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Jiang, Y., Li, D., Cao, C.C. et al. (2025) Clinical significance of skeletal fat-to-muscle ratio in idiopathic hyperaldosteronism. Clinical Endocrinology, 103 (4). pp. 429-435. ISSN: 0300-0664

https://doi.org/10.1111/cen.15274

Clinical Endocrinology

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Adrenal

Clinical Significance of Skeletal Fat-to-Muscle Ratio in Idiopathic Hyperaldosteronism

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Received: 11 February 2025 | **Revised:** 29 April 2025 | **Accepted:** 8 May 2025

Funding: This study was supported by grants from Natural Science Foundation of Shandong Province (ZR2020MH104).

Keywords: aldosterone-to-renin ratio | fat-to-muscle ratio | idiopathic hyperaldosteronism | insulin resistance

ABSTRACT

Objective: The objective of this study is to evaluate the correlation between the fat-to-muscle ratio (FMR) and insulin resistance (IR) with aldosterone production among patients with idiopathic hyperaldosteronism (IHA).

Methods: Patients with primary aldosteronism were screened from those with secondary hypertension and then subtyped via adrenal venous sampling. A total of 199 patients with IHA and 186 with essential hypertension (EH) (controls) were studied. Baseline clinical characteristics, including data on diabetes and IHA, were collected. The FMR was evaluated based on the distribution of adipose tissue and muscle, measured by a body composition analyzer.

Results: The prevalence of diabetes and prediabetes was significantly higher in patients with IHA compared to those with essential hypertension. IHA patients also had significantly higher hemoglobin A1c(HbA1c) levels, homeostatic model assessment of insulin resistance (HOMA-IR), and much lower quantitative insulin sensitivity check index scores than the EH group. FMR was positively associated with fasting insulin, HOMA-IR, aldosterone-to-renin ratio (ARR), and age. A higher FMR was linked to the prevalence of IHA, with a stepwise increase in risk observed from the lowest to the highest quartiles of FMR. Logistic regression analysis showed that both HOMA-IR and body mass index contributed to the elevated FMR. IHA may result from a substantial loss of muscle mass accompanied by fat accumulation.

Discussion: In this retrospective study, our findings suggest that FMR could serve as a valuable metric for early intervention and comanagement strategies in patients at risk of sarcopenic obesity. This approach could help block the progression from aldosterone-producing cell clusters to IHA, potentially inhibiting aldosterone overproduction in such patients.

1 | Introduction

Primary aldosteronism (PA) is the most common endocrine cause of secondary hypertension and is associated with increased cardiovascular morbidity [1]. The pathogenesis of the most common bilateral form of PA, idiopathic hyperaldosteronism (IHA), is believed to differ from that of aldosterone-producing adenoma (APA). Patients with IHA exhibit more metabolic disorders and a higher prevalence of obesity compared to those with APA, although the underlying cause is still not fully elucidated.

Adrenal hyperplasia is surrounded by perirenal adipose tissue and contains islets of adipocytes intermingled with adrenocortical cells, facilitating cell-to-cell communication. The interactions between adipocytes and steroidogenic cells appear to be bidirectional [2]. It has been identified that peri- and intra-adrenal adipocytes may exert control over aldosterone production [3].

Metabolic syndrome is more frequent in patients with PA than in those with essential hypertension (EH). Hypertension is strongly associated with metabolic syndrome through pathophysiological mechanisms involving obesity [4]. There is a significant relationship between higher body fat percentage and PA. Among patients with PA, the prevalence of obesity is significantly higher in IHA patients than in APA patients [5]. Additionally, aldosterone concentration has been found to decrease following weight loss in severely to morbidly obese individuals [6]. It is suggested [7] that obesity-related factors may contribute to the pathogenesis of IHA, and a positive association between plasma aldosterone concentration (PAC) and visceral fat area has been observed in patients with IHA only [6]. However, these studies did not consider fat and muscle together; factors such as sarcopenic obesity (SO) and insulin resistance (IR) have not yet been evaluated, despite their potential relevance to aldosterone production and adrenal hyperplasia. It has been reported that the fat-to-muscle ratio (FMR) is associated with IR and cardiometabolic disorders in diabetic patients [8]. These considerations prompted us to evaluate the distribution of adipose tissue and muscle in IHA patients. We aim to elucidate the correlation between FMR and IR with aldosterone production, with the goal of offering lifestyle recommendations that integrate both muscle and fat components to prevent the pathogenesis of IHA.

