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Hypertension and Chronic Kidney Disease: Cause and Consequence – Therapeutic Considerations

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1. Introduction

There is a strong relationship between hypertension and Chronic Kidney Disease (CKD). Hypertension is an important cause of End-Stage Renal Disease (ESRD), contributing to the disease itself or, most commonly, contributing to its progression. On the other hand, hypertension is highly prevalent in CKD patients, playing a role in the high cardiovascular morbidity and mortality of this particular population. This chapter will focus on the pathogenesis of hypertension-related CKD and its role on the progression of renal disease itself. The pathogenesis and treatment of hypertension resulting from CKD will also be addressed.

2. Hypertension as a cause of CKD

The relationship between abnormal blood pressure and kidney dysfunction was first established in the 19th century. The prevalence of both, and of the associated burden of cardiovascular morbidity and mortality, has been dramatically increasing worldwide (Kearney et al., 2005; Kearney et al., 2004; Ong et al., 2007; Schoenborn & Heyman, 2009; USRDS 2010; Meguid El Nahas & Bello, 2005). Data from several renal databases identifies systemic hypertension as the second most common cause of ESRD, with Diabetes mellitus being the first. In the United States (US), hypertension is the leading cause of ESRD in African-American patients (USRDS 2010; Klag et al., 1996; Hsu et al., 2005). Additionally, for any given cause of CKD, the elevation in systemic blood pressure accelerates the rate at which the glomerular filtration rate (GFR) declines (Perry et al., 1995). This is particularly true for patients with proteinuric nephropathies (Jafar et al., 2003).

2.1 Pathogenesis of hypertensive renal damage

The exact mechanisms of kidney damage in patients with hypertension still remain elusive. Two complementary pathogenic mechanisms ultimately ending in kidney fibrosis and scarring have been proposed. One starts with the changes in systemic and renal macro and microvasculature leading to the loss of renal auto-regulation with elevation of intraglomerular capillary pressure and the consequent hyperfiltration-mediated injury.

Hyperfiltration leads to transglomerular loss of proteins which promotes the release of cytokines and growth factors by mesangial cells and downstream tubular epithelial cells. The second mechanism proposes endothelial dysfunction and loss of endogenous vasodilators as precipitating factors of hypoxic-ischemic injury. The consequent activation of the intrarenal Renin Angiotensin System (RAS) and the increased release of cytokines and growth factors with recruitment of inflammatory cells stimulate apoptosis causing loss of normal kidney cells and increased matrix production, finally leading to progressive glomerular and interstitial fibrosis and scarring.

Evidence to support, this apparently straightforward, chain of events starting in systemic hypertension and culminating in ESRD, has been accumulating since the beginnings of the 20th century when Goldblatt conducted his first experiments in dogs driven hypertensive by the clipping of one renal artery: the two-kidney one clip model of hypertension (Goldblatt, 1964). The brilliancy of this model rests on the existence of a control organ: the clipped kidney was protected from the deleterious effects of blood pressure. In fact, vascular damage was not found in the clipped kidneys. More recently, other authors reported that the clipped kidney is also protected from the effects of immunological mediators (Wenzel et al., 2002).

Extension of this model to rats and rabbits confirmed Goldblatt findings (Eng et al., 1994; Wenzel et al., 2002). These later experiments also documented the pivotal role of changes in renal macro and microvasculature to induce and maintain a vicious cycle, where hypertension causes vascular lesions which in turn will further increase blood pressure, even after its primary cause has been removed (Rettig et al., 1990).

Further investigation on animal models, as well as on genetic models of hypertension, allowed the description of three different stages of preglomerular vascular change. The histopathological resemblance between these experimentally induced vascular lesions and those observed in benign and malignant nephrosclerosis in human kidneys have long been documented. Medial thickening with narrowing of the lumen resulting from hypertrophy of smooth muscle cells (Nordborg et al., 1983; Hampton et al., 1989; Vial & Boyd 1989; Lee, 1987; Mulvany & Aalkjaer 1990; Owens & Schartz, 1982; Chobanian et al., 1984; Ross, 1993) is followed by segmental hyalinosis of the vessel wall of interlobular arteries and afferent arterioles. In humans studies using light microscopy and immunofluorescence these lesions were better characterized and termed "benign nephrosclerosis" (Valenzuela, 1980; Fisher, 1966). Finally, the most severe type of hypertensive renal vascular lesion, similar to "malignant nephrosclerosis", is proliferation of the intima resulting in the typical onion-like appearance and extremely narrow vessels predominantly affecting the interlobular arteries and afferent arterioles (Klemperer & Otani, 1931). The previous existence of medial hypertrophy and, or, increased collagen content in the arterial wall were pre-requisites for the development of this final stage (Helmchen et al., 1984, Bidani et al., 1994). However, in humans even the early lesions of malignant nephrosclerosis affect the intima (Ellis, 1942; Heptinstal, 1953; Somers, 1958).

