Arterial Hypertension and the Kidney: The Fatal Duo of Chronic Non-Communicable Diseases

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Abstract: Chronic non-communicable diseases are the leading cause of death worldwide, among which cardiovascular diseases have the highest mortality. Hypertension is a major risk factor of cardiovascular diseases, which is usually asymptomatic until complications occur. There is a strong relationship between hypertension and the kidney, since hypertension is both, a major risk factor for the onset and progression of kidney diseases as well as a complication of kidney diseases.

Keywords: Arterial hypertension; Kidney; Chronic kidney disease; Chronic non-communicable diseases

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1. Introduction
Chronic non-communicable diseases are conditions that develop slowly and last over an extensive period of time, resulting in bodily deterioration [1]. These include cancer, diabetes, respiratory, renal, and cardiovascular conditions.

According to the World Health Organization (WHO), in 2016, 70% of deaths worldwide were attributed to chronic noncommunicable diseases [41]. Hypertension is one of the seven conditions that make up the entity known as cardiovascular disease (CVD). Epidemiological data have shown that hypertension is a major risk factor of cardiovascular disease [2], and in Mexico itself, the prevalence of arterial hypertension is 25.5% [3].

Chronic kidney disease (CKD) is related to several chronic non-communicable conditions, mainly arterial hypertension. In Mexico, the epidemiological data on CKD morbidity and mortality are very alarming [4]. There is a close relationship between hypertension and CKD, since hypertension is both a major risk factor of the onset and progression of CKD as well as a complication of CKD.

Therefore, in this review, we will analyze several aspects of arterial hypertension, including its prevalence, classification, etiology, heritability, and relationship with chronic non-communicable diseases, the importance of the kidney in regulating blood pressure, as well as chronic kidney disease, its relationship with hypertension, and its deleterious consequences for health.
2. Arterial hypertension
When there is an imbalance between vasoconstrictor and vasodilator factors in the body, hypertension occurs. Hypertension is characterized by a sustained and chronic elevation of blood pressure (increase in systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg) due to various factors. Environmental, genetic, and epigenetic factors are implicated in this imbalance. The latter constitutes the connection, whereby environmental factors (diet) directly intervene with genes and regulate their expression.

Hypertension can be classified according to blood pressure levels (Table 1).

Table 1. Classification of hypertension according to systolic and diastolic levels

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic pressure (mmHg)</th>
<th>Diastolic pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Normal blood pressure</td>
<td>120–129</td>
<td>80–84</td>
</tr>
<tr>
<td>High normal blood pressure</td>
<td>130–139</td>
<td>85–89</td>
</tr>
<tr>
<td>Hypertension grade 1</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Hypertension grade 2</td>
<td>160–179</td>
<td>100–109</td>
</tr>
<tr>
<td>Hypertension grade 3</td>
<td>&gt; 180</td>
<td>≥ 110</td>
</tr>
<tr>
<td>Masked hypertension</td>
<td>≤ 140</td>
<td>≤ 90</td>
</tr>
</tbody>
</table>

The term prehypertension, proposed in the Seventh Report of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, defines a group of people at increased risk for CVD who have blood pressure readings that are not considered to be significant by physicians. The defined blood pressure range for prehypertension is 120–139 mmHg systolic or 80–89 mmHg diastolic.

The relationship between blood pressure level and CVD risk events are continuous, consistent, and independent of other risk factors. According to observational studies of more than one million people, death from ischemia, heart disease, and stroke shows a linear increase from blood pressure levels as low as 115 mmHg systolic and 75 mmHg diastolic upwards. Epidemiological studies also support the hypothesis that in the relationship between blood pressure level and CKD risk, there is a linear progression.

Prehypertension is found associated with an intermediate level of CVD risk, higher than that for normotensive patients, but lower than that for patients with grade 1 hypertension.

3. Etiology of arterial hypertension
According to its etiology, hypertension can be classified into two major groups (Figure 1).

(1) Essential or primary hypertension
There is no specific medical cause for essential hypertension. It accounts for 90% to 95% of all identified cases, and it primarily affects people in an advanced age. It has a strong correlation with sedentary lifestyle habits and a diet rich in fats and carbohydrates, with low fruits and vegetable intake. Other risk factors include anti-inflammatory drugs, steroids, medications, salt (sodium chloride), alcohol, and hormone replacement therapy.

