, hemoglobin values, response to treatment with erythropoiesis stimulating medications,

calcium and phosphorus metabolism, and blood pressure control[11].

The clearance of small solutes is quantified using Kt/V, which is calculated according to the formula below and should be corrected for a body surface area of 1.73 m²:

$$\text{Total Kt/V} = \text{peritoneal Kt/V} + \text{renal Kt/V}$$

$$\text{Peritoneal Kt} = \frac{\text{dialysate volume in 24h (L)} \times \text{urea dialysate mg/dL} \times 7}{\text{Serum urea mg/dL}}$$

$$\text{Renal Kt} = \frac{\text{urine volume in 24 h (L)} \times \text{urinary urea mg/dL} \times 7}{\text{Serum urea mg/dL}}$$

V (litres) Watson formula:
Men = 2.447 - 0.09516 x age (years) + 0.1704 x height (cm) + 0.3362 x (kg)
Women = -2.097 + 0.10969 x height (cm) + 0.2466 x Weight (kg)

According to the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF KDOQI) PD adequacy guideline, in patients with residual renal function, the minimum total Kt/V dose (peritoneal + renal) should be at least 1.7 per week and should be evaluated at end of the first month of PD and every four months thereafter. Therefore, measures to preserve residual renal function should be taken, such as the use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers in hypertensive patients and avoidance of nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, aminoglycosides and iodinated contrasts[1].

For patients without residual renal function, the minimum offered dialysis dose should correspond to a peritoneal Kt/V of at least 1.7 per week. The dose should be measured in the first month of therapy and every four months thereafter[1].

In patients who do not reach this Kt/V, the clearance of small molecules may be improved by increasing the number of changes and/or infusion volume, while the clearance of medium molecules is more dependent on the period the dialysate stays in contact with the peritoneal membrane. In APD patients, the dialysis dose can be improved by introducing the wet cavity during the day or even adding a change during the day.

In addition, another determinant of solute clearance that should be evaluated to better define the prescription of PD is the category or type of peritoneal transport of each patient, which is assessed by the peritoneal equilibrium test (PET).

By convention, the PET involves infusing 2 L of dialysate (D) at 2.5% glucose in the peritoneal cavity and collecting samples of this dialysate at 0, 2 and 4 hours of permanence in the cavity. A plasma sample (P) is also obtained mid-period (2 h). According to the creatinine D/P ratio in the second and fourth hours, the glucose D/D0 in the same period and the volume of dialysate drained after 4 hours, patients can be classified into one of four categories (Table 1). Considering peritoneal transport, it should be noted:

High transporters: They quickly reach a D/P balance for creatinine and urea, but quickly absorb glucose with a rapid loss of osmotic gradients. They benefit from short-term changes.

Low transporters: Their creatinine D/P balance is slower and incomplete, and the osmotic gradient remains longer. They need changes with a longer permanence period and greater volume per change.

COMPLICATIONS IN PERITONEAL DIALYSIS

Pericatheter leak

Break-in is the period between catheter implantation and the beginning of PD. Break-in is a prophylactic procedure that is used to prevent mechanical and infections complications, and a period of two weeks is recommended for patients starting elective PD. As for an unscheduled beginning of PD, it is ideal to perform the therapy lying down and with a lower infusion volume[12]. If there is a leakage of pericatheter peritoneal fluid, PD may be temporarily interrupted or the dialysis scheme can be changed to intermittent nightly dialysis. If the leakage does not resolve, the catheter should be replaced[13].

Drainage failure (Catheter dysfunction)

Drainage failure occurs in two ways: the catheter infuses and does not drain, usually related to intestinal constipation, tip migration, or "sequestration of the omentum", or the catheter does not infuse and does not drain, which occurs due to folds and intramural obstruction[13].

The recommended procedures are:

1) Check the catheter angle in the abdominal wall (tunnel): if there are folds, catheter replacement is required.

2) Intestinal constipation: correction with a laxative solves 50% of cases of drainage failure.

3) Fibrin (treatment): prophylactic heparin at a

dose of 500 U/L is most commonly used; thrombolytic agents, such as alteplase, at a dilution of 1 mg/mL with a permanence of 2 to 4 hours can also be used[14].

4) Catheter translocation: the tip of the catheter can be viewed through a simple abdominal X-ray. When observing catheter tip migration, some measures can be used, such as laxatives, flexible guidewire replacement (with or without radioscopy), and peritoneoscopy, or a catheter change can be performed. In some situations, the catheter tip is properly positioned and may be blocked by the omentum. In this situation, the treatment should be omentectomy and/or omentopexy[13].

Hernias

Hernias can occur in 10% to 25% of PD patients as a result of increased intra-abdominal pressure and most often require surgical correction. There are potential risk factors, such as the volume infused, recent surgery, obesity and polycystic kidney disease[15]. If the patient has residual renal function, corrective surgery can be performed without interruption of therapy. As a result, PD can be resumed one or two days after surgery, initially with a lower volume of infusion[16].

Hydrothorax

Hydrothorax is a rare complication that occurs through passage of the dialysate into the pleural space via lymphatics or through a congenital diaphragmatic defect. The diagnosis is made by pleural fluid analysis, which reveals high concentrations of glucose and low concentrations of protein; technetium scintigraphy and contrast-enhanced tomography in the peritoneal cavity may be used. Treatment consists of discontinuation of dialysis for two to six weeks and measures to decrease intra-abdominal pressure, such as converting from CAPD to nocturnal APD with a dry peritoneal cavity during the day. If there is no improvement, pleurodesis, surgical repair and even method transfer may be necessary[17].

Edema and ultrafiltration failure

Hypervolemia is an independent risk factor for cardiovascular disease and death in dialysis patients, and it is associated with ventricular hypertrophy, nutritional alterations and inflammation[18]. The causes of hypervolemia in PD are excessive salt and water intake, loss of residual renal function, non-adherence to dialysis prescription, excessive absorption of dialysate during a long change, low use of a hypertonic solution, mechanical complications (dysfunctional catheter, leaks), discrepancy between dialysis prescription and patient PET, and ultrafiltration failure (UFF).

For patients with a reduced ultrafiltration volume, the reversible causes should be assessed, such as an inappropriate dialysis prescription (period of permanence and concentration of the bags), and ruled out to solve mechanical complications[19].

UFF is defined by the four rule – ultrafiltration lower than 400 mL after 4 hours of permanence with a 4.25% bag. After evaluating UFF, evaluate the membrane with the PET.

UFF is rated with the aid of the PET:

• Reduced ultrafiltration volume – fast solute transport: Type I UFF, which may be an intrinsic or acquired condition (e.g., after peritonitis, long time in PD) and results from osmotic gradient dissipation due to absorption of glucose into circulation.

• Reduced ultrafiltration volume – reduced solute transport: Type II UFF. The usual cause is a decrease in the effective peritoneal surface for exchange mainly due to fibrosis.

• Reduced ultrafiltration volume – normal solute transport: There are two possibilities. Type III UFF, when there is increased absorption of the direct peritoneal dialysate, especially lymphatics, or a functional deficit of aquaporins (ultra-small pores).

Treatment of UFF:

• Type I: avoid long periods of permanence or use icodextrin; a resting period for the peritoneum;

• Type II: difficult handling – change of dialysis method;

• Type III: optimize ultrafiltration with an increased glucose concentration, use lower exchange volumes and a shorter permanence; icodextrin[20].

Weight gain, hypertriglyceridemia and hyperglycaemia

Due to the absorption of dialysate glucose, a caloric overload with a consequent weight gain, hypertriglyceridemia and hyperglycaemia can occur. Treatment includes a low calorie diet, increased physical activity and restricted water intake, seeking to minimize the need for hypertonic bags. The use of renal function-corrected dose fibrates is a therapeutic option for hypertriglyceridemia. Hyperglycaemia may require an oral hypoglycaemic adjustment and/or insulin adjustment. If no improvement is obtained,

consider changing the dialysis method.

Encapsulating peritoneal sclerosis

Encapsulating peritoneal sclerosis is a rare complication of long-term PD patients that is associated with high morbidity and mortality, usually due to an intestinal obstruction and malnutrition. There are no well-defined diagnostic criteria, and diagnosis is based on structural and functional characteristics, such as the combination of intestinal obstruction and peritoneal fibrosis encapsulation characteristics[21]. Anorexia, nausea, vomiting and weight loss are common, as well as anemia and hypoalbuminemia. Encapsulating peritoneal sclerosis can also present as hemoperitoneum and recurrent sterile peritonitis. Laparotomy is the only way to make a definitive diagnosis, but it is not usually performed due to its high risk. Computed tomography findings include variable bowel loop diameters, dilated and adhered loops, septate ascites, calcification, and thickening of the intestinal wall and peritoneal membrane. In addition to providing nutritional support (usually parenteral), PD should be discontinued. Corticosteroids, tamoxifen and immunosuppression have been described as alternative therapies, but these are of inconclusive benefit. Surgical treatment can also be tried as a treatment[22].

Infectious complications

• Peritonitis: This is the most serious complication of PD and is still the main factor for the failure of the technique. PD patients with abdominal pain should always have the diagnosis of peritonitis ruled out. Abdominal pain, turbid dialysis fluid and a peritoneal reaction are symptoms that may be encountered, which are confirmed by a dialysate cell count greater than 100 leukocytes/μL, with a predominance of at least 50% polymorphonuclear cells. The dialysate culture establishes the type of organism that causes the process, but it is not advisable to wait for its result to start treatment, which can be performed with intraperitoneal (IP) or systemic antibiotics for 14 to 28 days, depending on the organism in question, with doses corrected for renal function. The IP route is preferable. Repeated infections of the peritoneal cavity lead to a decrease in the area of exchange of the peritoneal membrane, with a consequent decrease in the effectiveness of dialysis treatment.

Treatment with gram-positive and gram-negative coverage should be initiated soon after peritoneal fluid culture collection. The ISPD recommends antibiotic selection be performed considering the local history of sensitivities to agents. Thus, a first-generation cephalosporin or vancomycin (gram-positive coverage) combined with a third-generation cephalosporin or aminoglycoside (gram-negative coverage) can be chosen. Antibiotics administered via the IP route may be given continuously (at all dialysis changes) or intermittently (once a day; in this case, the antibiotic bag should remain in the cavity for at least 6 hours). Dose recommendations are provided in Table 2. After identification of the agent through the culture results, the antibiotic should be adjusted (for example, once a gram-positive agent is identified, gram-negative coverage is suspended). Treatment may be outpatient, provided that the patient has no impairment of their general condition or signs of a systemic infection. The main treatment is a follow-up with the improvement of symptoms and, mainly, with clearing of the effluent; if there is no response after five days of appropriate treatment, refractory peritonitis is diagnosed, which requires catheter removal and transfer to HD.

TABLE 1. CLASSIFICATION BY TYPE OF PERITONEAL TRANSPORT

Category	D/P Creatinine	D/D0 Glucose	Drained Volume 4h
High transporter	>0.81	<0.26	1,580–2,085 ml
Medium-high transporter	0.65–0.81	0.26–0.38	2,085–2,368 ml
Medium-low transporter	0.50–0.65	0.38–0.49	2,368–2,650 ml
Low transporter	<0.50	>0.49	2,650–3,226 ml

D/P creatinine: relationship between dialysate creatinine and plasma creatinine.D/D0 glucose: relationship between the dialysate glucose concentration after 4 hours (D) and at time zero (D0).

TABLE 2. INTRAPERITONEAL ANTIBIOTIC DOSE RECOMMENDATIONS IN CAPD[A]

	Intermittent (per change, once a day)	Continuous (mg/L; all changes)
Amikacin	2 mg/kg	AD 25; MD 12
Cefazolin or Cefalotin	15 mg/kg	AD 500; MD 125
Ceftazidime	1,000-1,500 mg	AD 500; MD 125
Vancomycin	15-30 mg/kg every 5-7 days	AD 1000; MD 25

AD: attack dose; DM: maintenance dose. **a.** In patients with residual renal function (defined as urine output >100 mL/day), antibiotic doses should be increased empirically by 25%. Adapted from Li et al[23].

Peritonitis is considered recurrent when it occurs within four weeks after the end of antibiotic therapy for a previous episode, with isolation of the same agent or with a sterile culture. In this case, catheter replacement, which can be performed in a single procedure (simultaneous removal and implantation of another catheter), is recommended, provided that the effluent is clear.

In cases of *Staphylococcus aureus (S. aureus)* peritonitis, treatment for 21 days is suggested; for cases of *Pseudomonas aeruginosa (P. aeruginosa)* peritonitis, association with a second antipseudomonal agent, such as oral (PO) ciprofloxacin, an aminoglycoside or ceftazidime IP, is suggested. In such cases, the duration of treatment should be 21 to 28 days. In cases of fungal peritonitis, the catheter should be immediately removed and the antifungal agent maintained for at least two weeks after catheter removal.

After catheter removal due to infection and consequent transfer to HD, a minimum period of two to three weeks should elapse before reinsertion of a new PD catheter[23].

• Catheter infection (at the exit-site on the skin or subcutaneous tunnel): Infection of the catheter outlet is diagnosed by the presence of local hyperaemia and exudate. The two main aetiological agents are *S. aureus* and *P. aeruginosa*. If an infection is suspected, take a swab culture and initiate treatment to prevent peritonitis. Additionally, topical antibiotics in the catheter outlet, such as mupirocin, are recommended to prevent infection. Treatment should be started with PO antibiotic therapy for at least 14 days. An empirical treatment should always provide coverage for *S. aureus* (e.g. cephalexin 500 mg PO every 12 hours or every 8 hours), and in patients with a history of an exit-site infection with *P. aeruginosa*, it is recommended to use an antibiotic with antipseudomonal action (e.g., ciprofloxacin 250 mg PO every 12 hours). In cases of a recurrent or slowly resolving *P. aeruginosa* infection, a second agent, such as an aminoglycoside or ceftazidime IP, may be added. Treatment should generally last for 14 days. If prolonged therapy with adequate antibiotic therapy is not sufficient to resolve the infection, catheter replacement in a single procedure (simultaneous removal and implantation of another catheter) under antibiotic coverage is recommended[23].

TECHNIQUE FAILURE

In some situations, it is necessary to change the dialysis method from PD to HD. In these cases, we state that the technique failed. Failure can happen in the following cases:

1) When it is not possible to reach the ideal Kt/V urea. In such cases, patients should be informed of the risks of remaining on PD with an adequacy level below that recommended by the physician.

2) Low fluid removal in patients without residual renal function.

3) High transporter patients who have inadequate ultrafiltration and/or excessive protein loss (relative contraindication, obviously discovered after initiation and first PET).

4) Development of severe hypertriglyceridemia.

5) Frequent peritonitis.

6) Development of technical/mechanical problems.

7) Severe malnutrition resistant to aggressive treatment (relative).

Authors' contribution

The authors have contributed equally in drafting and reviewing the text.

RESUMO

A diálise peritoneal (DP) é uma terapia renal substitutiva baseada na infusão de uma solução estéril na cavidade peritoneal através de um cateter, proporcionando a remoção de solutos e água usando a membrana peritoneal como superfície de troca. Essa solução, em contato com os capilares do peritônio, permite o transporte difuso de solutos e a perda de água por ultrafiltração osmótica, uma vez que é hiperosmolar ao plasma devido à adição de agentes osmóticos (normalmente, a glicose). A infusão e drenagem da solução dentro da cavidade peritoneal pode ser realizada de duas maneiras: manualmente (DP ambulatorial contínua), em que o paciente, geralmente, passa por quatro trocas de solução durante o dia, ou por DP mecânica (automatizada), em que a diálise é realizada com o auxílio de uma máquina de diálise que permite que as trocas sejam feitas durante a noite, enquanto o paciente está dormindo. A prescrição e o acompanhamento da DP envolvem a caracterização do tipo de transporte peritoneal e a avaliação da dose de diálise oferecida (depuração do soluto), bem como o diagnóstico e tratamento de possíveis complicações relacionadas ao método (infecciosas e não infecciosas).

PALAVRAS-CHAVE: *Diálise peritoneal. Terapia renal substitutiva. Doença renal crônica terminal. Insuficiência renal crônica.*

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REVIEW ARTICLE

Mesenchymal stem cell therapy in acute kidney injury (AKI): review and perspectives

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http://dx.doi.org/10.1590/1806-9282.66.S1.45

SUMMARY

INTRODUCTION: *Acute kidney injury (AKI) is highly prevalent today. It has a multifactorial aetiology and affects people of all ages, genders and ethnicities. Its treatment is essentially supportive of renal function substitution, so new treatment alternatives such as mesenchymal stem cell therapy (MSCs) should be investigated.*

METHODS: *This review encompasses our understanding of the main mechanisms of action of MSCs in preclinical models of AKI by renal pedicle clamping ischemia-reperfusion, chemotherapy (cisplatin) and kidney transplantation in small and large animals, as well as outcomes in patients with AKI due to ischemia and kidney transplantation.*

RESULTS: *Cellular therapy with MSCs has benefits in preclinical studies of AKI through various mechanisms, such as anti-inflammatory, antiapoptotic, oxidative anti-stress, antifibrotic, immunomodulatory and proangiogenic. In humans, MSC therapy is safe and effective. However, the challenges of MSC cell therapy include investigating protocols about the optimal dose of these cells, the route and frequency of appropriate administration, and the design of further biodistribution studies over a long follow-up period. In addition, a better understanding of molecular signalling and cellular interactions in the microenvironment of each organ and tissue is needed in order to define the best time to administer MSCs. Another challenge would be to mitigate the heterogeneity of the profile of cultured MSCs through preconditioning approaches.*

CONCLUSIONS: *Cellular therapy with MSCs is very promising and should be part of the treatment of AKI patients in combination with other approaches already available, helping to accelerate recovery and/or slow the progression to chronic kidney disease. Randomized, multicentre controlled studies are needed to develop robust protocols that validate population-based cell therapy with MSCs.*

KEYWORDS: *Acute kidney injury. Cell therapy. Outcomes. Clinical trials.*

INTRODUCTION

In the current review, we will be addressing the challenges of mesenchymal stem cell therapy (MSCs), as these cells are already being tested in human clinical studies.

MESENCHYMAL STEM CELLS (MSCS)

MSCs, also known as stromal stem cells, are a diverse cell population with a wide range of potential therapeutic applications for different organs and tissues. MSCs can be derived from many tissue

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sources consistent with their possibly ubiquitous distribution.

These cells are characterized by clonogenicity, self-renewal, differentiation in different lineages and by regenerating organs with certain lesions. The International Society for Cellular Therapy has proposed a series of criteria for defining human MSCs (H-MSCs), namely: (1) adherence to plastic under standard culture conditions; (2) expression of CD73, CD90, CD105 surface molecules in the absence of CD34, CD45, HLA-DR, CD14 or CD11b, CD79a or CD19; (3) differentiation capacity for osteoblasts, adipocytes and chondroblasts in vitro (1). These criteria have been established to standardize the isolation of MSCs from humans, but may not apply uniformly to other mammals.

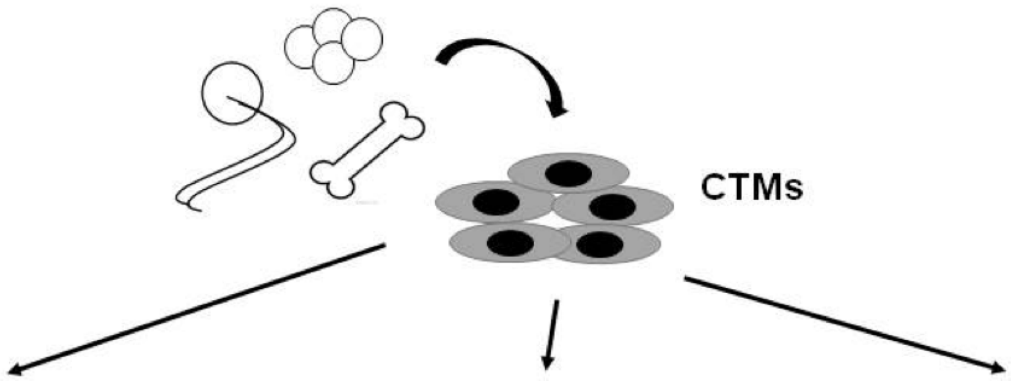
CELL THERAPIES USING MSCS IN SMALL ANIMALS

In Figure 1, we describe the main effects of MSCs extracted from different sites in the preclinical acute rodent models, including IR AKI by renal pedicle clamping, chemotherapy AKI (cisplatin), and kidney transplantation itself[2-9].