After this initial chain of events, increased glomerular perfusion and elevation of glomerular capillary pressure resulting in hyperfiltration, lead to further damage of the affected glomerulus (Brenner, 1985; Klahr et al., 1988) and to increased filtration of proteins to the tubular lumen. Enhanced tubular reabsorption induces the synthesis of inflammatory and fibrotic factors, resulting in tubulointerstitial ischemia, inflammation, up-regulation of

oxidative stress and epithelial-to-mesenchymal transdifferentiation eventually culminating in fibrosis (Ruggenti & Remuzzi, 2000; Mayer et al., 1993; Abbate et al., 1998; Fine et al., 1998; Sánchez-Lozada et al., 2003; Higgins et al., 2007; Tian et al., 2008; Leh et al., 2011; Dussaule et al., 2011). The involvement of inflammation in the progression of CKD was widely demonstrated in experimental models of non-immunologic kidney disease (Bottinger & Bitzer, 2002; Müller, 2000, 2001; Fujihara, 1998, 2000; Romero et al., 1999; Mazzali et al., 2001; Eddy & Giachelli, 1995; Largo et al., 1999; Gómez-Garre et al., 2001; Zoja et al., 1998; Takase et al., 2003; Alvarez et al., 2002).

Traditionally, the glomeruli have been in the centre of attention particularly in view of the hyperfiltration hypothesis involving the degradation and sclerosis of the remaining nephrons. However, the notion that tubulointerstitial fibrosis might rather cause than result from decreased glomerular function has gained strong evidence (Ong & Fine, 1994; Luft & Haller, 1995). Tubulointerstitial proliferation with incoming of inflammatory monocytes and macrophages, resulting from mechanical damage to the postglomerular interstitial vasculature, were also described, establishing the tubules and the interstitium as additional sites of early hypertensive damage (Eng et al., 1994). Furthermore, the up-regulation of the intrarenal RAS, hypothetically mediated by local ischemia, is associated with increased expression of Angiotensin Converting Enzyme (ACE) in proximal tubules and peri-tubular interstitium. Here, ACE can cleave angiotensinogen and bradykinins creating an imbalance in favor of the former with the consequent stimulation of proliferation, fibrosis and salt retention (Carlos & Jeanneret, 2003).

2.2 Epidemiology of hypertensive nephrosclerosis

The general term “nephrosclerosis”, both benign and malignant, has been used to describe these lesions since the beginning of the 20th century. The causal relationship between malignant hypertension with fibrinoid necrosis and renal failure is consensual. On the other hand, the evidence for a relationship between milder degrees of hypertension and either benign nephrosclerosis and ESRD remains controversial (Zucchelli & Zuccala, 1995; Freedman et al., 1995; Kincaid-Smith, 1999).

In the past 30 years, at the start of dialysis, an increasing number of patients have been labeled as having hypertension-related ESRD (USRDS 2003). Although, only few of them have undergone a kidney biopsy (Weisstuch & Dworkin, 1992) making it impossible to exclude other causes of ESRD, such as atheroembolic disease, ischemic nephropathy secondary to atheromatous disease, or glomerulonephritis (Zucchelli & Zuccala, 1998; Freedman et al., 1995). On the other hand, the increased life expectancy of the general population, due to better anti-hypertensive control and better survival from cardiovascular events, providing a longer time for hypertensive renal disease to progress, could in fact account for this increased prevalence (Caetano et al., 1999). The MRFIT study established a consistent relationship between increasing levels of systolic and diastolic blood pressure and ESRD that was independent of several other relevant variables. Nevertheless, several other literature reports originating in studies conducted in the US and in the United Kingdom concluded that benign nephrosclerosis did not significantly progress to ESRD (Tomson et al., 1999; Kincaid-Smith, 1982, 1999). However, the exception was provided by African-American patients in whom a higher risk of progression to ESRD was widely demonstrated in all age groups (Rostand, 1982; Fogo, 1997; Marcantoni et al., 2002). This disproportion

could not be explained by the higher prevalence and greater severity of hypertension in African-American patients or by socioeconomic determinants (Freedman 1993, 1995). Furthermore, in African-American patients progression for ESRD is faster across all levels of blood pressure (Klag et al., 1997; Shulman et al., 1989). Biopsy-proven hypertensive nephrosclerosis occurs earlier and is more severe in African-American than in Caucasian patients independently of blood pressure values and proteinuria (Tracy et al., 1991; Perneger et al., 1995; Marcantoni et al., 2002). Traditionally, this excess of kidney damage has been associated with genetically or environmentally induced impairment of renal auto-regulation and amplification of profibrotic mechanisms (Campese et al., 1991; Duru et al., 1994; Suthanthiran et al., 1998).

