Role of arterial hypertension and angiotensin II in chronic kidney disease (Review)

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Abstract. Chronic kidney disease (CKD) is a major public health issue, due to its effect on the quality of life of patients and by the huge costs incurred in treating this disease. It is an irreversible process, characterized by the progressive loss of functional nephrons. CKD ultimately requires the support of renal function by dialysis or even renal transplantation. It has a multiple etiology, but the most common causes remain arterial hypertension and diabetes. High arterial blood pressure affects the target organs (kidneys) and this leads to a vicious circle involved in maintaining high blood pressure. Arterial hypertension is closely related to the renal pathology of CKD. The result of excessive activation of the renin angiotensin system (RAS) is increased angiotensin II (Ang II), which acts upon the systemic circulation and especially upon the kidneys. The outcome is high blood pressure and also the stimulation of proinflammatory and profibrotic effects in the kidneys. Collectively these ultimately lead to CKD. The aim of this review was to provide a brief overview of the pathophysiological associations between CKD, arterial hypertension, and Ang II.

Contents

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1. Introduction

The kidney has excretory, metabolic and endocrine functions. Among all the organs of the human body, the kidney has one of the highest blood flow rates per gram of organ tissue. Based on its excretory function, it intervenes in maintaining the hydro-electrolytic balance of the body, by forming and eliminating urine in the adequate amounts and with the adequate concentrations of ions.

To perform such roles, the kidney requires its normal blood flow, which is ~20-25% of the resting cardiac output. Physiologically, the distribution of renal blood flow is not uniform. From the entire renal blood flow, the cortex receives 85-90%, the external medulla receives 10%, and the internal medulla receives only 2%. The kidney has multiple, complex, and interrelated mechanisms for the autoregulation of blood flow (1). It is well known that, in the human kidney, autoregulation occurs for values of the systemic arterial blood pressure (ABP) approximately between 60 and 180 mm Hg. Thus, the renal blood flow remains fairly constant despite ABP changes between these values. There is a linear association between ABP and renal blood flow beyond the respective pressure interval. As a result, variations in systemic blood pressure within the mentioned ABP range are accompanied only by transient changes in the glomerular filtration rate (GFR).

Stimulation of the sympathetic nervous system causes intrarenal vasomotor changes. It is well known that sympathetic hyperstimulation causes more pronounced vasoconstriction of the afferent arteriole, with reduced glomerular blood flow and reduced hydrostatic pressure in the glomerular capillaries. Consequently, the rate of glomerular filtration is markedly reduced. If blood pressure values remain high, renal dysfunction occurs, with the onset of chronic kidney disease (CKD).

One of the pathophysiological mechanisms involved in the increase of blood pressure and in the development of arterial hypertension is represented by the increase of the circulating level of angiotensin II (Ang II), due to the excessive activation

of the renin angiotensin system (RAS). Damage of the target organs, which occurs as a result of increased ABP, is accompanied by a higher risk of cardiovascular events. In addition, Ang II stimulates inflammation and atherosclerosis in the target organs (2).

Arterial hypertension is closely related to CKD, while CKD is promoted and perpetuated by the chronic kidney inflammation that involves the increased RAS activity (both the circulating one and local, renal one) (Fig. 1).

2. Chronic kidney disease

The renal function is assessed by evaluation of GFR, which is normally ~125 ml/min. Structural and/or functional changes of the kidneys may correspond to various extents of true renal injury/lesion. If renal injury is acute, then the kidney has the ability to recover, but if the damage is chronic, then the ability of the kidney to regenerate is affected/lost and CKD tends to develop and progress (3). This irreversible disease, which affects 5-7% of the population of the world, thus progresses to the final stage, a situation that requires the replacement of the kidney function by dialysis or transplantation (4).

CKD is a clinical syndrome characterized by GFR decrease below 60 ml/min/1.73 m^2, lasting at least three months. Arterial hypertension and diabetes are the main etiological causes of CKD, but CKD can also be a complication of other diseases such as infectious glomerulonephritis, urethral obstruction, genetic damage, vasculitis, autoimmune diseases, and drugs (5). CKD is a huge public health problem, due to the increasing incidence of arterial hypertension, diabetes (6), obesity, and life expectancy and it is the 18th leading cause of death worldwide. Some 30-40% of the individuals diagnosed with nephropathy develop kidney failure in 10-15 years and these individuals need to improve their kidney function, which involves huge costs (7).

Regardless of the cause of CKD, the common elements encountered are inflammation, followed by the development of fibrosis (8) and the progressive loss of kidney function. Over time, these renal changes lead to the progression of the final stage of CKD. Inflammation of low intensity, but persistent, is characterized by the presence of leukocyte infiltration and the secretion of proinflammatory cytokines. Inflammatory phenomena at the renal level occur a few years before the start of specific clinical symptoms (9) and represent a protective response to potential endogenous and/or exogenous aggressors (10).