Despite the evidence that cell therapy with MSCs contributes to the improvement of AKI, some challenges need to be overcome in order for such therapy to be successfully established, such as defining the best route of administration, the number of cells per administration and also the number of injections, the best strategy for MSCs to migrate to acute and chronic kidney injury, understanding the interaction between MSCs and other tissue cells, and to identify adverse effects of MSCs (poorly differentiated in vivo and tumour formation).

Meta-analysis studies evaluating the therapeutic effect of MSCs in small animals in chronic and acute models of renal injury with variable administration (arterial, venous or renal) have shown beneficial effect for renal regeneration[10]. However, it is suggested that the arterial route enables renal regeneration more efficiently than the intravenous route. Intrave-

FIGURE 1. MAIN EFFECTS OF MESENCHYMAL STEM CELLS EXTRACTED FROM BONE MARROW, ADIPOSE TISSUE AND UMBILICAL CORD IN SEVERAL MODELS OF AKI BY RENAL PEDICLE CLAMPING ISCHEMIA-REPERFUSION, CHEMOTHERAPY (CISPLATIN) AND KIDNEY TRANSPLANTATION.



AKI induced by ischemia-reperfusion
(clamping of the renal pedicle)

↑ *Tubular cell proliferation*
↑ *Tregs, IL-10, and macrophage M2*
↑ *Klotho, HGF, VEGF, heme-oxygenase-1*
↑ *Microvascular density*

↓ *Creatinine, urea, KIM-1*
↓ *Apoptosis (caspase 3), TNF-a, IL-1, IL-10, IL-6, IFN-y*
↓ *a-SMA*
↓ *Oxidative stress*
↓ *Collagen deposition and interstitial fibrosis*
↓ *Tissue damage*

AKI induced by chemotherapy
(cisplatin)

↑ *Tubular cell proliferation*
↑ *Animal survival*
↑ *IL-10, VEGF, heme-oxigenase-I*

↓ *Creatinine, urea, albuminuria*
↓ *Apoptosis, TNF-a, IL-1, IL-10, IL-6*
↓ *HGF, IGF-1, VEGF, p53*
↔ *HGF, TGF-01, and IGF-1*
↓ *Infiltration of T lymphocytes, neutrophils, and macrophages*
↓ *Oxidative stress*
↓ *Epithelium-mesenchymal transition*
↓ *Interstitial fibrosis*
↓ *Tissue damage*

Renal transplantation
(Fisher -> Lewis, allogeneic)

↑ *Tregs*
↑ *Renal graft survival*
↑ *TSG-6 (TNF-inducible gene 6 protein)*

↓ *Creatinine, urea*
↓ *Infiltration of T lymphocytes and macrophages*
↓ *MHC II+, CD80+, and CD86+ cells*
↓ *CD4+/CCD8+ ratio*
↓ *TGF-01*
↓ *Interstitial fibrosis and tubular atrophy*

nously, cell number, multiple injections, and cell size increase the chance of pulmonary entrapment. Although local intraparenchymal administration also has a beneficial effect on renal repair, this route is less practical for clinical application, especially since renal disease is diffuse.

Another emerging approach to MSC administration-based therapies includes understanding the role of exosomes in tissue regeneration. Exosomes (30-40 to 100-120 nm) are vesicles naturally secreted by membranes and present ubiquitous distribution. These extracellular vesicles are considered important mediators of cell-to-cell communication, also mediating the effects of MSCs on target cells, such as the transfer of receptors, proteins, and genetic information (mRNA and microRNAs), as well as having direct stimulation in target-cell.

A key aspect that may adversely affect the therapeutic potential of MSCs is the inflammatory environment at the site of injury, as it may directly impact survival and incorporation of these cells into the injured tissue. Thus, M2 macrophage-derived anti-inflammatory cytokines (IL-10, TGF-ß1, TGF-ß3 and VEGF) favour the growth of MSCs, while M1 macrophage-derived proinflammatory cytokines (IL-1ß, IL -6, TNF-α and IFN-ψ) inhibit the growth of MSCs in vitro[11]. This observation indicates that the timing of MSC injection is crucial to the success of tissue repair.

However, further studies on renal models are still needed to evaluate this paradigm of transition from immune privilege to immunogenic state in MSC.

CELL THERAPIES USING MSC IN HUMANS

The number of registered clinical trials worldwide and applications for Investigational New Drugs (IND) submitted to the US Food and Drug Administration (FDA) have recently increased, as well as the diversity in donor and tissue sources and therapeutic purposes, despite the considerable heterogeneity in the protocols[12]. Most MSC trials included allogeneic cells occurring in the US, Europe, and China: phase 1 only (26%), phase 1/2 (40.6%), phase 2 only (22.5%), phase 2/3 (3.8%), phase 3 (6.7%) and phase 4 (0.3%). In 2019, 887 studies with H-MSCs were reported, 5% of which in renal diseases only, including AKI, DKD (diabetic kidney diesease), kidney transplantation and nephritis, among others[13].

Another key aspect of MSC-based therapy is the isolation of MSCs from individuals with chronic diseases, such as DM, for autologous transplantation. Thus, AT-MSC obtained from diabetic donors present higher levels of cellular senescence and apoptosis than AT-MSC obtained from non-diabetic individuals, as well as the reduced capacity of osteogenic and chondrogenic differentiation[14]. Similarly, type 2 diabetic patients treated with allogeneic UC-MSC ($1x10^6$/kg), by intravenous injection followed by intrapancreatic endovascular injection, showed a reduction in glucose and glycated haemoglobin levels after a 12-month follow-up, as well as systemic inflammation markers (IL-1ß and IL-6) and T lymphocyte count (CD3 and CD4)[14]. C-peptide levels also improved and insulin requirement decreased by ~30%. Thus, allogeneic versus autologous transplantation based on

TABLE 1. CLINICAL OUTCOMES OF THE MAIN STUDIES ON MESENCHYMAL STEM CELLS AND ACUTE KIDNEY INJURY (AKI) DUE TO ISCHEMIA.

Study	Stage	Type of AKI	Number of patients	Type of MSCs	Site of extraction of the MSCs / Route of administration	Dose (cells per kg of weight x 106) / number of doses	Time of infusion of MSCs	Main findings
Togel et al., 2012	I	Ischemia after cardiac surgery	15, separated in low (n=5), intermediate (n=5), and high (n=5) doses	Allogenic	Bone marrow / Intra-aortic (suprarenal)	Evaluation of scaled doses (quantity?) / Single dose	During surgery	- Administration of MSCs is safe - Reduction of AKI to 0% (versus 20%) - Reduction in 40% of the time of hospitalization and hospital readmission rates
Swaminathan et al., 2018	II	Ischemia after cardiac surgery	156, 27 centers: - 67: MSCs - 68: controls	Allogenic	AC607 MSCs (Allocure) - Bone marrow / Intra-aortic (suprarenal)	2.0 / Single dose	48h after AKI (preoperative creatinine: 1.3±0.6 mg/dl; pre-treatment creatinine 2.1±0.7 mg/dl)	- Administration of MSCs is safe - No difference in the number of days for recovery from AKI - No difference in mortality after 30 days

TABLE 2. CLINICAL OUTCOMES OF THE MAIN STUDIES ON MESENCHYMAL STEM CELLS AND ACUTE KIDNEY INJURY DUE TO ISCHEMIA-REPERFUSION INJURY AND ACUTE DYSFUNCTION CAUSED BY REJECTION AFTER RENAL TRANSPLANTATION.

Study	Induction therapy	Maintenance therapy	Number of patients/type of donor	Type of MSCs	Site of extraction of the MSCs / Route of administration	Dose (cells per kg of weight x 106) / number of doses	Time of infusion of MSCs	Main findings
Perico et al. (2011)	rATG (0.5 mg/kg/day, days 0-6; Basiliximab (20 mg, days 0 and 4); steroids (days 0-7)	CSA, MMF	2 / LRD	Autologous	Bone marrow / Intravenous	1.7-2.0 / single dose	Day 7	-↑ Tregs/Memory CD8 lymphocytes ratio - Pulse with MP in the third week (↑ creat) - Absence of DSA class I and class II
Tan et al. (2012)	Basiliximab (20 mg, days 0 and 4) only in the control group	ICN, MMF, steroids:	159 / LRD: - 53: standard CNI group - 53: standard CNI group + MSCs - 53: 80% CNI group + MSCs	Autologous	Bone marrow / Intravenous	1.0 - 2.0	Days 0 and 14	-↓ acute rejection in 6 months (~ 7% versus 21.6%) -↓ viral infection (~ 9% versus 29%) - no difference in eGFR in 12 months
Perico et al. (2013)	rATG (0.5 mg/kg/day, days 0-6; steroids (days 0-7)	CSA, MMF	2 / LRD	Autologous	Bone marrow / Intravenous	2.0 / single dose	Day 1	-↑ Tregs/Memory CD8 lymphocytes ratio - Acute cellular rejection in 1 patient
Reinders et al. (2013)	Basiliximab (20 mg, days 0 and 4)	CNI, MMF, steroids	6 / LRD	Autologous	Bone marrow / Intravenous	1-2 / 2 doses with a 1-week interval	6-10 months: SCR with 4 weeks or SCR and/or IF/TA with 6-10 months in renal biopsy	- improvement of tubulate in the absence of IF/TA - 5/6 patients: reduction of specific lymphocyte proliferation to the in vitro donor
Peng et al. (2013)	Cyclophosphamide 200 mg/day for 3 days and MP for 3 days (750 mg/250 mg and 250 mg/day)	TAC, MMF, steroids	12 / LRD (6 controls and 6 with 50% TAC and MSCs)	Allogeneic	Bone marrow / Intravenous	5.0 via the renal artery and 2.0 intravenously / 2 doses	Renal artery on the day of the transplant and intravenous after 1 month	- no difference in acute rejection and in eGFR after 12 months - MSCs group: higher levels of B-lymphocytes after 3 months - Absence of chimerism after 3 months
Reinders et al. (2015) Stage Ib; Neptune Study	Basiliximab (20 mg, days 0 and 4)	CNI, MMF, steroids	10 / LRD	Allogeneic	Bone marrow / Intravenous	2.5 2 doses (1-week interval)	25 and 26 weeks	- Ongoing study - Primary outcomes: acute rejection confirmed by biopsy and renal graft loss - Secondary outcomes: fibrosis, DSA, immunological tests, eGFR, opportunistic infections
Mudrabettu et al. (2015)	rATG (1 mg/kg) for 3 consecutive days	TAC, MMF, steroids	4/ LRD and LUD	Autologous	Bone marrow / Intravenous	0.21-2.4 / 2 doses	1 day before transplantation and 1 month after transplantation	- No early or late dysfunction of renal graft - Absence of viral infection - ↑ Tregs - ↓ proliferation of CD4 lymphocytes
Pan et al. (2016)	Cyclophosphamide 200 mg/day for 3 days and MP for 3 days (750 mg/250 mg and 250 mg/day)	TAC, MMF, steroids	32 (16 controls and 16 treated with 50% TAC and MSCs) / LRD	Allogeneic	Bone marrow/ Renal artery and intravenous	5.0 via renal artery and 2.0 intravenously / 2 doses	Renal artery on the day of the transplant and intravenous after 1 month	- No difference in acute rejection, renal graft survival, serum creatinine, and eGFR - Absence of changes in responses to donor alloantigens in vitro - Immunophenotyping comparable of subpopulations of T lymphocytes
Sun et al. (2018)	rATG (50 mg/day, for 3 consecutive days)	CNI, MMF, steroids	42 (21 controls and 21 treated with and MSCs) / DD	Allogeneic	Umbilical cord/ Intravenous + Renal artery	2.0 Intravenously and 5.0 via renal artery / single doses on each route	Intravenous: 30 minutes before the renal transplantation/ Renal artery at the time of transplantation	- No difference in delayed renal graft function, acute rejection, eGFR, patient and renal graft survival after 12 months

Study	Induction therapy	Maintenance therapy	Number of patients/type of donor	Type of MSCs	Site of extraction of the MSCs / Route of administration	Dose (cells per kg of weight x 106) / number of doses	Time of infusion of MSCs	Main findings
Vanikar et al. (2018)	Protocol for induction of tolerance: non-myeloablative therapy with Bortezomib, MP, rATG, and Rituximab	No conventional immunosuppression	10 / LRD	Allogeneic	Hematopoietic cells of the bone marrow and adipose tissue / Intraportal	0.22 ±0.16 of CD34+ cells from bone marrow mixed with 0.19 ±0.09 of MSCs of adipose tissue	14 days before the transplant	- Acute cellular rejection: 3 patients (155 days, 33.4 months and 1.4 year) - Patient survival: 100% (2 years), 90% (3 years), and 80% (6 years): n= 1 pneumonia; n =1 sudden death and chronic graft dysfunction - Renal graft survival censored to death in 6 years: 90% (n=1 loss due to IF/TA) - 2 patients with DSA, but without graft dysfunction - 5 with conventional immunosuppression and 2 with mycophenolate - Serum creatine: 1.44± 0.41 mg/dl after 6 years
Erpicum et al. (2019)	Basiliximab (20 mg, days 0 and 4)	TAC, MMF and steroids (39% discontinued)	20 (10 controls and 10 treated with MSCs) / DF	Allogeneic	Bone marrow / Intravenous	mean 2.4 (2.0-2.6) / single dose	3 ± 2 days after the transplant (2-5 days variation)	- 1 patient with acute myocardial infarction 3 hours after infusion of MSCs - ↑ Tregs in 30 days, but no difference after 1 year - No difference in proliferation of B lymphocytes - No difference in acute rejection and opportunistic infections - No difference in eGFR after 1 year - 4 patients developed antibodies anti-MSCs (only 1 with MFI > 1,500)

MSCs = Mesenchymal Stem Cells; rATG = Rabbit anti-thymocyte globulin; CSA = Cyclosporine; MMF = Mycophenolate Mofetil; LRD = Living related donation; LUD= Living unrelated donation; MP = Methylprednisolone; DSA = Donor Specific Antibody; CNI = Calcineurin inhibitor; eGFR = Estimated Glomerular Filtration Rate; SCR = Subclinical rejection; IF/TA = Interstitial fibrosis/Tubular atrophy; TAC = Tacrolimus; DD = Deceased donor; MFI = Mean Fluorescence intensity

the use of MSCs requires further investigation in the setting of DKD. On the other hand, in patients with ischemic cardiomyopathy, allogeneic and autologous BM-MSC were equally safe and effective[15].

In addition, some obstacles need to be overcome to achieve greater safety in MSC-based therapies such as cytogenetic aberrations observed during the propagation of these cells in culture. In humans, malignant transformation of MSCs has not been described in vivo so far in clinical trials. Another important aspect that should be taken into account in MSC cell therapy is the fact that its beneficial effect may be neglected by the occurrence of adipogenic differentiation during long-term follow-up, which may contribute to glomerulosclerosis.

In tables 1 and 2, we describe the main studies with MSCs in humans in the AKI scenario[16,17] and after kidney transplantation[18-28], respectively. In Table 2, we describe both studies that evaluated safety and efficacy at the initial moment of transplantation and also at the later period. Currently, there are more than ten ongoing clinical studies involving a significant number of patients undergoing kidney transplantation, which means more than one thousand individuals[29]. We highlight an ongoing clinical study with the inclusion of individuals undergoing renal transplantation and injection of two doses of autologous MSCs at weeks 6 and 7, and alemtuzumab induction followed by maintenance with everolimus and discontinuation of Tacrolimus from week 8 onwards[30].

An important point for the use of MSCs after kidney transplantation is the interaction between immunosuppressive drugs and the function of these cells. In vitro studies have shown that all immunosuppressant drugs (steroids, cyclosporine, sirolimus and mycophenolate) interfere in some way with the function of MSCs, leading to reduced production of

trophic factors (HGF and VEGF) and TSG-6, which has immunomodulatory properties and antiapoptotic properties[31].

NEW PERSPECTIVES

Preconditioning or gene modifications of MSCs

Several approaches have been suggested to increase the efficiency of cell therapy with MSCs, such as preconditioning or gene modifications.

Preconditioning of MSCs

MSCs are generally grown in a 21% oxygen environment. However, physiologically, MSCs are found in an environment with a much lower oxygen tension (1% to 7%). Thus, the cultivation or preconditioning of MSCs in a hypoxic environment with 2% or 5% oxygen allows these cells to remain multipotent and have greater proliferative and migratory capacity, as well as lower senescence rates[32]. In addition, hypoxia-preconditioned MSCs do not differentiate into tumour-associated fibroblasts in vitro and do not induce tumours in vivo.

In order to reduce the heterogeneity of the MSC profile, which is defined by the different isolation and culture protocols, the preconditioning of these cells with proinflammatory factors has been the focus of investigation. Thus, preconditioning of MSCs by stimulating IFN-ψ, TNF-α, PGE2 and nitric oxide mitigated the heterogeneous behaviour of MSCs in T lymphocyte proliferation trials and late type hypersensitivity response[33].

MSCs: gene carriers or gene modifications

Due to their migratory capacity to lesion sites, MSCs represent a robust platform for "delivery" of genes associated with regeneration and repair of renal tissue, working as a "Trojan Horse". Thus, several genes associated with trophic factors have been studied for these purposes, IGF-1, HGF, EGF or VEGF, since they are renoprotective[7,34].

Our group has been studying two genes, HGF and klotho, which have promising therapeutic potential in the future. We are modifying MSCs with these genes and will be injecting them into acute and chronic models of kidney injury.

In the context of IR or cisplatin-induced AKI, HGF is associated with increased tubular epithelial cell proliferation and migration, as well as lower α-SMA expression, fibrosis, and apoptosis. In chronic models such as murine DKD, HGF gene therapy increased the expression of SDF-1, which is the ligand of CXCR4 and, consequently, bone marrow cell migration to the kidney. Consequently, there was an improvement in proteinuria, a reduction in glomerulosclerosis (lower collagen I and IV deposition, and fibronectin) and TGF-β1 levels, a reduction in glucose and GLUT1-mediated glucose uptake, thus reducing oxidative stress. Similarly, in the murine Lewis mouse transplant model, HGF also reduced tubulointerstitial fibrosis, glomerulosclerosis and inflammation, leading to increased renal graft and animal survival.

Klotho is highly expressed in the distal tubule of the kidney[35]. It is a co-receptor for fibroblast growth factor-23 (FGF-23) and participates in mineral homeostasis through interaction with other hormones such as parathyroid hormone (PTH) and 1,25-$(OH)_2$ vitamin D3 in various tissues such as the kidneys, bones, intestines and parathyroid gland. There is a molecular signature of murine model klotho deficiency and CKD in humans, both related to serum creatinine values related to klotho expression in renal tissue, serum phosphorus and FGF23 values, atherosclerosis and ectopic calcification. In the kidneys, the soluble form of klotho has several effects and, therefore, therapeutic targets, such as antioxidant effects on cells (decreased senescence and apoptosis, as well as increased autophagy), inhibition of fibrosis, phosphorus reduction and FGF23, proangiogenic agents and maintenance of the stem cell reservoir, as well as reducing myocardial remodelling. Similarly, understanding the factors that decrease klotho expression in the kidney is equally important for establishing combined therapies to mitigate AKI damage and reduce CKD progression and, consequently, renal fibrosis. Factors that decrease kidney klotho expression include reduced kidney functional mass, abnormal cytokine production (↑ TNF-α and ↑ IFN-ψ), increased oxidative stress (↑ lipid peroxidation and hydrogen peroxide), activation of the renin-angiotensin-aldosterone system (RAAS), reduction of vitamin D3, alteration of bone metabolism (hyperphosphatemia) and uremic toxins (↑ indoxyl sulphate).

