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HYPERTENSION IN CHRONIC RENAL FAILURE

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Hypertension is one of the most important complications resulting from chronic renal failure. Renal parenchymal disease is the most frequent form of secondary hypertension, comprising about 5% of all hypertension cases. The prevalence of hypertension in different parenchymal diseases is shown in Table 1. The prevalence of arterial hypertension is related to the severity of renal insufficiency, reaching 80–90% in end-stage renal failure.

Figure 1 shows the mechanisms by which chronic renal failure contributes to hypertension. Sodium and water retention play an important role due to their difficult elimination by the kidney. The consequences are an increase of exchangeable sodium, vascular wall sodium [1], and an expansion of the extracellular volume with an increase in cardiac output. The renin-angiotensin system is stimulated, especially in patients with mild to moderate chronic renal failure. This results in haemodynamic changes such as vasoconstriction, sympathetic nervous system activation, as well as non-haemodynamic actions such as the activation of endothelial cells, mesangial cells, inflammation and fibrosis. The outcome from this effect of angiotensin II is progressive renal damage and hypertension [2].

The sympathetic nervous system is activated with consequent increases in norepinephrine levels, peripheral resistance and cardiac output. Baroreceptor desensitization is also found in patients with end-stage renal disease [3]. Endothelium function is also impaired. Nitric oxide, a vasodilator agent, is reduced in chronic renal failure mainly due to an increase of the inhibitor asymmetrical dimethylarginine (ADMA) [4]. Prostaglandins and kinins have been found to be normal, high, or low in renal failure according to different authors; however, the administration of non-steroid anti-inflammatory drugs produces an increase in blood pressure, a decrease of the glomerular filtration rate and a reduction of urinary prostaglandins [5]. Endothelin and thromboxane, both of them vasoconstrictor agents, are elevated in chronic renal failure. The atrial natriuretic peptide is also elevated in renal failure favouring an increase of urinary sodium excretion, relaxation of the smooth muscle cells and inhibition of renin release [6].

Erythropoietin administration in patients with chronic renal failure is a common practice and can produce hypertension in about 20% of patients due to an increase in platelet cytosolic calcium [7].

The most important issues in the basal clinical evaluation of arterial hypertension in chronic renal failure are listed in Table 2 in which two sections are clearly differentiated: clinical history with physical examination and complementary examinations. Besides measuring blood pressure in the office and at home, 24-hour ambulatory blood pressure monitoring should be carried out because it has been demonstrated that patients whose night-time blood pressure does not decrease (non-dippers) have a worse prognosis with regard to morbidity, mortality and the progression of chronic renal failure [8].

Treatment

Arterial hypertension in chronic renal failure is a serious complication that may lead to end-stage renal disease in a short period of time. For this reason, both the European Society of Hypertension and Cardiology and the seventh report of the Joint National Committee Guidelines recommend a reduction in blood pressure below 130/80 mm Hg in all patients with renal failure and at least below 120/80 mm Hg particularly when proteinuria is superior to 1 g/24 h.

Table 1. Prevalence of hypertension in renal parenchymal disease

Focal glomerulosclerosis 75–85%	Diabetic nephropathy 65–75%
Membranoproliferative glomerulonephritis 60–70%	Membranous nephropathy 35–45%
Mesangioproliferative glomerulonephritis 30–40%	Ig A nephropathy 20–30%
Minimal change disease 10–15%	Interstitial nephritis 15–25%
Polycystic kidney disease 55–65%	

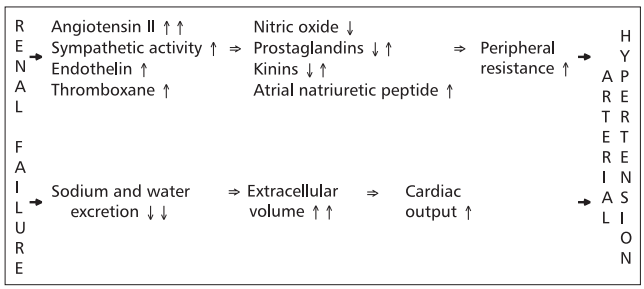

Figure 1. Mechanisms underlying arterial hypertension in chronic renal failure

Table 2. The following examinations are required for appropriate diagnosis of arterial hypertension in patients with chronic renal failure

Clinical history and physical examination	**Clinical history** Family background of renal disease (polycystic kidney, Alport and Fabry disease) Date of diagnosis of hypertension Background of diabetes mellitus Symptoms of haematuria, oedema, lithiasis Symptoms of peripheral artery disease, ischemic heart disease, cerebrovascular disease Chronic administration of analgesics, NSAID...
	Physical examination Blood pressure, weight, height and waist circumference Neck palpation and auscultation of both carotid arteries Pulmonary and cardiac auscultation Abdomen: abdominal masses and bruits Limbs: pulse palpation, oedema Fundoscopy: retinopathy degree
Complementary examinations	**Renal function** Determination of serum creatinine; cystatin C, creatinine clearance, MDRD or Cockcroft-Gault formulas Urine: quantification of proteinuria; micro- or macro--albuminuria; protein/creatinine ratio Urine sediment, microhaematuria, casts
	Renal morphology: renal ultrasonography
	Renal morphology and function: urography, scintigraphy and isotopic renal flow
	Blood sample determinations: haemoglobin, leukocytes, platelets, sugar, lipids, uric acid, calcium, phosphorus, transaminases, ionogram and acid-base measurements
	Systemic and viral disease with renal involvement markers: complement, cryoglobulins, ANA anti-DNA, immunoglobulins, ANCAS, viral B and C, and HIV serology
	Renal vascularization: scintigraphy, renal arteriography
	Renal histological study: renal biopsy