2 | Patients and Methods

2.1 | Patients

This was a retrospective observational study involving 385 patients, including 199 patients with IHA and 186 with EH, who served as the control group. The two subgroups were selected from a larger patient population consecutively referred to our institution over the past three years, and were matched for sex, age, and body mass index (BMI). Patients were excluded if they met any of the following criteria: (1) other known causes of secondary hypertension; (2) severe renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2, calculated using the CKD-EPI formula; or (3) severe heart failure, classified as New York Heart Association (NYHA) functional class III or above.

Before examination, anti-hypertensive medications that could influence plasma PAC and plasma renin activity (PRA) were discontinued and replaced with calcium channel blockers or α-blockers. PAC and PRA were measured using chemiluminescence detection, and urinary sodium and potassium excretion were determined using the ion-selective electrode (ISE) method.

This study was approved by the Ethical Committee of the Affiliated Hospital of Qingdao University, and written informed consent was obtained from all patients participating in the study.

2.2 | Anthropometric Measurements

BMI (kg/m^2) was calculated using height and body weight upon admission. Waist circumference (WC) was measured at the umbilical level. Obesity was defined as a BMI ≥ 25 kg/m^2 according to the 2016 Japanese guidelines for the management of obesity. Central obesity, an essential component of metabolic syndrome, was defined as WC ≥ 85 cm for men and ≥ 90 cm for women, based on Japanese criteria [9].

Body composition was assessed using a body composition analyzer (InBody 170, BIOSPACE, China). This single-frequency device utilizes eight polar electrodes and a single-point load-cell weighing system on the scale platform to provide separate body mass readings for different body segments. An algorithm incorporating impedance, age, and height was used to estimate total and regional body fat and fat-free mass. Fat mass, skeletal muscle mass, percentage body fat (PBF), and visceral fat area (VFA) were measured and recorded. Total fat and lean mass percentages, as well as appendicular lean mass (ALM), were calculated using standard formulas [10]. The skeletal muscle mass index (SMI) was calculated by dividing appendicular skeletal muscle mass (kg) by height squared (m^2). The FMR was calculated as body fat mass (kg) divided by muscle mass (kg) [11, 12].

2.3 | Screeing and Confirmatory Test for PA

The diagnostic procedure for PA at our hospital follows the guidelines established by the Working Group on Endocrine Hypertension of the European Society of Hypertension [13] and the expert consensus of the Chinese Society of Endocrinology [14]. Briefly, hypertensive patients with an aldosterone-renin ratio (ARR) > 20 ng/mIU and a plasma PAC > 10 ng/dL underwent either a captopril challenge test or a saline infusion test to confirm the diagnosis of PA. All medications were discontinued for 3 weeks (at least 6 weeks for spironolactone). In cases where antihypertensive treatment could not be discontinued, calcium-channel blockers and/or α-receptor blockers were administered at the necessary doses to maintain blood pressure control.

2.4 | Subtype Classification for PA

All patients with a confirmed diagnosis of PA underwent adrenal computed tomography (CT) scanning for preliminary classification. Adrenal CT findings were categorized into the following possibilities: (1) normal-appearing adrenal glands; (2) unilateral adrenal macroadenoma (> 1 cm); (3) bilateral adenomas with either macro- or microcharacteristics; or (4) minimal, unilateral adrenal limb thickening. It is particularly challenging to distinguish between subtypes in cases of small, inconspicuous APAs or nodular hyperplasia due to significant overlap in quantitative CT findings between APA and IHA. Therefore, patients willing to undergo adrenalectomy were referred for adrenal vein sampling (AVS).

The criterion used to determine the lateralization of aldosterone hypersecretion was established according to consensus guidelines [13–15]. The selectivity index (SI) for both the right and left adrenal veins was calculated as the ratio of each adrenal vein's cortisol level to the peripheral cortisol level. AVS was considered successful if the SI was greater than 2.0. The lateralization of aldosterone hypersecretion was assessed using the

lateralization index (LI), which is the ratio of the aldosterone-to-cortisol concentration on the dominant side to that on the contralateral side. Lateralization was defined as an LI ≥ 2.