In AKI patients, there is a proportional reduction in klotho expression according to the severity of the lesion. Thus, the administration of klotho protein, as well as the study of drugs that increase its production (statin and RAAS blockers, for example), reacti-

vation of endogenous expression of klotho by epigenetic mechanisms (demethylation and deacetylation) and/or cell therapy itself represent promising strategies. Thus, UC-MSC injection in rats subjected to IR injury restores kidney klotho expression, whereas genetically modified klotho-adenovirus MSCs lead to reduction of morphological and structural damage in the same model.

Other genetic modifications of MSCs, which are also quite promising in the context of AKI, include overexpression of erythropoietin, CXCR4, CTLA4Ig and IL-10/selectin, as well as transfection of biological drug-containing minicircles such as Etanercept, which is a TNF-α blocker and the transfection of nanoparticles containing iron oxide, polymers and plasmids.

Renal tissue-derived progenitors/stem cells

Several progenitors/stem cells specific to renal tissue have been studied in the literature, mainly in preclinical studies, and evaluated in acute and chronic models.

Recently our group demonstrated that c-Kit$^+$ cells present in renal tissues have cardinal progenitor/stem cell properties, such as the ability to differentiate in different lineages of the mesodermal and ectodermal layers, clonogenicity, self-renewal and therapeutic potential in the AKI by IR model and acute puromycin-induced nephrotic syndrome in rats[2,36]. In addition to paracrine effects, c-Kit cells have been incorporated around 10% in various renal compartments, such as tubular, vascular and glomerular, making them promising candidates for cell therapy. There is interest in defining whether MSCs can modulate c-Kit stem/progenitor cells in vivo or whether the combined infusion of these cells can have a more robust effect on renal tissue regeneration or interruption of AKI and CKD progression. Recently, we have reported the expression of c-Kit cells in kidneys of deceased donors[37], so future studies are needed to demonstrate the therapeutic potential of these cells in preclinical and human models.

Other approaches to renal regeneration: embryonic stem cells, inducible pluripotent stem cells (iPSCs), organoids and renal decellularisation

Embryonic stem cells and inducible pluripotent stem cells are capable of originating the three types of embryonic layers, giving rise to any cell type when appropriate culture conditions are applied. Modest clinical trials are underway with these cells[13].

IPSCs have been studied as a model for the re-creation of renal diseases and culture plate, studies of signalling pathways, therapeutic tests, drug screening[38], and the generation of renal and organoid progenitors that can be used for renal regeneration and for a better understanding of the pathways involved in renal development and pathobiological processes. Other robust platforms that can be used for this purpose include 3D printing techniques and kidney-on-a-chip microfluidic technology. Renal decellularisation presents a therapeutic alternative and its use has already been successfully tested in small animals, combined with recellularisation with endothelial cells, renal foetal cells and MSCs. Renal decellularisation studies in larger animals are needed, and in the future, kidney from pigs or from expanded criterion donors may be used as an alternative or as a bridge to kidney transplantation.

CHALLENGES TO CELL THERAPY

Heterogeneity of AKI causes.

Each scenario promotes a type of molecular signature, requiring specific interventions for each in order to regain homeostasis. Understanding the biological environment in which cells are being inserted is extremely important in order to design the best approach beforehand and to understand possible therapeutic outcomes after therapy.

High structural complexity of kidneys.

The kidneys are formed from two germinal foci, the ureteric bud and the metanephric mesenchyme, which differ in more than 30 different cell types in the adult kidney. Thus, an intense association between epithelium and vascular tissue is formed in various functions for hemodynamic balance and electrolyte balance.

Complicating factors of MSCs therapy itself

Exact understanding of the type of cell used

The acronym "mesenchymal (stromal) stem cell" refers to a diverse set of cell types and is therefore it is inaccurate. From the moment of cell extraction to the choice of tissue source, they already interfere with potential, function and transcripts.

Administration timing

Ideally, MSCs should be injected at the very beginning of AKI changes. The difficulty of this moment is the silent form of the lesion, without presenting typical symptoms. Good biomarkers should be established to identify as soon as possible the onset of AKI, quickly and early. Once this ideal moment of action is identified, it is necessary to have the cells ready for injection, requiring very well structured logistics and making it difficult to use autologous cells (due to the time of preparation and expansion in culture).

Compatibility between injected cells and receptors

Despite the well-established notion of MHC-II expression by MSCs, further understanding of the mechanisms related to the immune privilege or immunosuppression ability of MSCs is needed, which may be crucial for the successful integration of cells into the patient and the success of the therapy, as it happens in cases of bone marrow transplantation. This knowledge is even more necessary in the clinical setting, which often requires multiple dose applications to achieve the expected outcome in chronic diseases.

In favour of the use of autologous MSCs, a meta-analysis in heart failure patients favoured increased exercise capacity, left ventricular ejection fraction, quality of life and reduced mortality and hospital readmission rates[39]. In another meta-analysis, treatment with whole bone marrow autologous cells (dose ranged from 382.6 ± 10^7 to $2.8\pm1.9x10^9$) was effective for reducing glycated haemoglobin (HbA_{1c}) by 1.18% and for reducing the need for insulin at 3, 6, 9 and 12 months after treatment[40].

There is recent evidence that allogeneic MSCs would be as effective as autologous MSCs in improving the final diastolic volume and left ventricular ejection fraction of patients with ischemic cardiomyopathy[15]. Importantly, allogeneic MSCs did not promote immune response at the receptors. In renal transplant patients, injections of autologous[18] and allogeneic[26] MSCs were also considered safe.

Understanding the specific action mechanisms of different MSCs types

There is a lack of skill specification data that MSCs present according to their tissue origin, for the proper adaptation of the cell type to the clinical picture to be applied. Important qualifications of MSCs such as cell-type differentiation of damaged target tissue, immunosuppression and anti-inflammatory action have been tested in vitro and do not necessarily accurately predict actual clinical potency in each scenario. An interesting study has shown that for the immunosuppressive action of MSCs in patients with host disease against donor, cytotoxic immune attack of the host patient against injected MSCs is essential, inducing them to apoptosis. Patients who responded best to therapy were the ones with the highest cytotoxicity against injected MSCs. According to the evaluation of the existing literature, the decision of the moment of injection of the cells determines the microenvironment that they will find. MSCs, in response to the inflammatory microenvironment, activate their own anti-inflammatory mechanisms, defining the resultant patient-cell therapy interaction. This may explain some negative results obtained by clinical trials. For example, patients who received MSCs prior to kidney transplantation showed no difference from the control group in relation to the common adverse effects of the procedure, which can be explained by the microenvironment without the inflammatory IR insult installed and, consequently, the lack of activation of MSCs to the anti-inflammatory pattern[41].

Monitoring patients beforehand in order to identify these more responsive subgroups and understand the timing of the most appropriate pathogenesis for cell administration is extremely valuable in achieving the desired efficacy of the therapy.

Data from clinical trials are in progress

Most clinical studies are based on safety and efficacy outcomes and are not designed with large numbers of patients and have heterogeneity in injection dose and frequency. However, the occurrence of adverse events after treatment with MSCs does not appear to be different from the control group.

Cell dose per individual: uncertainties

There is a detrimental mismatch between data from preclinical and clinical studies regarding the appropriate amount for cell therapy with MSCs. Commonly, in rodents, the intravenous dose is 50 million/kg/weight. In humans, MSCs are usually transfused around 1-2 million/kg/ weight. However, weight adjustment may not be the best measure for comparing humans and rodents for therapeutic perspectives. Even so, considering that they respect the same biological mechanism of action and that the effects are

dose-dependent, this difference in methodology imposes a negative bias in clinical practice due to the lower dose used in humans.

Administration route: more effective biodistribution for the desired outcome

There is still no consensus on the best route of injection of MSCs in preclinical and clinical trials, and the intravenous route is widely used. Depending on the choice, there is a different dynamics of cell distribution in the body, affecting the mechanism of action and possibly the clinical outcome. Among the options, some choices have practical methodological ease in the routine application and also in the transition to clinical use, such as the extravascular (intraperitoneal, intramuscular and subcutaneous) pathways. Testing these pathways, it has already been shown that MSCs, when acting in a systemic manner, also end up benefiting the organ affected by the disease in question, even with the distance[42].

Regulated clean room

It is necessary to define production standards according to the disease and the type of patient. Isolation method, culture time and environment composition can all affect the potency and quality of the final product of MSCs. It is suggested that MSCs be injected until passage (P)2, when the amount of cells obtained is also sufficient. It is still necessary to consider the costs and complexity of these processes, and it is extremely important to evaluate measures that enable large-scale production at low cost, as it is done in the processes of blood transfusion centres.

One of the challenges of cell therapy with MSCs is a better understanding of the occurrence of chromosomal alterations, which, although rare (n=1/152), leads to the disposal of MSCs[43]. Thus, the genomic integrity of MSCs, assessed by karyotype, should always be considered, although the ideal moment, if soon after cell collection, in which passage or before infusion, is still a matter of debate.

Finally, the additional characterization of MSC manufactured products is essential for a better understanding of the phenotypic characteristics and their subpopulations, as well as for the evaluation of their therapeutic potential.

CONCLUSIONS

Cellular therapy with MSCs has benefits in preclinical studies of AKI through various mechanisms, such as anti-inflammatory, antiapoptotic, oxidative anti-stress, antifibrotic, immunomodulatory and pro-angiogenic. Such benefits may also explain many of the positive effects of that therapy on humans.

Authors' contribution:

C.S.S.; P.E.S.S.; M.T.B.R., A.O.L. wrote the review; E.B.R. wrote the review and gave the final approval.

Acknowledgment

This work was supported by the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (Fapesp) for Christian Sávio Silva (process 2017/18072-9), Poliana Evelyn Soinski de Sousa (process 2018/24562-1) and Érika Bevilaqua Rangel (process 2017/23195-2), in addition to the European Foundation for the Study of Diabetes (EFSD) for Érika Bevilaqua Rangel.

PALAVRAS-CHAVE: *Lesão renal aguda. Terapia celular. Desfechos. Ensaios clínicos.*

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REVIEW ARTICLE

Anemia in chronic kidney disease

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http://dx.doi.org/10.1590/1806-9282.66.S1.55

KEYWORDS: *Anemia; chronic kidney disease (CKD); functional iron deficiency; erythropoiesis- stimulating agentes (ESA); hypoxia-inducible fator (HIF) stabilizers.*

INTRODUCTION

Anemia, defined as hemoglobin (Hb) ≤ 12 g/dL in women and Hb ≤ 13 g/dL in men[1], was first linked to chronic kidney disease (CKD) in 1836 by Richard Bright[2]. This condition is highly prevalent, although treatable, whose frequency increases in the more advanced stages of the disease. It can be found in more than 50% of patients with the diagnosis of CKD in stages 4 and 5[3] and appears earlier in individuals with diabetes mellitus (DM)[4].

Anemia in CKD is typically normocytic, normochromic, and hypoproliferative. The discovery of a factor produced in the renal cortex and responsible for stimulating erythropoiesis, later identified as erythropoietin (EPO), led to the hypothesis that its deficiency could be the main cause of anemia in CKD patients[5].

PHYSIOPATHOLOGY

The erythropoietic system is responsible for maintaining the balance in the supply of red blood cells, thus, ensuring an adequate tissue oxygenation[4]. To maintain this balance, the senescent erythrocytes are replaced by new cells. Hypoxia plays an important role in stimulating erythrocyte production through its interaction with the HIF (hypoxia-inducible factor) system. The HIF is a heterodimer consisting of two subunits: alpha and beta. The production of HIF-alpha is continuous; however, its degradation occurs in the absence of tissue hypoxia. On the opposite situation, alpha and beta subunits join and bind in the nucleus of the cell, a DNA sequence called hypoxia-responsive elements. Thus, the production of erythropoietin is stimulated.

Erythropoietin, in turn, is a molecule of 165 amino acids and 4 chains of carbohydrates. Pro duced mainly in the interstitial cells of the renal cortex, with the reduction of glomerular filtration, the hepatic production increases significantly. The half-life of erythropoietin is 5 to 12 hours, and it acts as a true hormone that binds to receptors of bone marrow cells to produce erythrocytes[4-6].

Although the reduction in the production of erythropoietin significantly contributes to anemia in CKD, it is not the only cause. Iron deficiency is common, and it is estimated that patients on hemodialysis have an iron loss of around 1 to 3 grams per year[7]. Even in patients not receiving dialysis, low levels of iron are often found[4]. Frequent phlebotomies, blood loss in the hemodialysis apparatus, and impairment in its absorption may explain this finding[5]. The beginning of treatment with erythropoietin analogs showed how common iron deficiency is among CKD patients[5,8].

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Iron deficiency often occurs as a functional deficiency and is characterized by a low transferrin saturation index (TSI) and normal or increased ferritin. Ferritin can be increased in the presence of inflammation, infection, liver disease, and malignancy[2]. Thus, its high levels may not reflect stored iron. The regulation and maintenance of systemic iron homeostasis also depend on hepcidin[9.10]. Produced in the liver, it induces the degradation of ferroportin in duodenal enterocytes, hepatocytes, and macrophages, which prevents proper absorption and use of iron. Inflammatory cytokines are capable of inducing the transcription of hepcidin[5.6], and there is evidence of its increase in patients with CKD[5].

Anemia in CKD is, therefore, a process with multiple causes, which includes mainly the deficiency of erythropoietin, reduction in the life span of erythrocytes (of poorly defined etiology), and changes in the homeostasis of iron.

CLINICAL CONSEQUENCES

Anemia is associated with several symptoms that lead to reduced quality of life, such as fatigue, dyspnea, insomnia, and headache. It is also related to reduced cognitive capacity. However, these symptoms are nonspecific and could be, in patients with CKD, a consequence of uremia4. Since symptoms develop gradually, many patients do not report complaints spontaneously; however, when actively questioned, they may report limitations in their usual activities.

In addition, anemia is associated with left ventricular hypertrophy (LVH), an increased number of hospitalizations, a possible progression of CKD, and death[11.12]. The increase in mortality occurs mainly when Hb≤ 8 g/dL[13].

In relation to LVH, some studies have associated lower levels of hemoglobin, especially Hb < 7.7 g/dL, with the increase of left ventricular mass. Silberberg et al.[14] described that for each 1g/dL reduction of hemoglobin, there was an increase of 6% in the incidence of LVH.

The hypothesis that anemia may be related to the progression of CKD emerged from experimental studies. Since there is a direct relationship between the concentration of hemoglobin and tissue oxygenation, the presence of anemia could lead to hypoxia of the tubular cells, which, in turn, would contribute to the progression of the tubulointerstitial injury present in CKD. Furthermore, erythrocytes are described as an antioxidant component, and its reduction could be associated with increased oxidative stress[15]. In a post hoc analysis of the RENAAL study[16], the initial concentration of hemoglobin was an independent predictor of renal outcome. Even slightly decreased values were related to the risk of disease progression. However, it is important to remember that the prevalence of anemia increases with the progression of CKD, and, therefore, a cause-effect relationship cannot be established. In opposition to the RENAAL study, other observational and intervention studies [17.18] did not find a significant relationship between the evolution of the CKD and hemoglobin concentrations.

Before the start of treatment with erythropoietin analogs, lower hemoglobin levels were common among patients on dialysis- which exposed them to the risk of multiple blood transfusions and reduced functionality[11,12,17].

DIAGNOSIS AND TREATMENT

The presence of anemia in CKD does not imply that treatment with erythropoietin analogs should necessarily be initiated. It is recommended, however, to investigate its cause even with values slightly below normal (Hb < 12g/dL)[4].

The initial assessment is similar to that in other populations, although an emphasis on iron deficiency is suggested. It is common to find high levels of ferritin, which can reflect inflammation and does not exclude iron deficiency. TSI, the level of circulating iron, should also be analyzed. However, none of these two parameters, alone, can predict the actual iron status in CKD patients. When analyzed together and according to their fall or rise tendency, it is possible to predict response to treatment.

The dosage of erythropoietin should not be performed since its deficiency is relative. Tests results would not help in the diagnosis or treatment management[4].

In 1989, the approval of the first erythropoietin analog revolutionized treatment of anemia in CKD. Until then, patients were treated only when very symptomatic, with multiple blood transfusions[8]. The transfusions exposed them to the risk of infections, transfusion reactions and, in addition, often prevent renal transplantation.

Currently, the use of erythropoietin analogs is widespread. However, before starting these erythropoiesis-stimulating agents (ESA), iron deficiency must

be investigated. Iron replacement can be done orally or parenterally. The first route is used for most patients not receiving dialysis or undergoing peritoneal dialysis since there is a concern to preserve vascular access. However, in patients undergoing hemodialysis, the oral route presents reduced effectiveness[19].

An exception is ferric citrate supplementation, which is effective even for patients on dialysis.

Parenteral iron, on the other hand, presents excellent effectiveness and is the treatment choice for patients undergoing hemodialysis. Iron infusion can lead to hypotension or hypersensitivity reactions, although it is quite safe[20].

The doses recommended for iron replacement depend, among other factors, on the stage of the disease.

The recommendation by the Brazilian Society of Nephrology is that patients with CKD stages 1 and 2 should maintain the same levels of ferritin and TSI as the general population[21]. For patients in stage 3, 4, and 5 who are not on dialysis, serum ferritin and TSI should be kept higher than 100ng/mL and 20%, respectively. In dialysis patients, ferritin levels should remain over 200ng/mL and TSI > 20%. In the same way, the interruption of iron replacement is considered when ferritin > 500ng/mL and IST> 30%. Iron therapy should be suspended in the presence of active systemic infection[20].

In 2018, the PIVOTAL study[21] showed that higher doses of iron might be associated with a lower risk of cardiovascular events and reduced doses of ESA without an increase in the risk of infections. The beginning of treatment with erythropoietin analogs should occur, ideally, when iron deficiency is corrected.

The first erythropoietin analog used was epoetin alfa. Subsequently, darbepoetin was also approved. Both can be administred subcutaneously or parenterally. The use of erythropoietin analogs is not devoid of risks. It is important that blood pressures is controlled[4]. It should be avoided in the presence of active neoplasia, especially when cure is the anticipated outcome, and it is recommended to use with great caution in patients with previous stroke or malignancy[19].

After initiating treatment, an increase of hemoglobin at around 1g/dL is expected in the first month. In case of elevations above 1g/dL in two weeks, a dose reduction of 25-50% is recommended.

The optimal level of hemoglobin is still a controversial issue. Initial studies sought to correct anemia to maintain hemoglobin values similar to the general population. However, two large randomized trials[17,22] showed more cardiovascular events and a lack of improvement in the quality of life when the hemoglobin level was completely corrected. It has been questioned whether this increase in adverse events is related to the higher dose of erythropoietin analogs, and not to the hemoglobin levels reached[23].

The use of erythropoietin analogs has a clear benefit in patients with Hb<10 g/dL and increased risk when Hb>13g/dL. The recommendation to maintain a target of Hb between 10 and 11.5g/dL seems advisable to achieve the benefits of treatment without increased risks[4].

Recently, a new drug class (the HIF stabilizers) has been proposed for the treatment of anemia in CKD patients[6]. This medication acts through the enzymatic inhibition of prolyl-hydroxylase, leading to the stabilization of HIF factor. The HIF, as mentioned, is a determinant factor in the physiological response to tissue hypoxia. The stabilization of HIF stimulates the endogenous production of erythropoietin. However, its levels are lower than with the use of EPO analogs. This consistent, though less pronounced, increase can be related to a lower risk of cardiovascular events or access thrombosis than those attributed to EPO analogs. Besides stimulating the production of EPO, HIF stabilizers are involved in the iron metabolism. They act reducing the levels of hepcidin, which leads to improved intestinal absorption, as well as increased release of iron from macrophages to transferrin. An additional advantage of HIF stabilizers is its oral administration.

