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COMMENT

Visceral fat: a bad companion for mineralocorticoid receptor overactivation

Yuichi Yoshida[1] · Hirotaka Shibata[1]

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Aldosterone is a hormone secreted by the adrenal glands, and its secretion is regulated mainly by the renin–angiotensin system (RAS) and serum potassium level. Primary aldosteronism (PA) is characterized by excessive aldosterone production in the adrenal glands independent of the RAS. The two most common subtypes of PA are unilateral PA, which is caused predominantly by an aldosterone-producing adenoma (APA), and bilateral PA, caused mostly by bilateral adrenal hyperplasia (idiopathic hyperaldosteronism). Patients with PA are at high risk of cardiovascular complications due to robust inflammation and fibrosis via aldosterone-mediated mineralocorticoid receptor (MR) overactivation. The rates of obesity, impaired glucose tolerance, and sleep apnea syndrome are higher in patients with PA than in those with essential hypertension.

Obesity is strongly associated with hypertension. Excess aldosterone is implicated as an important mediator of obesity-related hypertension. Visceral fat has several pathophysiological roles: the RAS is activated by increased angiotensinogen secretion from adipose tissues; the sympathetic nervous system is activated by fat-derived leptin, and one complication is sleep apnea syndrome; and visceral fat may secrete as-of-yet unidentified "aldosterone-releasing factor(s)" [1]. All of these pathways may result in greater aldosterone secretion and MR-associated hypertension [2]. Visceral fat also secretes more humoral factors than does subcutaneous fat, including VEGF, IL-6, PAI-1, and PGE2 [3]; visceral fat may also result in MR overactivation, even in the absence of high plasma aldosterone levels.

In the present study, the authors showed that left ventricular mass index (LVMI) and the E/e' ratio were significantly correlated with the visceral fat volume (VFV), but not the subcutaneous fat volume (SFV), in PA patients [4]. Furthermore, in the PA group with a high plasma aldosterone concentration (PAC), the VFV/SFV ratio was significantly and positively correlated with the E/e' ratio. The authors previously showed that a higher VFV/SFV ratio was correlated with impaired renal function in PA patients [5]. Taking these reports together, the greater the visceral fat mass is, the more prevalent cardiovascular complications are. It is interesting to speculate that obesity-related hypertension with a high PAC may be more prone to cardiovascular complications (Fig. 1). Somlóová et al. reported that compared with APA, idiopathic hyperaldosteronism (IHA) has significantly stronger correlations with the prevalence of metabolic syndrome and BMI [6]. In IHA, Shibata et al. reported that BMI and insulin resistance are significantly correlated with urinary aldosterone excretion [2]. MR blockers (MRBs) are thought to be effective for treating PA, especially IHA because visceral fat accumulation is often accompanied by excessive salt intake, chronic kidney disease, and diabetes, which may further enhance MR activity.

In addition to MRB and adrenalectomy as treatments for PA, the authors noted that weight loss and sodium-glucose transporter 2 (SGLT2) inhibitor therapy may be effective in patients with PA with a high PAC to reduce the VFV/SFV ratio based on their results. In patients with PA, the combination of MRBs and SGLT2 inhibitors may be desirable for several reasons [7]. MRBs can cause hyperkalemia as a side effect; however, Neuen et al. reported that SGLT2 inhibitors promote urinary potassium excretion and prevent hyperkalemia in diabetic patients [8]. Bohm et al. reported that SGLT2 inhibitors also promote sodium excretion, resulting in a non-potent blood pressure-lowering effect [9].

✉ Hirotaka Shibata
hiro-405@cb3.so-net.ne.jp

[1] Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu city, Japan

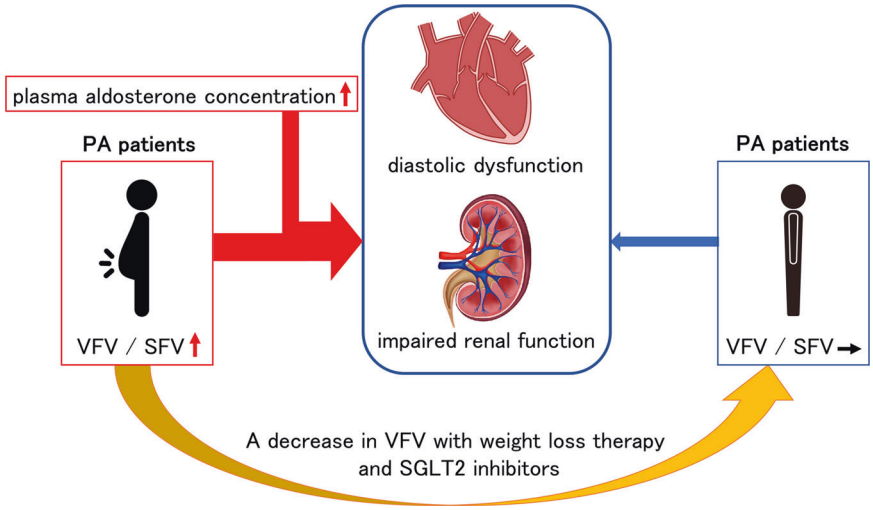

Fig. 1 Increased visceral fat mass in PA patients leads to more advanced cardiorenal dysfunction. PA primary aldosteronism, SFV subcutaneous fat volume, SGLT2 sodium-glucose transporter 2, VFV visceral fat volume

SGLT2 inhibitors have numerous reported protective effects against cardiac and renal impairment in patients with and without diabetes [9]. Based on these effects, it may be possible that the use of SGLT2 inhibitors in addition to MRBs for PA will become the standard of treatment. However, although SGLT2 inhibitors have been associated with weight loss and changes in body composition, it is not yet clear whether the weight loss is more significant for VFV or SFV [10]. In addition, Yoshida et al. showed that sleeve gastrectomy, a bariatric surgical procedure, has an independent antihypertensive effect in addition to its weight loss effect [11], so sleeve gastrectomy may be a treatment option when PA is complicated by severe obesity. Furthermore, Hundemer et al. reported that patients whose renin activity increased to ≥1 pg/mL/h after PA treatment with MRBs had significantly fewer cardiovascular events compared with those whose renin activity was lower after treatment [12]. Yoshida et al. reported the importance of salt restriction, as a change in salt intake was inversely correlated with renin in the low renin concentration group, even while on MRBs [13]. These considerations suggest that lifestyle changes, such as weight loss and dietary salt reduction, are very important in preventing the progression of primary aldosteronism complications.

This study raises several concerns. First, antihypertensive drugs may affect the sensitivity and specificity of PA diagnosis because the screening tests were conducted in patients on RAS inhibitors and beta-blockers. Second, patients with IHA more often have associated obesity compared with patients with APA. Subtype-dependent analysis remains to be conducted. Third, the VFV/SFV ratio was associated with LVMI and the E/e' ratio in PA patients; it remains to be elucidated whether the cardiovascular outcome is affected. Despite several limitations, this paper provided beneficial information suggesting that visceral fat is a bad companion for MR overactivation. When treating obese PA patients, it is important to know that both blocking MR overactivation by administering MRBs or unilateral adrenalectomy depending on PA subtype, as well as reducing visceral fat via weight reduction, play crucial roles in protecting against cardiovascular complications.

Compliance with ethical standards

Conflict of interest HS has honorarium from Daiichi-Sankyo Company, Mochida Pharmaceuticals, Astrazeneca, Novartis Pharma, Bayer, and Astellas. HS also received scholarship from Chugai and Bayer.

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