Early studies from animal models with Dahl salt-sensitive rats, Spontaneous Hypertensive Rats, Fawn-hooded rats and Brown and Norway rats as well as the AASKD trial suggested a genetic susceptibility to hypertensive vascular damage (Brown et al., 1996; Churchill et al., 1997; Freedman et al., 1998; Zarif et al., 2000; Agodoa et al., 2001). Several genetic alterations have been associated to a more rapid decline of renal function in African-American patients with hypertensive nephrosclerosis. Polymorphisms of the kallikrein (KLK1) gene promoter were associated with a higher risk of ESRD in the presence of hypertension in a population of African-American patients (Yu et al., 2002). Different genetic polymorphisms of the RAS have been linked to a greater progression to ESRD across a wide spectrum of populations and causes of CKD (Wong et al., 2008). Polymorphisms of TGF- β have also been implicated in hypertension and progressive fibrosis (August et al., 2000). Non-muscle myosin heavy chain 9 gene (MYH9) polymorphisms, leading to disruption of normal podocyte function, brought attention to the role of podocyte injury as a mechanism of kidney damage in hypertensive glomerulosclerosis (Freedman et al., 2009). Genetic variation within the loci of the adrenergic beta-1 receptor (ADRB1) gene is associated with increased adrenergic activity and an increased risk of progressive renal disease (Fung et al., 2009). Specific polymorphisms in the C - reactive protein gene predicted a higher risk for CKD progression, resistant to the action of ACE inhibitors in African-American patients (Hung et al., 2010). Finally, mutations in the human methylenetetrahydrofolate reductase (MTHFR) gene were associated with elevated levels of homocysteine and a faster decline of renal function over time in African-American patients (Fung et al., 2011). Very recently a study, conducted in a population of Hispanic descent reported an association between polymorphisms of vascular endothelial growth factor (VEGF) and hypertensive nephropathy with subsequent progression to ESRD (Yang et al., 2011).

3. Pathogenesis of hypertension in chronic kidney disease

Although the kidney is also involved in essential or primary hypertension, its insufficiency causes high BLOOD PRESSURE, contributing to 2-5 % of all cases of hypertension or half the cases of all forms of secondary hypertension (Kaplan, 2006b). The pathogenesis of hypertension-related to CKD is complex and multifactorial, mainly in the late stages of the renal disease. In addition to the classical factors, such as increased intravascular volume and excessive activity of the RAS, there are new recognized players such as increased activity of the sympathetic nervous system, endothelial dysfunction and alterations of several humoral and neural factors that promote an increase of the blood pressure. Hypertension is highly prevalent in CKD, being related with the level of renal function, the etiology of the kidney disease and the age of the patient. Patients with vascular disease, diabetes and polycystic

kidney disease (PKD) are more prone to be hypertensive (Ridao et al., 2001). It is also known that as renal function worsens the prevalence of hypertension increases. Therefore, more than 80 % of the patients beginning renal replacement therapy have high blood pressure (Ridao et al., 2001, USRDS, 2010).

3.1 Sodium and volume status

The fundamental role of the kidney in the control of sodium and volume homeostasis is well acknowledged since the seminal studies of Dahl and Guyton. During the last decades, a bulk of evidence shows that volume expansion is the first and major pathogenic mechanism for hypertension in CKD. In the early stages of CKD, patients have already an increased exchangeable sodium and blood volume, which are correlated with the blood pressure level (Beretta-Piccoli et al, 1976).

According to the Guyton's whole-body auto-regulation concept, many organs, including the kidney and the brain, have the ability to maintain a relatively constant blood flow in the presence of variations of the perfusion pressure (Coleman & Guyton, 1969). Guyton proposed that this auto-regulation could be responsible for the secondary increase of the peripheral resistance in the presence of blood volume expansion, as it occurs in CKD (Guyton et al, 1980). Therefore, initially, an augment of the blood volume increases the cardiac output and simultaneously the peripheral vascular resistance fell. Later, the auto-regulatory increase of the vascular resistance causes a pressure natriuresis (Navar, & Majid, 1996), with normalization of the cardiac output and maintenance of high blood pressure values.