Two phase-3 studies on the use of Roxadustat, a second-generation HIF stabilizer, have been published[24,25]. One of them showed the superiority of Roxadustat in the treatment of anemia in patients not receiving dialysis when compared to a placebo. The other highlighted the non-inferiority of this medication compared to epoetin alfa in patients undergoing dialysis. As additional effects, they found a reduction of hepcidin and total cholesterol, LDL, and triglycerides in patients who used the HIF stabilizer. Hyperkalemia was also more common with the use of Roxadustat.

This new drug option leads to questions regarding the proposed treatment for anemia in CKD. Further studies are needed to ensure that long-term adverse events are evaluated. In addition, it raises the question of whether HIF stabilizers could normalize the hemoglobin level of patients without the risks associated with erythropoietin analogs.

PALAVRAS-CHAVE: *Anemia. Insuficiência renal crônica. Deficiência de ferro.*

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REVIEW ARTICLE

Diet in Chronic Kidney Disease: an integrated approach to nutritional therapy

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http://dx.doi.org/10.1590/1806-9282.66.S1.59

SUMMARY

A healthy diet is an essential requirement to promote and preserve health, even in the presence of diseases, such as chronic kidney disease (CKD). In this review, nutritional therapy for CKD will be addressed considering not only the main nutrients such as protein, phosphorus, potassium, and sodium, which require adjustments as a result of changes that accompany the reduction of renal functions, but also the benefits of adopting dietary patterns associated with better outcomes for both preventing and treating CKD. We will also emphasize that these aspects should also be combined with a process of giving new meaning to a healthy diet so that it can be promoted. Finally, we will present the perspective of an integrated approach to the individual with CKD, exploring the importance of considering biological, psychological, social, cultural, and economic aspects. This approach has the potential to contribute to better adherence to treatment, thus improving the patient's quality of life.

KEYWORDS: *chronic kidney disease, diet, nutrition, dialysis*

INTRODUCTION

Proper nutrition is a basic requirement to promote and preserve health and is recognized as a determinant and conditioning factor for the health status of individuals and groups of people. In situations of chronic diseases, such as chronic kidney disease (CKD), diet is part of its treatment at all stages. Changes in lifestyle that include the practice of physical exercise, proper nutrition, and smoking cessation are important factors that, when associated with the control of blood pressure, blood glucose, and lipid profile, contribute to decrease the rate of progression of CKD. More recently, the approaches used to advise patients with CKD regarding diet have been discussed because of the difficulty in getting patients to adhere to the recommendations.[1] Furthermore, studies suggest that greater attention should be given to the quality of these patients' diets.[2,3] At the same time, the concept of a healthy diet has been discussed, and the need to give it a new meaning has become evident.[4,5] Due to the relevance of diet as part of any stage of the CKD treatment, it is necessary for health professionals who handle with CKD patients to have a basic

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understanding of what is a healthy diet, regardless of their area of specialization. In this context, to clearly delineate the concept of a healthy diet, it is necessary to take a closer look into history.

Healthy diet in CKD: giving it a new meaning to promote it

Historically, the concept of a healthy diet has been tied to an almost exclusively biological perspective of eating, often associated with the metabolism, digestion, absorption, and storage of nutrients (post-swallowing aspects). To Viana et al.,[6] we excessive rationalize the diet and nutritional process, reducing it to the physicalist perspective of nutrients and its influence on the body. The American gastronomic critic Steingarten[7] stated that "health authorities never consider the profound benefits that delicious food can bring to our miserable lives. In over 1,000 pages of federal reports on nutrition, I could not find a single occurrence of the words delicious, tasty, or flavorful.". In addition, this reductionist outlook on nutrition contributed to *Nutritionism,* which identifies food items just as the sum of its nutrients, minimizing or even excluding the sociocultural components of food and commensality, transforming nutrition into an exact and purely biological science.[8] However, eating is a complex process that, when seen only by this perspective, ignores the various determinants of food choices, which include interactions of factors related to food, the environment, and the individual including their own subjectivity.[9] Although satisfying nutritional needs is essential for survival, the meanings of food should not be understood only by means of nutritional indicators. Eating and sharing food ensures both our physiology as our humanity, because what you eat, how and when you eat it, are elements filled with meaning.[6] In this sense, considering pre-swallowing aspects, i.e., behavior, culture, society, and experiences around food, it is essential to understand and recommend a healthy diet. In fact, if we think that knowledge-based choices represent very little compared to the diverse influences that operate below the level of consciousness, we could say that focusing only on biological aspects is counterproductive.[10] As an example, just see how efforts to curb obesity rates have not shown good results; coincidently, they are often focused only on the biological aspects of nutritions and health.

On the other hand, studies about the so-called "French paradox" show that there are substantial differences in the dietary beliefs and concerns among countries. Attitudes such as spending more time eating; having more social moments around food; seeing food as a source of pleasure, not of guilt or concern; eating fresher food (regardless of nutrients), and relying on internal cues from the body to decide how much to eat, are among the main characteristics that differentiate the relationship of French and American individuals with food. However, the French have better health parameters than Americans.[13-16] When commenting on these results, Pollan[17] suggests, paradoxically, that considering food more than an end to bodily health, i.e., as also a source of pleasure, socialization, and identity, does not make people less healthy; in fact, there are reasons to believe that this could make them healthier. Thus, it is worth questioning: to those of which of the two countries (France or the United States) do our practices resemble?

In this sense, the most recent version of the Dietary Guideline for the Brazilian Population[18] represents a paradigm disruption in the dissemination and definition of a healthy diet, bringing in its chapters the importance of eating as a social activity and also of having pleasure from it. The Brazilian Guideline considers, as a principle, the need to promote the individual's autonomy regarding their diet and stresses that adopting a healthy diet is not merely a matter of individual choice, since several factors, such as the physical, economic, political, cultural, or social nature can positively or negatively influence the dietary patterns of individuals. The Guideline classifies foods into categories according to the processing level employed in their production (*in natura* or minimally processed food, processed food, and ultra-processed food), instead of their content of nutrients. Table 1 describes ten steps to a healthy diet, according to the Guideline.

In addition to the questions raised, to optimize the promotion of a healthy diet, it is necessary to have a better understanding of the individual's belief system, because the way we think about "food" and "healthy" predicts our eating behavior[19]. In a qualitative study, Kelly et al.[20] listened to patients with CKD in order to understand their experiences in relation to the dietary approaches employed. The patients reported a lack of support and regular feedback to sustain changes, that the guidelines provided do not consider the promotion of dietary autonomy, and that the ambiguity of information between health professionals, and the dichotomization of foods, as in 'allowed' and 'not allowed', 'good' and 'bad', contributes to making

them feel exasperatedly unable to adhere to the guidelines. Thus, patients value professionals who transmit tranquility, are positive, involve their families and/or caregivers, and focus on what is possible in their diet, and not on imposing restrictions[20]. In addition, it is necessary to have caution because extremely restrictive approaches with CKD patients can contribute to worsening diet quality[2].

Improving communication skills with patients is another step to improve adherence to nutritional therapy.[21,22] Simply sharing various nutritional information is not enough to change the patient's behavior and promote adherence, especially in the long term.[23] However, as already mentioned, it is first essential to understand "healthy" more broadly, and then move on to strategies. Considering the above, it is prudent to say that there cannot be a definition of what is a healthy eating without contextualizing "who, when, how, and where". Finally, in the presence of chronic diseases, the essence of any health intervention needs to be the individual, valuing, therefore, their subjectivity, culture, social, and economic aspects. Similarly, in the CKD, regardless of its stage, all these factors must be considered. The adjustments of some nutrients that require special care in CKD, such as protein, phosphorus, potassium, and sodium, will be discussed in this chapter and must be performed without disregarding the global nature of healthy eating.

PROTEIN

The control of the amount of protein has been one of the most discussed dietary practices in CKD. The acute ingestion of proteins influences the renal hemodynamics, increases the renal plasma flow, the intraglomerular pressure, and glomerular filtration rate. This physiological effect aims to increase the excretion of products derived from the protein metabolism through the kidneys.[24] In healthy individuals, a high intake of protein in the long-term does not seem to promote deleterious effects on renal function; however, increased protein intake was associated with a lower glomerular filtration rate (GFR) in individuals with some degree of CKD.[25] In this sense, it is suggested that the popular high-protein diets, used for various purposes, should be used with caution, since CKD is a silent condition, commonly underdiagnosed and of growing incidence.

Considering that glomerular hyperfiltration is one of the pathophysiological mechanisms of CKD progression, low-protein diets (0.6 to 0.8g/kg/day) have become popular as a dietary strategy in the non-dialysis stage. However, its benefit on the progression of CKD remains controversial, particularly after the widespread use of renin-angiotensin-aldosterone system (RAAS) inhibitors.[26] However, this strategy presents important benefits on the reduction of proteinuria and the need for dialysis.[27] Low-protein diet also contributes to reducing the endogenous production and accumulation of toxic metabolites, attenuating clinical manifestations of uremia. In addition, nutrients such as phosphorus, potassium, saturated fatty acids, sodium, and acid-producing compounds, are present in the main sources of protein, such as meats in general, eggs, and dairy products.[28] Thus, reduced ingestion of these foods helps in the prevention and treatment of eletrolyte, metabolic, and hormonal disorders in CDK. Recently, the short term reduction of protein intake, was accompanied by a decrease in serum concentrations of toxins from the intestinal microbiota.[29,30] Despite the benefits mentioned above, there are concerns that low-protein diets may promote malnutrition. However, to date, studies have not found any significant changes in

TABLE 1. TEN STEPS TO A HEALTHY DIET ACCORDING TO THE DIETARY GUIDELINE FOR THE BRAZILIAN POPULATION[18].

1. Make *in natura* or minimally processed foods the foundation of the diet.
2. Use oils, fats, salt, and sugar in small amounts to season and cook food and create culinary preparations.
3. Limit the consumption of processed foods.
4. Avoid the consumption of ultra-processed foods.
5. Eat regularly and thoughtfully, in appropriate environments and, whenever possible, with company.
6. Shop at places that offer a variety of in natura or minimally processed foods.
7. Develop, exercise, and share culinary skills.
8. Planning time to give eating the space it deserves.
9. Give preference, when away from home, to places that serve fresh meals.
10. Be critical about the information, guidance, and messages on nutrition published in commercial advertisements.

the nutritional status of CKD patients on low-protein diets.[31] However, it is necessary to monitor nutritional status and energy intake.

In addition to the quantity, the influence of the type of protein on renal function is also discussed in the non-dialysis stage of CKD. Population-based prospective studies have observed a direct relationship between the intake of red meat, the incidence of CKD,[32,33] and the need of dialysis.[34] Although these data indicate a possible advantage of replacing red by white meat, intervention studies with this purpose are scarce. In cross-over and randomized clinical trials, the replacement of red meat by chicken with the same amount of protein (1.4g/kg/day) decreased proteinuria in patients with diabetes mellitus type 2; the reduction was even greater with an ovo-lacto vegetarian low-protein diet (0.7g/kg/day).[35,36] In the same way, replacing animal protein for plant-based protein sources, particularly soybeans, without changing the total quantity of the nutrient, showed no positive impact on the GFR.[37] Thus, the benefits of controlling dietary protein at the non-dialysis stage of CKD is more related to the adjustment of the quantity than of the type of protein.

Clinical guidelines suggest a diet with 0.8 to 1.0g/kg/day, in stages 1 and 2 and, 0.6 to 0.8 in stages 3 and 4.[38] A more marked restriction (0.3 to 0.4g/kg/day) supplemented with keto-analogues and essential amino acids can also be employed in patients with GFR<30mL/min/1.73m2.[39] Despite the numerous benefits demonstrated with the use of keto-analogues, this approach has great difficulty of implementation due to its strict food restriction, high cost, high number of pills, among others.[39] For dialysis patients, higher protein content is recommended (1.1 to 1.3g/kg/day), due to the higher degree of protein catabolism and losses of amino acids/peptides in hemodialysis (HD), or proteins in peritoneal dialysis.[38] Providing healthy meals before, during, and after a dialysis session may attenuate the protein catabolism.[40]

PHOSPHORUS

The adjustment in the phosphorus intake is among the dietary-therapeutic objectives in CKD, especially in cases of hyperphosphatemia. However, it is important to emphasize that the prevention and treatment of hyperphosphatemia involve a multidisciplinary approach since its cause is multifactorial and includes the insufficient phosphorus removal by dialysis, use of vitamin D analogs, bone and mineral metabolism disorders, and the inappropriate use of phosphorus binders agents.[41]

Phosphorus is found in a wide variety of foods, in organic and inorganic forms. Organic phosphorus is found naturally, especially in foods that are sources of protein, both vegetable (legumes and nuts) or animal. However, the phosphorus content of animal-based foods is more easily absorbed by the gastrointestinal tract (GIT) than that of vegetable origin (> 70% *vs.* < 40%, respectively). In plants, part of the phosphorus is complexed to the phytate (carbohydrate not digested by the GIT enzymes), impairing the absorption of this mineral. Inorganic phosphorus, whose absorption by the GIT may reach 100%, is found in the form of chemical additives used in many processed and ultra-processed foods.[42,43] The intake of these foods has increased in recent decades, which can contribute to excessive intake of phosphorus in the general population and phosphorus overload in CKD.[44] The following topics describe some dietary strategies to decrease phosphorus intake.

ORGANIC PHOSPHORUS

In the early stages of CKD, the adjustment of protein intake also contribute to reduce phosphorus intake.[45] Although hyperphosphatemia is more prevalent in advanced stages, reducing phosphorus overload by dietary control in the earlier stages can help prevent or delay the development of secondary hyperparathyroidism.[46]

In HD, due to the increased protein need, strategies that promote the adequate intake of proteins with lower phosphorus content are required. There is evidence of lower mortality in patients with high protein intake and low serum phosphate, in comparison to those with high levels of both.[47] Thus, encouraging the intake of foods with lower phosphorus-to-protein ratio (Table 1) can be a good strategy. Although there is no recommendation regarding the ideal ratio, higher mortality was observed with a daily intake greater than 16mg of phosphorus per gram of protein.[48]

INORGANIC PHOSPHORUS

In Brasil, despite the description of additives on food labels, there is no obligation to inform the amount of phosphorus present in food, which makes it difficult to estimate its intake.[49] In a North American

study, authors found approximately 40% more phosphorus in foods and menus with phosphorus-based additives in comparison to those without additives.[50] Foods containing phosphorus-based additives frequently consumed by patients undergoing HD are: processed meats, bacon, restructured meats (e.g., nuggets®, hamburgers), some yogurts, UHT milk, processed cheeses, instant noodles, cookies, cake mixes, and juice powder.[51,52] The additives most commonly used are phosphoric acid, sodium diphosphate, and tricalcium phosphate.[51] After evaluating the influence of foods sources of organic or inorganic phosphorus on the phosphatemia of patients under HD, only inorganic phosphorus was associated with hyperphosphatemia.[52]

Thus, encouraging greater consumption of *in natura* and minimally processed foods, instead of processed ones, is a good strategy to control phosphatemia. This also contributes to the reduction of sodium intake and improves dietary quality. A controlled clinical trial showed a reduction of serum phosphorus of HD patients with persistent hyperphosphatemia, when instructed to replace foods with phosphorus additives by similar types of food without them.[51] Therefore, strategies should consider the individuality of each patient.

In addition to the diet, the use of phosphorus binder agents (when necessary) may contribute to reduce serum phosphorus.The binders should be used during meals, in an amount proportional to the phosphorus content of the food[41].

POTASSIUM

The adjustment of the potassium intake also deserves attention in CKD, particularly in the more advanced stages, due to the higher prevalence of hyperkalemia.[53] Besides the reduced renal excretion, other factors contribute to the increase of serum potassium, such as metabolic acidosis, intestinal constipation, diabetes *mellitus*, use of RAAS inhibitors, beta-blockers, potassium-sparing diuretics, and food intake. Thus, all these factors must be considered to prevent and treat hyperkalemia.[53]

Potassium is found in a wide variety of foods, both animal (meat and dairy) and plant-based, such as fruits, vegetables, legumes, and nuts are its main sources. However, it is important to point out that plant-based foods should not be excluded from the diet since they are also sources of vitamins, minerals,

TABLE 1. PHOSPHORUS-TO-PROTEIN RATIO IN USUAL PORTIONS OF FOOD[48]

Food	Amount (g)	Usual portion	Phosphorus (mg)	Protein (g)	Ratio phosphorus/ protein (mg/g)
Meat and eggs					
Chicken	80	1 medium breast fillet	150	23.0	6.5
Pork	80	1 medium pork chop	147	21.2	6.9
Beef	85	1 medium steak	209	26.0	8.0
Whitefish	84	1 medium fillet	241	20.6	11.7
Beef liver	85	1 medium steak	404	22.7	17.8
Sardine	34	1 unit	170	8.4	20.2
Whole egg	50	1 unit	90	6.0	15
Sausages					
Sausage*	60	1 unit	126	13.9	9.1
Ham*	48	2 medium slices	136	14	9.7
Milk and dairy products					
Cheese	30	2 thin slices	153	7.5	20.4
*Requeijão**	30	1 tablespoon	134	2.9	46.2
Natural yogurt	120	1 small cup	159	6.3	25.2
UHT milk*	150	1 glass	140	4.9	28.6
Legumes and nuts					
Cooked beans	154	1 medium ladle	133	6.9	19.3
Peanuts	50	1 small package	253	13	19.5

* may contain phosphorus-based additives.

and bioactive compounds. In addition, these foods may contribute indirectly to the control of hyperkalemia. Studies carried out in patients not on dialysis and with normal serum potassium found that the increased intake of fruits and vegetables had the same effect on correcting metabolic acidosis as the standard treatment with sodium bicarbonate, without inducing hyperkalemia.[54,55] There is no evidence regarding this strategy in the dialysis stage. In addition, the higher intake of fibers provided by these foods is associated with the regulation of bowel transit, and may increase fecal excretion of potassium. Thus, the assessment of diet intake is essential to achieve the proper adjustment of dietary potassium, taking into account patients' culture, habits, preferences, and the variety of foods needed to ensure the dietary quality and the intake of other nutrients. The following topics describe strategies to control potassium intake.

Selection of food based on the potassium content

There are no specific recommendations about the amount of potassium that CKD patients, with or without hyperkalemia, should ingest. In addition, the definition of food as "rich" or "poor" in potassium. In clinical practice, estimation of potassium intake is challenging because of the limited information regarding the potassium content in food composition tables, the non-obligation to declare it on the label of products, in addition to the difficulty in estimating portions due to the variations in the sizes of food and household utensils, and the subjectivity of the definition of portion (e.g., what is an "average unit of fruit?"). Thus, dietary advices should be individualized and focused on promoting autonomy for choosing or combining foods and stimulating changes within the patients' dietary repertoire.[56]

Cooking technique for reducing potassium in plant-based foods

Cooking vegetables in water is a good strategy to reduce the potassium content of food, which enables the maintenance of this important food group in the diet. Although some centers still employ the technique of cooking plant-based foods in water twice, there is evidence that the largest mineral loss occurs during the first cooking.[57] Thus, it is indicated to cook plant-based foods only once in abundant water, discarding the cooking water to remove part of the potassium content. In this procedure facilitates the preparation, and minimizes the loss of flavor and consistency, improving the acceptance and pleasure in eating.[57] Studies have also evaluated the technique of soaking, which was not efficient in removing the potassium content of foods.[57,58] It is noteworthy that not all plant-based foods need to be cooked, but it is important to evaluate the overall context of the diet so that the inclusion of raw vegetables does not contribute to hyperkalemia.

Attention to potassium additives

Many additives found in processed foods are potassium-based, and have greater absorption by the GIT than potassium naturally found on foods.[59] Sherman and Mehta[60] analyzed the amount of potassium additives in processed meats and observed an amount of potassium up to three times higher in comparison to "fresh" meat. The commonly used additives are potassium sorbate, potassium citrate, and potassium diphosphate[60]. In addition, potassium chloride has also been widely used to replace sodium chloride to reduce sodium in the diet, either in the form of "light" salt or in food products described as with reduced sodium content. Therefore, nutritional education that stimulates reducing the intake of processed foods can also be interesting for serum potassium control.

