Journal of Progressive Medical Sciences
ISSN: 3052-8518
J.P.M.S
DOI: https://doi.org/10.63939/j8gqak63

Vol. 2 , No. 6 , August 2026

RESEARCH Open Access

Alterations in Serum Vanillylmandelic Acid Levels in patients With Hypertension: A Case-Control Study

Hussein Bahaa Abd Alrzaaq[1], Ali Abdulhasan Abdulwahid[2] , Zainab sabah Al-khalidi[3]

[1]Department of Physiology, Faculty of Medicine, Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Najaf, Iraq. Email : hussein.bahaa@jmu.edu.iq.

[2,3]Department of Physiology, College of Medicine, University of Kufa, Najaf, Iraq. alia.abosaybaa@uokufa.edu.iq[2] , zainabs.alkhalidi@uokufa.edu.iq[3]

Corresponding Author : Hussein Bahaa Abd Alrzaaq.

Abstract

Background: The metabolic abnormalities and sympathetic activity are linked to hypertension. Catecholamine metabolism can be inferred indirectly from vanillylmandelic acid (VMA), which is the last metabolite of norepinephrine and epinephrine. However, it is unclear how serum VMA levels relate to antihypertensive medication, age, body weight, and hyperlipidemia in hypertensive individuals. **Aim**: The purpose of this study was to evaluate the connection between serum VMA levels and hyperlipidemia, age, body mass index, and antihypertensive medication in men with hypertension and healthy controls. **Methods:** Ninety men between the ages of thirty and fifty-nine were recruited from Al-Sader Teaching Hospital in Najaf to participate in case-control research. Of them, sixty had hypertension and thirty appeared healthy. The presence or absence of hyperlipidemia, treatment status (newly diagnosed or on antihypertensive medication), and body mass index were used to further categorize the hypertensive subjects. ELISA was used to measure the levels of serum VMA. The t-test and one-way analysis of variance (ANOVA) were used to compare groups; $p < 0.05$ was deemed statistically significant. **Results:** Compared to healthy controls, hypertension patients had considerably higher serum VMA levels ($p <$

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

0.0001). VMA concentrations were highest in hypertensive patients who also had hyperlipidemia, and they increased with age. VMA levels were higher in newly diagnosed individuals than in those on antihypertensive medication. Furthermore, serum VMA levels rose gradually in all BMI groups, with obese individuals showing the highest levels. **Conclusions:** Increased sympathetic activity and altered catecholamine metabolism may be the cause of elevated blood VMA levels in hypertensive men, especially those with hyperlipidemia, obesity, advanced age, and recently diagnosed hypertension. More longitudinal investigations are required to confirm the clinical importance of serum VMA as a possible measure of cardiometabolic risk in hypertension.

Keywords: VMA, Hypertension, Hyperlipidemia, Catecholamines, Obesity, Ageing.

Introduction

Globally, approximately 1.9 billion people are affected by hypertension, which is associated with a high annual mortality rate due to cardiovascular complications, according to the WHO Hypertension Report 2025 [1]. The clinical impact of hypertension is further increased by its frequent association with metabolic disorders, particularly obesity and dyslipidemia, while advancing age may also contribute to increased cardiovascular risk and target-organ damage [2]. The pathophysiology of hypertension is complex and involves interactions among neurogenic, renal, vascular, hormonal, metabolic, and inflammatory mechanisms [3][4]. Among these mechanisms, excessive sympathetic nervous system activity has increasingly been recognized as an important contributor to the development and maintenance of hypertension [5].

Catecholamines are chemical molecules derived from tyrosine that function as both neurotransmitters and hormones. The main catecholamines, dopamine, norepinephrine, and epinephrine, play important roles in the regulation of blood pressure, heart rate, and the body's response to stress [6]. VMA is a final end-product of catecholamine catabolism, particularly of norepinephrine and epinephrine, and is primarily excreted in the urine [7]. High concentrations of catecholamines or their metabolic product, VMA, can cause episodic or sustained hypertension through increased vascular resistance and cardiac activity [8].

