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Revisión

Aldosterone: a cardiometabolic risk hormone?

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Abstract

Introduction: **A aldosterone is a component of the renin–angiotensin–aldosterone system, classically known for its role in sodium and water retention. Besides its effects, has been shown that the aldosterone is associated with the pathogenesis and progression of metabolic syndrome components. A better understanding of this system and interfering factors could help develop pharmacotherapeutic alternatives for several disorders.**

Objectives: **Investigate the relationship between diet and aldosterone, and its influence on cardiometabolic risk factors.**

Results and Discussion: **Diet can affect plasma aldosterone levels; high fructose and fat intake can lead to increased aldosterone levels, whereas the effect of sodium intake remains controversial. Adipose tissue, particularly visceral tissue, appears to produce a lipid-soluble factor that increases aldosterone production. Patients with metabolic syndrome have higher aldosterone levels; moreover, an increased cardiometabolic risk associated with insulin resistance could be partially mediated by the action of aldosterone via mineralocorticoid receptors. Even a subtle activation of this hormonal system may have deleterious effects on the glucose and lipid metabolism related to metabolic syndrome. Nevertheless, additional studies are required to better understand the interactions among adipose tissue, aldosterone, and cardiovascular risk as well as the possible role of diet.**

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Key words: *Aldosterone. Obesity. Metabolic syndrome. Cardiovascular diseases.*

ALDOSTERONA: ¿HORMONA DE RIESGO CARDIOMETABÓLICO?

Resumen

Introducción: **La aldosterona es un componente del sistema renina-angiotensina-aldosterona, clasicamente conocida por su papel en la retención de sodio y agua. Además de estos efectos, ha sido demostrado que la aldosterona está asociada a la patogénesis y progresión de componentes del síndrome metabólico. Una mejor comprensión de este sistema y de los factores interferentes podría ayudar a desarrollar alternativas farmacoterapéuticas para varias enfermedades.**

Objetivos: **Investigar la relación entre dieta y aldosterona, y su influencia sobre factores de riesgo cardiometabólico.**

Resultados y Discusión: **La dieta es capaz de modular las concentraciones plasmáticas de aldosterona; alto contenido de fructosa y la ingestión de grasa pueden llevar al aumento de los niveles de aldosterona, mientras que el efecto de la ingestión de sodio permanece polémico. El tejido adiposo, particularmente el visceral, parece producir un factor liposoluble que aumenta la producción de aldosterona. Pacientes con síndrome metabólico tienen concentraciones más elevadas de aldosterona; Además de eso, un aumento del riesgo cardiometabólico asociado con la resistencia a la insulina puede ser parcialmente mediada por la acción de la aldosterona a través de los receptores mineralocorticoides. Aunque la activación sutil de este sistema hormonal parece ejercer efectos deleterios en el metabolismo glicémico y lipídico, asociado con el síndrome metabólico. Sin embargo, otros estudios son necesarios para el entendimento de las interaciones entre tejido adiposo, aldosterona y riesgo cardiovascular, así como el posible papel de la dieta.**

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Palabras claves: *Aldosterona. Obesidad. Síndrome metabólico. Enfermedades cardiovasculares.*

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Abbreviations

BMI: Body mass index.
CI: Confidence interval.
CYP11B2: Aldosterone synthase.
HDL: High density lipoprotein cholesterol.
HF: High-fat diet.
HOMA-IR: Homeostasis model assessment-estimated insulin resistance.
ICAM-1: Intercellular adhesion molecule-1.
LDL: Low density lipoprotein cholesterol.
LF: Low-fat diet.
MCP-1: Monocyte chemotactic protein-1.
mRNA: Messenger ribonucleic acid.
NAD(P)H: Nicotinamide adeninedinucleotide phosphate.
NF-κβ: Factor nuclear kappa B.
PAI-1: Plasminogen activator inhibitor-1.
PPAR-γ: Peroxisome proliferator-activated receptor.
OR: Odds ratio.
RAAS: Renin-angiotensin-aldosterone system.
StAR: Steroidogenic acute regulatory protein.
TNF α: Tumor necrosis factor α.
VLDL: Very low density lipoprotein cholesterol.

Introduction

The discovery of aldosterone by Simpson et al. in 1950 had a marked effect in the field of medicine[1]. At present, aldosterone is well known to play a role in electrolyte transport, wherein it promotes the increased absorption of sodium as well as excretion of potassium. Aldosterone binds to mineralocorticoid receptors on epithelial cells such as those in the kidneys as well as non-epithelial tissues including cardiomyocytes, hippocampal cells, blood vessel walls (i.e. smooth muscle and endothelial cells), and monocytes[3].

Aldosterone is synthesized from cholesterol in the zona glomerulosa of the adrenal glands. However, the synthesis of aldosterone in other areas such as the heart, blood vessels, and brain has also been proposed[4-7]. Aldosterone synthesis is stimulated by several factors, particularly by the lipid-soluble factor produced in adipose tissue, especially in the abdominal region[8,9].