(2) Secondary hypertension
Secondary hypertension is the result of pre-existing conditions, which can be categorized based on systems: renal (tubular monogenic syndrome, subcapsular compression, reninoma, polycystic kidney disease, and chronic kidney disease); vascular (aortic coarctation, atherosclerotic renal stenosis, and fibromuscular dysplasia); endocrine (hyperaldosteronism, hypercortisolemia, acromegaly, pheochromocytoma, steroid synthesis disorders, hyperthyroidism, and hypothyroidism); neuronal
(obstructive sleep apnea and autonomic failure). It accounts for 5% to 10% of all cases, and it primarily affects people in their 40s[5,6].

![Classification of arterial hypertension](image)

**Figure 1. Classification of arterial hypertension**

Blood pressure also has a hereditary trait. It has been estimated that 30% of the variation in blood pressure is related to genetic factors. A common feature of most forms of hypertension with Mendelian inheritance is the alterations in sodium homeostasis. Genome studies have identified more than 65 loci that affect blood pressure, but most of these include genes that would not have been expected to affect blood pressure based on the pathophysiology of hypertension[9]. In recent years, it has been proposed that intrauterine metabolic programming might also have a role in the development of hypertension[6].

Epidemiological data and experimental data in humans and animals, respectively, have shown that alterations in the intrauterine environment due to various factors, such as alterations in maternal nutrition, are associated with the onset of arterial hypertension in adults and animals[10]. One approach to understanding the relationship between fetal metabolic programming and the development of hypertension in adults is through epigenetics[11]. Epigenetics studies how environmental factors (nutrients) chemically modify DNA without changing its sequence, allowing it to be inherited, and eventually producing a specific phenotype[12].

The difficulty in interconnecting all the mechanisms that regulate blood pressure leads to the fact that even if there is a primary factor responsible for causing hypertension, others could be responsible for its maintenance. Most theories agree that the disorder in its regulation is due to endogenous or exogenous factors. Endogenous factors are multifactorial, including genetic ones, whereas exogenous factors are those that trigger genetic predisposition, and they mainly include high salt intake, poor diet (food rich in saturated fat and carbohydrate), and some psychogenetic factors (stress)[13].

Hypertension often presents with a set of additional risk factors related to chronic non-communicable diseases, such as insulin resistance, diabetes, obesity, and dyslipidemia, all of which can cause hypertension. For example, increased body weight is related to sodium retention, due to increased activity of the renin-angiotensin-aldosterone system. Also, in obese people, the increase in triglyceride concentration favors the formation of atheroma, which narrows the vascular lumen, and thus increases blood pressure. Similarly, insulin resistance causes a compensatory increase in insulin to maintain adequate blood glucose levels, in which hyperinsulinemia has been reported to be a major risk factor of atherosclerosis that contributes to elevated blood pressure due to narrowed vascular lumina[14,15].

Arterial hypertension is characterized by endothelial dysfunction related to a decrease in vasorelaxant factors, such as nitric oxide (NO), bradykinin, and prostacyclin, but an increase in vasoconstrictor factors, such as adrenaline, serotonin, endothelin, thromboxane A2, and reactive oxygen species[16]. There is also an inability of blood vessels to modify their structure in response to hemodynamic and mechanical changes due to hyperstimulation of the renin-angiotensin-aldosterone system and hypersensitivity of the
sympathetic nervous system \[6,17\]. Moreover, increased PAI-1 (plasminogen activator inhibitor-1) also plays a role in remodeling the vascular endothelium structure and participates in blood vessel thrombosis \[18\].

The fact that endothelial dysfunction is a promoter of hypertension highlights the relationship between hypertension and other diseases that disrupt the endothelial function, such as diabetes, obesity, and dyslipidemia \[19\]. Prospective studies have shown that chronic stress and anxiety also promote the development of hypertension by constant activation of the sympathetic system \[20\].