2.5 | Evaluation for Insulin Sensitivity

Insulin sensitivity was assessed using three different methods based on 75 g OGTT values. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting plasma insulin (μU/ml) and plasma glucose (mmol/l), divided by 22.5. Insulin sensitivity was also evaluated using the quantitative insulin sensitivity check index (QUICKI), proposed by Katz et al., calculated as 1/[log (fasting plasma insulin) + log (fasting plasma glucose)]. Additionally, the insulin sensitivity index (ISI) proposed by Matsuda and DeFronzo [16] was calculated as ISI composite = 10,000/√([mean plasma insulin × mean plasma glucose during OGTT] × [fasting plasma glucose × fasting plasma insulin]). IC, IA, GAD, and IA-2 antibodies were measured to exclude type 1 diabetes.

Patients were evaluated when normokalemic and on normal sodium intake, assessed by measurement of 24-h urinary sodium excretion.

2.6 | Statistical Analysis

All analyzes were performed using SPSS version 25 (IBM Corp., released 2017). Continuous variables were expressed as mean ± SD or median and interquartile range, as appropriate. Correlations were analyzed using the Spearman rank correlation coefficient. Continuous variables were compared using the *t*-test or the Mann-Whitney U test, depending on the data distribution. The comparison of frequencies between two groups was estimated using the chi-square test or Fisher's exact test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Two-tailed *p*-values of < 0.05 were considered statistically significant.

Given that FMR may be correlated with aldosterone production, we conducted further analyzes stratified by FMR. To evaluate the correlation between FMR quartiles and aldosterone secretion in IHA, logistic regression was used to calculate univariate and multivariate logistic regression coefficients.

3 | Results

3.1 | Baseline Characteristics

Demographic, anthropometric, and biochemical characteristics of the IHA and EH patients are presented in Table 1. The mean age in the IHA group was 65.04 ± 10.09 years, which was significantly higher than that in the EH group (61.11 ± 11.49 years). IHA patients had significantly higher PAC and ARR compared to the EH group, as well as lower serum K^+ and PRA levels ($p < 0.05$ and $p < 0.001$, respectively). However, there were no significant differences between the two groups in terms of total cholesterol (TC), triglycerides (TG), uric acid, and eGFR.

Among the metabolic parameters, the prevalence of diabetes and prediabetes was significantly higher in IHA patients than in EH patients. Additionally, IHA patients exhibited significantly higher HbA1c, fasting insulin levels, and HOMA-IR compared to the EH group. Accordingly, QUICKI was much lower in the IHA group than in the EH group. Other laboratory values showed no statistically significant differences between the two groups.

3.2 | The Distribution of Adipose Tissues and Muscles in IHA Patients

IHA patients had significantly higher BMI compared to the EH group ($p < 0.05$) in Table 2. Additionally, the IHA group exhibited higher VFA and lower appendicular lean mass (ALM) than the EH group ($p < 0.05$), leading to a significantly lower ALM/BMI ratio in IHA patients (all $p < 0.05$). Furthermore, the percentage of body fat (PBF) was 28.05 ± 7.65% in the IHA group, which was significantly higher than that in the EH group (24.27 ± 8.45%, $p < 0.001$). Finally, the FMR (FMR) was also significantly different between IHA and EH patients [0.41 (0.32, 0.51) vs. 0.36 (0.27, 0.50), respectively, $p < 0.05$]. Other laboratory values showed no statistically significant differences between the two groups.

3.3 | Relationship Between FMR and RAAS in IHA Patients

The correlation of FMR with RAAS and biochemical metabolic variables is shown in Table 3. FMR was positively associated with fasting insulin, HOMA-IR, ARR, and age, regardless of gender. In contrast, FMR was inversely associated with PRA.

3.4 | FMR Quartile

As shown in Table 4, both HOMA-IR and BMI contributed to the elevated FMR. Additionally, multinomial logistic regression analysis demonstrated that the multivariable-adjusted odds ratios for ARR in FMR quartile 4 compared to quartiles 1, 2, and 3 were 6.710, 0.082, 1.701, and 3.269, respectively. No significant differences were observed in the trend analysis for other variables when stratified by FMR quartiles.

