African Journal of
Clinical Medicine and Pharmacy Research

ISSN: 1595-7993

Index: Harvard, Boston, Sydney University, Dimensions, Lens, ResearchGet Scilit, Semantic, Google Scholar, Base etc

https://doi.org/10.58578/AJCMPR.v3i3.11826

Role of Heme Oxygenase-1 (HO-1) in the Pathogenesis of Hypertension among Young Adults: Association with Oxidative Stress, Inflammatory Markers, and Metabolic Profile

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Article Info:

Submitted:	Revised:	Accepted:	Published:
Jul 4, 2026	Aug 1, 2026	Aug 13, 2026	Aug 18, 2026

Abstract

Hypertension in young adults is increasingly recognized as a multifactorial condition associated with oxidative stress, inflammation, endothelial dysfunction, and metabolic imbalance. This study investigated the relationship between heme oxygenase-1 (HO-1) and hypertension among young adults, with particular attention to oxidative stress markers, inflammatory mediators, and metabolic profiles. A case–control study was conducted involving 170 hypertensive and normotensive participants. Sociodemographic and clinical characteristics were assessed alongside blood pressure, body mass index (BMI), body weight, and biochemical markers, including HO-1, vascular endothelial growth factor (VEGF), insulin, nitric oxide (NO), iron, and adenosine deaminase (ADA). Compared with normotensive controls, hypertensive participants had significantly higher systolic and diastolic blood pressure ($p < 0.05$), as well as higher BMI and body weight. HO-1 concentrations were markedly lower in hypertensive participants ($p < 0.00001$), indicating reduced antioxidant capacity.

Conversely, VEGF concentrations were significantly elevated ($p < 0.00001$), consistent with altered vascular regulation. Hypertensive participants also exhibited increased insulin concentrations ($p < 0.01$), reduced NO concentrations ($p < 0.00001$), and elevated iron and ADA concentrations ($p < 0.00001$), collectively reflecting metabolic dysregulation, impaired endothelial function, oxidative stress, and inflammatory activity. Correlation analysis revealed no significant associations between HO-1 and adenosine, ADA, or xanthine oxidase ($p > 0.05$). These findings identify a distinct biochemical profile of young-adult hypertension characterized by reduced HO-1 and NO concentrations alongside increased VEGF, insulin, iron, and ADA concentrations. Although the case–control design does not establish causality, the results highlight HO-1 as a relevant component of the oxidative and vascular alterations associated with hypertension and support further longitudinal and mechanistic investigation.

Keywords: Endothelial Dysfunction; Heme Oxygenase-1; Hypertension; Oxidative Stress; Young Adults

INTRODUCTION

Arterial hypertension has become an increasingly important public health challenge, particularly among young adults, where its early onset is now associated with accelerated vascular aging and long-term cardiovascular complications. The rising prevalence in this age group is concerning because prolonged exposure to elevated blood pressure during early adulthood significantly increases the risk of stroke, myocardial infarction, and chronic kidney disease later in life. Increasing evidence suggests that the development of hypertension in young adults is not merely a consequence of lifestyle factors alone but results from a complex interaction of biological mechanisms involving oxidative stress, chronic low-grade inflammation, and metabolic imbalance (Jacobs et al., 2025).

The pathophysiology of hypertension is strongly influenced by oxidative stress, which occurs when the production of reactive oxygen species overwhelms the body's antioxidant defense systems. This imbalance leads to endothelial dysfunction, impaired nitric oxide bioavailability, and increased vascular stiffness. At the same time, inflammatory processes play a central role in sustaining vascular injury, as pro-inflammatory cytokines contribute to endothelial activation and promote structural remodeling of blood vessels. These processes are further amplified by metabolic disturbances such as obesity, insulin

resistance, and dyslipidemia, all of which are increasingly prevalent among young adults and contribute to early cardiovascular risk (Martínez-Casales et al., 2021; Omar et al., 2021).

Within this interconnected pathological environment, Heme Oxygenase-1 (HO-1) has emerged as a critical endogenous defense mechanism. HO-1 is a stress-inducible enzyme responsible for the degradation of heme into biologically active products, including biliverdin, carbon monoxide, and free iron, which is subsequently sequestered by ferritin. These byproducts exert powerful antioxidant, anti-apoptotic, and anti-inflammatory effects that help maintain vascular homeostasis. By limiting the accumulation of free heme and reducing oxidative burden, HO-1 plays an essential role in protecting endothelial cells from injury and preserving normal vascular function (Aluia et al., 2022; Ryter, 2022).

Despite its protective functions, the HO-1 system may become insufficient or dysregulated under conditions of persistent oxidative and inflammatory stress. In such cases, the compensatory induction of HO-1 may fail to adequately counteract ongoing vascular damage, thereby contributing to endothelial dysfunction and progressive arterial remodeling. This failure of adaptive response is particularly relevant in young individuals exposed to chronic metabolic stressors, where sustained oxidative load may overwhelm endogenous protective pathways and accelerate the transition from subclinical vascular dysfunction to established hypertension (Matraguna et al., 2025; Micieta et al., 2025).