As a component of the renin–angiotensin–aldosterone system (RAAS), aldosterone is classically known for its role in sodium and water retention[10]. Besides its effects on the RAAS, aldosterone is strongly associated with the pathogenesis and progression of metabolic syndrome components[11-16]. In this case, aldosterone appears to promote adipogenesis and affect glucose metabolism, thus leading to insulin resistance via several mechanisms including oxidative stress, inflammation, and interference with the synthesis of enzymes involved in glucidic metabolism[9,17,18]. The pro-inflammatory and prothrombotic effects of aldosterone on the cardiovascular system promote cardiac hypertrophy and remodeling; this suggests a strong etiologic association between the aldosterone pathway and the atherosclerotic process[2,10]. Considering the complexity and incomplete understanding of the pathogenesis of metabolic syndrome, the objective of this review study was to critically investigate the relationship between diet and aldosterone, and the influence of this in the development and progression of cardiometabolic syndrome.

Methodology

The electronic bibliographic index (Web of Science, Science Direct, Pubmed and Scopus) and a multidisciplinary database for Ibero-America (Scielo) were searched from the earliest available online indexing year through March 2014, without language or filters restrictions. The study was conducted using the following keywords: "aldosterone" and/or "diet", "sodium intake", "obesity", "insulin resistance", "blood pressure", "dyslipidemia", "inflammation", "oxidative stress", "metabolic syndrome", "cardiometabolic syndrome", and "cardiovascular disease". Papers were selected which related to population studies and clinical trials with humans or animals, published from 2004 to 2014, as well as other relevant studies published prior to these dates.

Aldosterone and the Renin–Angiotensin System

Aldosterone is the most important mineralocorticoid that is naturally present in humans[19]. Even a subtle activation of the aldosterone pathway may lead to slight changes in its serum concentrations, and consequently, a quick onset of action[10].

Activation by angiotensin II is the primary stimulus for aldosterone secretion, followed by renin secretion, excess potassium, and sodium deficiency. Additional factors that stimulate aldosterone synthesis include atrial natriuretic peptide, adrenocorticotropic hormone[20], and the lipid-soluble factor produced by adipose tissue, especially in the abdominal region[8,9]. Aldosterone plays a key role in electrolyte homeostasis and blood pressure regulation by controlling sodium transport via mineralocorticoid receptors; these receptors are widely distributed, thus corroborating evidence of the deleterious effects of abnormal aldosterone levels[3,21].

Studies on the factors involved in aldosterone regulation led to the discovery of the RAAS, and consequently, to the further clarification of the mechanisms of blood pressure regulation[1]. The RAAS is associated with obesity, dyslipidemia, insulin resistance, and high blood pressure[22].

Once renin is secreted, it acts on the circulating angiotensinogen (a renin substrate), leading to the production of angiotensin I, which in turn is converted

into angiotensin II in the lungs by the angiotensin-converting enzyme. Angiotensin II increases the expression of aldosterone synthase (CYP11B2) and steroidogenic acute regulatory protein (StAR), a transport protein that regulates cholesterol transfer within mitochondria, leading to the synthesis of pregnenolone, one of the precursors of aldosterone. This mechanism strongly stimulates aldosterone synthesis. Moreover, angiotensin II is a potent vasoconstrictor and plays a direct role in intravascular volume depletion[2].

Dietary Factors and Aldosterone Modulation

Excessive food intake and quality of nutrients including fat, carbohydrates, and salt, is associated with increased adipose tissue[23] and levels of RAAS components[9]. Experimental studies demonstrate that excessive aldosterone levels associated with insulin resistance may lead to myocardial rigidity and diastolic dysfunction in response to excessive food intake[16]. Rats fed a high-fat diet for 8–11 weeks showed twice the angiotensinogen gene expression levels in retroperitoneal adipose tissue as well as increased plasma levels of angiotensin II, which are correlated with mean arterial pressure[24] (Table I).

A double-blinded randomized placebo-controlled study evaluated the effects of buttermilk consumption (45 g/day) on blood pressure and markers of the RAAS in humans[25]. Buttermilk consumption for 4 weeks significantly reduced arterial blood pressure (−1.7 mmHg), particularly systolic blood pressure (−2.6 mmHg), as well as angiotensin I-converting enzyme levels (−10.9%), compared with the placebo. However, it did not affect the plasma levels of angiotensin II or aldosterone (Table I).

The serum concentrations of sodium and potassium are among the main factors that stimulate aldosterone synthesis. However, the effects of a high-sodium diet on plasma aldosterone levels are unknown. Although the concentrations of these electrolytes are strictly regulated by diverse homeostatic mechanisms, a high-sodium diet is expected to lead to increased serum sodium and potassium levels, and consequently, to decreased aldosterone synthesis. The opposite is expected to occur with a sodium-restricted diet, which would lead to increased aldosterone synthesis by the adrenal glands and a consequent increase in sodium absorption by the kidneys. A meta-analysis demonstrates an association between sodium restriction and increased serum levels of aldosterone and renin[26]. However, high salt intake in rats is postulated to increase inflammation and oxidative stress, thus leading to diastolic dysfunction in the presence of elevated concentrations of aldosterone and angiotensin II[27]. A study performed in sheep evaluated the effects of high- and low-sodium diets for 2 months during gestation[28]. The results demonstrate associations among kidney function, hormone levels, and the mRNA (messenger ribonucleic acid) expressions of proteins of the RAAS in both fetuses and offspring. Some alterations observed in fetuses, including increased angiotensinogen gene expression, angiotensin-converting enzyme, and angiotensin I and II receptors, were still present after birth, suggesting possible risks for the development of cardiovascular and kidney diseases (Table I). These results provide further evidence of the benefits of reduced sodium intake along with a healthy diet, particularly decreased blood pressure[29].