4 | Discussion

Our study demonstrated that IHA patients had significantly higher HbA1c and fasting glucose levels compared to the EH group. Correspondingly, the prevalence of diabetes and prediabetes was significantly higher in IHA patients than in EH patients, consistent with our previous findings [17]. It is known that the prevalence of obesity and diabetes is higher in IHA than in APA, and insulin resistance (IR) is a leading cause of glucose intolerance in IHA [18]. In this study, fasting insulin levels and HOMA-IR were significantly higher in IHA patients compared to the EH group, while QUICKI was significantly lower. Notably, our previous study also indicated that IHA subjects had a higher prevalence of insulin resistance than EH

TABLE 1 | Baseline characteristics of patients with IHA and EH.

	IHA ($n = 199$)	EH ($n = 186$)	*p*-value
Age (years)	65.04 ± 10.09	61.11 ± 11.49	< 0.05
Sex (male/female)	111/88	115/71	> 0.05
Presence of type 2 diabetes (%)	44.22	33.87	< 0.01
Presence of prediabetes (%)	42.71	32.26	< 0.01
SBP (mmHg)	178.03 ± 22.29	173.87 ± 23.73	> 0.05
DBP (mmHg)	100.00 ± 16.85	103.33 ± 15.43	> 0.05
PAC (pg/mL)	140.60 (105.34, 176.75)	102.90 (78.69, 138.90)	< 0.05
PRA (ng/mL/h)	0.17 (0.09, 0.34)	1.99 (0.79, 3.09)	< 0.001
ARR	57.02 (36.54, 142.66)	6.84 (3.54, 11.92)	< 0.001
Serum potassium (mmol/L)	3.73 ± 0.46	3.80 ± 0.35	< 0.05
TC (mmol/L)	4.88 ± 1.05	5.03 ± 0.96	> 0.05
HDL (mmol/L)	1.34 ± 0.21	1.41 ± 0.25	> 0.05
LDL (mmol/L)	2.76 ± 0.77	2.83 ± 0.79	> 0.05
TG (mmol/L)	1.37 (0.98, 2.10)	1.42 (1.07, 2.31)	> 0.05
Uric acid (mmol/L)	356.68 ± 83.01	363.70 ± 97.31	> 0.05
eGFR (%)	73.33 ± 13.65	73.93 ± 13.89	> 0.05
HbA1c (%)	6.70 (6.26, 7.11)	6.20 (5.60, 7.10)	< 0.001
FPG (mmol/l)	5.87 (5.18, 6.55)	5.41 (4.73, 6.23)	< 0.001
Insulin (μU/ml)	11.76 (7.86, 17.15)	10.00 (6.60, 14.10)	< 0.05
HOMA-IR	3.21 (1.94, 4.81)	2.35 (1.52, 3.67)	< 0.01
QUICKI	0.23 (0.21, 0.26)	0.25 (0.23, 0.28)	< 0.01

Data were presented as mean ± SD, median (interquartile range), or number (%). IHA, idiopathic hyperaldosteronism; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone–renin ratio; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, HOMA of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

TABLE 2 | Anthropometric characteristics and body composition patterns in IHA and EH patients.

	IHA ($n = 199$)	EH ($n = 186$)	*p*-value
BMI (kg/m^2)	26.34 ± 3.39	25.75 ± 2.86	< 0.05
WC (cm)	83.72 ± 10.86	84.13 ± 9.48	> 0.05
BMR	1529.00 (1329.00, 1758.00)	1578.50 (1399.50, 1711.75)	> 0.05
VFA (cm^2)	75.40 (60.20, 95.90)	70.96 (52.54, 92.96)	< 0.05
BF (kg)	20.18 (16.20, 24.57)	19.30 (15.55, 23.38)	> 0.05
PBF (%)	28.05 ± 7.65	24.27 ± 8.45	< 0.001
ALM (kg)	28.85 (23.35, 34.69)	30.77 ± 6.21	< 0.05
ALM/BMI	1.09 (0.95, 1.26)	1.18 ± 0.22	< 0.001
FMR	0.41 (0.32, 0.51)	0.36 (0.27, 0.50)	< 0.05

BMI, Body Mass Index; WC, waist circumference; BMR, basal metabolic rate; VFA, visceral fat area; ALM, Appendicular lean mass; BF, body fat; PBF, percentage of body fat; FMR, fat-to-muscle ratio.

subjects. Thus, IR emerges as a major contributor to the increased risk of aldosterone production.