Progressive renal sclerosis, which develops after the uncontrolled inflammatory response, is a major risk factor, by increasing the pressure in the glomerular capillaries (11). Several changes occur: A decrease in the number of podocytes, loss of the electrical charge of the glomerular basement membrane, and mesangial distension. All these, together with the endothelial dysfunction, lead to glomerulosclerosis.

Fibrosis, which develops after kidney inflammation, involves tissue repair, and is characterized by excessive accumulation of extracellular matrix components, which gradually affects the cellular tissue architecture (12,13). The progression of CKD to the final stage is the consequence of losing the renal cells and their replacement with extracellular matrix, in the glomeruli and in other renal tissue structures (11). With a role

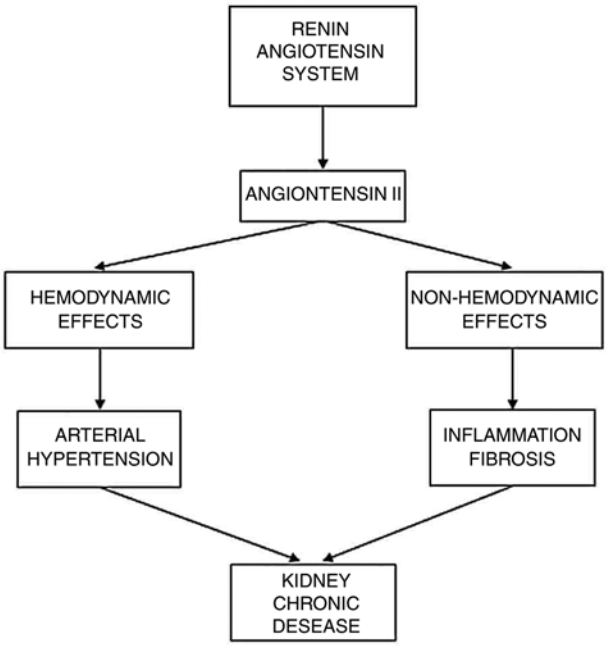

Figure 1. Association between angiotensin II and chronic kidney disease.

in preserving renal function, the processes of inflammation and fibrosis affect the specialized renal cells (tubular epithelial cells, podocytes, and glomerular mesangial cells), as well as the vascular cells (13). Glomerulosclerosis, vascular sclerosis and tubulo-interstitial fibrosis appear in the final stage of CKD (3).

3. Role of hypertension in chronic kidney disease

Arterial hypertension, the leading modifiable risk factor for a variety of cardiovascular diseases, continues to be underdiagnosed and undertreated and/or untreated worldwide. The kidneys, heart, brain, blood vessels, and eyes are the main target organs that are affected by increased ABP. Over 90% of hypertension in CKD patients is closely related to endothelial dysfunction and it is either an etiological factor or a complication of CKD. It is not known exactly whether impaired renal function in CKD is the cause and/or consequence of increased blood pressure. Being surpassed only by diabetic nephropathy, hypertensive nephropathy is the second cause of CKD progression to the final stage (14) and it is considered an independent risk factor for the decline of the GFR (15).

The GFR physiologically has a linear association with ABP, classically designated pressure diuresis. Furthermore, chronically high ABP produces renal effects at multiple levels including vascular, glomerular, interstitial, tubular, and also that of the renal immune system. High ABP, the cause and effect of CKD, promotes and perpetuates inflammation and fibrosis at the glomerular, interstitial, and tubular levels and in addition causes important changes in renal microcirculation. Renal disease followed by increased ABP, hypertensive nephropathy or hypertensive nephrosclerosis, is associated with histopathological changes in the pre- and intraglomerular microvascularization and with tubulo-interstitial changes (16-18). From a pathophysiological point of view,