Sodium

As in the general population, the sodium intake in CKD patients is high, and several benefits from the reduction of this mineral have been reported. In the non-dialysis stage, studies show that reducing the intake of sodium potentiates the action of antihypertensive drugs and decreases blood pressure and proteinuria.[61,62] In HD, the adjustment of sodium intake contributes to lower interdialytic weight gain, which, in turn, is associated with better clinical outcomes.[63] The dietary challenges to adjust the sodium intake consist not only in reducing the consumption of processed foods but also of sodium chloride and artificial seasonings used to prepare meals. Therefore, in addition to patient-centered strategies that seek the use of natural foods and seasonings, there is also a need for public policies that aim to simplify information found on food labels and to promote greater consumption of *in natura* and minimally processed food, so that it is possible to reduce sodium intake.[64] Such measures would be in line with the Dietary Guidelines for the Brazilian Population mentioned before.[18]

Dietary Patterns and Chronic kidney Disease

For a long time, research in nutrition has focused on isolated nutrients, which does not portray the complexity of food choices and the wide dietary variety of a meal or eating habit. In addition, the biological effects of an isolated nutrient can be altered by its interaction with other components of the same food or other foods in the diet. Thus, a global analysis of the diet or eating patterns enables to capture the potential synergy between food and nutrients, in addition to allowing more adequate dietary comparisons between different population groups.

The modern lifestyle has led to important changes in dietary patterns, especially in western societies, characterized by excessive consumption of red meat, refined grains, dairy products, soft drinks, fried foods, and processed products.[65] This pattern has been associated with an increased risk for weight gain, cardiovascular complications, mortality due to cardiovascular diseases (CVD), and cancer.[66-68] On the other hand, dietary patterns with a higher contribution of *in natura* or minimally processed plant-based foods, and less animal-based and processed ones, have been associated with a lower risk for type 2 diabetes mellitus, obesity, CVD, CKD, and all-cause mortality.[69-71] In addition to the effects on health, patterns based in plant-based foods are more environmentally sustainable, compared to those rich in animal-based products.[72] It is important to emphasize that we are not encouraging a vegetarian or vegan diet, since a moderate consumption of poultry, fish, and dairy products does not seem to bring adverse consequences to health.[72]

In CKD, the findings point out to the same direction. A meta-analysis showed that, in general, patterns based in plant-based foods and with a smaller presence of meat, especially red, salt, and refined sugar was associated with lower mortality.[73] Recently, in patients in stages 3 and 4 of CKD, an adequate intake of fruits and vegetables, combined or not to other health behaviors, was associated with lower mortality and a delay in the progression of the disease.[74]

FINAL CONSIDERATIONS

The act of eating is immersed in a wide and varied collection of cultural practices that interact with the subjectivity of each individual; therefore, understanding them is essential to draw better strategies for nutritional therapy. In addition, adjustments in the intake of nutrients, such as protein, phosphorus, potassium, and sodium, all common in the treatment of CKD, should be performed considering the global context of the diet, in order to ensure quality. The Dietary Guidelines for the Brazilian population can be used as a tool to guide dietary strategies in CKD since it promotes the consumption of foods with less processed foods, hence helping out the control of phosphorus, sodium, and potassium. In addition, the guidelines also encourages a broader look on a diet by proposing a rediscovery of culinary practices and commensality and criticizes the aspects involved in the purchasing and advertising of foods.

In the integrative care of the patient, it is urgent to consider the individual besides the disease and the diet beyond nutrients. Thus, it is important that health professionals, regardless of the area, reflect on their own beliefs and relationship to food in order to improve patients'care in the promotion of healthy eating. Finally, more studies are needed to assess different strategies to promote dietary behavior change, particularly in patients with CKD in less advanced stages, in order to prevent the various complications associated with the disease.

Conflict of interest

The authors declare there are no conflicts of interest.

Contribution of the authors

All authors contributed to the drafting and final revision of the article.

RESUMO

Uma dieta saudável é essencial para promover e preservar a saúde, mesmo na presença de doenças como a Doença Renal Crônica (DRC). Nesta revisão, a terapia nutricional para pacientes de DRC será abordada levando em conta não só os principais nutrientes que precisam ser ajustados devido às alterações que acompanham a redução das funções renais, tais como proteínas, fósforo, potássio e sódio. Abordaremos também os benefícios da adoção de padrões alimentares associados a desfechos melhores tanto para a prevenção quanto para o tratamento da DRC. Também enfatizaremos que esses aspectos devem ser aliados a um processo de ressignificação do conceito de dieta saudável para que seja possível a sua promoção. Por último, apresentaremos a perspectiva de uma abordagem integrada para o indivíduo com DRC, explorando a importância de considerar aspectos biológicos, psicológicos, sociais, culturais e econômicos. Essa abordagem tem o potencial de contribuir para uma melhor adesão ao tratamento, melhorando assim a qualidade de vida do paciente.

PALAVRAS CHAVE: *Terapia nutricional. Alimentação. Insuficiência renal crônica.*

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REVIEW ARTICLE

Acute kidney injury

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http://dx.doi.org/10.1590/1806-9282.66.S1.68

KEYWORDS: *Acute kidney injury. Water balance. Critical Care. Renal replacement therapy. Furosemide.*

Acute kidney injury (AKI) is a set of syndromes defined by the abrupt decrease in glomerular filtration rate (GFR). An AKI episode is associated with negative short-term outcomes, such as hypervolemia, acid-base disorders, immune system dysfunction. In addition, there is higher mortality in individuals who have suffered an episode of AKI up to 10 years after the event when compared to the general population.[1]

The current classification of AKI, KDIGO AKI (Kidney Diseases Improving Global Outcomes Acute Kidney Injury)[2] comes from a laboratory criterion, the serum creatinine value, and a clinical criterion, urinary output. If there is a staging divergence between the criteria, the greatest prevails.[1]

Stage	Serum creatinine concentration	Diuresis
Diagnosis	• Increased 0.3 mg/dL in 48h, or • Increase 50% (1.5x) of the baseline creatinine	• < 0.5 mL/kg/h for 6 hours
Stage 1	• 50-99% (1.5 to 1.9x) of the baseline creatinine, or • Increased 0.3 mg/dL of the baseline creatinine	• < 0.5 mL/kg/h from 6 to 12 hours
Stage 2	• 100-199% (2.0 to 2.9x) of the baseline creatinine	• > 0.5 mL/kg/h per period of 12 hours
Stage 3	• 200% (3x) of the baseline creatinine, or • Increased creatinine 4.0 mg/dL, or • Renal Replacement Therapy, or • In patients younger than 18 years, reduction in GFR < 35 mL/min/1.73m^2	• < 0.3 mL/kg/h per period of 24 hours, or • Anuria per period 12 hours

The incidence of AKI varies depending on the age, adult vs. pediatric, and the patient's location within the hospital structure, intensive care unit (ICU) vs. infirmary. Worldwide, AKI characteristics (epidemiology, etiology, outcomes), contrast between developed vs. developing countries. Nevertheless, the presentations of AKI in urban centers are similar to those found in developed countries.[1]

KIDNEY ATTACK

In 2013, in order to highlight AKI, Ronco[3] coined the term "Kidney Attack", an analogy to "Heart Attack"/ acute coronary syndrome. Obviously, this term is not a formal nomenclature. In the publication, an additional criterion proposed for the classification of AKI is a marker of renal tubular injury, NGAL (neutrophil gelatinase-associated lipocalin)[3]. It is important to emphasize that creatinine is a marker of renal function, whereas NGAL is a marker of injury. In this analogy, increased creatinine would represent an ST-segment elevation. Whereas Increased NGAL would mean an increase in troponin levels. There are four possible scenarios:

1. Normal creatinine and NGAL → Absence of AKI.

2. Increased creatinine and normal NGAL → functional AKI. Example: introduction of drugs that modify glomerular perfusion without causing a tubular lesion. Drugs commonly related: Angiotensin-converting

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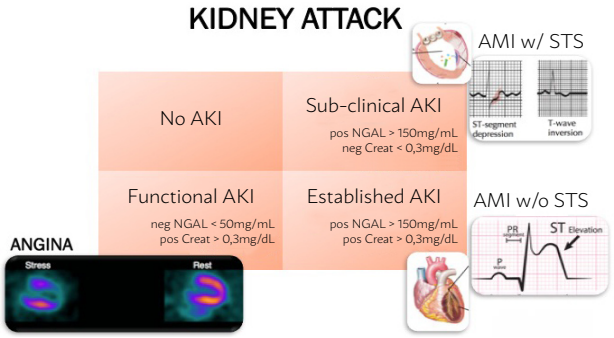
enzyme inhibitors (Enalapril); angiotensin 2 receptor blockers (Losartan), calcineurin inhibitors (Tacrolimus); Gliflozins, sodium-glucose co-transporter type 2 inhibitors (Empagliflozin). Clinical situations such as Parathyroidectomy.[4] The parathyroid hormone has vasodilating action in the afferent arteriole of the glomeruli. Its sudden reduction causes a decrease in glomerular perfusion, a decrease in the glomerular filtration rate, increase of serum creatinine, without causing a tubular lesion.[4] Both the pharmacological and clinical causes would be equivalent to positive myocardial perfusion scintigraphy.[3]

3. Normal creatinine and increased NGAL → subclinical AKI. Example: AKI induced by intravenous iodine contrast with an increase of less than 0.3 mg/dL in serum creatinine. It would be equivalent to an acute myocardial infarction (AMI) without ST-segment elevation.

4. Increased creatinine and NGAL → established AKI. AMI with ST-segment elevation.[3]



FLUID BALANCE

The arbitrary definition of positive fluid balance would be an increase of more than 5% of the body mass related to the accumulation of fluids.[5] In these patients, there is a greater propensity to deleterious effects on multiple systems.

Central nervous system → Cognitive deficit, delirium.

Cardiovascular → Conduction disorders, decreased inotropism, diastolic dysfunction.

Respiratory → Reduction of gas exchange, decreased pulmonary compliance.

Hepatic → Cholestasis, reduced protein production.

Digestive → Malabsorption syndrome, paralytic ileus.

Skin and soft tissue → Cicatrization deficit, wound infections, pressure injuries.

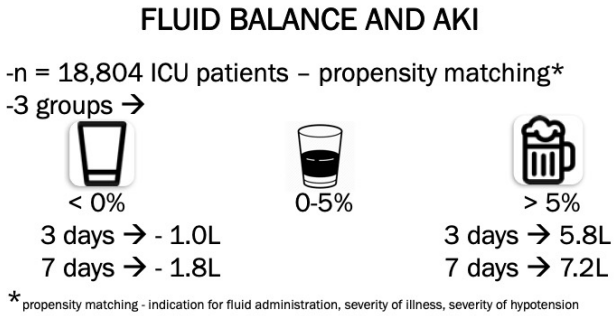
Renal → Increased interstitial pressure, reduced renal perfusion, retention of water and sodium, uremia. Due to the low compliance of the renal capsule, the interstitial edema leads to renal compartmental syndrome.[5]

In 2017, Balakumar et al.[6] published a retrospective study that included 18,804 patients admitted to an ICU. They were divided into three groups. The primary outcomes were mortality and recovery of renal function. The fluid balances on the third and seventh-day post-admission were analyzed. In one group, the fluid balance was negative. In the other group, the balance was positive, but less than 5%. In the last group, the balance was positive, exceeding 5% of the body mass. The individuals in the last group, when compared with the other two, showed a higher incidence of AKI, oliguria, length of hospital stay, and need for RRT, in addition to lower recovery of renal function and increased mortality after one year.[6]

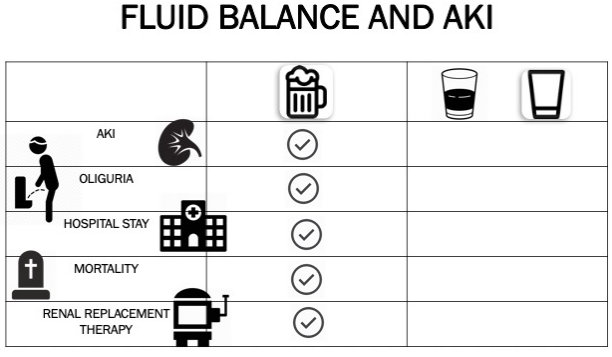
CHANGE OF PARADIGMS

In 2018, Ricci et al.[7] published an article with 10 incorrect concepts commonly spread on Nephrointensivism. Some to know:

1. Acute tubular necrosis is the predominant histologic finding in AKI → FALSE. In patients admitted to



Adapted from Balakumar et al.[6]



Adapted from Balakumar et al.[6]

the ICU with AKI who underwent kidney biopsy, the finding of acute tubular necrosis was only focal. This is because, in various etiologies of AKI, mechanisms other than renal ischemia have been found.

2. The main cause of septic AKI is the reduction of renal perfusion → FALSE. On the contrary, in septic AKI, there is an increase in renal perfusion. However, changes occur in the renal microcirculation (shunts), with lower perfusion of the glomeruli despite a higher global renal perfusion. This phenomenon is corroborated by the low incidence of the histological finding of acute tubular necrosis in septic AKI.

3. Fluid challenge is always indicated in oliguric patients → FALSE. In several scenarios, oliguric patients do not present a volemic deficit. An emblematic example is patients with right ventricular failure. They are usually patients with increased central venous pressure. Consequently, there is an increase in renal venous pressure, which is transmitted to the kidney, causing renal congestion. If these patients are oliguric, fluid challenge will be harmful, because it will increase the pressure in the renal veins.

4. An mean arterial pressure of 65 mmHg is the main target in patients with AKI → FALSE. This is an analogy to the perfusion of the central nervous system. This perfusion results from the difference between the mean systolic arterial pressure and intracranial pressure since the skull has insignificant compliance. The renal perfusion pressure would be the difference between the mean systolic arterial pressure and the central venous pressure, extrapolating that the latter represents the renal intracavitary pressure. This analogy is made due to the low compliance of the renal capsule. However, there are no studies that define a target pressure for renal perfusion. It is also noteworthy that in patients who were previously hypertensive with septic shock, a target of 80 to 85 mmHg is related to a reduction in mortality.

5. The return to baseline creatinine pre-AKI means a full recovery of renal function → FALSE. After an episode of AKI, there are always irreversible lesions of some glomeruli and nephrons, so there is always a sequel. What happens is that the creatinine can return to the baseline value for two reasons. The first, the reduction of lean body mass/sarcopenia after admission to the ICU. In this situation, the generation of creatinine would be smaller. The second reason is the use of the renal functional reserve. It is known that there is adaptive renal capacity, and, faced with AKI episodes, the capacity of filtration of the remaining glomeruli is enhanced at the expense of the renal functional reserve.

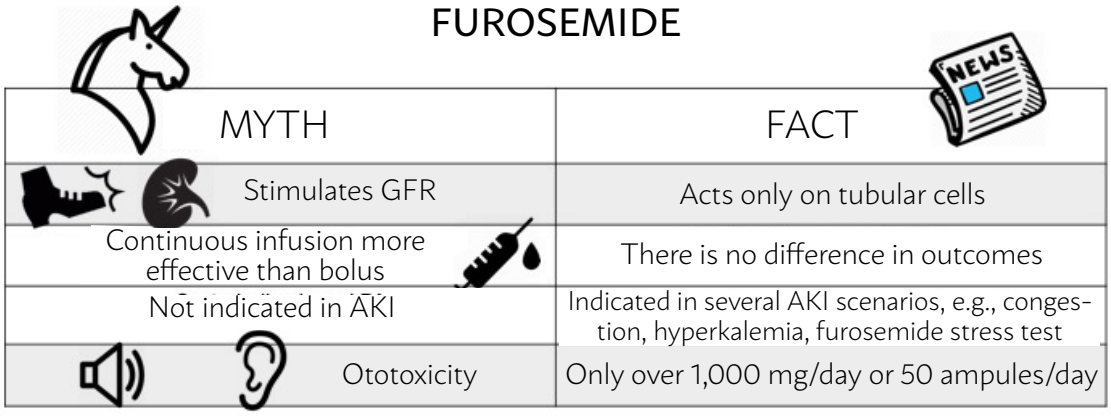
6. The Right Internal Jugular Vein is the best access for hemodialysis → FALSE. Current evidence shows that both femoral veins present similar rates of infection related to the catheter and patency of the catheter, except in obese patients with a body mass index above 30 kg/m^2, among whom the rates of catheter colonization and infection are higher.[7-9] In addition, catheters in the right jugular vein, there is an indication to place the tip of the device within the right atrium and not in the transition between the superior vena cava and the right atrium. In a study comparing these two positions, catheters with the tip in the atrium were related to a higher rate of patency of the hemodialysis filter, and there were not a higher rate of arrhythmias, right atrium perforation nor cardiac tamponade.[10]

7. In anuric patients, the suspension of the dialysis should be associated with volemic expansion and initiation or increase in the dose of diuretics (furosemide) → FALSE. The most important parameter for the weaning of renal replacement therapy should be the spontaneous increased of diuresis above 400 mL in 24 hours for patients who are not on diuretics. For patients on diuretics, diuresis exceeding 1000 mL in 24 hours is an indicator of renal recovery. When the urinary output in 24 hours is greater than this value, the suspension of dialysis can be considered.[11]

In 2019, Joannnidis et al.[12] published an editorial about myths related to furosemide. Some to know:

1. Furosemide promotes an increase in renal function → FALSE. The renal function is given by the glomerular filtration rate. Furosemide does not increase the glomerular filtration rate. Its action occurs in the lumen of the renal tubules. In summary, it promotes lower reabsorption of water in the glomerular ultrafiltrate, leading to an increase of diuresis.

2. Infusion by continuous infusion pump is more effective than bolus infusion → FALSE. Based on the current scientific evidence, there is no indication to prescribe furosemide in continuous infusion since there is no change in outcomes with this strategy. In addition, the cost of using an infusion pump may be up to R$ 1,000.00 per day. This is an unjustifiable cost for therapy with no added benefits.



Adapted from Joannidis et al.[12]

3. Furosemide should be stopped if there is a progressive increase of creatinine → FALSE. In situations of renal venous congestion/renal compartment syndrome, such as Cardiorenal Syndrome, even with daily increases in creatinine, there is an indication to maintain furosemide if the patient still has residual diuresis. In these situations, diuresis forced by furosemide and other measures that favor a negative fluid balance, such as extracorporeal ultrafiltration, low sodium diet, fluid restriction, are beneficial for the reversal of fluid overload status. In the same way, even if the patient is undergoing renal replacement therapy/hemodialysis, it is advisable to use furosemide to control the fluid balance.

4. In AKI, there is a contraindication to Furosemide → FALSE. In situations such as hypervolemia, hyperkalemia, and for the furosemide stress test, the use of this diuretic is encouraged.

5. Ototoxicity → FALSE. Only doses above 1,000 mg/day in adults have an ototoxic potential. The commercial presentation available on the national market is a 20 mg vial. Thus, only a dose exceeding 50 vial/day would put the patient at risk of cochlear lesion.[2]

PREVENTION

In 2017, Joannidis et al.[13] published guidelines on the prevention of AKI. The recommendations are classified according to the subjective level (1-Strongly recommended, 2-Weakly recommended) and to the evidence strength (A-high, B-moderate, C-low, D-very low). Some positions are noteworthy:

1. Volume expansion → Use of hypotonic solutions such as Ringer's lactate instead of 0.9% saline solution (2C).

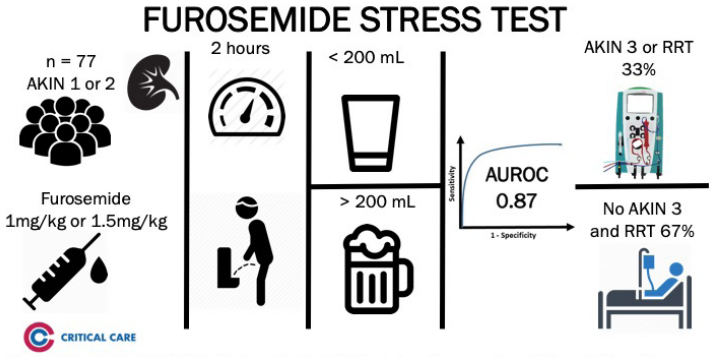
2. Use of loop diuretics (furosemide) to avoid/minimize positive fluid balance (2D).