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

Furthermore, enhanced sympathetic nervous system activity is associated with essential hypertension and increased catecholamine turnover, which may result in elevated urinary VMA levels [9]. In addition to its role in blood pressure regulation, sympathetic nervous system activity is closely involved in metabolic homeostasis [10]. Increased sympathetic stimulation can affect adipose tissue lipolysis, fatty acid mobilization, and hepatic lipid metabolism, suggesting a potential link between altered catecholaminergic activity and lipid disturbances [11] [12]. Despite the established role of catecholamines in blood pressure regulation, the association between VMA levels and the coexistence of essential hypertension and dyslipidemia in men remains insufficiently characterized. In particular, limited data are available comparing VMA levels between hypertensive men with dyslipidemia and healthy men. Therefore, investigating VMA levels in these groups may help clarify the potential relationship between catecholamine metabolism and cardiovascular risk factors.

Materials and Methods

2.1. Study design and setting: A case-control study was conducted to estimate serum VMA levels in men with hypertension and to compare them with those of an apparently healthy control group.

2.2. Population and groups: A total of 90 men were included in the study, comprising 60 hypertensive patients and 30 healthy controls with normal blood pressure and lipid profiles. Men were included to minimize biological variability and confounding. Hypertension was defined according to established diagnostic criteria as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg, measured on two separate occasions (1).

The participants' ages ranged from 30 to 59 years. The hypertensive participants were subsequently categorized according to the presence or absence of hyperlipidemia. Additional clinical and demographic information was recorded, including treatment status (newly diagnosed or receiving antihypertensive therapy) and body mass index (BMI), categorized as normal weight, overweight, or obesity. Samples were obtained from participants who attended Al-Sader Teaching Hospital in Al-Najaf City.

Inclusion criteria: The study included hypertensive men aged 30–59 years.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

Exclusion criteria: Female participants, Participants who did not meet the defined diagnostic criteria for hypertension in the hypertensive group.

2.3. Clinical and demographic data collection

Clinical information, including age, body mass index (BMI) and treatment, was collected from all participants.

2.4. Specimens and laboratory workflow

Five milliliters of venous blood was collected under aseptic conditions into sterile gel tubes. The samples were allowed to clot and then centrifuged at 3500 rpm for five minutes to obtain serum. The supernatant serum was collected into Eppendorf tubes and stored at −20°C until analysis. Serum VMA levels were measured using a bioassay ELISA kit from (Elabscience Biotechnology Inc., Wuhan, China), according to the manufacturer's standard operating procedures. Participants were classified into two groups based on their lipid status: patients with hypertension alone and those with hypertension accompanied by hyperlipidemia. Hyperlipidemia was determined from documented clinical diagnoses and relevant information recorded in the participants' medical records. Lipid profile parameters were not directly

2.6. Statistical analysis:

Statistical analysis was performed using International Business Machines Statistical Package for the Social Sciences (IBM SPSS), version 26. The t-test was used to assess differences in mean values between two groups, while differences in mean values among the three groups were assessed using one-way analysis of variance (ANOVA). A probability value of $P < 0.05$ was considered statistically significant. Values were expressed as mean ± standard deviation (mean ± SD)

2.7. Ethics:

Ethical approval for the study was obtained from the Ethics Committee of Jaber Ibn Hayyan University of Medical and Pharmaceutical Sciences. Written informed consent was obtained from all participants before their enrollment in the study.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

3. Results

In the present study, the patient group demonstrated a significant increase ($p < 0.0001$) in serum VMA concentration compared with the healthy control group. The mean serum VMA level was 36.22 ± 0.66 in the hypertensive patient group, compared with 4.52 ± 0.17 in the healthy control group (Figure 1).

