The Renin Angiotensin Aldosterone System in Obesity and Hypertension

Roles in the Cardiorenal Metabolic Syndrome

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KEYWORDS

• Obesity • Insulin resistance • Angiotensin II • Adipocyte • Hypertension

KEY POINTS

- The seminal role of hypertension in the pathogenesis of the cardiorenal metabolic syndrome (CRS) has significantly evolved over the past 5 years. The physiology of this is rooted in the concept that hypertension in the setting of obesity and CRS is partly due to the excess body mass leading to an expanded plasma volume, resulting in an increase in cardiac output.
- Impaired handling of sodium is another of the more salient features common to both hypertension and CRS. A review of the literature, which portrays that in states of insulin resistance such as with obesity, an activated systemic renin angiotensin aldosterone system (RAAS) appears to play an important role in the pathogenesis of hypertension and other components of CRS.
- Evidence shows the benefits of RAAS blockade in correcting many of the maladaptive aspects of the CRS, especially in patients with insulin resistance and obesity.
- Currently, there are inadequate guidelines for the optimal pharmacologic management of hypertension in patients with obesity and CRS and the inherent need for them be more clearly delineated.

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PATHOPHYSIOLOGY

All components of the cardiorenal metabolic syndrome (CRS) are linked to metabolic abnormalities and obesity.[1–4] Hypertension, in the setting of obesity and the CRS, is partly due to an expanded plasma volume resulting in an increase in cardiac output.[5,6] A second important factor in the pathogenesis of hypertension coupled with the CRS and obesity is increased peripheral vascular resistance.[5,6] Expanded plasma volume and hyperinsulinemia lead to increased renal filtration, which affects renal sodium handling and promotes renal dysfunction characterized early by albuminuria.[5,6] The increase in vascular resistance impairs blood flow to skeletal muscle tissue, which leads to more insulin resistance and hyperinsulinemia, creating a vicious cycle that promotes more volume expansion and renal hyperfiltration.[7] In obesity-related hypertension, the expanded intravascular blood volume and increased peripheral vascular resistance, over time, lead to both concentric and eccentric left ventricular hypertrophy and impaired cardiac diastolic relaxation.[6–9]

The Contribution of Renal Sodium Handling

One of the more salient features common to both hypertension and other components of the CRS is the impaired handling of sodium. Early studies showed a direct association between increased insulin and sodium absorption through increased nephron sodium transporters. This leads to a decrease in sodium excretion and thus an increased intravascular volume.[6] There is also increasing evidence that insulin resistance in cardiovascular (CV) tissues contributes to impaired cardiac and vascular relaxation and increased CV stiffness.[5,6] More contemporary studies have delved further into this topic, elucidating the role that inflamed adipose tissue (eg, in visceral and perivascular fat) may play in hypertension associated with CRS.[10–13] This inflammation of adipose tissue likely contributes to RAAS activation related to increased pro-inflammatory adipokine secretion. The resulting systemic activation reduced activation of nitric oxide (NO) synthase and increased destruction of NO with resultant reductions in bioavailable NO in CV tissue.[10–13]

The Role of the Renin Angiotensin Aldosterone System

In states of insulin resistance such as obesity, an activated systemic RAAS is critical to the pathogenesis of hypertension and other components of the CRS.[6] Increasingly, it is apparent that expanded inflamed visceral and perivascular adipocyte tissue is key to driving RAAS activation. Adipocyte production of angiotensinogen may contribute up to 30% of circulating angiotensinogen.[12] The notion that adipocyte production of angiotensinogen contributes to an activated RAAS is strengthened by observations of angiotensinogen knockout mice being immune to developing obesity, insulin resistance, and hypertension.[14,15] In other murine studies with ablation of adipose-derived angiotensinogen, no obesity-related hypertension developed. However, some mice did go on to develop obesity.[16] This evolving research underlines the important link between adipocyte-derived angiotensinogen and HTN, particularly in the context of CRS.[17]

There is a burgeoning body of evidence indicating that adipocytes are an important source of extra-adrenal-derived aldosterone.[18] This concept is supported by the observation that obese persons, especially females, have increased circulating levels of aldosterone.[6] Recent studies have shown that aldosterone-induced mineralocorticoid receptor (MR) activation in vascular tissue can itself be an instigating factor in the promotion of vascular stiffness by promotion of oxidative stress, inflammation, maladaptive immune modulation, and fibrosis.[19,20] Therefore, this MR activation may