In an experimental study, rats fed a fructose-rich diet exhibited decreased ectopic deposition of intramuscular lipids caused by RAAS blockade[30]; moreover, rats fed a fructose- and fat-rich diet had reduced fat tissue hypertrophy and macrophage infiltration as well as fewer metabolic alterations (e.g. steatohepatitis, dyslipidemia, high blood pressure, and glucose intolerance/insulin resistance) when administered spironolactone for 12 weeks[31]. Furthermore, aldosterone increases glucose intolerance and insulin resistance induced by fructose via the activation of mineralocorticoid receptors[32] (Table I).

Diet may have different effects on aldosterone, thus suggesting that this hormone is influenced by mechanisms other than the sodium homeostasis feedback mechanism and blood pressure. The consumption of fat- and/or fructose-rich diets is associated with higher aldosterone levels. However, the various mechanisms involved in this process as well as patterns and diet components associated with hormonal status are not fully understood.

Aldosterone and Obesity

Adipose tissue is considered an integral part of the endocrine and immune systems[33]. Obesity, characterized by an increase in the amount of adipose tissue, is associated with the increased synthesis of pro-inflammatory and atherogenic substances such as angiotensinogen, leptin, non-esterified fatty acids, reactive oxygen species, resistin[34], tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1), and prothrombotic factors such as plasminogen activator inhibitor-1 (PAI-1) as well as reduced synthesis of adiponectin and peroxisome proliferator-activated receptor gamma (PPAR-γ)[35]. These alterations in adipokine production are directly related to the activation of the RAAS by adipose tissue, which is partially mediated by angiotensin II[22].

Aldosterone is hypothesized to promote adipogenesis; the resultant adipose tissue then mutually increases aldosterone synthesis[18]. Thus, the control of aldosterone synthesis may differ according to the location of the adipose tissue. Abdominal adipocytes are more closely associated with the hypersecretion of trophic factors that result in aldosterone biosynthesis[21]. Angiotensinogen and angiotensin II receptor gene expression levels are higher in visceral adipose tissue than in abdominal

Table I

Clinical trials in which the association between aldosterone and cardiometabolic risk factors were investigated

Study	*Type of study*	*Sample*	*Intervention*	*Parameters accessed*	*Results*
Manrique et al (2013)[16]	Controlled clinical trial	Young C57BL6/J female and male rats	High-fructose/high-fat western diet for 8 weeks.	- Insulin sensitivity. - Cardiac function. - Aldosterone levels.	Excessive aldosterone levels associated with insulin resistance may lead to myocardial rigidity and diastolic dysfunction in response to excessive food intake.
Boustany et al (2004)[24]	Controlled clinical trial	Male Sprague-Dawley rats	Low-fat (LF: 11% kcal as fat) or high-fat diet (HF: 32% kcal as fat) for 8–11 weeks.	- Quantification of mRNA expression of RAAS components (angiotensin I, angiotensin II, angiotensinogen, renin and angiotensin-converting enzyme genes) in retroperitoneal adipose tissue. - Plasma concentration of RAAS components. - Blood pressure.	Increased plasma levels of angiotensin II (LF: 390±48 ng/ml; HF: 530±22 ng/ml; P<0.05) and angiotensinogen gene expression (2 -fold) in HF rats. Mean arterial blood pressure was increased in HF rats (LF: 97±2; HF: 105±1 mmHg; P<0.05).
Conway et al (2014)[25]	Crossover double-blinded randomized placebo-controlled	Men and women (n=34) with normal blood pressure and low-density lipoprotein cholesterol	Diet with buttermilk consumption (45 g/day) or with 45 g/day of a macro-/micronutrient-matched placebo in random order (4 weeks for each diet).	- Blood pressure and RAAS plasma markers (angiotensin II, aldosterone and angiotensin I-converting enzyme).	Buttermilk consumption significantly reduced arterial blood pressure (−1.7 mmHg; P=0.015), particularly systolic blood pressure (−2.6 mmHg; P=0.009), as well as angiotensin I-converting enzyme (-10.9%; P=0.003) levels compared with placebo.
Whaley-Connell et al (2013)[27]	Crossover randomized controlled	Transgenic (mRen2)27 (Ren2) rats or age-matched Sprague–Dawley	High (4%) salt or normal diet for 3 weeks.	- Cardiac function. - Aldosterone, angiotensin II and renin plasma levels. - Blood pressure. - Heart tissue measurement of 3-nitrotyrosine content. - Quantification of peri-arterial cardiac fibrosis. - Quantitative insulin sensitivity check index. - In vivo cine-magnetic resonance imaging of left ventricular diastolic function.	The high salt diet increases in type 1 collagen, 3-nitrotryosine content, diastolic dysfunction, ultrastructural findings of pericapillary fibrosis, increased left ventricular remodeling, and mitochondrial biogenesis without increasing insulin resistance.
Mao et al (2013)[28]	Controlled clinical trial	Sheep during gestation, fetuses and offspring	Pregnant sheep were fed high-salt diet or low-salt diet for 2 months.	- Renal functions. - Plasma hormones. - mRNA and protein expressions of the renal RAAS key elements All were measured in fetuses and offspring.	Increased angiotensinogen gene expression, angiotensin-converting enzyme, and angiotensin I and II receptors, were present on fetuses and offspring following maternal high salt intake. Maternal and fetal plasma antidiuretic hormone was elevated, while plasma angiotensin II was decreased in the high-salt diet group.

