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COMMENT

Fat mass: the most sensitive predictor of persistent hypertension in unilateral primary aldosteronism

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Primary aldosteronism (PA) is characterized by excessive autonomous aldosterone secretion, suppressed plasma renin activity, and hypertension and is frequently complicated by cerebro-cardiovascular events. The mechanism is thought to be stimulation of mineralocorticoid receptor (MR) activity in the kidney by excessive aldosterone, which increases Na^+ reabsorption and circulatory blood volume, resulting in hypertension. In addition, the enhanced MR activity in the heart and vasculature leads to marked inflammation and fibrosis, resulting in a high incidence of cerebro-cardiovascular diseases. The two most common subtypes are unilateral PA (uPA), due mostly to an aldosterone-producing adenoma, and bilateral PA (bPA), due to bilateral adrenal hyperplasia.

Obesity is associated with hypertension, diabetes, dyslipidemia, and sleep apnea, resulting in a high incidence of cardiovascular events. Medina-Inojosa et al. reported that waist circumference and the waist-to-hip ratio are predictors of cardiovascular events, suggesting that the accumulation of visceral fat impairs the cardiovascular system [1]. It has also been postulated that adipocytes are endocrine organs that secrete components via the tissue renin–angiotensin–aldosterone (RAA) system [2]. Obesity can also activate the RAA system by activating the sympathetic nervous system via stress and inflammation. However, obese patients have high dietary intakes that include excessive salt, which can suppress plasma renin and aldosterone levels, although excessive salt may enhance MR activity by facilitating nuclear MR translocation via activation of Rac1. Obese patients with diabetes mellitus are thought to be more likely to activate MR directly due to chronic hyperglycemia-mediated O-linked N-acetylglucosamine modification, resulting in progressive hyporeninemia and hypoaldosteronemia [3]. In other words, the effect of obesity on the RAA system varies individually, and hormonal changes are likely not generalizable, although multiple mechanisms may contribute to MR overactivation.

Huang et al. evaluated patients with uPA using a body composition monitor (BCM) before treatment to assess whether the hypertension remitted after adrenalectomy [4]. This study is unique in that it used BCM to examine obesity status in three groups: clinically obesity (BMI ≥ 25 kg/m^2), normal weight obesity (fat mass (FM) ≥ 35% in women and FM ≥ 25% with BMI < 25 kg/m^2 in men), and no obesity (FM < 35% in women and FM < 25% with BMI < 25% in men). They showed that uPA patients had a higher FM and lower lean tissue mass compared with essential hypertensive patients, although there was no significant difference in BMI. Higher plasma renin activity (PRA) and a lower serum creatinine level were also correlated with increased FM. In addition, compared with the no obesity group, the normal weight obesity (NWO) and obesity groups, which have high FM values, had refractory hypertension after adrenalectomy (OR = 2.89) and a long history of hypertension (OR = 1.065) and left ventricular hypertrophy, which may make hypertension intractable (Fig. 1).

In a similar study using abdominal computed tomography (CT), Haze et al. reported that PA patients with a higher visceral to subcutaneous fat volume ratio had lower renal function [5]. They also showed that PA patients with a high visceral to subcutaneous fat volume ratio and high plasma aldosterone concentration are more likely to have future cardiovascular events because of the higher E/e' on echocardiography compared with essential hypertension [6]. In other words, the results suggest that PA patients with a