Metabolic abnormalities further complicate this process by interfering with antioxidant defense mechanisms. Conditions such as obesity and insulin resistance have been shown to impair the expression and activity of HO-1, thereby weakening its protective effects against oxidative injury. As metabolic dysfunction worsens, inflammatory signaling pathways become increasingly activated, creating a feedback loop that intensifies vascular injury and promotes sustained elevation of blood pressure. This interplay between metabolic imbalance and impaired antioxidant response highlights the importance of considering metabolic profile parameters when evaluating hypertensive risk in young populations (Backston et al., 2025; Triantafyllidi et al., 2025).

In addition, emerging evidence suggests that integrating oxidative stress markers, inflammatory biomarkers, and metabolic indicators may significantly improve the understanding and prediction of hypertension risk in young adults. Biomarkers such as high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-alpha reflect the inflammatory status of the vascular system, while markers of lipid and glucose metabolism

provide insight into underlying metabolic disturbances. Together, these parameters create a more comprehensive representation of the physiological environment in which hypertension develops (Gaybiyev & Bobojonov, 2025; Latif, 2025).

HO-1 occupies a central position within this biomarker network because of its ability to modulate both oxidative and inflammatory pathways simultaneously. By degrading pro-oxidant heme molecules, HO-1 reduces reactive oxygen species formation and suppresses downstream inflammatory signaling cascades. This dual action helps to preserve endothelial integrity and maintain vascular tone under conditions of physiological stress. However, when HO-1 response is inadequate or suppressed, the balance shifts toward a pro-oxidant and pro-inflammatory state, thereby increasing susceptibility to hypertension and vascular dysfunction (Akhigbe & Ajayi, 2021; Wu et al., 2022).

Given the increasing burden of early-onset hypertension, particularly in young adults, there is a growing need to identify key regulatory mechanisms that determine susceptibility to vascular dysfunction. Understanding the role of HO-1 in relation to oxidative stress, inflammatory mediators, and metabolic alterations may provide valuable insight into the biological basis of hypertension development. Such knowledge could also support the identification of early diagnostic biomarkers and potential therapeutic targets aimed at preventing disease progression.

Therefore, this study investigates the role of Heme Oxygenase-1 in the pathogenesis of hypertension among young adults and examines its association with oxidative stress markers, inflammatory mediators, and metabolic profile parameters, with the aim of improving early detection and understanding of hypertension in this vulnerable population.

METHODS

Study Design

This study adopted a hospital-based cross-sectional analytical design to investigate the role of Heme Oxygenase-1 (HO-1) in the pathogenesis of hypertension among young adults and its association with oxidative stress, inflammatory markers, and metabolic profile.

Study Area

The study was conducted in Ekiti State, Southwestern Nigeria, specifically in the cardiology and medical outpatient units/department of ABUAD Multisystem Hospital, Ado-Ekiti; Federal Teaching Hospital, Ido-Ekiti; and Ekiti State University Teaching Hospital, Ado-Ekiti.

Study Population

The study population comprised young adults aged 18–40 years, including:

- Diagnosed hypertensive patients (cases)
- Apparently healthy normotensive individuals (controls)

Inclusion Criteria

Participants included in the study were:

- Young adults aged 18–40 years
- Confirmed cases of primary hypertension (for case group)
- Apparently healthy individuals with normal blood pressure (for control group)
- Individuals who gave informed consent

Exclusion Criteria

The following participants were excluded:

- Pregnant women
- Individuals with secondary hypertension
- Patients with chronic kidney disease, liver disease, or autoimmune disorders
- Individuals who had used antioxidant or anti-inflammatory drugs within the preceding three months

Sample Size Determination

The sample size was determined using an appropriate statistical formula for comparing two independent groups, based on prevalence estimates from previous related studies on oxidative stress and hypertension among young adults. An additional 10% was included to compensate for possible non-response or incomplete data.

Sampling Technique

A systematic random sampling technique was used to recruit eligible participants from the outpatient clinics of the selected hospitals until the required sample size was achieved. Controls were matched with cases based on age and sex where applicable.

Data Collection Procedures

Socio-demographic and Clinical Data

Data were collected using a structured questionnaire to obtain information on age, sex, lifestyle factors (dietary habits, smoking, alcohol consumption, and physical activity), and medical history.

Blood Pressure Measurement

Blood pressure was measured using a calibrated automated sphygmomanometer. Measurements were taken after 5–10 minutes of rest in a seated position, and the average of two to three readings was recorded.

Laboratory Analysis

Blood Sample Collection

Venous blood samples (5–10 mL) were collected aseptically after an overnight fast of 8–12 hours. Samples were centrifuged, and the serum/plasma obtained was stored at −20°C until analysis.