Table I (cont.)
Clinical trials in which the association between aldosterone and cardiometabolic risk factors were investigated

Study	*Type of study*	*Sample*	*Intervention*	*Parameters accessed*	*Results*
Furuhashi et al (2004)[30]	Controlled clinical trial	Male Sprague–Dawley rats	Two groups: those fed with standard chow (control) and those fed with fructose-rich chow for 6 weeks and RAAS blockade (olmesartan and termocapril).	- Insulin sensitivity. - Blood pressure. - Serum levels of triglyceride, free fatty acid and insulin. - Sizes of adipocytes derived from epididymal fat and triglyceride content in the soleus muscle.	RAAS blockade decreases adipocyte size without change in epididymal %fat pads accompanied by improvement in insulin sensitivity.
Wada et al (2013)[31]	Clinical trial	Wild-type C57BL/6 and liver-specific SREBP-1c Tg rats	High-fat and fructose diet and spironolactone for 12 weeks.	- Macrophage infiltration in adipose tissue. - Vascular and hepatic histological features. - Lipids levels. - Blood pressure. - Glucose intolerance. - Insulin resistance.	The spironolactone reduced fat tissue hypertrophy, macrophage infiltration and metabolic alterations.
Sherajee et al (2013)[32]	Controlled clinical trial randomized placebo-controlled	Male Sprague-Dawley rats	Rats uninephrectomy were divided into five groups for 6 weeks treatment: 1) placebo. 2) aldosterone. 3) fructose. 4) aldosterone +fructose. 5) aldosterone + fructose + spironolactone.	- Blood pressure. - Insulin resistance. - Oral glucose tolerance test. - Plasma level of non-esterified fatty acid, triglyceride, adiponectin and insulin. - mRNA expressions of glyceraldehydes-3-phosphate dehydrogenase.	Aldosterone + fructose rats manifested hypertension, and induced glucose intolerance and insulin resistance compared to fructose intake rats. Spironolactone significantly improved the aldosterone-accelerated glucose intolerance and suppressed upregulated mineralocorticoid receptor target gene.
Dall'Asta et al (2009)[39]	Clinical trial	40 (31 women, 9 men) hypertensive and 55 (44 women, 11 men) normotensive obese subjects.	1 year after significant weight loss obtained through laparoscopic adjustable gastric banding.	- Weight. - Waist circumference. - Blood glucose, insulin, electrolytes (sodium and potassium), lipids and supine and upright renin and aldosterone.	Weight loss is associated with reduction of blood pressure and of renin activity and aldosterone levels in obese hypertensive subjects.
Yamashita et al (2004)[12]	Controlled clinical trial	ICR female rats	Aldosterone administration.	- Blood glucose levels. - Expression of the genes involved in gluconeogenesis (glucose-6-phosphatase, fructose-1,6-biphosphatase and phosphoenolpyruvate carboxykinase).	Aldosterone administration to rats resulted in a dose-dependent increase in blood glucose levels caused by increased expression of the genes involved in gluconeogenesis.

Table I (cont.)
Clinical trials in which the association between aldosterone and cardiometabolic risk factors were investigated

Study	*Type of study*	*Sample*	*Intervention*	*Parameters accessed*	*Results*
Kawahito et al (2013)[15]	Controlled clinical trial	ApoE-deficient rats uninephrectomized and sham control rats	High-cholesterol diet for 4 or 6 weeks.	- Monocytes/macrophages counts. - mRNA expression levels of inflammatory cytokines, angiotensinogen and the angiotensin II on periaortic adipose tissue. - Insulin resistance.	The angiotensinogen mRNA expression and the angiotensin II concentration in the periaortic adipose tissue were significantly higher after 6 weeks of intervention than in the control.
Sun et al (2002)[51]	Controlled clinical trial	Male Sprague-Dawley rats uninephrectomized	Five animal groups were studied for 4 weeks (n=8 in each group): 1) controls. 2) diet + aldosterone. 3) diet + aldosterone + aldosterone receptor antagonist. 4) diet + aldosterone + pyrrolidine dithiocarbamate antioxidant. 5) diet+aldosterone+N-acetylcysteine antioxidant.	- mRNA levels of ICAM-1, MCP-1, and TNF-α - NF-κβActivation. - Aldosterone plasma level.	Elevation in circulating aldosterone contributing to a proinflammatory/ fibrogenic cardiac phenotype that appears within both the normotensive right and hypertensive left ventricles of the rat heart.
Cooper et al (2013)[56]	Controlled clinical trial	Overweight and normotensive young adults (n=285)	Diet intervention with or without sodium restriction and physical activity during 1 year.	Body weight, serum aldosterone, 24-hours sodium and potassium excretion, and obesity related factors.	Decreases in aldosterone were associated with decreases in C-reactive protein, leptin, insulin/ insulin resistance, heart rate, tonic cardiac sympathovagal balance, and increases in adiponectin (all $P<0.05$).