Arterial hypertension is a disease that can be asymptomatic until non-reversible complications occur, which is why it is known as a silent killer. The complications of hypertension are related to organ damage, particularly the heart, brain, and kidneys. In the heart, the long-standing change in cardiac output leads to heart failure, which is manifested as effort intolerance, fatigue, and renal dysfunction. Stroke, thrombosis, embolism, or ictus may occur when hypertension damages the blood vessels in the brain. Depending on the part of the brain affected, stroke can lead to paralysis, blindness, memory loss, language problems, or even death. Similarly, hypertension damages the kidneys by causing the loss of nephrons, leading to renal failure and ultimately death \[6,21\].

4. Kidney and blood pressure control
Anatomically, each kidney is covered by a tough, fibrous, rigid capsule made of connective tissue that serves to limit the sudden changes in volume occurring in response to an elevation in blood pressure. The kidney is divided into two main regions: cortex and medulla; it can be further divided into four zones: cortex, outer fringe of the outer medulla, inner fringe of the outer medulla, and inner medulla \[22\]. The functional and structural unit of the kidney is the nephron, which contains a cluster of capillaries, called the glomerulus. It filters a large volume of blood, and the filtered fluid produces urine as it travels to the renal pelvis \[23,24\].

   The kidney plays a very important role in the control of blood pressure by governing the excretion and reabsorption of both, water and sodium, as well as the synthesis and release of hormones that regulate the two major systems: the renin-angiotensin-aldosterone system and the adrenergic system \[23\]. All these mechanisms are involved in a feedback loop; therefore, when there is an imbalance, structural and functional renal alterations occur, but these alterations have cumulative consequences that are associated with the onset and maintenance of arterial hypertension (Figure 2).

   ![Figure 2](image)

   **Figure 2.** Relationship between the kidney and arterial hypertension. The kidney is known to regulate blood pressure, so when there is an imbalance, there is an increase in blood pressure, which conditions the occurrence of renal alterations (structural and functional) that favor the onset of arterial hypertension; this, in turn, causes greater renal alterations that favor the maintenance and progression of arterial hypertension.
The kidneys have a preponderant role in the long-term control of blood pressure, since they excrete large amounts of water and sodium. This control is related to the hemostatic control of fluid volume in the body. When blood volume increases, without a change in vascular capacitance, there will be an increase in blood pressure. With the increase in pressure, the kidney will excrete more fluid into the urine, so that the blood pressure will normalize. When blood pressure decreases, the kidney will excrete less fluid than is ingested, so that blood pressure will increase through fluid retention. Renal elimination of water is known as pressure diuresis. The increase in blood pressure also causes an increase in sodium elimination, which is known as pressure natriuresis [23].

The kidneys can also regulate blood pressure in the short term, by means of the renin-angiotensin-aldosterone system. This system contributes to the control by regulating sodium reabsorption by aldosterone and the synthesis of angiotensin II (Ang II). Besides increasing myocardial contractility, Ang II stimulates the secretion of aldosterone and the release catecholamines from the adrenal medulla and sympathetic nerve endings, which increases sympathetic nervous system activity and water reabsorption in the kidney [25]. In addition, the acute stimulation by Ang II regulates water-sodium homeostasis and vasoconstriction, which modulates blood pressure; whereas its chronic stimulation promotes dysfunction of vascular smooth muscle cells, cardiac muscle, and renal fibrosis [26].

5. Hypertension and chronic kidney disease
Chronic kidney disease is defined by KDIGO (Kidney Disease: Improving Global Outcomes) as decreased renal function, with a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for more than three months, along with histological alterations and albuminuria or proteinuria greater than 30 mg/dL. Chronic non-communicable diseases, such as diabetes and hypertension, are significant risk factors of chronic kidney disease [1].

The issue of whether renal dysfunction is the result of chronic hypertension or the primary cause of the hypertensive state is still being debated [22,27,28]. However, what is not debatable is the involvement of the kidney in the development and maintenance of arterial hypertension [29]. Changes in renal function are thought to be attributable to structural factors and functional alterations in the kidney as a result of increased perfusion pressure.

It has been discovered that increased basal blood pressure can exacerbate structural changes in the kidney of hypertensive patients, resulting in secondary hypertension. Similarly, increased total peripheral resistance due to various causes has also been shown to induce increased renal vascular resistance, changes in kidney function, and arterial hypertension [22,29].