3.2 The Renin-Angiotensin System

The relevance of the RAS, in physiological terms, is based on its capacity to regulate arterial pressure and sodium balance. When the blood pressure or perfusion fall, or the sympathetic activity increases, the juxtaglomerular cells secrete renin, which cleaves angiotensinogen, leading to an increase in angiotensin II (AII) levels. This octapeptide is a powerful vasoconstrictor and stimulates the production of aldosterone, which, in turn, increases renal sodium reabsorption, and closes the regulatory feedback loop. However, if the blood volume is normal, the increased activity of the RAS produces an abnormal rise in the blood pressure.

Only a small proportion of CKD patients have a measurable increase of the RAS (Acosta, 1982). However, this activity in most of these patients is inappropriately high in the volume-expanded milieu of CKD (Davies et al, 1973; Mailloux, 2001). Furthermore, in CKD, mainly secondary to vascular disease, diabetes or PKD, in areas of renal injury or ischemia there is a greater production of local and intra-renal AII which then exacerbates systemic hypertension (Acosta, 1982; Rosenberg et al, 1994).

3.3 Oxidative stress and nitric oxide antagonism

“Oxidative stress is an imbalance between oxidants and anti-oxidants in favor of the oxidants, potentially leading to damage” (Sies, 1997). In CKD there is an excess of oxidant molecules such as superoxide and hydrogen peroxide and a decrease of anti-oxidant ones,

such as catalase, superoxide dismutase and glutathione dismutase (Vaziri et al., 2002). The excess of reactive oxygen species may directly stimulate vascular contraction or reduce nitric oxide, contributing to hypertension in CKD (Hu et al., 1998). In addition, it is known that anti-oxidant agents can reduce the blood pressure in animal models of hypertension (Vaziri et al., 1997). The endothelial-derived nitric oxide has the capacity to maintain the vascular tone and to produce vasodilatation, through the activation of guanylate cyclase. In CKD, there is an increase of asymmetric dimethylarginine, an inhibitor of nitric oxide synthase (Leone et al., 1992). Moreover, as we pointed out before, the increase amount of reactive oxygen species in CKD impair nitric oxide effects. These two factors are responsible for a decrease nitric oxide activity in CKD which contribute to endothelial dysfunction and increased blood pressure.

3.4 Sympathetic Nervous System and Renal Dopaminergic System

The Sympathetic Nervous System activity is increased in CKD, as was demonstrated almost 20 years ago (Converse et al., 1992). Afferent signals from the diseased kidney are transmitted to the vasomotor control center in the brain increasing the blood pressure (Rump et al, 2000). In addition, increased plasma noradrenaline levels are often high in CKD patients. Evidence for the role of sympathetic nervous system is provided by the fall of blood pressure after renal sympathetic denervation or after bilateral nephrectomy (Khawaja et al, 2011).

Dopamine, a precursor of noradrenaline, has a natriuretic effect by inhibiting Na-K-ATPase in proximal tubular segments. Patients with CKD have reduced urinary excretion of dopamine (Casson et al, 1983) and decreased activity of the renal dopaminergic system, which correlates well with the degree of renal dysfunction (Pestana et al, 2001). These data show that the reduced activity of renal dopaminergic system in CKD, by decreasing the sodium excretion, may be another factor connected with the hypertension of CKD.

3.5 Miscellaneous

Endothelin is a family of four 21 amino acid peptides and ET-1, the predominant isoform, is produced by endothelial cells. It can mediate vasoconstriction when binds to its A and B receptors in vascular smooth muscle cells. Vasodilation results from the interaction with the B receptor in endothelial cells. In CKD, endothelin levels are increased and the use of selective endothelin A receptor antagonist produces reduction of blood pressure associated with renal vasodilatation (Goddard et al, 2004).

Parathormone starts to rise early in CKD. Its role in the pathogenesis of hypertension remains controversial. It has been shown, by some but not all authors that the parathormone can increase intracellular calcium and aggravate hypertension and that parathyroidectomy may improve blood pressure control.

The role of Endogenous Digitalis-like Factors (EDLFs) in sodium or volume dependent hypertension was elucidated only recently, after several decades of intense research. The EDLFs include quite a few substances, produced in the adrenal gland or in the hypothalamus, that inhibit the Na-K-ATPase in cell membranes, being at the same time natriuretic and vasoconstrictors (Takahashi et al, 2011). The high levels of EDLFs in CKD

(Hamlyn et al, 1996; Komiyama et al, 2005), secondary to an increased sodium content and expanded blood volume, may also contribute to the hypertension commonly seen in this population.