Abbreviations: Low-fat (LF), high-fat diet (HF), mRNA (messenger ribonucleic acid), RAAS (renin-angiotensin-aldosterone system), ICAM-1 (Intercellular adhesion molecule-1), MCP-1(monocyte chemotactic protein-1),TNF-α (tumor necrosis factor α), NF-κβ (factor nuclear kappa B).

subcutaneous adipose tissue; this is associated with higher growth and proliferation of adipocytes in visceral adipose tissue[36]. However, the lower activity of the RAAS in gluteofemoral adipose tissue may explain why the fat from this area is less metabolically active[9].

A recent study investigated the effects of adiposity on the plasma levels of aldosterone in children and adolescents; the results show significant associations between aldosterone level and body mass index (BMI), waist and hip circumference, and tricipital and subscapular skinfolds for Caucasian but not African-American subjects[37]. Another study shows associations between plasma aldosterone level and BMI, waist circumference, and waist-to-height ratio in African-American adult subjects[38].

The fact that obese subjects have lower plasma aldosterone levels as well as decreased insulin resistance after experiencing weight loss further corroborates the association between aldosterone and adipose tissue content[39] (Table I).

Therefore, the studies described above demonstrate a strong association between adipose tissue and aldosterone, in which high concentrations of this hormone are related to adiposity, particularly abdominal fat. Furthermore, the location of the fat appears to play an important role in adrenal steroidogenesis, and fat from the gluteal muscles appears to exhibit an inverse relationship. Despite these findings, the pathophysiological mechanisms involving the RAAS and adipose tissue are not fully understood.

Aldosterone and Insulin Resistance

A study involving African-American subjects revealed differences in plasma fasting glucose levels, blood insulin levels, and homeostasis model assessment-estimated insulin resistance (HOMA-IR) with respect to aldosterone levels; subjects with "moderate" concentrations of aldosterone had higher values than those with "low" concentrations[40].

Kidambi et al.[38] also found positive associations of aldosterone with blood insulin levels and HOMA-IR. They proposed that the increased synthesis of aldosterone likely occurs because of hyperinsulinemia or the release of adipokines by visceral adipose tissue. It is important to note that cross-sectional studies preclude the establishment of causal relationships, because the cause and effect factors cannot be identified. Increased angiotensin II synthesis also interferes with insulin signaling in muscles because of oxidative stress and endothelial dysfunction as well as decreased resistin production[9].

Hyperaldosteronism associated with obesity not only aggravates pancreatic β-cell function but also leads to decreased insulin signaling in skeletal muscle[18]. Another proposed mechanism involves a reduction in the gene expression of the insulin receptor by aldosterone. Aldosterone may also affect insulin sensitivity by interfering with potassium metabolism[17]. Aldosterone administration in rats resulted in a dose-dependent increase in blood glucose levels through the increased expression of the genes involved in gluconeogenesis[12].

Experimental and epidemiologic studies suggest a relationship between increased aldosterone levels and the presence of insulin resistance. Several pathophysiological mechanisms have been proposed; they include genomic mechanisms, such as interference with the synthesis of hepatic enzymes involved in glucose metabolism, as well as non-genomic mechanisms, such as increased synthesis of inflammatory adipokines, which aggravate insulin resistance.

Aldosterone and Dyslipidemia

Plasma aldosterone and not renin is associated with the levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides[38]. Excessive aldosterone levels stimulate adipocyte dysfunction, leading to an increased release of free fatty acids, which may cause an increase in very-low-density lipoprotein (VLDL), and thus result in hepatic steatosis and ectopic fat accumulation[9]. The resultant increased levels of VLDL produced by the liver reach the circulation, where lipid changes occur between the subclasses of LDL and high-density lipoprotein (HDL), which become smaller and denser. This results in increased HDL uptake and subsequent renal excretion, thus consequently decreasing serum levels of HDL and the associated protection. LDL particles become more easily oxidized, and hence more atherogenic; there is also an increase in the synthesis of other lipoproteins. This pattern of dyslipidemia is often observed in patients with type 2 diabetes mellitus and/or with metabolic syndrome[33].

Furthermore, Goodfriend et al.[41] demonstrate a strong negative correlation between aldosterone and HDL. However, patients with higher aldosterone levels also had higher BMI and waist-to-hip ratio, suggesting that adipose tissue and not aldosterone caused the observed dyslipidemia. Moreover, the Framingham Heart Study, which included 2,891 subjects, did not show a correlation between low HDL levels and high aldosterone levels[42]; this indicates that high blood pressure and not aldosterone is associated with the observed effects on lipid homeostasis. Nevertheless, additional studies are required to better understand the direct and indirect effects of aldosterone on the lipid profile.

Aldosterone and High Blood Pressure

As a component of the RAAS, aldosterone is classically known as a factor contributing to the development of high blood pressure, owing to its role in sodium and water retention[10]. The activation of the RAAS along with increased aldosterone levels is strongly associa-

ted with high blood pressure as well as other components of metabolic syndrome in humans[11,13,14,38,43] and animal models[12,15,16] (Table I). This can be explained by the fact that aldosterone inhibits nitric oxide-mediated endothelium-dependent relaxation by decreasing its bioavailability because of the increased reactive oxygen species level. Thus, an increased aldosterone level is associated with greater endothelial dysfunction and the subsequent development of high blood pressure[18].