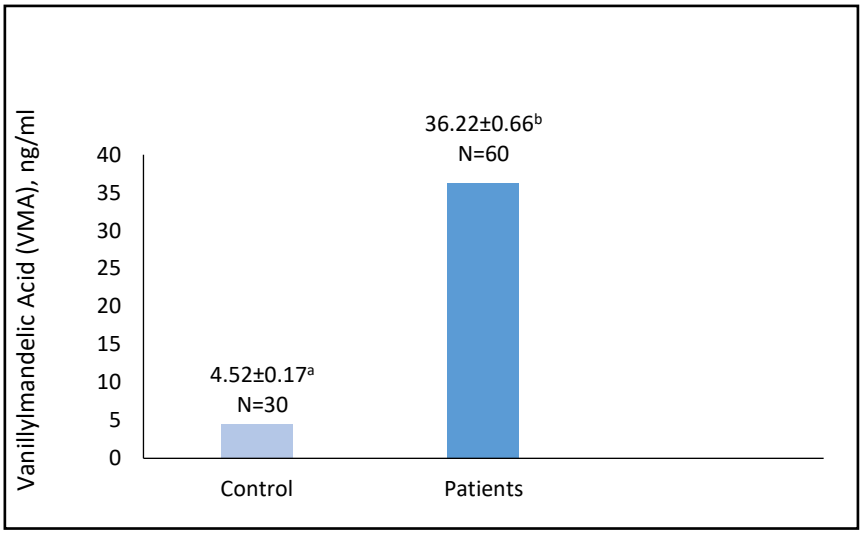

Figure 1: Comparison of serum VMA levels between hypertensive men and control group.

***Different letters indicate significant differences ($p < 0.0001$), while the same letters indicate nonsignificant differences.**

As shown in Figure 2, the present investigation revealed a significant progressive increase ($P<0.05$) in serum VMA concentration across the different age groups. The mean VMA level was lowest among individuals aged 30–39 years (29.94 ± 0.58), followed by those aged 40–49 years (36.96 ± 0.34), and reached the highest level in the 50–59 years age group (41.32 ± 0.25). The VMA concentration was significantly higher in the 40–49 and 50–59 years age groups compared with the 30–39 years group.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

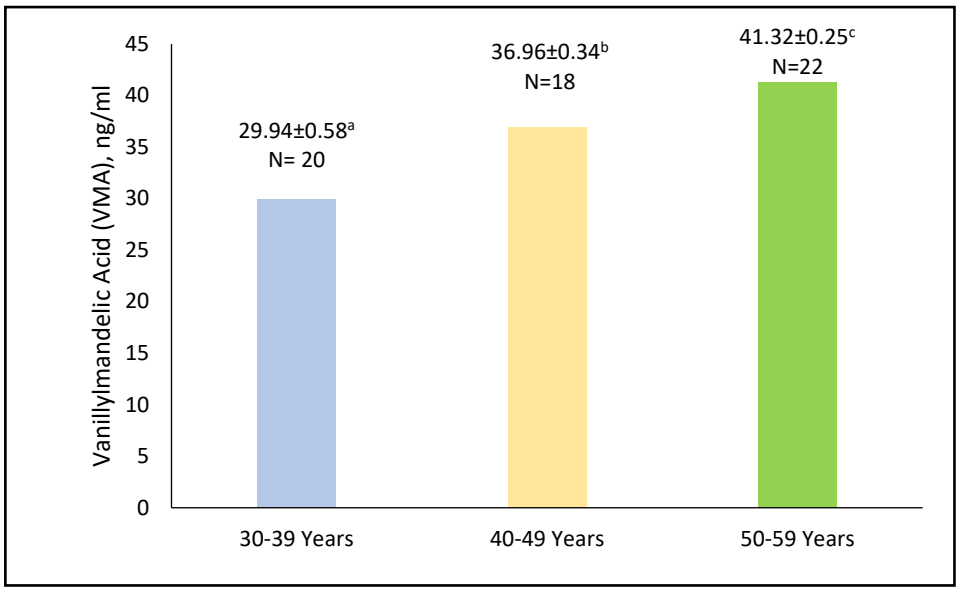

Figure 2: Association between age and serum VMA concentration in men hypertensive.

***Different letters indicate significant differences ($p < 0.0001$), while the same letters indicate nonsignificant differences.**

The results demonstrated a highly significant elevation ($p < 0.0001$) in serum VMA concentrations among patients with hypertension, with the highest levels observed in those with concomitant hyperlipidemia (39.97 ± 0.35), followed by patients with hypertension alone (30.95 ± 0.62), compared with the healthy control group (4.52 ± 0.17). Furthermore, VMA levels were significantly higher ($p < 0.0001$) in hypertensive patients with hyperlipidemia than in those with hypertension alone, as presented in Figure 3.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