4. Considerations about hypertension treatment in CKD

The treatment of hypertension in CKD has three main goals: blood pressure control; delaying the progression of CKD itself; decreasing the risk of cardiovascular complications in this particular population. The role of non-drug therapy is frequently underestimated. However, salt restriction and lifestyle modifications are invaluable to achieve the goals defined above. Drug therapy is fundamental, and at later stages of CKD, double or multiple drug associations are often needed. RAS antagonists should be the preferred drugs and their association with diuretics mandatory.

4.1 Salt restriction and life style modifications

Given that one of the main causes of CKD related hypertension is increased extracellular volume (or exchangeable sodium), dietary sodium restriction makes every sense. Excess dietary salt, typical of Western Countries, is clearly associated with the massive number of hypertensive patients in modern societies and, in the other extreme, it is well known that in primitive civilizations with low sodium intake, the prevalence of hypertension is irrelevant (Carvalho et al, 1989). Guidelines on CKD recommend a low sodium ingestion (70–100mmol/day) in patients with CKD (KDOQI, 2004; Joint Specialty Committee Guidelines, 2006; Levin et al, 2008). This suggestion is based on the evidence that a lower sodium intake is associated with a reduction of the blood pressure values (Sacks et al, 2001), increases the protective effect of ACE inhibitors in patients with proteinuria (Heeg et al, 1989) and, possibly, declines the progression of renal failure (Ciancaruso et al, 1998). Concerning life style changes, it is recommended to CKD patients to have a healthy life. Cigarette smoking, a well known cardiovascular risk factor also works as a renal risk factor. Smoking increases blood pressure by stimulating the sympathetic nervous system and also by rising plasma endothelin levels (Orth, 2003; Halimi & Mimran, 2000). The related excessive production of oxygen-free radicals can produce endothelial dysfunction and consequently be another factor implicated in the increase of blood pressure. It is critical to stop smoking, because this preventable risk factor can hasten the progression of chronic renal insufficiency in diabetic and non-diabetic nephropathies, independently of gender and race (Orth, 2003). Reduction of alcohol ingestion is also another useful decision, not because it is related with worsening of the renal function itself, but rather because it can be associated with smoking and obesity (Suter & Schutz, 2008). Weight loss in hypertensive obese patients is associated with reductions of the blood pressure, proteinuria and left ventricular hypertrophy, with benefits in terms of total cardiovascular outcomes. In CKD patients a favorable impact was also demonstrated: a decrease in proteinuria and better blood pressure control (Praga & Morales, 2006). Weight reduction may improve insulin resistance and decreases inflammation and oxidative stress beyond positive actions on the RAS and sympathetic nervous system. Furthermore, it may also slow down the progression to ESRD. The regular practice of exercise also has a beneficial effect on CKD patients. A high-quality exercise program can improve many indicators of physical performance, as well as all cardiovascular indices. Exercise may improve the control of blood pressure and endothelial function and decrease

inflammation and insulin resistance (Johansen, 2007). Moreover, physical exercise has no untoward effect on progression of CKD. However, since this population has a potential bigger risk of musculoskeletal injuries and cardiac events it is mandatory to perform an accurate medical checkout before enrolling any exercise program.

4.2 Pharmacological therapy

The need to employ anti-hypertensive drugs mainly in the late stages of the disease is mandatory in almost all CKD patients. It is, often, necessary to use multiple drug regimens to control the blood pressure levels adequately and a constant evaluation of patient compliance and frequent medical reassessment meetings are required.