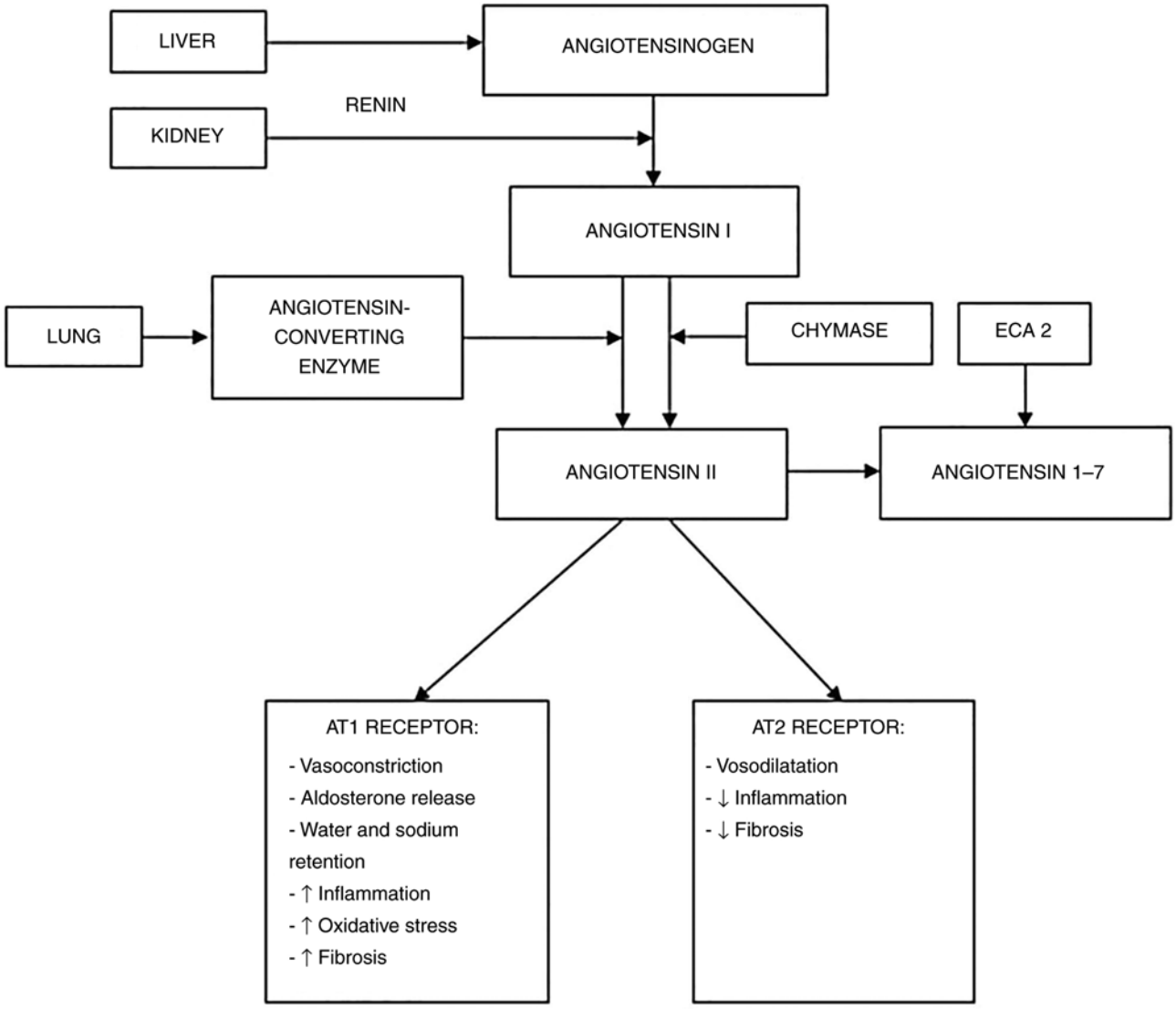

Figure 2. Renin angiotensin system.

nephrosclerosis can set in slowly, with progressive changes in the intima of the arteries and arterioles of the renal parenchyma, or rapidly, with histological changes in fibrinoid necrosis and/or proliferation of myointimal cells.

In addition, atherosclerotic changes (hyalinization) occur in the afferent arterioles. Both processes contribute to the occurrence of pulsating blood flow in the renal arterioles (19) which causes ischemic glomerular changes (focal and segmental glomerular sclerosis) and tubular atrophy, accompanied by interstitial fibrosis. Tubulo-interstitial hypoxia is instated and, together with hormonal vasoconstriction (including RAS and/or Ang II), it progresses CKD to the final stage (20). The immune system can also be an important etiopathogenic contributor to the development and maintenance of high ABP, as further discussed in the next section.

4. Renin-angiotensin system

RAS is an important regulator of systemic ABP, but other hormones are also involved, such as catecholamines, thyroid hormones, corticosteroids, and sex hormones (12).

Classically, the biologically active product of RAS, which is Ang II, is formed by a cascade of enzymatic reactions (Fig. 2), which involves two important enzymes: Renin and angiotensin-converting enzyme (ACE). Secreted by exocytosis from the cells of the renal juxtaglomerular apparatus (RJA), renin acts upon angiotensinogen (a serpentine polypeptide, synthesized mainly in the liver) and forms angiotensin I (Ang I) (apparently an inactive decapeptide). Low ABP, hypovolemia, hyponatremia, and sympathetic stimulation increase renin synthesis in RJA.