Primary hyperaldosteronism resulting from adrenal hyperplasia or aldosterone-producing adenoma has an estimated prevalence 0.5–4.8% in a population with essential hypertension and 4.5–22% among those with treatment-resistant hypertension[44,45]. Primary hyperaldosteronism is associated with a higher frequency of treatment-resistant hypertension[45], which is the most common form of endocrine hypertension[8]. In such cases, high blood pressure is unresponsive to medications unless the therapeutic regimen involves the use of mineralocorticoid receptor antagonists such as spironolactone or eplerenone[46]. However, the phenomenon known as "aldosterone breakthrough" (i.e. aldosterone escape or breakthrough), which involves excess aldosterone biosynthesis in response to the use of RAAS inhibitors, decreases the effectiveness of these antagonists in lowering blood pressure. In this context, a proposed alternative involves the use of calcium channel antagonists to inhibit aldosterone synthesis[47].

In a cohort study of 1,688 normotensive subjects, aldosterone was associated with increased blood pressure, suggesting that higher levels of this hormone-even if within normal parameters-is a predisposing factor to the development of high blood pressure[48].

Thus, it appears that the development and progression of high blood pressure are the most evident cardiometabolic alterations related to the adverse effects of excess aldosterone. Mineralocorticoid receptor antagonists have been shown to be effective for the treatment of patients with treatment-resistant hypertension and associated metabolic alterations.

Aldosterone in Subclinical Inflammation and Oxidative Stress

Aldosterone appears to affect the development of cardiovascular diseases via mechanisms besides mineralocorticoid receptors. This process involves higher infiltration of macrophages into the adipose tissue, which contributes to increased oxidative stress caused by NAD(P)H oxidase through the stimulation of the expression of pro-inflammatory genes such as those from adhesion molecules and chemokines. This ultimately increases cardiovascular risk[49]. Oxygen radicals may promote oxidative damage, structural remodeling, inflammation, and atrial fibrillation; these in turn activate angiotensin II and independent cascades, leading to increased aldosterone synthesis, which is associated with tissue damage[50].

In animal experiments, systemic aldosterone administration causes oxidative stress and myocardial inflammation. Moreover, the inhibition of reactive oxygen species prevents inflammation and adverse cardiac remodeling in rats, suggesting that these mechanisms are involved in the adverse effects of aldosterone on the myocardium[51] (Table I).

A cohort study performed with 3,770 hypertensive human subjects investigated the relationship between the degree of inflammatory activation and urinary aldosterone concentration[52]. The results show that aldosterone is associated with C-reactive protein and serum amyloid A protein, which suggests that aldosterone is involved in the occurrence of subclinical inflammation at least in individuals with essential hypertension. After adjusting for age, sex, race, diabetes mellitus, smoking habit, heart rhythm, left ventricular mass, and BMI, in individuals with heart failure caused by systolic dysfunction (n = 58), aldosterone was not correlated with C-reactive protein (an inflammatory marker) but rather with 8-iso-prostaglandin F2α (an oxidative stress marker), intercellular adhesion molecule 1 (ICAM-1) (an endothelial dysfunction marker), and tissue inhibitor of metalloproteinases-1 (a marker of turnover of tissue matrix). The authors state that aldosterone may have distinct effects on the different aspects of inflammation, during which ICAM-1 is present on the surfaces of endothelial cells and myocytes, and C-reactive protein is produced in the liver and acts as an acute phase reactant and a marker of generalized inflammation. However, it is important to mention that the small sample size of this study is a limiting factor; thus, additional relationships between aldosterone and other biomarkers may be detected with a larger sample size[13].

It is important to note that oxidative stress increases inflammation, which in turn aggravates endothelial dysfunction, leading to increased oxidative stress. Both factors may affect the interstitial matrix by acting on the synthesis and degradation of myocardial collagen[53].

However, further studies, particularly intervention and cohort studies, are required to better understand the endocrinal associations between the various markers of subclinical inflammation and oxidative stress with respect to the clinical and ethnic aspects of various populations.

Aldosterone and Metabolic Syndrome

Aldosterone is associated with metabolic syndrome and its components (i.e. waist circumference, blood pressure, and HDL) in non-Caucasians[43] but not in Caucasians[54]. Thus, ethnicity/race appears to play an important role in the associations between race and metabolic syndrome components; this relationship appears to be stronger in non-Caucasian subjects[38,43].

Evidence supports the hypothesis that aldosterone levels can predict the onset of high blood pressure and metabolic syndrome. In the Framingham Offspring

Study, 2,292 subjects were evaluated to determine the relationships between the incidence of metabolic syndrome and 8 markers associated with homeostasis, inflammation, endothelial dysfunction, and neurohormonal activity. Following adjustment for confounders, only the levels of PAI-1 and aldosterone were associated with metabolic syndrome. PAI-1 is known to contribute to tissue fibrosis, and aldosterone increases PAI-1 expression levels[55]. PAI-1 is significant and positively associated with longitudinal changes in systolic arterial pressure, plasma fasting glucose levels, and triglycerides, while aldosterone is associated with systolic arterial pressure[14].

