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COMMENT

Perirenal fat: a missing link between mineralocorticoid receptor activation and cardiovascular-kidney-metabolic syndrome in primary aldosteronism

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Obesity is a risk factor for metabolic diseases, including hypertension, type 2 diabetes, and dyslipidemia. These metabolic disorders cause vascular complications such as cardiovascular disease (CVD) and chronic kidney disease (CKD). Adipose tissue comprises a large number of adipocytes and is traditionally classified into visceral adipose tissue and subcutaneous adipose tissue based on its morphological appearance and location [1]. Perirenal fat (PRF), a component of the visceral adipose tissue that surrounds the kidney, was originally presumed to provide only mechanical support. However, PRF has been shown to have a closer relationship with renal disease among individuals with obesity, compared with other visceral fat deposits [2]. In addition, excess PRF has been identified as an independent risk factor for CKD and a contributor to the development of CVD [3].

In obese patients with hypertension who underwent bariatric surgery, a positive correlation was observed between PRF thickness and a reduction in the use of antihypertensive drugs. PRF thickness was greater in obese and hypertensive patients than in lean and normotensive subjects [4]. After bariatric surgery, a greater reduction in PRF is associated with a more effective amelioration of hypertension. Furthermore, PRF thickness positively correlates with serum creatinine levels and negatively with the glomerular filtration rate estimated by serum creatinine, indicating an important relationship between PRF thickness and renal function [4]. Measurement of PRF thickness, especially by noninvasive and rapid ultrasound, or alternatively by more expensive methods, such as computed tomography or magnetic resonance imaging, might help identify obese patients at higher risk of obesity-related hypertension.

Excessive PRF compresses the kidney, increases the intrarenal pressure, and reduces the flow rate in the loop of Henle. These changes elevate sodium reabsorption in the proximal tubule, decrease sodium delivery to the macula densa, inhibit tubuloglomerular feedback, cause preglomerular vasodilation, and increase renal blood flow, glomerular hyperfiltration, and renin secretion.

Moreover, PRF produces adipocytokines such as leptin, interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), which may also contribute to obesity-related hypertension by stimulating inflammatory responses. Excess PRF can affect the kidneys via systemic or local secretion of inflammatory cytokines. PRF secretes TNF-α, which directly impairs renal arterial endothelial dysfunction, an early sign of vascular damage [5].

PRF stimulates the sympathetic nervous system (SNS). Efferent nerves innervate the PRF, while afferent nerves have been distributed in adipose tissue. The physiological function of PRF neural activity is presumably related to these anatomical characteristics. The afferent nerves of PRF may control the SNS through a negative feedback loop. Renal sympathetic activation increases with enhanced afferent signaling from PRF, followed by elevated arterial blood pressure, known as the "adipose afferent reflex." Injection of leptin into PRF also activates this reflex without affecting serum levels of sympathetic-activating substances, suggesting that PRF directly regulates the cardiovascular system through the SNS [6].

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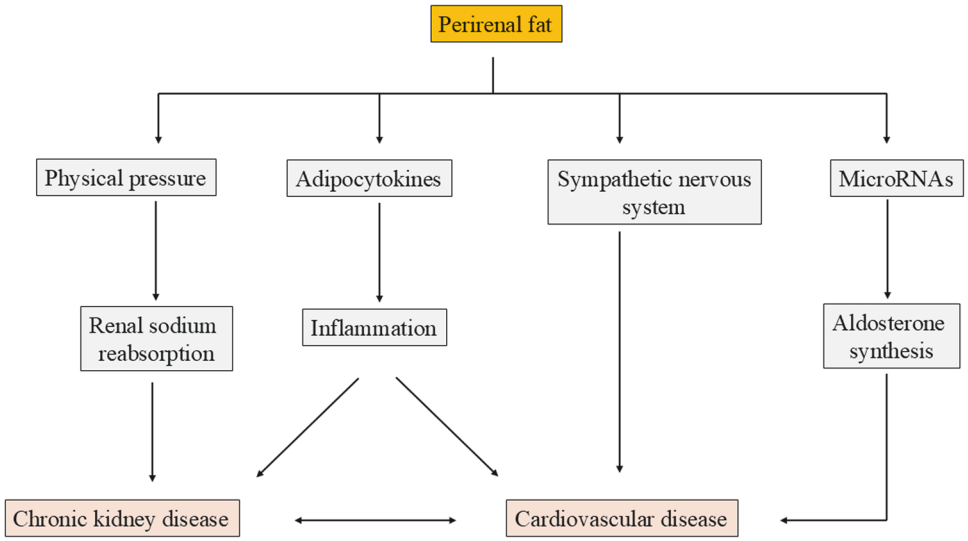

Fig. 1 Relevant mechanisms for perirenal fat in chronic kidney disease and cardiovascular disease

A recent study by Mitsuno et al. showed that PRF accumulation is involved in the mechanisms linking mineralocorticoid receptor (MR) activation with cardiometabolic and renal dysfunction in patients with primary aldosteronism (PA). Moreover, PRF could be not only a prognostic factor but also a potential therapeutic target for MR antagonist (MRA)-resistant hypertension. These findings provide new insight into why MR overactivation results in the development and progression of cardiovascular-kidney-metabolic syndrome [7]. Here, we discuss the association between PRF microRNAs (miRNAs) and aldosterone levels. MiRNAs, non-coding RNAs consisting of 19–22 nucleotides that regulate gene expression, have been identified in tissues, circulation, and urine, and serve as potential biomarkers and mediators in various diseases, including CVD [8]. Recently, attention has focused on miR-24-3p derived from PRF, as a previous study has shown that miR-24-3p targets CYP11B2 in PA, affecting aldosterone synthesis [9]. In fact, miR-24-3p is significantly upregulated in the PRF of patients with PA than in those with non-adrenal disease (exclusion criteria: secondary hypertension [Cushing's syndrome, pheochromocytoma, renal and renovascular hypertension, hyperthyroidism, or aortic stenosis], use of glucocorticoids, or medications affecting the renin–angiotensin–aldosterone system). Furthermore, miR-24-3p expression in the PRF of patients with PA positively correlates with plasma aldosterone concentration, left ventricular posterior wall end-diastolic thickness, body mass index, and PRF thickness [10]. These findings indicate that PRF-derived miR-24-3p may contribute to poor responsiveness to MRA in patients with PA, and that the upregulation of miR-24-3p in PRF may be involved in the high risk of CKD in this population (Fig. 1).

However, little is known about the relationship between circulating miR-24-3p and CKD, or whether miR-24-3p is directly involved in MR signaling. Additional preclinical and clinical studies are required to address these questions.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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