3. Target mean arterial blood pressure → In previously hypertensive patients who evolve with septic shock, the target is 80-85 mmHg (1C).

4. Statins to prevent AKI in the postoperative period of cardiac surgery → contraindicated for ineffectiveness (1A).

MANAGEMENT

In 2013, Chawla et al.[14] published a manuscript about the usefulness of furosemide as a prognostic tool in the AKI, the Furosemide Stress Test. They performed a retrospective analysis of 77 individuals with AKI KDIGO 1 and 2. Patients who were already on furosemide received a dose of 1.5 mg/kg of furosemide via bolus. Patients who were not on the medication received 1.0 mg/kg via bolus. They used 200 mL as the cutoff point of diuresis 2 hours after the administration of furosemide. They were able to anticipate the outcomes of progression to KDIGO 3 and/or need



Adapted from Chawla et al.[14]

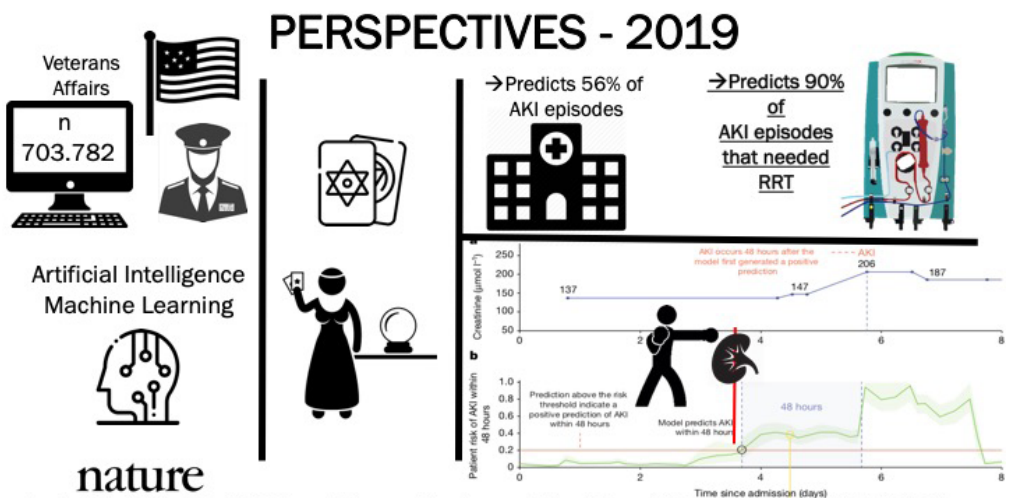
SCAMP - Standardized Clinical Assessment and Management Plan				
Complete on Day 1				
Site of Nephrology Evaluation:	□ Room	□ ICU		
Nephrology Evaluation was (timing): □ Early		□ On time	□ Late	
AKIN Etiology: □ Sepsis	□ Hypotension	□ Iodinated contrast	□ Glomerulonephritis	□ Nephrotoxin
□ Pre-renal	□ Tubulointerstitial nephritis	□ Rhabdomyolysis	□ Thrombotic microangiopathy	
□ Hepatorenal Sy.	□ Cardiorenal Sy.	□ Hemolysis	□ Vasculitis	
□ Post-renal/Obstructive	□ Other:			
KDIGO: DI	□ 2	□ 3		
DIAGNOSIS HYPOTHESIS:				
HISTORY:				
□ DRC 5D				
ETIOLOGY	START OF RRT (year):	ACCESS:	DRY WEIGHT:	RESIDUAL: GAIN:
SEROLOGIC TESTS:	HD PRESCRIPTION:	CLINICAL:	NEPHROLOGIST	
What is your estimate of in-hospital mortality of the patient? SAPS II -->				
□ Unlikely (<25%)	□ Possible (25-74%)	□ Very Likely (75-94%)	□ Almost certain (>95%)	
Do you consider initiating RRT?				
□ YES (proceed to the next question)		□ **NO: (Move on to indications for RRT start)->**		
Would RRT be a futile measure?				
□ **NO: (move on to indications for RRT start)->**				
□ YES, because:				
□ Base disease severity:				
□ Metastatic cancer				
□ Irreversible acidosis (10 mmol/L)				
□ Irreversible sepsis (3 vasopressors, SBP < 90 mmHg, presence of infection)				
□ Irreversible neurological damage				
□ Other:				
Even so, will you initiate RRT?				
□ YES, because:			□ NO:	
□ Request from the ICU team	□ Decision of the family		□ Prior choice of the patient	
□ No time for discussion			□ Other:	

INDICATIONS FOR START OF RENAL REPLACEMENT THERAPY

	Emergency	Urgency	Not urgent
A-E-I-O-U			
Acidosis	□ pH < 7.20	□ pH 7.20-7.30	□ pH > 7.30
Electrolytes	□ K > 6.5 or abnormal ECG	□ K 6.0 - 6.5	□ K < 6.0
Ingestion:	□ Toxin:		
Overloaded/Hypervolemia	□ Severe anasarca □ IRpA FiO2 >70% □ Diuresis < 100mL/ 24h	□ Edema 2+ to 3 + □ FiO2 50-70% □ Diuresis 100-500mL/ 24h	□ Edema 1 + □ No edema
Uremia	□ Uremic symptoms □ Neurological abnormality	□ Urea 130- 280	□ Urea < 130
SCAMP RECOMMENDS --->	□ 1 -> RRT	□ 3 -> RRT □ 1-2 -> No RRT	□ 4-> No RRT

SELECT the option that will be deployed -> (IT IS NOT NECESSARY TO JUSTIFY IF THE OPTION IS THE SAME RECOMMENDED BY SCAMP)

□ RRT	□ No RRT
Justification to start RRT if SCAMP recommends NOT STARTING RRT (complete only if there is a disagreement between the SCAMP RECOMMENDATION and the option that will be deployed)	**Justification to NOT start RRT if SCAMP recommends STARTING RRT (complete only if there is a disagreement between the SCAMP RECOMMENDATION and the option that will be deployed)**
□ Hypervolemia (relative seriousness)	□ could accelerate a death outcome
□ Predicted worsening of renal function	□ Is not relevant to the therapeutic objective
□ Hyperkalemia (not severe < 6.0)	□ Predicted improvement of renal function
□ Other:	because:
	□ Useless therapy/Base disease:
	□ Metastatic cancer
	□ Irreversible lactic acidosis
	□ Irreversible sepsis
	□ Irreversible neurological damage
	Other:
	□ Other:



Adapted from Tomašev et al.[16]

for renal replacement therapy with good accuracy. Individuals with diuresis less than 200 mL showed a tendency of evolution of the renal lesion. On the other hand, diuresis exceeding 200 mL had the contrary prognosis in relation to the progression of the renal lesion. The AUCROC (area under the curve receiving operating characteristic) was 0.87.

In an article published in 2017, Mendu et al.[15] presented an algorithm on decision-making in relation to the use of renal replacement therapy in patients with acute kidney injury, the protocol named by the acronym SCAMP (standardized clinical assessment and management plan). The SCAMP form is filled out with the data of the patient. At the end of the flow chart, there is a suggestion to start or not renal replacement therapy. However, there is no obligation to follow the protocol's suggestion. It is up to the physician alone to justify the conduct chosen if it is contrary to the SCAMP suggestion. In-hospital mortality and mortality at 60 days were the primary outcomes.

Patients whose nephrologists agreed with the protocol had lower in-hospital mortality (42 vs 63%; P<0.01) and 60-day mortality (46 vs 68%; P<0.01). However, this protective effect was only observed in patients whose predictive mortality at the first evaluation was below 50%.

PROSPECTS

In an article published in Nature magazine in 2019, the discriminatory power of prognosis of a multifactorial analysis via artificial intelligence was tested.[16] In a retrospective analysis of the Veteran Affairs records, with 703,782 individuals, by means of software with artificial intelligence, it was possible to discern, 48 hours in advance, 56% of the AKI episodes. The same tool can point out in 90% of the cases which AKI patients will require renal replacement therapy.

Note

The visual abstracts were created by this author; they were not taken from other sources.

Abbreviations

- AKI: acute kidney injury.
- GFR: glomerular filtration rate.
- KDIGO AKI: *Kidney Diseases Improving Global Outcomes Acute Kidney Injury.*
- RRT: renal replacement therapy.
- NGAL: *neutrophil gelatinase-associated lipocalin.*
- AMI: acute myocardial infarction.
- ICU: intensive care unit.

PALAVRAS CHAVE: *Lesão renal aguda. Balanço hídrico. Cuidados Críticos. Terapia de Substituição Renal. Furosemida.*

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REVIEW ARTICLE

HIV-related nephropathy: new aspects of an old paradigm

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http://dx.doi.org/10.1590/1806-9282.66.S1.75

SUMMARY

The scenario of infection by the human immunodeficiency virus (HIV) has been undergoing changes in recent years, both in relation to the understanding of HIV infection and regarding the treatments available. As a result, the disease, which before was associated with high morbidity and mortality, is now seen as a chronic disease that can be controlled, regarding both transmission and symptoms. However, even when the virus replication is well controlled, the infected patient remains at high risk of developing renal involvement, either by acute kidney injury not associated with HIV, nephrotoxicity due to antiretroviral drugs, chronic diseases associated with increased survival, or glomerular disease associated to HIV. This review will cover the main aspects of kidney failure associated with HIV.

KEYWORDS: *HIV. Renal insufficiency, chronic. AIDS-associated nephropathy.*

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) was recognized in 1981 in the United States. The human immunodeficiency virus (HIV) was isolated in patients with AIDS in 1983, initially as HIV 1 and, in 1986, HIV 2 was identified[1]. HIV is a retrovirus with an RNA genome that belongs to the Retroviridae family. It is through the reverse transcriptase enzyme that the virus is able to transcribe viral RNA into DNA and, then, integrate the host[1].

According to data from UNAIDS, approximately 37 million people worldwide were living with HIV in 2017, and 940,000 people died of AIDS-related causes[2]. National data show that, in Brasil, over 42,000 new cases of HIV infection were diagnosed in 2017. However, what is observed over the years is a reduction in the detection rate of new AIDS cases, which is attributed to the recommendation of "treatment for all" implemented in 2013[3].

HIV infection is associated with various forms of renal involvement; this spectrum includes an involvement directly associated with the viral infection or immune response and also to the treatment against the virus[3,4]. Renal involvement associated with HIV was first described in 1984 and was characterized by kidney failure and proteinuria. Since then, different forms of nephropathy have been described, both as a result of the direct effects of the virus on the kidney and of the medications, which involve acute kidney injury, chronic kidney disease, and renal toxicity[5,6].

The pathogenesis of kidney disease associated with HIV is still poorly understood. The mechanisms proposed include direct injury of the parenchymal cells caused by viruses or indirect injury caused by the release of cytokines. However, we still have not been able to identify how the virus enters the cell[7]. In patients infected by HIV, kidney disease has become

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an important cause of mortality[7,8]. The development of combination antiretroviral therapy prolonged patient survival and changed the spectrum of kidney diseases in HIV-infected patients, decreasing the prevalence of glomerular diseases and increasing the prevalence of nephrotoxicity and comorbidities[8].

ACUTE KIDNEY INJURY IN HIV INFECTION

Acute kidney injury (AKI) is defined by the guidelines of the Kidney Disease Improving Global Outcomes (KDIGO 2012) as the presence of one of the following criteria: increased level of serum creatinine at 0.3 mg/dl or more at 48h, increased serum creatinine level at 1.5 times or more the basal level in 7 days, or urinary debt lower than 0.5 ml/kg/h for 6 hours[9]. It is known that AKI is more frequent among individuals infected by HIV than in those not infected, and its incidence varies considerably between studies since most are heterogeneous retrospective analyses in relation to the characteristics of the patients and follow-up time[8,10]. However, the lowest incidence rate of AKI is reported in outpatients, ranging from 5.7 to 9.4%, reaching up to 66% in more severe patients[8].

The identification of risk factors is fundamental to develop prevention and early diagnosis strategies. The presence of previous kidney disease is one of the most important risk factors for AKI, as well as the severity of the disease. However, the incidence of AKI seems to have decreased with the use of antiretroviral therapy, with reports of 10-fold reduction after 3 months of the start of the treatment[8,10].

The etiology is multifactorial, but pre-renal causes and acute tubular necrosis remain as significant causes of AKI. The main etiologies are sepsis, volume depletion, and nephrotoxicity, corresponding to approximately 40% of the cases[8,10,11]. Nephrotoxicity evolves with varied presentations of AKI, such as acute tubular necrosis, interstitial nephritis, mainly associated with antiviral drugs or drugs such as sulfamethoxazole/trimethoprim, acyclovir and amphotericin B, crystalluria/obstruction, renal tubular disorders, and pre-renal disorder[8]. AKI of post-renal etiology is unusual in patients infected by HIV; crystalluria is induced by medication, causing deposition of insoluble crystals and obstruction, one of its main causes[8].

CHRONIC KIDNEY DISEASE IN HIV INFECTION

The prevalence of HIV-associated chronic kidney disease varies geographically and depends on the definition used[12]. In addition to having a higher risk of kidney disease, individuals infected by the virus also present greater speed of progression of renal dysfunction compared to non-infected individuals[13].

The introduction of antiretroviral therapy has increased the survival of individuals infected by HIV. However, this decrease in mortality rates has been accompanied by an increase in other related diseases, such as chronic kidney disease, which has become increasingly common in HIV-infected patients and can occur at any stage of HIV infection, even before seroconversion[13,14]. These patients have a combination of traditional risk factors, such as advanced age, black ethnicity, diabetes and arterial hypertension, in addition to the factors related to HIV, such as low CD4 lymphocyte count, high viral load, co-infection by the hepatitis C virus, use of injectable drugs, and exposure to antiretroviral therapy[11].

Since the treatment for HIV nephropathy may postpone the decline of renal function, it is recommended to screen for the disease regularly by measuring the arterial pressure, evaluating the renal function (creatinine and estimated glomerular filtration rate) and through urine examination to investigate the proteinuria, which is a common manifestation of the disease[7,14].

As a general rule, it is recommended to use antiretroviral drugs with caution in patients with chronic renal disease, avoiding nephrotoxic drugs, and adjusting the dose, with a reduction or extension of the administration period [15]. Some antiretroviral drugs, such as tenofovir, are associated with an increased risk of both the development and progression of chronic kidney disease[12]. The guidelines recommend avoiding the use of tenofovir if the glomerular filtration rate is less than 60 ml/min/1.73m^2. For patients in use of tenofovir who evolve with a decline greater than 25% in glomerular filtration rate in relation to the baseline renal function, it is recommended to replace the antiretroviral treatment by another one[12]. There is no evidence that demonstrates the best dialysis modality for HIV-positive patients. Survival in dialysis patients is similar to that of non-infected patients. There is no recommendation for isolation, nor for the exclusive use of machines in hemodialysis sessions[12].

Based on data from retrospective studies, it is known that renal transplantation is highly viable in recipients infected by HIV. One of the major challenges

is to achieve therapeutic and non-toxic levels immunosuppressants due to their interaction with antiretroviral drugs. It is recommended to avoid antiretroviral agents that act on the cytochrome P450 pathway so that it is possible to achieve a better therapeutic level of calcineurin inhibitors and decrease the incidence of renal graft rejection; integrase inhibitors are some options in this context. Induction therapy with antithymocyte immunoglobulin should be restricted to patients at a high immune risk of rejection[16].

Despite the higher rates of acute rejection in recipients infected by HIV in relation to those not infected, kidney transplant seems to be a viable renal replacement therapy in HIV patients, but some strategies need to be improved to minimize rejection and manage drug interactions[16].

EVALUATION OF KIDNEY FUNCTION

An accurate assessment of the kidney function in patients infected by HIV is essential since antiretroviral drugs are eliminated by the kidney and require dose adjustments according to the renal function, in addition to their associated effects, such as nephrotoxicity[17]. Therefore, it is recommended to screen for renal disease at the time of diagnosis and start or modification of the antiretroviral therapy[18].

Serum creatinine is the biomarker of choice for estimating the glomerular filtration rate in clinical practice, and cystatin C should be considered in cases of patients who received medications that alter the tubular secretion of creatinine, such as ritonavir or sulfamethoxazole-trimethoprim, in addition to providing a better prediction of long-term mortality[18.19].

Several equations have been used to estimate the glomerular filtration rate; CKD-EPI is currently the most noteworthy of them, having been evaluated and considered the most accurate for various populations and recommended as the first method of choice to evaluate renal function by the Guidelines of the European AIDS Clinical Society (EACS)[17]. Urine analysis should be performed in all HIV-infected patients to detect the onset or worsening of proteinuria or hematuria, and, if possible, it is recommended to measure the proteinuria (albumin/creatinine or protein/creatinine ratio).

HIV-ASSOCIATED NEPHROPATHY (HIVAN)

HIV-associated nephropathy (HIVAN) was the renal involvement initially described in HIV-infected individuals and is one of the most important causes of end-stage renal disease in this population[5.7]. In recent years, its incidence has decreased sharply. The reported prevalence is approximately 20% of HIV-infected patients, corresponding to the third main cause of end-stage renal disease among African-Americans aged between 20 and 64 years[11,20,21]. It is often found in populations with no access to antiretroviral therapy, which is the case in some regions of Africa, where the decline is less pronounced, probably due to the lower availability of antiretroviral medication[5.20].

Other factors associated with a greater incidence of

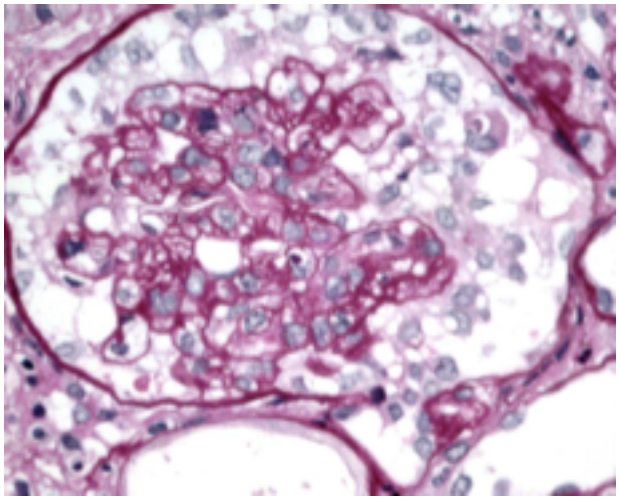

FIGURE 1. GLOBAL COLLAPSE OF THE CAPILLARY LOOPS, SURROUNDED BY HYPERTROPHIC PODOCYTES, WITH DEGENERATIVE CHANGES. (SBP - 400X). IMAGE KINDLY PROVIDED BY PROF. DR. LUIZ A. MOURA.

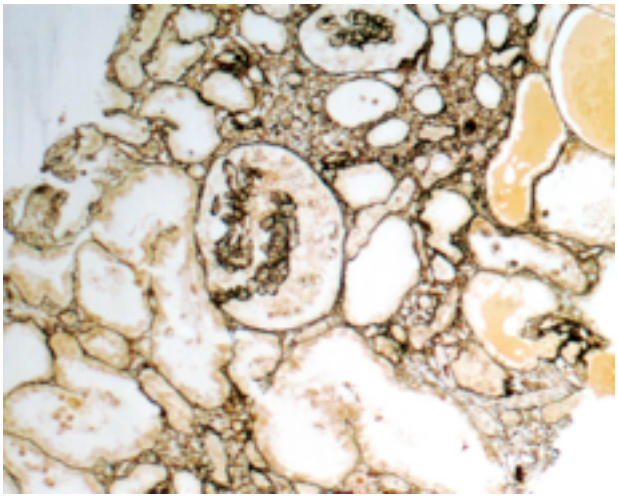

FIGURE 2. A GLOMERULUS WITH COLLAPSED CAPILLARY LOOPS AND DILATED TUBULES, WITH HYALINE CYLINDERS (INDICATED BY THE BLUE ARROW). (JONES' SILVER - 100X). IMAGE KINDLY PROVIDED BY PROF. DR. LUIZ A. MOURA.