The first studies that linked hypertension with renal changes were carried out by Guyton and several other researchers. They postulated that the alterations in renal function are predisposing factors for any type of arterial hypertension, since in order to achieve natriuresis, arterial pressure must be raised, with the aim of increasing glomerular filtration pressure to increase the filtered load and eliminate sodium [23,30]. Subsequently, Brenner, Garcia, and Anderson proposed that a reduction in the number of nephrons is also related to hypertension, since a decrease will cause compensatory glomerular hyperfiltration to maintain global glomerular filtration and sodium filtration; this effect is attributable to the increase in Ang II, which causes efferent vasoconstriction, increase in glomerular pressure, and hypertension [31]. Another study was that of Rettig, which involved transplanting kidneys from rats genetically conditioned to develop hypertension (SHR, Spontaneous Hypertensive Rats) to compatible normotensive recipient rats, which eventually developed hypertension; hence, it was concluded that the kidneys of the hypertensive rats had intrinsic damage that caused hypertension [32].

On the other hand, Curtis investigated the significance of kidney transplantation in the remission of hypertension in a recipient with arterial hypertension, who received a transplant from a healthy donor.
(normotensive). He found that there was remission of essential hypertension in the hypertensive individual who received the transplant from the normotensive donor. Although these studies point to the kidney as the cause of hypertension, renal structural alterations alone cannot be considered as the sole factor causing hypertension.

It has been discovered that hypertension can cause further injury to the glomeruli and renal blood vessels, and it is a major contributor to the development of end-stage renal disease. In contrast, renal dysfunction can lead to arterial hypertension. The relationship between hypertension and nephropathy can be described as a vicious cycle. Primary renal injury increases blood pressure, which in turn further injures the kidneys; the cycle continues until terminal nephropathy develops. Vascular disorders of the kidneys related to arterial hypertension include partial or complete occlusion of vessels of various caliber, which affects the glomeruli, and as a consequence, progressive renal failure develops; thus, arterial hypertension further aggravates hypertension. Hypertension is highly prevalent in patients with chronic kidney disease, thus contributing to the high cardiovascular morbidity and mortality in this population.

In general, two mechanisms have been proposed to explain renal damage in patients with hypertension. (1) Changes in the renal macro- and microvasculature occur, leading to a loss of renal autoregulation and an elevated glomerular capillary pressure, which is consequently damage by glomerular hyperfiltration. (2) Renal endothelial dysfunction and the loss of endogenous vasodilators favor ischemic vascular injury, leading to the activation of the renin-angiotensin-aldosterone system and a release of cytokines as well as growth factors. This, in turn, results in the recruitment of inflammatory cells that stimulate apoptosis, causing the loss of nephrons and an increase in extracellular matrix synthesis, thus resulting in renal fibrosis.

In addition, the renal regulation of the renin-angiotensin-aldosterone system, mediated by local ischemia, is associated with an increase in angiotensin-converting enzyme (ACE) activity in the proximal tubules and peritubular interstitium, which increases Ang II production and, therefore, vasoconstriction and changes in vascular structure. Ang II regulates cell growth in the kidney, and its secretion favors the development of glomerulosclerosis and tubulointerstitial fibrosis. It also stimulates the synthesis of endothelin I and decreases nitric oxide synthesis, which enhance its vasoconstrictor effect. Hypertension, in turn, causes afferent arteriolar sclerosis with tubular ischemia, interstitial inflammation, and Ang II release, all of which contribute to renal fibrosis and functional deterioration.

6. Conclusion

Chronic non-communicable diseases are a major health problem, both, in Mexico and around the world. Among them, arterial hypertension and chronic kidney disease have a high incidence of morbidity and mortality. In addition, arterial hypertension, in most cases, seldom manifests symptoms that allow it to be detected early, which may lead to serious complications as it is a risk factor of myocardial infarction and chronic kidney disease, thus making it the silent killer of chronic diseases. Regardless of the mechanism that causes arterial hypertension, renal alterations will contribute to maintaining and aggravating arterial hypertension.

Regardless of the cause of CKD, hypertension will contribute to worsening CKD and in turn lead to health complications, which can be life-threatening. The prospect for a decrease in the prevalence of hypertension and chronic kidney disease is bleak. Therefore, it is crucial to ensure that patients suffering from either one of these two diseases are aware of the care they should receive, because the occurrence of either one conditions the event of the other, resulting in a progressive deterioration of health and a significant risk of mortality.
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Disclosure statement
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References


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