The results of a cross-sectional study evaluating the influence of aldosterone on metabolic syndrome development indicated correlations between aldosterone level and blood pressure, waist circumference, blood insulin levels, HOMA-IR, and dyslipidemia. Individuals with metabolic syndrome are reported to have higher aldosterone and aldosterone/renin levels[38]. Another similar study showed that aldosterone levels and waist circumference in men were correlated and that aldosterone levels increased with age. Moreover, subjects with metabolic syndrome had aldosterone levels approximately 20% higher than those of metabolically normal individuals[43].

In order to corroborate these findings, a clinical triage study was conducted to monitor diet intervention (i.e. with or without sodium restriction) and physical activity for 1 year in 285 overweight young adults without additional risk factors[56] (Table I). After adjusting for age, sex, time and type of intervention, and sodium and potassium excretion, the results indicated associations of decreased aldosterone levels with decreased C-reactive protein, leptin, insulin, HOMA-IR, and heart rhythm values and increased adiponectin levels. These findings suggest that favorable changes in obesity-related factors are associated with decreased circulating levels of aldosterone, thus reinforcing the role of aldosterone as an emergent and important cardiometabolic risk factor.

The studies summarized above suggest increased aldosterone levels may be a relevant risk factor for the development and progression of metabolic syndrome, which is supported by the parallel relationship between the control of metabolic syndrome components and hormonal decline. Thus, aldosterone can be used to help identify individuals with higher cardiometabolic risk. Furthermore, this hormone may be considered a component of metabolic syndrome in the future.

Aldosterone and Cardiovascular Disease

Exposure to high levels of aldosterone, such as in cases of primary aldosteronism, leads to higher rates of cardiovascular morbidity and mortality. The results of a case-control study that compared patients with primary aldosteronism to those with essential hypertension indicated higher blood pressure levels, family history of early cardiovascular disease, left ventricular hypertrophy, and higher cardiovascular risk in cases of primary aldosteronism[57]. Another study comparing patients with primary aldosteronism to those with essential hypertension shows that primary aldosteronism is associated with a 2-fold greater prevalence of left ventricular hypertrophy, even after adjusting for the duration of hypertension as well as higher prevalence of coronary arterial disease (odds ratio [OR] = 1.9), myocardial infarction (OR = 2.6), heart failure (OR = 2.9), and atrial fibrillation (OR = 5.0)[58].

The cardiovascular effects of aldosterone stem from its influence on the excretion of electrolytes and fluids, which in turn affects blood volume and pressure[45]. However, independent of its effects on electrolyte and fluid reabsorption, aldosterone also acts specifically on the heart muscle, leading to effects such as hypertrophy, cardiac arrhythmia, sympathetic nervous system activation, parasympathetic nervous system inhibition, endothelial dysfunction, vascular inflammation, and myocardial fibrosis and congestion; these effects on the heart muscle appear to result from vascular fibrosis, inflammation, and endothelial dysfunction[17,59].

The pro-inflammatory and prothrombotic effects of aldosterone on the cardiovascular system promote hypertrophy and remodeling of the left ventricle; they are also associated with increased cardiovascular morbidity/mortality and total mortality in populations with high cardiovascular risk, including those with cardiac insufficiency, myocardial infarction, and a high risk of coronary arterial disease[2]. A study of 129 hypertensive subjects evaluated several markers of cardiovascular risk, including lipids, blood glucose levels, blood insulin levels, HOMA-IR, C-reactive protein levels, microalbuminuria, homocysteine levels, aldosterone levels, renin levels, and endothelin levels. Among these, aldosterone and endothelin levels were the most important determinants of left ventricular hypertrophy[60].

Despite its effects on high-risk groups, aldosterone also affects subgroups of patients with stable and low risks of coronary arterial disease; this was evident in an observational prospective study demonstrating the relationships among aldosterone, vascular events, and atherosclerotic load in 2,699 outpatients with coronary arterial disease (age >60 years; 82 men)[10]. During a median follow-up period of 4.7 years, the vascular outcomes of myocardial infarction, ischemic stroke, or vascular death were noted in 355 (13%) patients. Moreover, aldosterone levels were independently associated with future vascular events (incidence ratio: 1.56, 95% confidence interval [CI]: 1.13–2.15) and vascular death (incidence ratio: 1.95, 95% CI: 1.27–3.00). Bivariate analysis also demonstrated significant associations of aldosterone levels with the presence and degree of atherosclerosis in additional vascular territories (i.e. cerebrovascular disease or peripheral artery disease; $p = 0.026$). These results collectively suggest a strong etiologic association between the aldosterone pathway and the atherosclerotic process,

although this cannot be generalized to other populations. This relationship is very important in clinical practice because it is relevant to the evaluation of high-risk patients, thus enabling easier and more effective monitoring as well as identification of patients who will benefit from therapeutic strategies that are more intensive[10,60].

The Ludwigshafen Risk Cardiovascular Health Study (a prospective study) involved 3,153 patients (mean age: 63.5 years; 30.1% women) who underwent coronary angiography; after a median follow-up period of 7.7 years, the aldosterone levels of the second (incidence ratio: 1.58, 95% CI: 1.15–2.16), third (incidence ratio: 1.39, 95% CI: 1.01–1.90), and fourth (incidence ratio: 1.63, 95% CI: 1.20–2.20) quartiles were significantly associated with higher mortality from cardiovascular disease than those of the first quartile. The results of specific causal analysis demonstrate strong associations of aldosterone level with increased risks of stroke and sudden cardiac death[61].