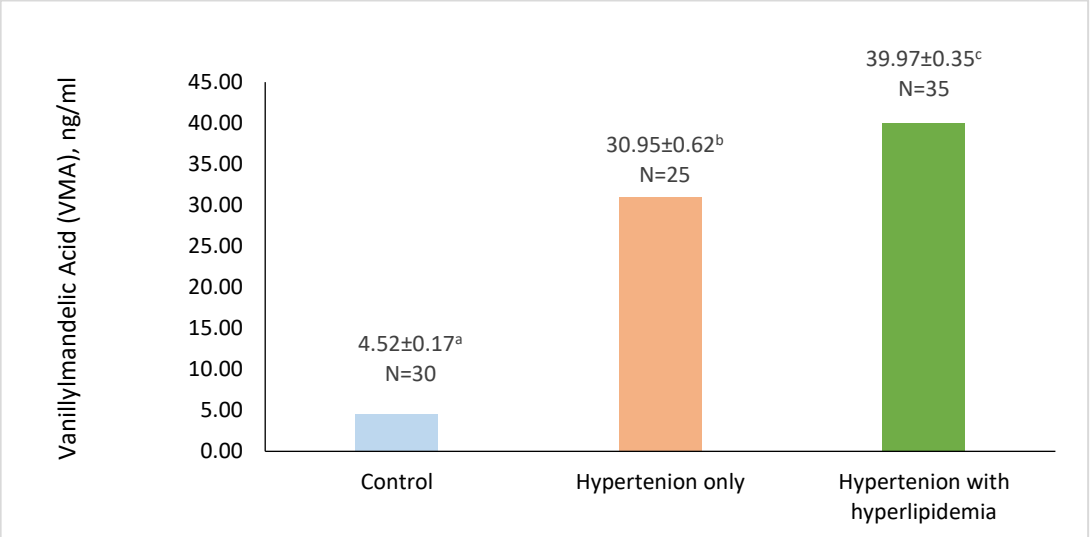

Figure 3: Comparison of serum VMA levels among hypertensive patients with and without hyperlipidemia and control group.

***Different letters indicate significant differences ($p < 0.0001$), while the same letters indicate nonsignificant differences.**

The results shown in Figure 4 demonstrated a highly significant difference ($p < 0.0001$) in serum VMA concentrations between newly diagnosed and treated patients. The mean VMA level was significantly higher in newly diagnosed patients (40.69 ± 0.30) than in treated patients (32.30 ± 0.67).

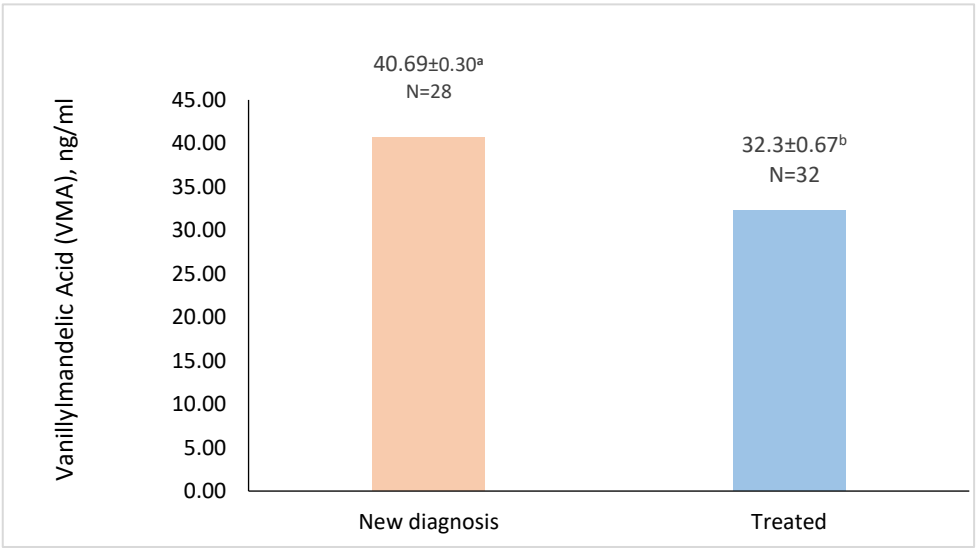

Figure 4: Comparison of serum VMA levels in newly diagnosed and treated men hypertensive.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

***Different letters indicate significant differences ($p < 0.0001$), while the same letters indicate nonsignificant differences.**

The effect of body weight on serum VMA levels is shown in Figure (5). The results revealed a significant increase ($p < 0.0001$) in serum VMA levels in the overweight (35.86±0.40) and obese (40.99±0.28) groups compared with the normal-weight group (28.73±0.44). Furthermore, obese individuals showed a significant increase ($p < 0.0001$) in VMA levels compared with the overweight group.