4.2.1 What should be the target blood pressure?

Nearly all guidelines concerning CKD patients support that blood pressure should be targeted to less than 130/80 mmHg (Chobanian et al, 2003; KDOQI, 2004; Levin et al, 2008). Despite major well designed randomized controlled trials (RCT) (Klahr et al, 1994; Estacio et al, 2000; Wright et al, 2002; Ruggenenti et al, 2005), there is no clear evidence that a blood pressure target < 130/80 mmHg is better, in terms of renal disease progression in CKD patients. A recently published systematic review did not show any advantage, regarding progression of CKD, in keeping blood pressure < 130/80 mmHg (Upadhyay et al, 2011). Post-hoc analysis of the MDRD and ABCD studies showed some benefits in the group of patients with a better control of the blood pressure, and two meta-analyses (Makki et al, 1995; Casas et al, 2005) also showed a protracted progression of the CKD in patients with lower blood pressure levels. Furthermore, another meta-analysis including 11 RCT with non-diabetic CKD patients, showed that those with systolic blood pressure between 110-119 mmHg, had the lowest risk of progression of CKD, and that this risk was greatly increased in patients with systolic blood pressure > 130 mmHg (Jafar et al, 2003). Finally, Appel and co-workers demonstrated that in African-American patients with CKD and proteinuria, intensive blood pressure treatment decreased the risk of progression of renal failure (Appel et al, 2010). Secondary analysis from large RCT with antagonists of the RAS, such as the HOPE, IDNT and ADVANCE studies, proved that hypertension treatment in CKD patients can reduce the risk of cardiovascular events (Mann et al, 2001; Pohl et al, 2005; Heerspink et al, 2010). However, insofar no RCT was able to prove that a blood pressure < 130/80 mmHg is better in terms of cardiovascular outcomes. On the other hand, it must be kept in mind that lowering the blood pressure < 120/70 mmHg, mainly in older patients, can increase the progression of renal failure (van Bommel et al, 2006) and enhance the probability of a cardiovascular event (Pohl et al, 2005; Hirsh et al, 2008). In brief, there is no strong evidence to have a blood pressure target < 130/80 mmHg, and we should maintain the goal of blood pressure < 140/90 mmHg, mostly in the elderly. However, in patients under 60 years with proteinuria a lower target might be allowed.

4.2.2 Which anti-hypertensive drug must we choose?

We must choose a drug to control the blood pressure, with the ability to slow down the inexorable progression of CKD and decrease the cardiovascular risk of this population. Hypertension control, by itself, can delay the progression of CKD, as Mogensen reported

more than 30 years ago, using diuretics and a Beta Blocker in type I diabetic patients with nephropathy (Mogensen, 1976). Notwithstanding, in the last decades, the superiority of the ACE inhibitors, and lately of the angiotensin receptor blockers (ARB), in terms of preventing the progression of CKD and also in terms of reducing cardiovascular morbidity and mortality have been widely reported in medical literature. The benefits of ACE inhibitors and ARB are far beyond and independent of blood pressure control. The mechanisms of renal protection result from hemodynamic and non-hemodynamic actions: decrease of intraglomerular hydrostatic pressure, decrease of protein excretion, and decrease of AII activity (Sica, 2003). This octapeptide is also a powerful cytokine with non-hemodynamic properties such as proinflammatory and profibrotic actions. AII upregulates the production of adhesion molecules, cytokines and chemokines, increasing the number of inflammatory cells in the kidney. It also stimulates extracellular matrix accumulation through the production of profibrotic factors, such as transforming growth factor- β . The decrease of AII activity observed with these drugs explains, in part, the extra advantages of their use in CKD patients. Several RCT and meta-analysis, in type 1 and 2 diabetic patients as well as in non-diabetic patients, confirmed that ACE inhibitors and ARB must be first choice drugs in renal patients, since they effectively slow the progression of CKD (Jafar et al, 2003; Lewis et al, 1993; Lewis et al, 2001; Brenner et al, 2001; Jafar et al, 2001). In addition, these particular drugs have the ability to reduce cardiovascular morbidity and mortality. In a post hoc analysis of the HOPE study, treatment with ramipril in patients with slight to moderate CKD decreased significantly the number of cardiovascular events (Mann et al, 2001). In the PEACE trial, trandolapril reduced the mortality in 27 % only in the subgroup of patients with renal insufficiency (Solomon et al, 2006) and in a recent meta-analysis, Balamuthusamy and co-workers found that RAS blockade in patients with non-diabetic renal disease was associated with a significant reduction in cardiovascular outcomes (Balamuthusamy et al, 2007). Concerning the secondary effects of these anti-hypertensive agents in renal patients, special attention must be given to: possible slight increase of the creatinine level (< 25 %), reflecting a decrease of the glomerular hyperfiltration, which means good news on the long run; a major increase of the creatinine level is suggestive of volume depletion (concomitant use of diuretics) or of bilateral renal artery stenosis; hyperkalemia is usually insignificant, but when severe it might be fatal; we must be aware of the potassium intake and of the use of other potentially hyperkalemic drugs, like aldosterone antagonists or non-steroid anti-inflammatory drugs; finally, we must also take into consideration that these drugs may also increase the need for higher dose of erythropoiesis stimulating agents (Neves et al, 2007).