The expansion of the role of aldosterone as a risk factor for cardiovascular events is primarily based on the efficacy of mineralocorticoid receptor antagonists under these conditions[21,61]. Left ventricular hypertrophy, an independent cardiovascular risk factor, was reduced and normalized in 57% of patients who were administered low-dose spironolactone for 3 years[62]. Aldosterone antagonists act by suppressing the deleterious effects of this hormone on the components of metabolic syndrome, thus decreasing the risk of the development of cardiovascular diseases (Figure I).

The inappropriate activation of the RAAS and inability of the body to decrease aldosterone levels in response to a sodium-rich diet, which is typical at nowadays, illustrate the poor adaptation of this regulatory system[61].

Conclusions and Perspectives

Studies performed since the discovery of aldosterone demonstrate that in addition to its classical roles in electrolyte homeostasis and blood pressure regulation, aldosterone plays important roles in metabolic disorders and cardiovascular diseases. Obesity, particularly in the visceral area, has been recognized as an important regulatory mechanism for aldosterone synthesis, which may partially explain the association between adipose tissue and metabolic syndrome. Quantitative and qualitative dietary factors affect aldosterone level; high fructose and fat intake leads to increased aldosterone levels, while the effects of a sodium-rich diet on aldosterone remain controversial. Therefore, additional research is required to clarify the effects of sodium on aldosterone as well as the roles of other diet components.

Indeed, the studies presented herein consider aldosterone to be a hormone related to cardiometabolic risks due to its associations with high blood pressure, insulin resistance, dyslipidemias, oxidative stress/subclinical inflammation, and increased cardiovascular morbidly and mortality.

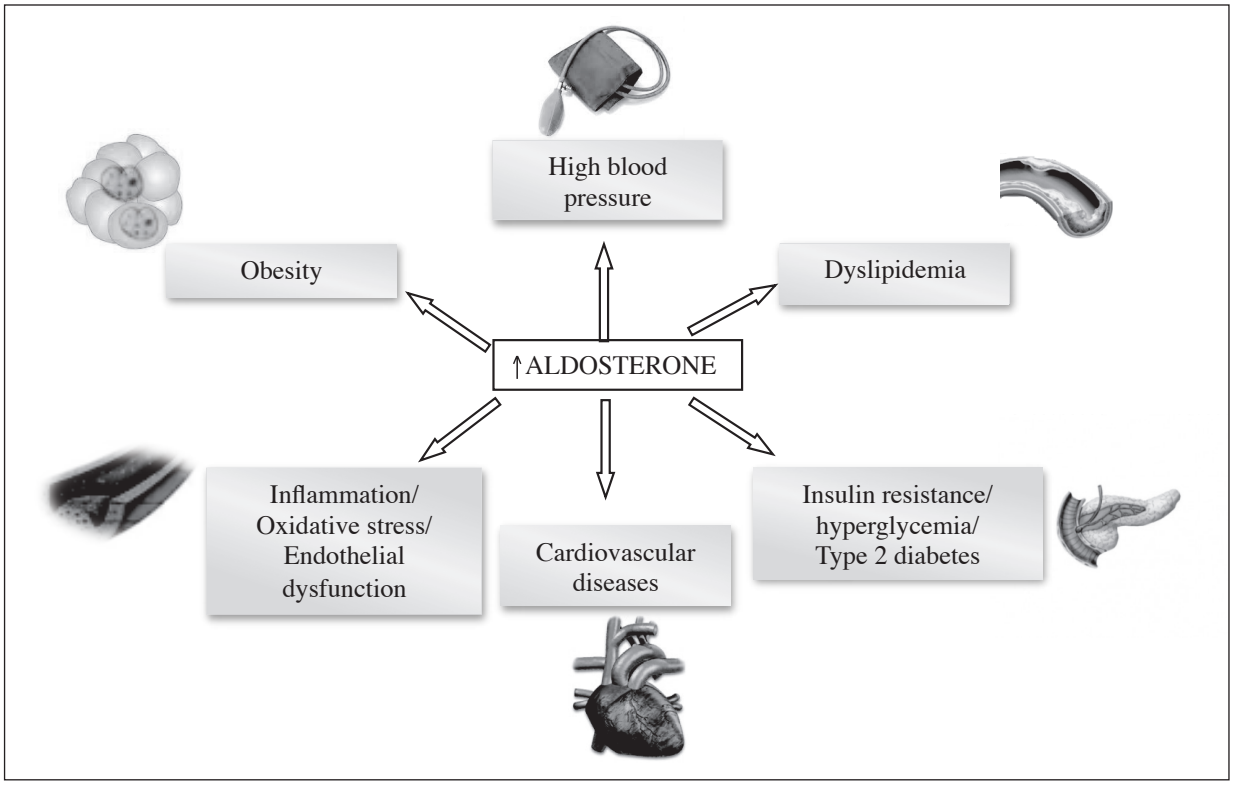

Fig. 1.—Effects of aldosterone on cardiometabolic factors.

Acute and chronic elevations of circulating levels of aldosterone, even if within normal parameters, are associated with increased risks of infarction, stroke, and mortality due to cardiovascular events. In this context, the use of mineralocorticoid receptor antagonists to inhibit the complex RAAS represents a promising therapeutic option for the prevention and treatment of these comorbidities.

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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