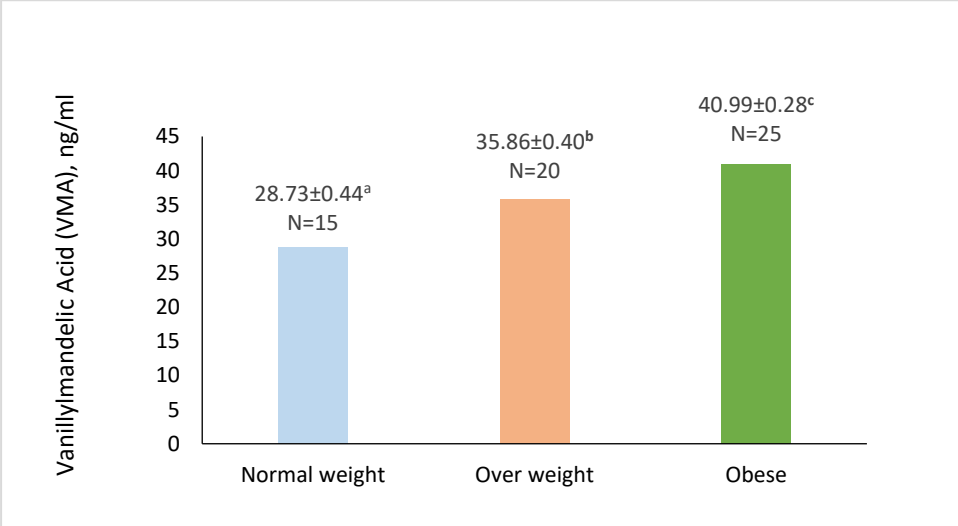

Figure 5: Comparison of serum VMA levels across body weight categories.

***Different letters indicate significant differences ($p < 0.0001$), while the same letters indicate nonsignificant differences.**

Discussion

In the present study, serum VMA concentrations were significantly higher in men with hypertension than in normotensive controls. This finding is consistent with recent metabolomic evidence reporting elevated VMA in hypertensive individuals, supporting its potential role as a marker of altered catecholamine metabolism [13] . VMA is the principal terminal metabolite of norepinephrine and epinephrine, formed through monoamine oxidase (MAO)- and COMT-mediated pathways; therefore, increased circulating VMA may reflect enhanced systemic catecholamine turnover and sympathetic overactivity [14]. This observation is consistent with evidence indicating that sympathetic overactivity is a central mechanism in the initiation and maintenance

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

of essential hypertension, promoting vasoconstriction, sodium retention, renin release, and progressive cardiovascular and renal remodeling [13] [15].

Among hypertensive patients, serum VMA concentrations tended to increase with advancing age. This pattern is biologically plausible, as ageing is associated with alterations in cardiovascular autonomic regulation and increased sympathetic activity. In this regard, Shantsila et al. (2015) reported higher muscle sympathetic nerve activity (MSNA), along with increased catecholamine concentrations and noradrenaline spillover, in older individuals [16]. Similarly, a meta-analysis of healthy adults across different age groups found that older adults had higher blood pressure, reduced heart rate variability and baroreflex function, and a shift in the sympathetic–vagal balance toward greater sympathetic influence on cardiac function. The same analysis also demonstrated increased MSNA and higher plasma noradrenaline concentrations with advancing age [17]. These findings may therefore provide a physiological explanation for the age-related increase in serum VMA observed in the present study.

In the present study, serum VMA levels were significantly higher in hypertensive patients with concomitant hyperlipidemia than in those with hypertension alone. This finding may indicate an association between altered sympathetic activity and metabolic abnormalities in hypertensive individuals. Adipose tissue closely interacts with the adrenal glands in the regulation of metabolism and energy balance. Recent evidence suggests that catecholamines regulate adipose tissue lipolysis and lipid flux through β-adrenergic signaling, while chronic sympathetic overactivity may contribute to dyslipidemia, insulin resistance, and ectopic fat deposition, all of which are closely associated with elevated blood pressure. Under physiological conditions, this bidirectional interaction contributes to metabolic and cardiovascular homeostasis. However, excessive sympathetic or adrenal hormonal activity may disrupt adipose tissue function and contribute to adverse metabolic profiles, visceral adiposity, and hypertension [18] [19]