Table 3. Non-pharmacological treatment

Sodium intake < 60 mmol/day	Cholesterol intake restriction
Protein intake 0.8–1.2 g/kg/day	Potassium intake restriction
Phosphorus intake < 750 mg/day	Smoking cessation and alcohol restriction
Caloric intake > 35 calories/kg/day	Moderate physical activity
Increased calcium intake	Weight loss

Table 4. Pharmacological treatment

Angiotensin converting enzyme inhibitors (ACEI)	Combination therapy ACEI or ARB + diuretics
Angiotensin II receptor blockers (ARB)	ACEI or ARB + calcium-antagonist
Diuretics	ACEI + ARB
Calcium antagonists	Beta-blockers + diuretics
Beta-blockers	
Alpha-blockers	

Non-pharmacological treatment

Non-pharmacological treatment is very important to control blood pressure in chronic renal failure; the indications are listed in Table 3. The strictness of the diet depends on the degree of renal failure. Sodium intake should be reduced to less than 60 mmol/day, and daily intake of proteins will depend upon renal function, but an average of 0.8-1.2 g/kg/day is recommended. Phosphorus intake is related to protein intake and must be less than 750 mg/day. Total caloric intake should never be less than 35 calories/kg/day, with carbohydrates around 50–60%, and saturated fats should be between 30–40% of total calories as long as plasma lipids are not elevated, in which case cholesterol should be reduced in the diet. Other dietary treatments are an increase in calcium intake, weight loss, moderate physical activity and tobacco/alcohol restriction [9].

Pharmacological treatment

The principal drugs used in the treatment of arterial hypertension in chronic renal failure are shown in Table 4. When a glomerular injury is present, especially with elevated proteinuria, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are used most often, both in diabetic [10] and non-diabetic patients [11]. They have a vasodilator effect on efferent arteriole reducing intraglomerular pressure and the mesangial fibrotic process. In significant renal failure, these drugs produce hyperkalaemia, especially when they are associated with distal tubule diuretics or eplerenone. ACEI doses should be reduced in advanced renal failure (GFR < 15 ml/min), but this is not necessary with ARB. Both drugs have fetal toxicity and are contraindicated during pregnancy.

Calcium antagonists have been recommended in chronic renal failure treatment due to their important antihypertensive and natriuretic effects. Dihydropiridines can cause vasodilatation of the afferent arteriole producing an increase in intraglomerular pressure [12]. Diltiazem and verapamil seem to provide greater kidney protection. Manidipine has demonstrated the greatest reduction of proteinuria due to its vasodilatation effect on both the afferent and efferent arterioles. The most important side effects of calcium antagonists are local ankle oedema, headaches, flushing, tachycardia and gingival hyperplasia.

Diuretics are widely used medications in these types of patients since they are characterized by sodium and water retention [13]. When GFR is greater than 50 ml/min, thiazide diuretics alone, or in association with distal diuretics such as amiloride, triamterene and spironolactone, can be administered. However, when GFR is less than 30 ml/min loop diuretics such as furosemide, bumetanide, ethacrynic acid, or torasemide should be administered, but not distal diuretics due to the possible increment of serum potassium. The most prominent side effects of diuretics are hypokalaemia, hyperuricaemia, dyslipidemia, glucose intolerance, insulin resistance, hyponatraemia and hypomagnesemia. Distal diuretics may cause hyperkalaemia, skin rash, and gynaecomastia.

Beta-blockers can be administered in order to counteract activation of sympathetic nervous system, but they can accumulate in advanced phases of renal failure. They should be carefully used in type 1 diabetic patients because they might inhibit hypoglycaemic signs and increase blood glucose levels [14]. In patients with severe peripheral vascular disease, they should be avoided. A significant side effect is bradycardia, especially in combination with other drugs like verapamil, diltiazem and digoxin. Asthenia, dyslipidaemia, glucose intolerance, impotence and hyperkalaemia are other possible side-effects.

Alpha-blockers can be used not only for their vasodilator properties but also for their antiproliferative, platelet antiaggregant, and antiatherogenic effects. They are indicated in benign prostatic hypertrophy. The side effects are orthostatic hypotension, headache, mouth dryness, fatigue and weakness.

Drug combinations of two, three, or even more drugs are the rule in chronic renal failure, especially in diabetic patients. The most frequent combination is ACEI or ARB with diuretics. If this is not sufficient, a calcium antagonist or a beta-blocker can be added. Combination therapy of ACEI and an ARB has been evaluated with very good results, especially in patients with heavy proteinuria [15]. Combining an ACEI or ARB with a calcium antagonist has also been used. ARB alone can be given in high doses [16]. In many circumstances of chronic renal failure, an integrated treatment (antihypertensive, statin and anti-platelet therapy) should be considered.

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