HIVAN, besides the African-American descent (which means an estimated risk 18 times greater of developing the disease), are: advanced stage of immunosuppression with high viral load and low CD4 lymphocyte count and nephrotic proteinuria, which are associated with the risk of both development and progression to end-stage chronic renal disease[7,12]. APOL1 is a gene of the chromosome 22 whose variants APOL1 G1 and G2 were strongly associated with HIVAN[12]. The association between the genetic variants of the apolipoprotein 1 (APOL1) and HIVAN has been recognized since 2010, especially among the African population[22].

The classical presentation of HIVAN is defined as collapsing glomerulopathy, with nephrotic proteinuria, tubulointerstitial involvement with dilation and formation of tubular microcysts, interstitial inflammation, and tubular injury, whose manifestations may include hematuria, rapidly progressive kidney failure, and arterial hypertension[6,11,18]. In electronic microscopy, endothelial tubuloreticular inclusions (viral footprints) are highly specific and classical characteristics of HIVAN[11,18].

It is recommend the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARB) in patients with suspected or confirmed HIVAN or clinically significant albuminuria (in diabetes mellitus, DM, with over 30mg of albumin/day, and in patients without DM with over 300 mg albumin/day), combined or not with corticosteroid therapy with the purpose of reducing proteinuria and preserving renal function, although the recommendation is based on consensus and small studies[6,9,12].

Kidney disease associated with immune complex deposition

Another form of renal involvement in HIV infection is related to intraglomerular immune complex deposition (HIVICK), which includes a spectrum of renal diseases, among them membranous and membranoproliferative nephropathy, and IgA nephropathy[20,23].

Unlike HIVAN, it is predominant among European and Asian populations and rarely affects people of African descent[12,24]. It usually occurs after years of the disease, in patients undergoing treatment with antiretroviral drugs, with lower viral load and CD4 lymphocyte counts, also unlike HIVAN, which tends to occur earlier, besides presenting a lower probability of progression to end-stage kidney disease[20,23].

Its pathogenesis is associated with changes in immune regulation and increased gamma globulin, which contributes to the formation of immune complexes[25]. Renal manifestations can be varied, depending on the extent and location of the glomerular deposits; some examples are proteinuria, hematuria, decreased glomerular filtration rate, and consumption of supplement[25]. Histologically, it is characterized by deposits of immune complexes in the capillary loops and mesangium, besides mesangial expansion and tubulointerstitial inflammation[12].

The long-term progression of renal disease associated with the deposition of immune complexes is not well defined. There are few studies on the therapy; it is assumed that the HIV infection should be controlled and that conservative measures for blood pressure and proteinuria control should be implemented[14].

Kidney biopsy: when to indicate it?

Proteinuria and renal dysfunction are not findings exclusive of HIVAN, and ultrasound parameters (kidney size and changes in the echogenicity of the renal parenchyma), proteinuria in nephrotic levels and low CD4 lymphocyte counts are not able to predict renal involvement due to HIVAN.

The indication of kidney biopsy is based mainly on the clinical presentation, typical or atypical, and the possibility of alternative diagnoses, as well as to guide the prognosis and therapy, particularly when there is significant proteinuria present[12,24].

Nephrotoxicity associated with antiretroviral therapy

The introduction of ARVT has changed the natural history of HIV infection, reducing the risk of HIVAN; however, some antiretroviral drugs can be harmful due to their direct tubular toxicity, obstruction induced by crystals, or interstitial nephritis, which makes it important to monitor the renal function during the treatment[11,26].

The antiretroviral drugs most significantly involved with renal injury are the protease inhibitors (in particular the indinavir and atazanavir) and tenofovir disoproxil fumarate[5].

Atazanavir

The risk of nephrolithiasis may be greater with atazanavir than with other protease inhibitors, especially in individuals with higher plasma concentrations of the medication, with alkaline urinary pH, dehydration, and associated kidney disease[5,26,27]. The use of atazanavir can cause three types of renal involvement,

nephrolithiasis, acute interstitial nephritis, and crystal nephropathy. Nephrolithiasis is the most common adverse event associated with the use of the medication and usually occurs after two years from the start of the antiretroviral therapy, which suggests something related to the cumulative exposure to the drug. In general, kidney function is preserved, and urine examination under polarized light can reveal the birefringence of needle-shaped crystals[27].

Tenofovir

After the introduction of antiretroviral therapy, several classes of drugs emerged targeting different points of the viral cycle; among them, the reverse transcriptase enzyme inhibitors, in 2001, of which tenofovir is the most used, since it is recommended as the first-line therapy by the "Clinical Protocol and Therapeutic Guidelines for the Management of HIV Infection in Adults" (2018) by the Ministry of Health, but also by the American Academy of HIV Medicine and European AIDS Society[4,20,28].

Tenofovir is a prodrug that is filtered by the glomeruli but also secreted by the tubules, with a good safety profile and, since it has a prolonged intracellular half-life, it facilitates the dosage and adherence to treatment; however, it is one of the ARVs more frequently involved with kidney disease[4,11,29,30].

The main site of toxicity of tenofovir is the proximal tubule due to its intracellular accumulation, which leads to transport defects and mitochondrial injury, after the entry in tubular cells through the pericellular space and organic anion transporters1 and 3[4.11]. Tenofovir can cause renal dysfunction, such as acute tubular necrosis, nephrogenic diabetes insipidus due to distal tubular dysfunction, and, in more severe cases, Fanconi's syndrome, characterized by excessive urinary excretion of amino acids, glucose, phosphate, bicarbonate, and uric acid[4,14,29].

The diagnosis of tenofovir toxicity is usually clinical, and kidney biopsy is not necessary in cases of classic presentation[5]. The tenofovir dose should be reduced in patients with previous kidney failure and, if the estimated glomerular filtration rate is less than 60 ml/min, it should not be used[28.29]. If there is an alternative therapy available, the recommendation is to discontinue tenofovir[5].

The prodrug tenofovir alafenamide is associated with a lower risk of kidney toxicity compared to tenofovir disoproxil fumarate, because it is not a substrate for organic anion transporters 1 and 3 and, therefore, does not accumulate in the proximal tubular cells, in addition to resulting in lower plasma concentrations[4.5].

HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

The first case of HIV-associated thrombotic microangiopathy (TMA) was reported in 1984; however, TMA is rarely the initial manifestation of the virus infection[24]. It manifests with microangiopathic hemolytic anemia and thrombocytopenia, presence of schistocytes in peripheral blood, and decreased

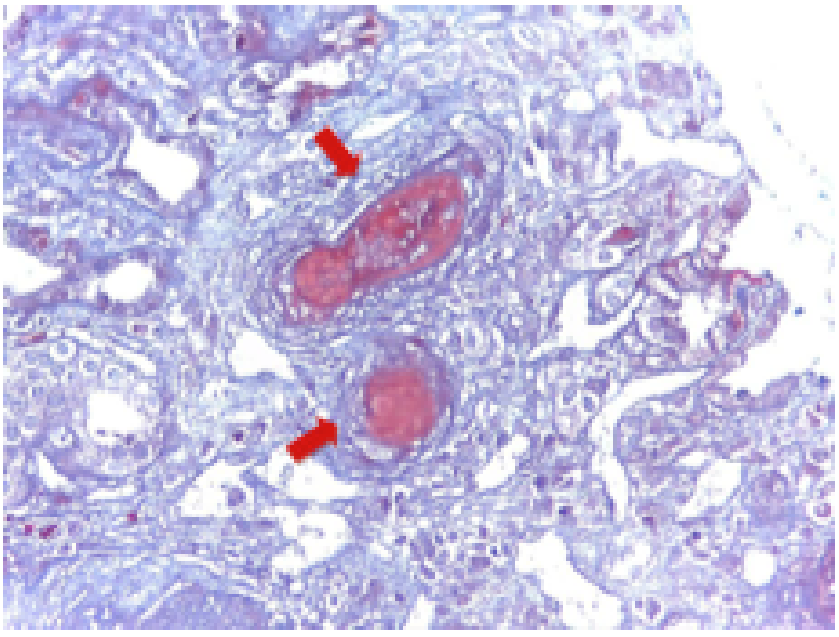

FIGURE 3. INTERLOBULAR ARTERY BRANCHES WITH DISSOCIATED WALL AND LUMEN OCCLUDED BY FIBRINOID MATERIAL (INDICATED BY THE RED ARROWS). (MASSON'S TRICHROME - 400X). IMAGE KINDLY PROVIDED BY PROF. DR. LUIZ A. MOURA.

haptoglobin levels. Clinically, HIV-associated TMA presents acute onset with rapid progression of kidney failure, hematuria, and proteinuria[19].

Its mechanism of pathogenesis can be associated with the direct cytopathic effects of the viruses that cause endothelial injury, leading to TMA, as well as to a systemic inflammatory response triggered by HIV or an opportunistic infection[4,19]. Some conditions, such as opportunistic infections and antiretroviral therapy, may be involved in the pathogenesis; a high viral load and decreased CD4 count may also be involved in the development of TMA, which, therefore, generally occurs in more advanced stages of the disease[4,19].

The treatment decision can often be a challenge due to the difficulty in making differential diagnoses (thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome). After the introduction of antiretroviral therapy, there was a substantial decline of HIV-associated TMA; therefore, for this condition, antiretroviral therapy is strongly recommended, as well as the treatment of opportunistic infections[19]. In addition, good results have been reported with the use of immunosuppressants, corticosteroids, infusion of fresh frozen plasma, plasmapheresis, and eculizumab[19].

CONCLUSION

The spectrum of kidney diseases associated with HIV has changed with the introduction of antiretroviral therapy. Currently, HIVAN is understood as a secondary effect to medications, despite the recognized interaction between the virus and the host. It is also noted an increase in renal injury associated with comorbidities that are not exclusively related to the virus, such as diabetes mellitus and hypertension.

The management of HIV-associated nephropathy is based on the suppression of viral replication and minimizing kidney injury in the long term, with emphasis on the importance of antiretroviral therapy. The screening and early detection of kidney failure in strongly recommended for the start of the treatment so that the outcomes of patients infected with HIV can be increasingly improved.

The proposed goal is that, by 2020, 90% of all people living with HIV know that they have the virus, with 90% of the people diagnosed receiving antiretroviral therapy and, then, 90% of all individuals receiving antiretroviral therapy will have viral suppression; it is known and recognizable that an undetectable viral load means that the virus is not transmissible.

Regarding the kidney disease scenario, the change was significant over the last 20 years with the effectiveness of HIV treatment. The understanding of the pathogenesis of interactions associated with kidney injury and the monitoring of current development can provide a better service for these individuals.

Acknowledgments

We would like to thank the illustrious Professor Dr. Luiz Antônio Ribeiro Moura for his contribution by providing the figures.

Contribution of the authors

Érica Lofrano Reghine, drafting of the text; Renato Demarchi Foresto, drafting and revision of the text; Gianna Mastroianni Kirsztajn; drafting and revision of the text.

RESUMO

O panorama da infecção pelo vírus da imunodeficiência humana (HIV) vem sofrendo alterações nos últimos anos, tanto em relação ao entendimento da infecção pelo HIV quanto aos tratamentos disponíveis. Como resultado, a doença, que antes estava associada a alta morbimortalidade, é agora considerada uma doença crônica que pode ser controlada, tanto em relação à transmissão quanto aos sintomas. No entanto, mesmo quando a replicação viral é bem controlada, o paciente infectado tem um alto risco de desenvolver complicações renais, seja através de lesão renal aguda não relacionada ao HIV, por nefrotoxicidade causada por drogas antirretrovirais, por doenças crônicas associadas com o aumento da sobrevida ou por doença glomerular associada ao HIV. Esta revisão abordará os principais aspectos da insuficiência renal associada ao HIV.

PALAVRAS-CHAVE: *HIV. Insuficiência renal crônica. Nefropatia associada a AIDS.*

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REVIEW ARTICLE

Drug-induced nephrotoxicity

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http://dx.doi.org/10.1590/1806-9282.66.S1.82

SUMMARY

Acute kidney injury is a very common diagnosis, present in up to 60% of critical patients, and its third main cause is drug toxicity. Nephrotoxicity can be defined as any renal injury caused directly or indirectly by medications, with acute renal failure, tubulopathies, and glomerulopathies as common clinical presentations. Some examples of drugs commonly associated with the acute reduction of glomerular filtration rate are anti-inflammatories, antibiotics, such as vancomycin and aminoglycosides, and chemotherapeutic agents, such as cisplatin and methotrexate. Cases of tubulopathy are very common with amphotericin B, polymyxins, and tenofovir, and cases of glomerulopathies are common with VEGF inhibitors, bisphosphonates, and immunotherapy, and it is also common to have more than one clinical presentation related to a single agent. Early diagnosis is essential for the good evolution of the patient, with a reduction of renal exposure to the toxic agent, which requires knowing the risk factors and biomarkers. General measures such as correcting hydroelectrolytic disorders and hypovolemia, monitoring the serum level, avoiding combinations with the synergy of renal injury, and looking for similar options that are less toxic are the foundations for the treatment of complications that are still common and often preventable.

KEYWORDS: *Drug-related side effects and adverse reactions. Acute kidney injury. Kidney tubules.*

INTRODUCTION

Acute kidney injury (AKI) is a very common diagnosis in both hospital and pre-hospital environments and may reach 60% of patients hospitalized in an intensive therapy unit. There has been a growth in its incidence in recent decades, which can be explained by an increase in risk factors such as advanced age, chronic kidney disease (CKD), and diabetes mellitus. Epidemiological studies show that nephrotoxicity is the third most common cause of AKD, with has become worst in recent decades due to the more frequent use of drugs with the potential to cause kidney damage, with studies showing a frequency up to 20% of nephrotoxic drug use in critical patients[1].

Although safety studies are necessary for the release of new drugs, side effects are often detected only after they are put into the market, when they start being used by different populations on a global scale. The reason for such high rates of drug-induced kidney injury is the function of drug and metabolite excretion performed by the kidneys, with the consequent exposure of its structures with high energy need (glomeruli and tubules) to the high concentration of exogenous substances[2,3].

Drug-induced nephrotoxicity is defined by the presence of any kidney injury caused directly or indirectly by medication. The presentation varies from an acute or chronic reduced glomerular filtration rate (GFR) to nephrotic syndrome and hydroelectrolytic disorders (HED) related, respectively, to glomerular and tubular damage. For epidemiological purposes, most studies only consider an increase in creatinine, hindering a precise analysis of the true magnitude of the problem[1].

The loss of GFR is a late marker of kidney injury, and other biomarkers are being researched to allow

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for an earlier intervention, which could improve the prognosis of these patients. Although there is no benefit proven by high-quality studies, there are some promising candidates:

• KIM - 1 (Kidney Injury Molecule - *V1*), adhesion molecule produced in the proximal convoluted tubule (PCT), which is increased in urinary concentration in situations of ischemia and drug toxicity, with accuracy demonstrated for cisplatin, gentamicin, and cyclosporine, in some cases with increase 48 hours after the introduction of the toxic agent and before the GFR reduction.

• Beta-2 microglobulin is a protein produced mainly by lymphocytes that increases its urine concentration in inflammatory diseases, including infections, and autoimmune diseases. It is filtered at the glomerulus, reabsorbed in the TCP, and considered a marker of tubular injury. A study on kidney transplantation showed an increase before the worsening of kidney function in patients with toxicity by calcineurin inhibitor (CNi), with high accuracy to differentiate rejection.

• Clusterin, a protein involved in the process of apoptosis and antiapoptosis found in various organs, including the kidney. It is not filtered and, in the tubules, is produced in stress situations to prevent cell death. Its greater accuracy in the diagnosis of tubular damage has been demonstrated, when compared to creatinine, with the use of cisplatin, vancomycin, tacrolimus, and gentamicin. It presents as much early increase as KIM-1 and does not increase in patients with glomerular damage.

• Cystatin C, a protein produced by all nucleated cells and filtered freely. It is completely reabsorbed in the proximal tubule and classically used as a way of estimating the GFR in conditions under stable kidney function conditions, in which the creatinine clearance is less reliable, such as in cirrhotic patients. Studies on amphotericin B, polymyxin, vancomycin, and cisplatin have shown a better correlation with renal toxicity when compared to creatinine[4].

EPIDEMIOLOGY

The AKI epidemiology varies according to the criteria used and the profile of the hospitals included in each study, but the proportion related to drug toxicity reaches 25% of the cases. Approximately 20% of the cases require renal replacement therapy, which is related to increased mortality, with rates of over 60% in developing countries[1,5].

A common problem when investigating the main etiology of AKI is the absence of tests to define the predominant mechanism of the injury. In clinical practice, it is common to have patients that are septic, hypotensive, with signs of dehydration, and on medication that is possibly toxic, all common causes of kidney injury.

To suggest causality, some criteria are proposed[6]:

• Exposure to the agent for at least 24 hours.

• Injury mechanism related to a drug compatible with the condition presented.

• Investigation of other causes of nephropathy with evolution or clinical manifestations that are not completely compatible.

Knowing the risk populations is essential for the prevention and early diagnosis of nephrotoxicity. The main risk factors are related to the reduction of the renal functional reserve (glomeruli without the ability to increase the filtration rate), a larger concentration of drugs on the tubules, and synergistic injury mechanisms. Some examples are drugs with vasoconstrictor effect associated with diuretics and drugs that compete for the transporter responsible for tubular secretion, increasing the cytoplasm concentration, such as in the combination of cisplatin and aminoglycoside[7].

TABLE 1. RISK FACTORS RELATED TO NEPHROTOXICITY BY DRUGS

Advanced age	Hypovolemia	Chronic kidney disease
>1 nephrotoxic	Hypoalbuminemia	Cardiopathy
Genetic polymorphisms	Diabetes	Obesity
High doses	Hypotension	

Renal toxicity can be divided into dose-dependent and idiosyncratic. In the first type, both the prevention and the treatment involve minimizing the duration and concentration of the drug, especially in situations associated with higher risk, such as the concomitant use of other nephrotoxic substances, renal ischemia, and patients with CKD. In the second type, there are few measures associated with the prevention and, in general, the treatment involves completely avoiding the drug. Examples of the first type are vancomycin, aminoglycosides, cisplatin, methotrexate, nonsteroidal anti-inflammatories, while the second are causes of acute interstitial nephritis, like proton pump inhibitors, beta-lactams, and some causes of thrombotic microangiopathy (TMA), such as CNi.

TABLE 2. COMBINATIONS OF DRUGS WITH SYNERGISTIC NEPHROTOXICITY

Cyclosporine/NSAIDS + Diuretic/ACEI/ARB
Aminoglycoside + Cisplatin/Cephalothin
Vancomycin + Piperacillin-tazobactam
Cyclosporine + Simvastatin
Methotrexate + Penicillins/Salicylate/Sulfas

To facilitate the diagnostic approach, it is important to know the clinical manifestations that are characteristic of each nephrotoxic drug; some of the most common are acute and chronic reduction of GFR, tubulopathies, and glomerulopathies, which will be illustrated below. To make matters more complicated, several agents present mixed characteristics, and it is common to have non-oliguric AKI with signs of PCT injury. We will not include drugs whose mechanisms of renal injury are indirect since they are not considered as primarily nephrotoxic, although they may be a cause for AKI. Some examples are loop diuretics, which can lead to dehydration, and renin-angiotensin-aldosterone system (RAAS) inhibitors, which cause vasodilation of the efferent arteriole, reduced intraglomerular pressure, and consequent worsening of renal function in risk situations, such as in patients who are septic, dehydrated, or with renal artery stenosis.