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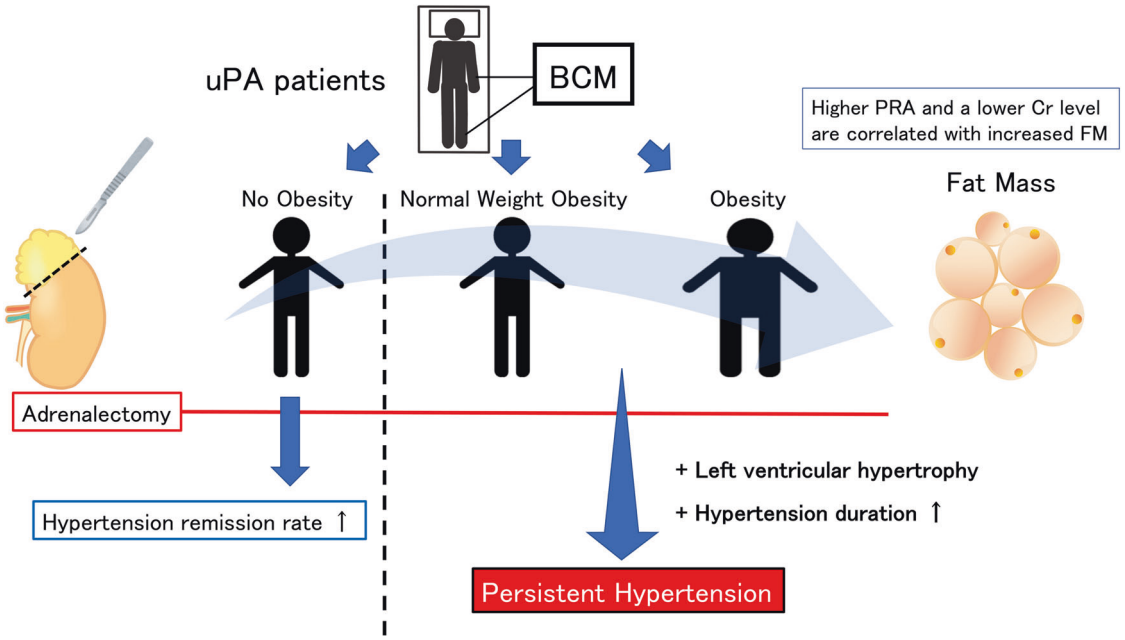

Fig. 1 Hypertension is refractory in uPA patients with a high fat mass as assessed by a BCM. BCM body composition monitor; Cr creatinine; FM fat mass; PRA plasma renin activity; uPA unilateral primary aldosteronism

high FM and plasma aldosterone concentration may have very negative cardiovascular outcomes.

The present study by Huang et al. differs from previous reports. The first difference is that bPA, compared with uPA, was reported to be more strongly correlated with the rate of metabolic syndrome complications and a higher BMI [7]. Shibata et al. also reported that BMI and insulin resistance were significantly correlated with urinary aldosterone excretion in bPA [8]. Based on those reports, it was believed that bPA, but not uPA, is related to obesity. The results of the present study, suggest that it is important to manage weight to avoid increasing FM in uPA as well as in bPA patients. The second difference is that high PRA is correlated with FM volume; i.e., patients are more likely to be NWO or obesity, which may ultimately lead to refractory hypertension. Hundermer et al. reported that PA patients with PRA ≥ 1 ng/mL/h after mineralocorticoid receptor blocker (MRB) therapy had significantly fewer cardiovascular events than those with PRA < 1 ng/mL/h [9]. The results suggest that patients in whom PRA suppression is improved by sufficient inhibition of MR activity by MRBs are less likely to have cardiovascular events. Yoshida et al. also showed that PA patients with a plasma active renin concentration (ARC) ≥ 5 pg/mL (corresponding to PRA ≥ 1 ng/mL/h) after MRB treatment had improved salt sensitivity, whereas those with an ARC < 5 pg/mL might remain salt sensitive [10]. These reports indicated that a higher renin level after treatment with MR antagonists is associated with a reduction in salt sensitivity and better cardiovascular outcomes. In general, PA without renin suppression is considered to be a milder form of PA, meaning that the effect of MR overactivation due to excess aldosterone may be mild. In comparison, the results of the current study showed that a higher pre-treatment renin level tended to be associated with a greater FM, suggesting that RAA system activation due to a higher FM may have enhanced the hyperaldosteronism in uPA. One of the reasons for this increased FM in uPA patients with higher renin levels may be concomitant sleep apnea, which was not examined in this study. Other reasons for the adverse effect of higher renin levels may be drugs that affect the RAA system during the preoperative hormonal evaluation, as described in the Limitations section. New studies should examine uPA patients, evaluating sleep apnea and drugs that affect the RAA system.

This study proposes a potential method to assess the degree of obesity in a less invasive manner and to predict future cardiovascular events. The results show that both NWO (BMI < 25) and obesity uPA patients have a low hypertension remission rate. This may not be assessed by measuring waist circumference or the waist-to-hip ratio as proposed by Medina-Inojosa et al. [1]; rather, assessing FM using a BCM may be an accurate and valid method. In addition, the studies by Haze et al. required CT imaging [5, 6]. The examinations for diagnosing PA include CT imaging to confirm the presence or absence of an adrenal tumor. If there is no adrenal tumor on CT, follow-up serial CT is not desirable; a BCM is a better modality for monitoring FM in terms of medical costs and radiation exposure. Thus, this is an excellent paper showing that FM

quantification using a BCM is a more sensitive marker than BMI for predicting the prognosis of hypertension after uPA adrenalectomy.

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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