Newly diagnosed hypertensive patients had higher serum VMA concentrations than patients receiving antihypertensive treatment. Several antihypertensive drugs can reduce sympathetic outflow and its cardiovascular and renal effects through different mechanisms. Centrally acting agents, such as clonidine and methyldopa, decrease sympathetic outflow from the brainstem, which may result in reduced norepinephrine

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

release, heart rate, and peripheral vascular resistance [20]. β-adrenergic blockers act mainly by blocking β_1-adrenergic receptors in the heart and juxtaglomerular cells, leading to a reduction in heart rate, myocardial contractility, and renin secretion, and consequently limiting activation of the renin–angiotensin–aldosterone system. In addition, some lipophilic β-blockers may have modest central sympatholytic effects and can reduce presynaptic norepinephrine release, although the extent of these effects differs between individual β-blocking agents [21]. Consequently, the reduction in sympathetic outflow may decrease catecholamine release and turnover, which may subsequently lead to lower VMA concentrations.

A progressive increase in serum VMA concentration was observed with increasing body weight, with the highest concentrations found among obese patients. Obesity is commonly accompanied by insulin resistance and compensatory hyperinsulinemia, both of which have been associated with increased sympathetic activity. Obesity is also associated with elevated leptin and other adipokines that act centrally to increase sympathetic nerve activity. Leptin stimulates glutamatergic inputs onto pre-sympathetic neurons in the paraventricular nucleus, enhancing efferent sympathetic discharge to the kidney, vasculature, and adipose tissue [22]. Excess visceral adipose tissue may further contribute to sympathetic activation through the release of pro-inflammatory cytokines and other adipose-derived mediators that can alter autonomic regulation [23]. Increased renal sympathetic activity may also play an important role by promoting renal vasoconstriction, sodium retention, and renin release, thereby contributing to activation of the renin–angiotensin–aldosterone system and maintenance of elevated blood pressure [24]. These metabolic, inflammatory, and neurohumoral abnormalities can act together to maintain a state of sympathetic overactivity in individuals with obesity. Persistent sympathetic activation may increase norepinephrine turnover, resulting in greater formation of its terminal metabolite VMA.

Overall, the findings of the present study suggest that hypertension, ageing, obesity, and metabolic abnormalities may represent different clinical contexts associated with altered sympathetic and catecholamine regulation, which could contribute to the observed variation in serum VMA concentrations. The higher VMA concentrations observed across these clinical conditions may therefore reflect differences in catecholamine turnover and metabolism rather than a single underlying

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

mechanism. Taken together, these findings support the potential association between serum VMA and alterations in catecholamine regulation among hypertensive patients. ional studies.

Conclusions:

Men with hypertension had considerably greater serum VMA concentrations than healthy controls, suggesting that essential hypertension may be associated with altered catecholamine metabolism and increased sympathetic activity. Higher VMA levels were also found among patients with hyperlipidemia, older participants, newly diagnosed patients, and those with greater body weight, particularly those classified as obese. These results suggest that serum VMA may be useful as a biochemical marker of the connection between metabolic abnormality, sympathetic activity, and cardiovascular risk in hypertension. Therefore, more prospective studies with larger sample sizes are needed to validate these relationships and determine the clinical value of VMA in managing hypertension and assessing cardiovascular risk.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclaimer

Not declared.

Conflict of interest

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of this study.

