The Relationship between Obesity, Insulin Resistance and Aldosterone Levels

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Abstract

The epidemic of obesity is associated with elevated risk of type 2 diabetes mellitus, hypertension, obstructive sleep apnea, coronary heart disease and stroke. Primary aldosteronism, the most prevalent etiology of endocrine hypertension, is discussed in the present review as a cause-effect relationship between aldosterone and the cardio-metabolic syndrome. Emerging findings have shown that aldosterone levels are excessive in obesity and contribute to both cardiovascular dysfunction and insulin resistance which is associated with obesity and sleep apnea. According to the updated Endocrine Society Clinical Practice Guideline, the application of aldosterone:renin ratio is now indicated to all patients with sustained blood pressure above 150/100mm Hg, which could, in the future, result in the primary aldosteronism detection in a large number of patients. Within this clinical context, hypertensive patients with obesity and diabetes are candidates to be “at-risk” population in prevalence studies of aldosteronism.

Keywords: Obesity; Diabetes mellitus; Aldosteronism; Insulin resistance; Sleep apnea; Metabolic syndrome.

Introduction

Arterial hypertension prevalence is rapidly enhancing with obesity associated with insulin resistance and dyslipidemia, all components of cardiometabolic syndrome [1]. The metabolic syndrome impact on cardiovascular outcomes is well established, with high morbidity and mortality, and, for such fact, the renin-angiotensin-aldosterone system on metabolic syndrome has been the target of many studies [2]. On the one hand, obesity causes arterial hypertension, and on the other hand, endocrine hypertension caused by aldosterone anomalous production is associated with metabolic syndrome development.

Primary aldosteronism and hypertension

Primary aldosteronism (PA), the most important etiology of endocrine hypertension, results from the independent renin-angiotensin system production of aldosterone [3]. It is potentially curable and the most common cause of secondary hypertension. PA has a wide range of conditions, but two major causes of primary aldosteronism are bilateral adrenal hyperplasia (BAH), accounting for 65-70% of PA patients, and aldosterone-producing adenomas (APA), accounting for 30-35% of PA [4]. Several hormone receptors have been shown to be involved in the renin-independent regulation of aldosterone secretion in PA [5]. New evidence points toward increasing metabolic dysfunction rates and vascular events in PA patients in comparison with essential primary hypertensive patients [6].

According to the updated Endocrine Society Clinical Practice Guideline, the screening of aldosterone:renin ratio is now indicated to all patients with sustained blood pressure above 150/100mm Hg; resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalemia; adrenal incidentaloma; hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 year) and all hypertensive first-degree relatives of patients with PA [3]. This could result in the primary aldosteronism detection of a large number of patients in the future [3,7]. Early diagnosis and therapy of PA (adrenalectomy or mineralocorticoid receptor antagonist) prevent its cardiovascular, metabolic, and renal morbidities. Patients will benefit from surgical or medical therapy according to a multistep approach to diagnosing and subtyping PA which includes conformationary tests and adrenal vein sampling to differentiate lateralized from bilateral sources of PA [8,9]. Plasma aldosterone concentrations >10ng/dL in concert
with plasma renin activity <1ng/mL/h indicates that additional investigation should be performed [3]. In the clinical practice, hypertension in PA responds well to specific treatments directed against aldosterone excess. Therefore, it is possible that PA screening is not performed when we consider the technical difficulty in performing all stages of the investigation, including withdrawal of antihypertensive medication, salt-loading protocols and invasive vascular examination. Thus, many hypertensive patients are treated with mineralocorticoid receptor antagonists and potassium-sparing diuretics and are not further evaluated for the diagnosis of PA.

**Obesity, metabolic syndrome and aldosterone**

Adipocyte production of angiotensinogen, angiotensin and aldosterone have been described, which amplify adrenal steroidogenesis [10,11]. Moreover, adipocyte-derived factors such as leptin exert a direct action on adrenal glomerulosa, increasing aldosterone synthesis [12]. The variation on aldosterone levels in obesity may challenge the accuracy of PA detection since it represents a nonlinear correlation with its plasma concentration [13].

Aldosterone levels are associated with cardiometabolic events, promoting systemic inflammation, endothelial dysfunction, vascular stiffness, hypertension, cardiac hypertrophy, and these associations are partly independent of aldosterone effects on blood pressure [3]. Also, it has been described an independent association between aldosterone and metabolic syndrome, due to impaired pancreatic β cell function, skeletal muscle insulin sensitivity, fatty liver disease, and increased release of proinflammatory cytokines from adipose tissue [12,14]. As an important component of the cardiometabolic syndrome, sleep apnea is also related to obesity, diabetes, and aldosterone levels [15-17]. Obstructive sleep apnea was found in 33.9% of hypertensive patients with PA [15] and in 85% of resistant hypertensive patients [18]. Thus, aldosterone overproduction seems to contribute to the worsening of underlying obstructive sleep apnea related to obesity and hypertension.

**Insulin resistance and aldosterone**

Aldosteronism can modify glucose metabolism, leading to insulin resistance, but some of the physiological pathways of mineralocorticoid effects are still discussed [11,19]. Aldosterone effects include direct action on pancreatic beta-cell mineralocorticoid receptors (MR), compromising their functional and structural integrity and reducing insulin release; induction of insulin resistance by the MR activation in adipose tissue; indirect effects related to hypokalemia states; and recent reported non-genomic mechanisms on various target organs such as vascular cells [2,11]. Both hyperglycemia and diabetes are more prevalent in hypertensive patients with PA than in those with essential hypertension [20,21].

Elevated levels of aldosterone may also act similarly to hyperglycemia state, causing oxidative stress, reducing nitric oxide production and activating inflammatory pathways leading to vasculopathy, once again resulting in improved cardiovascular risk [22]. Aldosterone levels are directly correlated with mortality rate by cardiovascular causes in type 2 diabetes [11].

**Conclusion**

Aldosterone has been recognized to play an important role in the development of cardiovascular and endocrine-metabolic diseases. According to the current guidelines, clinicians should consider PA screening for most patients with hypertension. Hypertensive patients with obstructive sleep apnea, obesity and insulin resistance are groups with potentially high prevalence of PA. In addition to adrenocortical cells, adipose tissue is also able to secrete aldosterone; although some cross-talk mechanisms are not well established, the cardiometabolic complications are well acknowledged.

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