The etiology of IHA is not yet fully understood. Several studies have shown that the prevalence of obesity is significantly higher in patients with IHA than in those with EH [6], and IHA patients tend to have higher BMI and VFA than APA patients, which is often associated with subclinical hypercortisolism. These findings suggest that there may be a unique metabolic cause of IHA that differs from APA and EH. However, there has been a lack of studies examining subtype-specific metabolic risks and body composition in IHA patients. To our knowledge, this is the first study to explore the relationship between FMR and aldosterone levels in IHA patients [19].

TABLE 3 | Correlations of FMR with metabolism parameters and RAAS in patients with IHA with diabetes or prediabetes.

	HbA1c (%)	FBG mmol/l)	INS (μU/ml)	HOMA-IR	PRA (ng/mL/h)	PAC (pg/mL)	ARR	BMI (kg/m^2)	Age (y)
r	0.262	0.353	0.408*	0.167*	−0.431*	0.564	0.130*	−0.019	0.825*
p	0.530	0.389	0.015	0.043	0.0285	0.145	0.032	0.963	0.011

*Statistically significant differences with p value < 0.05; r, correlation coefficient; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, plasma aldosterone-to-renin ratio; HbA1c, glycated hemoglobin; FBG, Fasting blood glucose; INS, Fasting Insulin; HOMA-IR, HOMA of insulin resistance.

TABLE 4 | Univariate and multivariate logistic regression analysis of predictive factors associated with FMR in IHA.

	Q1	Q2	Q3	Q4
BMI (kg/m^2)	−0.104*	−0.083	0.09*	0.113*
PAC (pg/mL)	0.004	−0.001	−0.001	−0.001
PRA (ng/mL/h)	−0.096	−0.161	−0.209	0.394
ARR	0.082*	1.701*	3.269**	6.710**
HbA1c (%)	0.209	−0.112	−0.36	0.214
HOMA-IR	0.915	2.019**	4.474**	20.245***
QUICKI	−0.095	0.074	0.009	−0.193

*Statistically significant differences with p value < 0.05; BMI, Body Mass Index; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, plasma aldosterone-to-renin ratio; HbA1c, glycated hemoglobin; HOMA-IR, HOMA of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

The present results suggest that obesity-related factors contribute to the pathogenesis of IHA [6], though the effects of adiposity on PA development have shown conflicting results. Additionally, an increase in muscle mass has been linked to reduced IR and protection against the development of type 2 diabetes. Aldosterone has been associated with sarcopenia, and lower skeletal muscle mass has been observed in patients with PA [20, 21]. Myosteatosis and sarcopenia are linked to autonomous cortisol secretion in APA patients, which leading to a higher prevalence of obesity, diabetes and increased cardiovascular events [22]. Autonomous cortisol secretion may result in increased intermuscular adipose tissue area (IMAT) and reduced skeletal mass. Urinary aldosterone was related to sarcopenic indices and may be involved in the pathogenesis of sarcopenia [23]. Therefore, myosteatosis and sarcopenia is a crucial but overlooked complication of PA [24].

However, the protective effects of muscle and the impact of substantial muscle loss combined with fat accumulation on the pathogenesis of IHA have not been clearly elucidated. FMR has emerged as a promising metric for assessing the imbalance between muscle and fat. While a growing number of studies have examined the role of FMR in cognitive dysfunction [25, 26], there is a notable gap in research on patients with hypertension.

In this study, we investigated the association between aldosterone and FMR in IHA and EH patients. We found that IHA patients had significantly higher VFA and PBF, along with lower ALM, compared to the EH group. Correspondingly, FMR was significantly higher in IHA patients. FMR was positively associated with fasting insulin, HOMA-IR, and ARR, while being inversely associated with PRA. Univariate and multivariate logistic regression analysis demonstrated that HOMA-IR and BMI contributed to the elevated FMR.

Several potential mechanisms for the interaction between FMR and aldosterone production can be hypothesized. A decrease in muscle mass is often linked to chronic inflammation and pro-inflammatory states, which can lead to activation of mineralocorticoid receptors and endothelial dysfunction [27]. Additionally, skeletal muscle is the primary site of insulin-mediated glucose uptake, and lower muscle mass is clearly associated with decreased insulin sensitivity [28]. As IR is a well-known factor associated with increased aldosterone production and mineralocorticoid receptor activation, this relationship may further explain the connection between muscle mass and aldosterone.