4.2.3 Which drug association must we favor?

As stated previously, most patients will need two or more drugs to control hypertension and a stepwise approach should be pursued. After the prescription of an ACE inhibitor or an ARB, if there are no contra-indications, the choice of another anti-hypertensive agent must be dictated by any specific conditions of each patient. Diuretics are very useful and almost always mandatory, mainly in later stages of the disease, because of the presence of fluid overload. Thiazides can be used when the GFR > 30 ml/min/1,73 m² body surface area, being ineffective beyond this level. Then, we should rather use a loop diuretic such as indapamide or furosemide (KDOQI, 2004). Diuretics have the ability to diminish sodium reabsorption, thereby reversing hypervolemia and reducing the blood pressure. By reducing

the blood volume and stimulating the renin activity, diuretics intensify the effect of ACE inhibitors and ARB. Potassium sparing agents must be avoided or used very carefully due to the risk of life threatening hyperkalemia, particularly if the patient is also under an ACE inhibitor or ARB (KDOQI, 2004). For all these reasons, in the CKD patient, diuretics should be the first class of anti-hypertensive drugs to be added to an ACE inhibitor or an ARB. Calcium Channel Blockers (CCB) are potent vasodilators and also have a relevant role in the control of the blood pressure in CKD patients. They are particularly indicated if the patient has angina or heart failure secondary to diastolic dysfunction (KDOQI, 2004). Due to distinct renal hemodynamic effects, the type CCB to use should not be indiscriminate. In fact, dihydropyridines by inhibiting the renal auto-regulatory capacity and by increasing the glomerular permeability, intensifying proteinuria (Nathan et al, 2005), are harmful in terms of CKD progression. This observation was well demonstrated in the AASK and IDNT trials (Wright et al, 2002, Lewis et al, 2001), where the dihydropyridine amlodipine was worse than the ACE inhibitor or the ARB regimen. However, the non-dihydropyridines, do not interfere with glomerular auto-regulation, and therefore do not exhibit deleterious effect in terms of proteinuria and renal function (Nathan et al, 2005; Bakris et al, 1996). In renal patients with proteinuria, the non-dihydropyridine CCB are a good choice to add to an ACE inhibitor to an ARB. On the contrary, they should be avoided in patients with second and third degree heart block or with congestive heart failure due to systolic dysfunction (KDOQI, 2004). Once the dihydropyridines have detrimental effects on renal function, it is recommended that they must be given in combination with kidney protecting drugs, such as the AII antagonists. In fact, in the ACCOMPLISH trial, the risk of progression of the CKD was lower in the group of patients treated with a combination of an ACE inhibitor with amlodipine than in the group treated with the ACE inhibitor and a diuretic (Bakris et al, 2010).. This study may support, at least in some patients, the use of a CCB as the first drug to add to an AII axis antagonist. It has been shown that this association may have a greater anti-inflammatory effect. Beta-Adrenergic Blockers comprise a heterogeneous group of drugs organized in classes according to their receptor selectivity, lipid-solubility, intrinsic sympathetic activity and membrane stabilizing capacity (Kaplan, 2006a). The use of a Beta-Adrenergic Blocker, in a renal patient, is almost always justified by the coexistence of ischemic heart disease. This class of drugs is specially indicated in patients with prior angina or myocardial infarction or with atrial tachycardia or fibrillation (KDOQI, 2004). The water soluble Beta-Adrenergic Blockers (atenolol, sotalol) are excreted by the kidney and may accumulate in CKD; the lipid soluble ones (propranolol, metoprolol) are metabolized in the liver and may be associated with central nervous system side effects. Both types can cause hyperkalemia. Beta-Adrenergic Blockers do not worsen renal function but, beyond blood pressure control, they do not protect the kidney (Hannedouche et al, 1994). Carvedilol is a Beta-Adrenergic Blocker with non-selective α_1 activity that displays some advantages: beneficial effects on lipid profile (Stafylas & Sarafidis, 2008), increase of insulin sensitivity, and the capacity to reduce albumin excretion (Bakris et al, 2004). Respecting renal hemodynamics, carvedilol preserves the renal blood flow and the glomerular filtration rate (GFR), whereas decreases the renal vascular resistance. Furthermore, has anti-oxidant activity. Contradictory results concerning the favorable effect of Beta-Adrenergic Blocker on cardiovascular morbidity and mortality of CKD patients have been reported in medical literature. Prospective RCT are needed to ascertain whether these anti-hypertensive drugs really do have a positive influence on the survival of renal patients or not. Aldosterone antagonists can be used in renal patients, but with great caution if the GFR is below 30 ml/min, the patient is taking an ACE inhibitor or an ARB, or has additional risk factors for