ACUTE RENAL DISEASE / ACUTE KIDNEY INJURY

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Medication widely used around the world, usually of easy access without prescription and considered one of the main causes of nephrotoxicity caused by drugs. The main risk factor is relative or absolute hypovolemia due to its action inhibiting the prostaglandins, causing vasoconstriction of the afferent arteriole. Examples of susceptible populations are patients with sepsis, decompensated congestive heart failure, cirrhosis, dehydration, or in use of agents that act on the renal hemodynamics (cyclosporine, iodinated contrast, RAAS inhibitors).

NSAIDS have the ability to cause injury in virtually any renal compartment; its main effects are described in table 3. Most renal side effects are observed on all subclasses; however, a recent study showed that the incidence of nephrotic syndrome could be more related to the use of the non-selective type, especially when for more than 15 days and up to 2 years after exposure to the drug. Preventive measures involve choosing other options for analgesia in patients with increased risk of AKI, maintaining it for the minimum time possible, and correcting hypovolemia when present[8,9].

VANCOMYCIN

A widely used antibiotics against gram-positive hospital bacteria, it is a cause of AKI in 5 to 15% of the patients, depending on different specific risk factors, such as daily dose > 4g, treatment time > 14 days, and high serum concentration, although there are cases even at therapeutic level (15 to 20 mg/L). Oral vancomycin, due to its low absorption, is not a cause of toxicity.

The injury mechanism is unclear, but some experimental studies suggest the induction of tubular ischemia due to oxidative stress. Recently, the formation of vancomycin cylinders with uromodulin has been demonstrated, especially with high plasma values, and with early increased creatinine when compared with other nephrotoxic drugs[2]. The association with other potentially nephrotoxic drugs is a well-determined risk factor, as well as in other cases. For reasons that are not well described, the combination with piperacillin-tazobactam causes a synergistic effect for renal injury, something unexpected due to the non-toxicity of the drug alone[10].

The treatment of choice is changing the medication by others with a similar spectrum of action, such as linezolid and daptomycin. Some studies suggest that teicoplanin could have a better safety profile, despite being in the same class, but there is no consensus regarding that information. In cases which it is not possible to interrupt the use of the drug, the most effective preventive measure is to monitor serum levels. After the end of the treatment, renal function tends to return to baseline levels[11].

AMINOGLYCOSIDES

The emergence of multidrug-resistant gram-negative bacteria susceptible to this ancient class of antibiotics is responsible for its growing use in recent decades, despite the high incidence of renal toxicity. Drugs are filtered in the glomerulus, with partial resorption in the PCT, via a receiver named Megalin. Inside the tubular cell, there is a connection with membrane phospholipids, with loss of protein synthesis and reduction of the mitochondrial

function and consequent cell death, which happens in a greater proportion with more cationic molecules, such as gentamicin.

Their more severe adverse effects are nephro and ototoxicity, with an incidence of up to 50% of non-oliguric AKI in high-risk patients, often with EHD, such as hypokalemia and hypomagnesemia. Several factors influence the ability to cause damage, such as concomitant renal ischemia, high serum concentration, and dosage with multiple daily doses.

Due to the high prevalence of renal toxicity, the KDIGO (Kidney Disease Improving Global Outcomes) recommendation is to avoid aminoglycosides whenever there is another less toxic antimicrobial option, which unfortunately is not often possible. In these cases, specific measures to minimize the damage must be carried out, such as the correction of hypokalemia and hypomagnesemia before the infusion, short time of use (<10 days, preferably), avoid use in hypovolemic patients, dosage one time per day, and dose adjusted according to the serum level. In the case of amikacin, the suggested concentration in the first hour is > 20 µg/mL and after 18-24h < 5 to 8 µg/mL. High valley values are related to nephrotoxicity incidence and must be corrected by increasing the intervals between infusions[5].

After discontinuation of the drug, the patient can continue presenting worsening of renal function for days, due to the slow clearance mechanism of the medication in the tubular cell. Despite this, the prognosis is apparently good, with a return to baseline renal function in most cases after the medication has been interrupted. However, some authors suggest irreversible damage and hyperfiltration of the remaining glomeruli as the mechanism responsible for the apparent recovery of renal function[12].

CISPLATIN

Platin derivates are old chemotherapeutic agents that remain widely used for the treatment of various cancers, such as those of the digestive tract and lungs. The risk of AKI was evaluated in a 6-year cohort that included over 800 patients, with an incidence of 34%; however, there were no cases of progression to end-stage kidney disease.

The damage is caused mainly in PCT, where the drug is internalized in the S3 segment through the OCT-2 (organic cationic transporter 2), and, in high concentrations, it causes DNA injury, with consequent cell death. Cisplatin also has a vasoconstrictor effect, and there have been rare reports of TMA cases. In addition to reducing the GFR, it also causes hypophosphatemia, glycosuria, and hypomagnesemia (the latter in > 40% of the cases). As prophylaxis in high-risk patients, it is recommended to reduce the dose of the medication, perform absolute or relative hypovolemia correction, and replacement the drug by carboplatin or oxaliplatin, when possible[13,14].

METHOTREXATE

An immunosuppressant frequently used in the treatment of autoimmune diseases that is related to AKI in high doses (> 500 mg/m², only used in chemotherapy against hematological neoplasms and sarcomas), with an incidence of up to 12%. There is the formation of crystals in the distal tubule, which causes local inflammation and necrosis through the formation of oxygen free radicals. The main risk factors are toxic drug interactions (sulfas, beta-lactams, salicylates), the dose used, the presence of ascites or pleural effusion, and the characteristics classically associated with nephrotoxicity.

Preventive measures include high doses of folinic acid and intravenous hydration, preferably with an isotonic bicarbonate solution, to correct possible hypovolemia and to alkalinize the urine; these measures are effective to reduce the medication crystallization. Some protocols suggest infusion up to 200 mL/hour with a total of up to 2 liters before initiating methotrexate, with a measurement of urinary pH every hour and extra infusions if the target of > 7.0 could not be reached. The plasma concentration of the drug can be measured with specific targets depending on the protocol used (most suggests < 0.1 µmol/L). In cases of injury that is already established, there is the option of glucarpidase, which acts with high efficiency in the enzymatic cleavage of the drug; another option is intermittent or extended high-flow hemodialysis, with special care regarding rebound in plasma concentration[13,15].

GLOMERULAR

VEGF (vascular endothelial growth factor) Inhibitors

VEGF is produced by podocytes and is responsible for maintaining the proper functioning and integrity of the glomerular basement membrane.

Inhibition can be direct through receptor inhibitor ligands (bevacizumab) or indirect with anti-angiogenic tyrosine kinase inhibitors (sorafenib and sunitinib). These are classes of chemotherapeutic agents widely used, especially in gynecological and pulmonary neoplasms.

Two of the main side effects are hypertension and proteinuria, with incidences respectively up to 22 and 72%, with a dose-dependent effect. However, less than 5% of cases present nephrotic proteinuria. Renal biopsies have shown several findings, including TMA and collapsing glomerulopathy. Suspending the drug is the treatment of choice, but there are cases of proteinuria persistence even after suspension. Nephroprotection with RAAS blockers is then recommended.

CHECKPOINT INHIBITORS

Monoclonal antibodies called immunotherapy that act by increasing the T lymphocyte response against cancer cells. The main subclasses are the CTLA-4 (cytotoxic T-lymphocyte-associated protein) inhibitors, with ipilimumab as an example, and PD-1/PDL-1 (programmed cell death ligand), such as nivolumab and pembrolizumab. They are available for the treatment of multiple metastatic neoplasms, such as lung cancer and melanoma, with excellent results considering advanced staging.

The main side effects are of immune mechanism, and the most common renal manifestations involve both acute interstitial nephritis and glomerulonephritis with different histological patterns (DLM, crescentic, membrane proliferative, membranous). There have been reports of proteinuria and hypertension in 16% of the patients who used nivolumab and multiple agents with evolution to acute interstitial nephritis and a reported incidence of AKI of 2% among users of this class of medications.

Because of the various possible causes related to renal dysfunction in oncologic patients, the current recommendation is to perform a renal biopsy whenever there is doubt about the etiology and, in the presence of acute interstitial nephritis, the recommendation is to start prednisone 1 mg/Kg and maintain the medication in mild cases, suspending it in cases of stage KDIGO 2 or 3 of AKI. It is not recommended to resume the use of medication in cases of improvement when the initial involvement was considered severe due to the high rate of recurrence[16].

BISPHOSPHONATE

Class of drugs used as first-line treatment for osteoporosis and hypercalcemia of malignancy that acts by inhibiting osteoclasts, with a consequent reduction in the reabsorption of the bone matrix. It is composed of several different agents, but regarding renal damage, the main ones involved are pamidronate and zoledronate.

The main clinical manifestation is proteinuria, and collapsing FSGS is the most typical anatomopathological finding. There have also been reports of AKI soon after the infusion, with a mechanism that likely involves the apoptosis of tubular cells, and this is reported mainly when the infusion is faster than recommended. Both clinical presentations are rare, and the prognosis is relatively good after discontinuation of medication[17].

TUBULOPATHY

Amphotericin B

Medication used to treat various systemic mycoses with at least three presentations available on the market, deoxycholate, liposomal, and lipid complexes. The main difference between them is the degree of renal toxicity, with the first being the most toxic, with rates up to 80%. The injury mechanism involves diffuse and direct tubular injury through the increase of permeability of the cell membrane, and ischemia that is induced by vasoconstriction of the afferent arteriole, which explains why hypotension, use of RAAS inhibitors, and low intravascular effective volume are important risk factors.

The most common clinical manifestations are hypokalemia, hypomagnesemia, urinary concentration defect, and metabolic acidosis, in addition to reduced GFR, and they begin, in general, after one week of medication use. In patients with a high risk of kidney toxicity who evolve with an increase in serum creatinine after the beginning of medication, it is recommended to change it for less toxic formulations or different classes of antifungal agents, particularly echinocandins and voriconazole. In cases in which there is no alternative to the use of amphotericin deoxycholate, it is recommended to increase the time of infusion, hydration pre-infusion (500 to 1000 mL), and HED monitoring and correction as preventive measures for AKI. The use of amiloride and spironolactone showed good results in the prevention of hypokalemia. Although the recovery of renal function is common after some weeks of

discontinuation of the drug, the incidence of severe acute renal dysfunction was 10% and was associated with an increased risk of mortality[5].

POLYMYXINS (COLISTIN)

Class of antibiotics whose use made a comeback in recent decades due to the emergence of multidrug-resistant gram-negative bacteria, like aminoglycosides, which also has a high rate of nephrotoxicity, with an incidence of up to 60% of AKI, often associated with hypokalemia and hypomagnesemia. There are two agents in clinical use currently, polymyxins B and E (colistin), which present important differences in terms of pharmacokinetics, and a need for adjusting the dose based on renal function in the case of colistin. The injury mechanism involves increased permeability of the cell wall and consequent edema and lysis, particularly in PCT.

Regarding the difference in toxicity, there is controversy about whether there is a lower incidence of renal toxicity with polymyxin B, and there is a prospective study that shows a lower incidence of the advanced stage of AKI, although with no difference in mortality[18]. Part of the difference may have occurred due to the difficulty in determining the optimum dose of medication according to the renal function. Despite the good renal prognosis after discontinuation of the drug, this is often not possible due to the importance of adequate treatment of the infection, in many cases with evolution to severe renal lesion requiring renal replacement therapy. There is no specific treatment for nephrotoxicity, so the recommendation is to monitor and correct EHD and prioritize the treatment for the infection, with a tendency to correct the dose of colistin based on renal function, but not polymyxin B[8,19].

TENOFOVIR

Antiretroviral therapy classified as nucleotide reverse transcriptase inhibitor and with widespread use since the beginning of the century for the treatment of HIV and hepatitis B. It is an integral part of the first-line regimen in Brasil due to its good tolerance, low resistance induction, and favorable dosage. However, it is not free from side effects; proximal renal tubulopathy and bone dystrophy, in particular, have been well described. The drug is internalized in the PCT cell by OAT-1 and 3 (organic anion transporter), where, in high concentrations, it inhibits essential functions associated with substance transport. The initial clinical manifestations are proteinuria, hypophosphatemia, and glycosuria, in some cases evolving to CKD.

The exponential increase of users of this medication, with the broadening of indication of HIV treatment and the emergence of pre and post-exposure prophylaxis (currently, all patients are treated, regardless of CD4 and frequent communication) has made its toxicity even more evident. Several authors have demonstrated more frequent loss of renal function in patients who were chronic users of tenofovir, both as prophylaxis and treatment, and even over relatively short periods (6 to 48 months). Some specific risk factors related to tubular damage are the time of drug use, association with protease inhibitors, especially atazanavir and ritonavir, previous reduction of GFR, systemic arterial hypertension, and age > 50 years.

It is recommended to frequently monitor the renal function and markers of tubular injury, such as glycosuria and phosphaturia. Brazilian guidelines for the treatment of HIV from 2018 advocate for the replacement of the drug in patients with a reduction of 25% of the baseline GFR or when < 60 mL/min/1.73m^2. Currently, the wide variety of classes against HIV allows the exchange without prejudice for the control of the disease. In addition, since 2015, there is a prodrug with much lower renal toxicity approved by the FDA (Food and Drug Administration) called TAF (tenofovir alafenamide), but it is not available in Brasil. In high-risk patients, one option is to suspend the medication depending on the progression of PCT lesion markers, even before the reduction of GFR[20,21].

CHRONIC KIDNEY DISEASE

Calcineurin inhibitors

Class of immunosuppressive agent essential in the prevention of rejection in solid organ transplantation and in the treatment of various glomerulonephritis. It is represented by cyclosporine and tacrolimus. Several mechanisms associated with CNi can cause renal injury, among the main ones are vasoconstriction of the afferent arteriole, hypertension, TMA, and induction of tubule-interstitial fibrosis and atrophy, with some authors suggesting a more pronounced hemodynamic effect with cyclosporine. The clinical presentation is also quite varied and may cause loss of glomerular filtration rate both acutely, by acute renal ischemia, and progressively over the years, with arteriolar and interstitial injury.

TABLE 3. CORRELATION BETWEEN CLINICAL SYNDROMES, INJURY MECHANISMS, AND MEDICATIONS.

Medications	Syndromes	Injury mechanism
NSAIDs	AKI CKD Glomerulopathy	Vasoconstriction AA / AIN TAIF MID / MG
CNi	AKI CKD	Vasoconstriction AA / TMA TAIF
Aminoglycosides Cisplatin	Tubulopathy AKI	Proximal tubular injury Diffuse tubular injury
Polymyxins Amphotericin B	Tubulopathy AKI	Diffuse tubular injury Vasoconstriction AA
Tenofovir	Tubulopathy CKD	Proximal tubular injury Chronic interstitial nephritis
VEGF inhibitors Gemcitabine ImTOR	Glomerulopathy AKI	Podocyte injury TMA
Checkpoint Inhibitors	Glomerulopathy AKI	Glomerulonephritis AIN
PPI Beta-Lactams Allopurinol Any drug	AKI	AIN
Topiramate Amoxicillin PI Acyclovir Methotrexate	Nephrolithiasis AKI	Formation of crystals with induction of formation of calculi and tubular toxicity
Pamidronate Infliximab	Glomerulopathy	Collapsing FSGS
Vancomycin	AKI	Generalized tubulopathy Cylinder formation
Dextrans IVIG	AKI	Hyperosmolarity

AA = afferent arteriole, MID = minimal injury disease, GM = membranous glomerulopathies, TAIF = tubular atrophy and interstitial fibrosis, imTOR = inhibitors of mammalian target of rapamycin, PPI = proton pump inhibitors, PI = protease inhibitors, FSGS = focal segmental glomerulosclerosis, IVIG = intravenous human immunoglobulin.

The prevalence of nephrotoxicity is quite varied and is directly related to the exposure time and high plasma concentrations. In patients with glomerulonephritis and kidney transplantation, there are many confounding factors that complicate the analysis of incidence, but in other solid organs, the prevalence of CKD reaches 30%, with studies suggesting the use of CNi as one of the main factors associated with it.

For the treatment, it is recommended to monitor plasma concentrations closely, but the decision to continue using the medication depends on the disease. In glomerulopathies, it is feasible to try other options of immunosuppressants, but in transplantations, the risk of nephrotoxicity, so far, is considered lower than that of rejection, so changing the medication is only suggested in particular situations, such as in some cases of TMA. Scenarios that evolve with AKI mainly associated to the vasoconstrictor effect tend to be reversible, unlike the slow and gradual loss associated with chronic nephrotoxicity[22].

DISCUSSION

The evolution in the treatment of severe diseases, such as cancer and infections, with the emergence of increasingly effective drugs with different mechanisms of action, is a reality in medicine today. However, these medications bring various side effects, new and old, and nephrotoxicity is one of the most common and with the greater morbidity.

The focus of the treatment is trying to minimize the harm that can be caused by renal toxicity. Thus, early recognition of the condition is essential. In addition to the biomarkers already described in this text, other measures are emerging to minimize this problem. The use of electronic systems that alert the nephrologist for evaluation when the laboratory detects an increase in serum creatinine, with or without prescription of nephrotoxic drugs, has been well studied recently. Although still controversial, there is a tendency toward improvement this mechanism

is used due to early application of measures against nephrotoxicity, such as the correction of dose, minimization of non-essential medications or particularly toxic combinations, and correction of hypovolemia, in addition to the investigation of other causes for renal disease[23].

Another point that is being well studied is pharmacogenetics. It is known that some patients have a genetic predisposition to certain side effects related to the medication. One of the mechanisms already known involve transporters of drugs present in the PCT, with OAC and MRP (multidrug resistance protein transporter) mutations and proven involvement in more serious cell damage. This information can be useful when deciding to prescribe potentially toxic medications and the best way to follow-up these patients. In addition, in the future, they may become specific therapeutic targets, with the creation of medications with structures that allow lower concentration in the tubular cell, as is the case of tenofovir alafenamide[2].

Since, so far, technology has not created perfect drugs exempt from adverse effects, the priority in cases of nephrotoxicity is based on the knowledge of risk populations, early diagnosis, and in general measures that can minimize the damage, such as correcting the dose of the medication based on the patient's renal function, something simple that, unfortunately, is not always carried out appropriately. Replacing nephrotoxic medications by others similar and less harmful, correcting the hypovolemia and HED, reducing the time of treatment when possible, monitoring the serum levels, and avoiding particularly toxic combinations are cost-effective ways to significantly decrease the incidence of drug-induced renal injury, a common complication that can have great repercussion in patient's treatment.

There is no conflict of interest in the present study.
There was no external funding.

Contribution of the authors:

Gabriel Teixeira Montezuma Sales[1]; Renato Demarchi Foresto contributed substantially to the planning, drafting, and revision of this article.

RESUMO

A lesão renal aguda é um diagnóstico muito comum, presente em até 60% dos pacientes críticos, e sua terceira maior causa é a toxicidade de medicamentos. A nefrotoxicidade pode ser definida como qualquer lesão renal causada por medicamentos, direta ou indiretamente, tendo a insuficiência renal aguda, tubulopatias e glomerulopatias como apresentações clínicas comuns. Alguns exemplos de drogas comumente associadas à redução aguda da taxa de filtração glomerular são anti-inflamatórios, antibióticos, como a vancomicina e aminoglicosídeos, e agentes quimioterápicos, tais como cisplatina e metotrexato. Casos de tubulopatia são muito comuns com anfotericina B, polimixinas e tenofovir, já casos de glomerulopatias são comuns com inibidores de VEGF, bisfosfonatos e imunoterapia; também é comum ocorrer mais de uma apresentação clínica relacionada a um único agente. O diagnóstico precoce é essencial para a boa evolução do paciente, com a redução da exposição ao agente tóxico, o que requer conhecimento dos fatores de risco e biomarcadores. Medidas gerais, tais como a correção de distúrbios hidreletrolíticos e da hipovolemia, o monitoramento do nível sérico, evitar combinações com sinergia de lesão renal e procurar opções semelhantes e menos tóxicas são os alicerces do tratamento de complicações que são comuns e, muitas vezes, evitáveis.

PALAVRAS CHAVE: *Efeitos colaterais e reações adversas relacionados a medicamentos. Lesão renal aguda. Túbulos renais.*

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