Ehrhart-Bornstein et al. [29] reported that secretory products from isolated human adipocytes stimulate aldosterone secretion from human adrenocortical cells. The candidate mediators responsible for stimulating aldosterone secretion have been identified as CTRP1, leptin, and resistin [30]. Hyperinsulinemia has also been reported as a contributor to the activation of the renin-angiotensin-aldosterone system (RAAS) [31]. Consequently, high FMR is thought to induce hyperaldosteronism through the actions of adipocytokines and activation of the RAAS. Simultaneously, hyperaldosteronism may exacerbate IR by promoting adipose maturation and muscle loss via mineralocorticoid receptor activation, creating a vicious cycle [6].

Several studies have explored the correlation between FMR quartiles and the risks of related diseases, such as chronic kidney disease and diabetes. Notably, these studies have found a sequential increase in risks from the lowest to the highest quartiles of FMR [32]. Supporting this, our results also showed that higher FMR was associated with a higher prevalence of IHA, with the multivariable-adjusted odds ratios for ARR being the highest in FMR tertile 4 compared to the lower tertiles. Logistic regression analysis further indicated that HOMA-IR and BMI contributed to the elevated FMR. The combination of BMI and FMR highlights the important roles of muscle loss and insulin resistance in the development of hyperaldosteronism. Given the interaction between FMR and aldosterone, we emphasize the protective role of muscle and recommend monitoring the distribution and ratio of body composition in IHA patients.

PA is becoming increasingly common in the elderly [33], and age over 60 is a known risk factor for PA. Recent studies have confirmed that renin-independent aldosteronism and dysregulated aldosterone physiology are more prevalent with advancing age [34]. Consistently, our study found that IHA is more common in older patients compared to EH, which may be due to an increased incidence of metabolic syndrome and higher FMR [7], as well as a decrease in PRA from reduced production and an increase in PAC from autonomous secretion of aldosterone

by aldosterone-producing cell clusters (APCCs). APCCs have been proposed as a transitional step toward PA, and their accumulation with age may contribute to the increased prevalence of IHA in older adults [35]. The increase in visceral fat and the decrease in skeletal muscle mass, which are specific to aging, further elevate the risk of IHA pathogenesis. Thus, adjusting lifestyle and intervening to improve insulin resistance and sarcopenia or pre-sarcopenia status may offer a novel, personalized treatment strategy for IHA.

Our study underscores the independent relationship between FMR and the heightened risk of IHA, especially in older patients. IHA may result from substantial muscle mass loss accompanied by fat accumulation. These findings suggest that FMR could serve as a valuable metric for early intervention and co-management strategies in patients at risk for sarcopenic obesity. Additionally, it holds therapeutic prospects that might potentially block the transition from APCC to IHA and inhibit aldosterone overproduction in some IHA patients. A limitation of this study is the lack of long-term follow-up data on interventions, which should be addressed in future prospective studies. Further research, including 'muscular fat mapping,' is needed to elucidate skeletal muscle quality's role in preventing cardiovascular and metabolic sequelae in IHA patients.

Author Contributions

All authors contributed to the revision and approval of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. M. Reincke, I. Bancos, P. Mulatero, U. I. Scholl, M. Stowasser, and T. A. Williams, "Diagnosis and Treatment of Primary Aldosteronism," *Lancet Diabetes & Endocrinology* 9, no. 12 (2021): 876–892.

2. S. Stanciu, E. Rusu, D. Miricescu, et al., "Links Between Metabolic Syndrome and Hypertension: The Relationship With the Current Antidiabetic Drugs," *Metabolites* 13, no. 1 (2023): 87.

3. H. Lefebvre, C. Duparc, A. Naccache, A.-G. Lopez, M. Castanet, and E. Louiset, "Paracrine Regulation of Aldosterone Secretion in Physiological and Pathophysiological Conditions," *Aldosterone* 109 (2019): 303–339.

4. Y. Rochlani, N. V. Pothineni, S. Kovelamudi, and J. L. Mehta, "Metabolic Syndrome: Pathophysiology, Management, and Modulation by Natural Compounds," *Therapeutic Advances in Cardiovascular Disease* 11, no. 8 (2017): 215–225.