Financial support and sponsorship

Nil.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

References

1. World Health Organization. Global report on hypertension 2025: high stakes—turning evidence into action. Geneva: World Health Organization; 2025.
2. Swarup S, Ahmed I, Grigorova Y, Zeltser R. Metabolic syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
3. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003;139(9):761-776.
4. Saxena T, Ali AO, Saxena M. Pathophysiology of essential hypertension: an update. Expert Rev Cardiovasc Ther. 2018;16(12):879-887.
5. Seravalle G, Grassi G. Sympathetic nervous system and hypertension: new evidences. Auton Neurosci. 2022;238:102954.
6. Berends AMA, Eisenhofer G, Fishbein L, van der Horst-Schrivers ANA, Kema IP, Links TP, et al. Intricacies of the molecular machinery of catecholamine biosynthesis and secretion by chromaffin cells of the normal adrenal medulla and in pheochromocytoma and paraganglioma. Cancers (Basel). 2019;11(8):1121.
7. Abd-Allah NM, Hassan FH, Esmat AY, Hammad SA. Age dependence of the levels of plasma norepinephrine, aldosterone, renin activity and urinary vanillylmandelic acid in normal and essential hypertensives. Biol Res. 2004;37(1):95-106.
8. Bima C, Lopez C, Tuli G, Munarin J, Maccario M, De Sanctis L. Prevention and management of hypertensive crises in children with pheochromocytoma and paraganglioma. Front Endocrinol (Lausanne). 2024;15:1460320. doi:10.3389/fendo.2024.1460320.
9. Engberink MF, Brink EJ, van Baak MA, Gans ROB, Navis G, Bakker SJL. Dietary protein, blood pressure and renal function in renal transplant recipients. Nutr Cardiovasc Health Ren Transplant Recipients. 2013;1:41.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

10. Willows JW, Blaszkiewicz M, Townsend KL. The sympathetic innervation of adipose tissues: regulation, functions, and plasticity. Compr Physiol. 2023;13:4985-5021.

11. Clayton TL, Fitch A, Bays HE. Obesity and hypertension: Obesity Medicine Association (OMA) clinical practice statement (CPS) 2023. Obes Pillars. 2023;8:100083.

12. Bigalke JA, Young BE, Cleveland EL, Fadel PJ, Carter JR. Aging and sympathetic transduction to blood pressure in humans: methodological and physiological considerations. Am J Physiol Heart Circ Physiol. 2024;326(1):H148-H157.

13. Parati G, Amir A, Refaat Abd El Meguid K, Sabbour H, Centonze C, Tsabedze N, et al. Managing the patient with hypertension and elevated heart rate in the routine care setting: expert opinion and narrative review. Curr Med Res Opin. 2026;42(6):1093-1111. doi:10.1080/03007995.2026.2682073.

14. Kamal S, Lappin SL. Biochemistry, catecholamine degradation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545235/

15. Grassi G, Drager LF. Sympathetic overactivity, hypertension and cardiovascular disease: state of the art. Curr Med Res Opin. 2024;40(Suppl 1):5-13.

16. Shantsila A, et al. Influence of age on respiratory modulation of muscle sympathetic nerve activity, blood pressure and baroreflex function in humans. Exp Physiol. 2015;100(9):1039-1051.

17. D'Souza AW, Klassen SA, Badrov MB, Lalande S, Shoemaker JK. Aging is associated with enhanced central but impaired peripheral arms of the sympathetic baroreflex arc. J Appl Physiol (1985). 2022;133(2):349-360. doi:10.1152/japplphysiol.00045.2022.

18. Ahmadian M, et al. Fatty acids promote uncoupled respiration via ATP/ADP carriers in white adipocytes. Nat Metab. 2026;8(3):572-586.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin

19. Jiang M, Stifel U, Blüher M, Lefebvre H, Bornstein SR, Bechmann N. Adrenal-adipose tissue crosstalk in health and disease. Eur J Endocrinol. 2025;193(6):R83-R96. doi:10.1093/ejendo/lvaf252.

20. Khalil H, Zeltser R. Antihypertensive medications. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.

21. Park J, Hamanaka A, Park I, Abdelhady HG. Chronic β-blockade and systemic homeostasis: molecular integration of cardiorenal and immune pathways, a narrative review. Biomolecules. 2025;15(12):1653. doi:10.3390/biom15121653.

22. Pongwattanapakin K, Care C, Sitticharoon C, Wilasrusmee KT, Keadkraichaiwat I, Maikaew P, et al. Interplay between key metabolic hormones, metabolic factors, renal function, and heart rate variability in humans with obesity. Sci Rep. 2025;15(1):37873. doi:10.1038/s41598-025-21757-1.

23. Patel M, Braun J, Lambert G, Kameneva T, Keatch C, Lambert E. Central mechanisms in sympathetic nervous dysregulation in obesity. J Neurophysiol. 2023;130:1414-1424. doi:10.1152/jn.00254.2023.

24. Evans LC, Dayton A, Osborn JW. Renal nerves in physiology, pathophysiology and interoception. Nat Rev Nephrol. 2025;21(1):57-69.

Published by DAC Democratic Arabic Center
DAC Democratic Arabic Center GmbH, Berlin