Under the action of ACE, released by the lung tissue, Ang II is formed from Ang I. ACE2 is a homologous enzyme of ACE, which generates angiotensin 1-9 (Ang 1-9) from Ang I and angiotensin 1-7 (Ang 1-7) from Ang II. Due to its vasodilating and Ang II-antagonizing effects, Ang 1-7 is considered a mechanism of counter-regulation of the classical RAS. Ang II can also be generated from Ang I, through the action of an enzyme called chymase.

In order to exert its effects, Ang II acts on specific receptors: The angiotensin receptor type 1 (AT1) and the angiotensin receptor type 2 (AT2) (Fig. 2). Ang II binding to AT1

mediates the following: Sodium retention, vasoconstriction (preferentially in the renal efferent arteriole), thirst stimulation, increased sympathetic activity, and increased release of aldosterone from the glomerular area of the adrenal gland. In the fetus, Ang II binding to the AT2 receptor counteracts the effects of AT1 receptor activation by Ang II and has vasodilator, anti-inflammatory and antifibrotic effects, but in adults these effects are irrelevant.

All RAS components can be produced locally, in tissues and organs, and act independently of systemic RAS. The kidney possesses all the components of RAS, and the amount of Ang II produced in the kidney is 1,000 times higher than the circulating one (21). Ang II influences both renal hemodynamics and tubular function. Ang II decreases renal blood flow and decreases the GFR, exerting effects both on renal microvasculature and on the glomerular mesangium. Ang II predominantly contracts preglomerular arterioles. When the pre- and post-glomerular resistance increases in parallel, the outcome is an increased GFR. Regarding tubular function, Ang II has the following effects: It causes sodium and water retention (mediated by Ang II-stimulated aldosterone secretion and modulated by hemodynamic changes in the peritubular capillaries); it causes cellular hypertrophy; and it induces oxidative stress. Local Ang II production directly causes podocyte impairment via AT1 receptor activation, regardless of hemodynamic changes (22,23).

Decreased blood pressure in response to Ang II inhibition is more pronounced during a low sodium diet. Normally, in hypertensive patients with kidney disease, ACE-I and sartans are used with other drugs, generally diuretics. It has been observed that ACE-I and sartans lead to a marked decrease in systemic ABP, accompanied by decreased GFR, when the volume of extracellular fluid is reduced. In patients with severe kidney disease, the related arterioles become less responsive to ACE-I and sartans (24).

Beyond the hemodynamic effects it possesses, Ang II behaves similar to a cytokine, with proinflammatory and profibrotic properties. Ang II-induced fibrosis is achieved by a dual mechanism: i) By a direct effect on the process of synthesis/degradation of the extracellular matrix; and ii) indirectly, by increasing the expression of profibrotic factors with a crucial role in mesangial proliferation (25), such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) (26). Renin and aldosterone also possess profibrotic effects by increasing TGF-β expression. Both the renal cells (especially the glomerular ones) and the macrophages recruited in the kidneys express TGF-β (27). TGF-β is involved in modulating the renal immune response by regulating the proliferation, differentiation and migration of inflammatory cells (23), while stimulating the proliferation of fibroblasts (28). Together with Ang II, TGF-β induces oxidative stress and stimulates extracellular matrix synthesis, in parallel with inhibition of proteases that degrade the extracellular matrix. Ang II exerts these effects through AT1 receptors. Furthermore, following renal injury, an increase in apoptosis is observed, a phenomenon induced by Ang II through AT2 receptors. Animal studies have shown the possible involvement of the AT2 receptor in the regression of renal fibrosis, by reducing post-aggression vascular damage. Renal fibrosis, associated with glomerulosclerosis and interstitial renal fibrosis is characterized by atrophy and tubular dilation, and increased fibrogenesis and collagen deposits in the extracellular matrix (29,30).

In previous studies by the authors some systemic and renal aspects of the proinflammatory effects of Ang II were investigated, using the Ang II-induced hypertension rat model (17,18,31). In fact, in these studies an attempt was made to gain insight into the associations among Ang II, hypertension, and inflammation. This trilateral association could be relevant to the topic of the present review, particularly regarding the disease stages just before and/or immediately after the true onset of CKD (as defined in terms of diminished GFR for at least three months).

5. Conclusions

In conclusion, Ang II acts on the kidney through a dual mechanism: Indirectly, by increasing systemic ABP and directly, by stimulating the inflammatory and fibrotic processes in the vascular wall and in the renal tissue. Kidney inflammation associated with high ABP is an area open to research due to insufficient available data. Expanding pathophysiological knowledge with regard to hypertension and kidney disease has an applicative potential, opening up new directions in the therapeutic approach of these diseases.

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Authors' contributions

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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