5. M. Okazaki-Hada, A. Moriya, M. Nagao, S. Oikawa, I. Fukuda, and H. Sugihara, "Different Pathogenesis of Glucose Intolerance in Two Subtypes of Primary Aldosteronism: Aldosterone-Producing Adenoma and Idiopathic Hyperaldosteronism," *Journal of Diabetes Investigation* 11, no. 6 (2020): 1511–1519.

6. Y. Ohno, M. Sone, N. Inagaki, et al., "Obesity as a Key Factor Underlying Idiopathic Hyperaldosteronism," *Journal of Clinical Endocrinology and Metabolism* 103, no. 12 (2018): 4456–4464.

7. Y. Shibayama, N. Wada, S. Baba, et al., "Relationship Between Visceral Fat and Plasma Aldosterone Concentration in Patients With Primary Aldosteronism," *Journal of the Endocrine Society* 2, no. 11 (2018): 1236–1245.

8. F. Huang, X. Ji, Z. Wang, et al., "Fat-to-Muscle Ratio Is Associated With Insulin Resistance and Cardiometabolic Disorders in Adults With Type 1 Diabetes Mellitus," *Diabetes, Obesity and Metabolism* 25, no. 11 (2023): 3181–3191.

9. K. Yamagishi and H. Iso, "The Criteria for Metabolic Syndrome and The National Health Screening and Education System in Japan," *Epidemiology and Health* 39 (2017): e2017003.

10. S. Hong and K. M. Choi, "Sarcopenic Obesity, Insulin Resistance, and Their Implications in Cardiovascular and Metabolic Consequences," *International Journal of Molecular Sciences* 21, no. 2 (2020): 494.

11. R. Ramírez-Vélez, H. A. Carrillo, J. E. Correa-Bautista, et al., "Fat-to-Muscle Ratio: A New Anthropometric Indicator as a Screening Tool for Metabolic Syndrome in Young Colombian People," *Nutrients* 10, no. 8 (2018): 1027.

12. N. Wang, Y. Sun, H. Zhang, et al., "Total and Regional Fat-To-Muscle Mass Ratio Measured by Bioelectrical Impedance and Risk of Incident Type 2 Diabetes," *Journal of Cachexia, Sarcopenia and Muscle* 12, no. 6 (2021): 2154–2162.

13. P. Mulatero, S. Monticone, J. Deinum, et al., "Genetics, Prevalence, Screening and Confirmation of Primary Aldosteronism: A Position Statement and Consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension ⋆," *Journal of Hypertension* 38, no. 10 (2020): 1919–1928.

14. C. So Endocrinology, "Expert Consensus on the Diagnosis and Treatment of Primary Aldosteronism," *Journal of Clinical Endocrinology & Metabolism* 36, no. 9 (2020): 727.

15. P. Dogra, I. Bancos, and W. F. Young, "Primary Aldosteronism: A Pragmatic Approach to Diagnosis and Management," *Mayo Clinic Proceedings* 98, no. 8 (2023): 1207–1215.

16. H. Ren, L. Qin, W. Wang, et al., "Abnormal Glucose Metabolism and Insulin Sensitivity in Chinese Patients With Gitelman Syndrome," *American Journal of Nephrology* 37, no. 2 (2013): 152–157.

17. C. Cao, Z. Zeng, Y. Zhou, et al., "Relationship Between Insulin Resistance and Aldosterone Level in Patients With Metabolic Syndrome," *Chinese Journal of Diabetes* 17, no. 01 (2009): 33–35.

18. Y. Akehi, T. Yanase, R. Motonaga, et al., "High Prevalence of Diabetes in Patients With Primary Aldosteronism (PA) Associated With Subclinical Hypercortisolism and Prediabetes More Prevalent in Bilateral Than Unilateral PA: A Large, Multicenter Cohort Study in Japan," *Diabetes Care* 42, no. 5 (2019): 938–945.

19. S. S. Park, C. H. Ahn, S. W. Kim, J. W. Yoon, and J. H. Kim, "Subtype-Specific Body Composition and Metabolic Risk in Patients With Primary Aldosteronism," *Journal of Clinical Endocrinology & Metabolism* 109, no. 2 (2024): e788–e798.