hyperkalemia. The association of aldosterone antagonists with AII antagonists is justified by the called aldosterone escape phenomenon. The hypothetical advantage of this add-on therapy is attributed to the anti-fibrotic and anti-hypertensive properties of aldosterone antagonists. Although there are some beneficial effects in terms of proteinuria, the addition of an aldosterone antagonist to an ACE inhibitor or to an ARB does not slow the progression of renal failure. Besides, the risk of hyperkalemia is markedly increased. Renin Inhibitors, a new class of antagonists of the RAS that blocks the conversion of angiotensinogen to angiotensin I, have recently started to be used worldwide. Aliskiren, the first compound of the class, shows an effective blood pressure control and reduces albuminuria successfully in type 2 diabetic patients, when given alone (Persson et al, 2009) or in combination with losartan (Parving et al, 2008). This renoprotection is independent of its blood pressure lowering effect. Further studies are needed to determine if aliskiren, alone or in association, is able to reduce hard renal and cardiovascular end-points in CKD patients. The utilization of α -adrenergic agents or the potent vasodilator minoxidil is only justified if blood pressure control was still not achieved with the previous described classes of anti-hypertensive drugs. They are extremely potent agents but present many adverse side effects. Furthermore, minoxidil must always be associated with a Beta-Adrenergic Blocker and a diuretic in order to control the reflex tachycardia and the fluid retention induced by the former (KDOQI, 2004).

4.2.4 What about the dual blockade of the RAS?

The rationale for using two antagonists of the RAS is sustained by the existence of the AII escape phenomenon. After long-term ACE inhibition, it was demonstrated that AII synthesis via non-ACE pathways increases. Moreover, there are some limitations of ACE inhibitors in decreasing the local production of AII (Arici & Erdem, 2009). The ARB blocks the binding of AII to its receptors, reducing both its systemic and local effects (Arici & Erdem, 2009). There are advantages and drawbacks of combination therapy (Wolf & Ritz, 2005), but, in clinical terms, the aim of combination therapy is to block of the RAS more effectively (Arici & Erdem, 2009). Although several studies showed a greater decrease of albuminuria with the dual blockade (Mogensen et al, 2000; Campbell et al, 2003; Jennings et al, 2007), there are no RCT demonstrating a true slow down of CKD with combination therapy. In the ONTARGET study, the group of patients under ramipril plus telmisartan presented a higher renal impairment - doubling of serum creatinine or dialysis - and there were no differences in respect to cardiovascular outcomes (Yusuf et al, 2008). The ValHeFT and the VALIANT studies also showed more kidney dysfunction in the combination groups (Conn et al, 2001; Pfeffer et al, 2003), despite better cardiovascular results in the ValHeFT (Conn et al, 2001). In summary, concerning CKD progression, despite the theoretical advantages of combination therapy, presently there are no RCT demonstrating such benefit. Furthermore, the dual blockade is not harmless, and is associated with the risk of hyperkalemia and of greater renal impairment. Probably, studies with selected patients (with proteinuria > 1g/24h) or a different type of dual blockade with a renin inhibitor, will demonstrate a clear superiority of an association of two antagonists of the RAS. At the moment this association cannot be recommended.

5. Conclusion

Hypertension and CKD are both the chicken and the egg in this story. CKD resulting from hypertension and hypertension resulting from CKD are complex and multifactorial. A better

understanding of the physiopathology mechanisms is imperative to improve our treatment strategies and reduce renal and cardiovascular adverse events. After decades of intense basic and clinical research in this area many questions remain unanswered: Is essential hypertension a cause of CKD in Caucasians? Which is the prevalent physiopathological mechanisms underlying CKD related hypertension in a particular patient? Which is the better anti-hypertensive therapy in our CKD patients and particularly in a specific patient?

6. References

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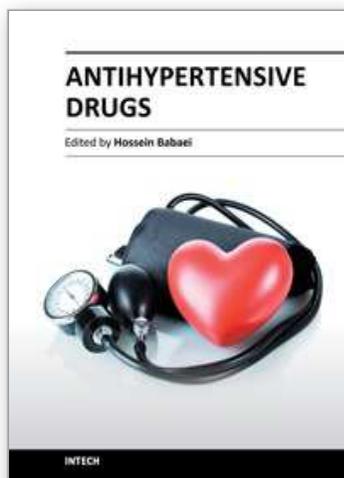
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Hypertension, known as a "silent killer" is widely prevalent and a major risk factor for cardiovascular diseases. It afflicts more than one billion population worldwide and is a leading cause of morbidity and mortality. The authors of the chapters look from different angles to hypertension, sharing their new knowledge and experience in the direction of deep understanding and more clarification of the disease providing an invaluable resource not only for clinicians, but also for all medical sciences students and health providers.

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