20. L. A. Burton, M. E. T. McMurdo, and A. D. Struthers, "Mineralocorticoid Antagonism: A Novel Way to Treat Sarcopenia and Physical Impairment in Older People?," *Clinical Endocrinology* 75, no. 6 (2011): 725–729.

21. M. K. Kwak, S. E. Lee, Y. Y. Cho, et al., "The Differential Effect of Excess Aldosterone on Skeletal Muscle Mass by Sex," *Frontiers in Endocrinology* 10 (2019): 195.

22. B. C. Lee, Y. L. Chang, P. T. Chen, et al., "Myosteatosis and Sarcopenia Are Linked to Autonomous Cortisol Secretion in Patients With Aldosterone-Producing Adenomas," *Hypertension Research* 48, no. 2 (2025): 519–528.

23. M. Mogi, K. Kohara, Y. Tabara, K. Tsukuda, M. Igase, and M. Horiuchi, "Correlation Between the 24-h Urinary Angiotensinogen or Aldosterone Level and Muscle Mass: Japan Shimanami Health Promoting Program Study," *Hypertension Research* 41, no. 5 (2018): 326–333.

24. Y. Yoshida and H. Shibata, "Unrecognized Association Between Autonomous Cortisol Secretion and Myosteatosis in Patients With Aldosterone-Producing Adenoma," *Hypertension Research* 48, no. 2 (2025): 813–815.

25. C. Fürnsinn, W. Ma, H. Zhang, et al., "Relationship Between Obesity-Related Anthropometric Indicators and Cognitive Function in Chinese Suburb-Dwelling Older Adults," *PLoS One* 16, no. 10 (2021): e0258922.

26. W. Wang, Y. Luo, Z. Zhuang, et al., "Total and Regional Fat-to-Muscle Mass Ratio and Risks of Incident All-Cause Dementia, Alzheimer's Disease, and Vascular Dementia," *Journal of Cachexia, Sarcopenia and Muscle* 13, no. 5 (2022): 2447–2455.

27. D. Armanini, M. Boscaro, L. Bordin, and C. Sabbadin, "Controversies in the Pathogenesis, Diagnosis and Treatment of PCOS: Focus on Insulin Resistance, Inflammation, and Hyperandrogenism," *International Journal of Molecular Sciences* 23, no. 8 (2022): 4110.

28. S. De Cosmo, C. Menzaghi, S. Prudente, and V. Trischitta, "Role of Insulin Resistance in Kidney Dysfunction: Insights Into the Mechanism and Epidemiological Evidence," *Nephrology Dialysis Transplantation* 28, no. 1 (2012): 29–36.

29. A. W. Krug and M. Ehrhart-Bornstein, "Aldosterone and Metabolic Syndrome," *Hypertension* 51, no. 5 (2008): 1252–1258.

30. A.-C. Huby, G. Antonova, J. Groenendyk, et al., "Adipocyte-Derived Hormone Leptin Is a Direct Regulator of Aldosterone Secretion, Which Promotes Endothelial Dysfunction and Cardiac Fibrosis," *Circulation* 132, no. 22 (2015): 2134–2145.

31. G. Z. Kalil and W. G. Haynes, "Sympathetic Nervous System in Obesity-Related Hypertension: Mechanisms and Clinical Implications," *Hypertension Research* 35, no. 1 (2011): 4–16.

32. F. Wu, Y. Liu, C. Lin, et al., "Correlation Between Fat-to-Muscle Mass Ratio and Cognitive Impairment in Elderly Patients With Type 2 Diabetes Mellitus: A Cross-Sectional Study," *BMC Geriatrics* 24, no. 1 (2024): 352.

33. X. Bu, F. Sun, H. Zhang, et al., "Clinical Characteristics of Target Organ Damage in Primary Aldosteronism With or Without Metabolic Syndrome," *Journal of Diabetes Research* 2022 (2022): 1–7.

34. K. Nanba, A. Vaidya, G. H. Williams, I. Zheng, T. Else, and W. E. Rainey, "Age-Related Autonomous Aldosteronism," *Circulation* 136, no. 4 (2017): 347–355.

35. F. A. Pauzi and E. A. Azizan, "Functional Characteristic and Significance of Aldosterone-Producing Cell Clusters in Primary Aldosteronism and Age-Related Hypertension," *Frontiers in Endocrinology* 12 (2021): 631848.