Biochemical Parameters

a. Heme Oxygenase-1 (HO-1)

Serum HO-1 levels were determined using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions.

b. Oxidative Stress Markers

- Malondialdehyde (MDA) as a marker of lipid peroxidation
- Superoxide dismutase (SOD) activity
- Glutathione peroxidase (GPx) levels

c. Inflammatory Markers

- High-sensitivity C-reactive protein (hs-CRP)
- Interleukin-6 (IL-6)
- Tumor necrosis factor-alpha (TNF-α)

d. Metabolic Profile

- Fasting blood glucose
- Total cholesterol, HDL-C, LDL-C, and triglycerides

Data Analysis

Data were analyzed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages.

- Independent t-test was used to compare means between hypertensive and control groups.
- Chi-square test was used for categorical variables.
- Pearson or Spearman correlation analysis assessed relationships between HO-1, oxidative stress, inflammatory markers, and metabolic parameters.
- Multivariate regression analysis was performed to identify independent predictors of hypertension.

A p-value of < 0.05 was considered statistically significant.

Ethical Clearance

Ethical approval was gotten from the ethics and research committee of Afe Babalola University Ado Ekiti (ABUADHRE/06/01/2025/535), Ekiti State University Teaching Hospital (EKSUTH/A67/2023/11/005), Federal Teaching Hospital, Ido-Ekiti (Protocol number: ERC/2024/01/15/1066B) and ABUAD Multisystem Hospital (Reference: AMSH/REC/BOO/184), Ado-Ekiti, respectively.

Informed consent was obtained from all participants. All information were kept confidential.

RESULTS AND DISCUSSION

Table 1: Sociodemographic characteristics of the study population

Variables	Hypertensives	Control	Statistical indices
Sex			
Male	61 (65.4)	40 (66.6)	χ^2=2.024; p=0.191[β]
Female	49 (44.6)	20 (33.3)	
Educational Status			
No formal Education	2 (1.3)	0 (0.0)	LR=3.26; p=0.354[γ]
Primary	3 (2.6)	1 (1.7)	
Secondary	8 (6.5)	2 (3.3)	
Tertiary	97 (88.2)	57(95.0)	
Marital Status			
Single	48 (43.64)	41 (68.33)	LR=10.2064;
Married	61 (55.45)	19 (31.67)	p= 0.006[γ]
Divorced	1 (0.9)	0 (0.00)	

The findings in Table 1 further emphasize that traditional demographic variables such as sex and educational status did not significantly differentiate hypertensive from normotensive young adults, suggesting that early-onset hypertension in this cohort is less influenced by conventional socioeconomic markers and more by underlying metabolic and psychosocial mechanisms. The absence of a significant association with sex (p = 0.191) and educational status (p = 0.354) indicates that biological dysregulation, particularly pathways involving oxidative stress, inflammation, and impaired endothelial protection, may play a more central role in disease development than demographic characteristics.

In contrast, the significant association observed with marital status (p = 0.006) highlights the potential influence of psychosocial stress and lifestyle restructuring on blood pressure regulation. Marital transitions and responsibilities may introduce chronic stressors that activate inflammatory cascades and oxidative pathways, thereby contributing to vascular dysfunction. This aligns with evidence suggesting that psychosocial stressors linked to marital status can trigger inflammatory responses that exacerbate hypertension progression in young adults (Jalo et al., 2025). Such stress-mediated mechanisms may also

interact with metabolic disturbances, reinforcing endothelial injury and disrupting normal vascular homeostasis.

Furthermore, emerging literature indicates that early-onset hypertension is predominantly driven by metabolic dysfunction rather than classical demographic factors, reinforcing the importance of focusing on oxidative stress biomarkers and systemic inflammation in risk assessment (Howaidy et al., 2022; Suh et al., 2021). Lifestyle-related changes associated with marital status, including dietary patterns, reduced physical activity, and weight gain, may further intensify metabolic imbalance and inflammatory activation (Chong et al., 2023; Shin et al., 2023). These interconnected pathways highlight the need to consider psychosocial determinants alongside biological markers in understanding hypertension etiology.

These findings support a multifactorial model in which psychosocial stressors, metabolic dysregulation, and oxidative imbalance converge to influence hypertension development, consistent with evidence that effective clinical management should extend beyond demographic profiling to include inflammatory and metabolic biomarkers (Baoum et al., 2023; Meher et al., 2023; Naik et al., 2025).

Table 2: Clinical characteristics of all the study population

Variables	Hypertensives	Control	Statistical indices
Age(years)	34(23-42)	29(25-38)	z = 1.234; 0.217#
Pulse rate	83 (72-94)	79.5 (72-87)	z = 1.601; 0.1094#
SBP (mmHg)	146 (±18.7)	121.15(±11.22)	t = 9.29; <0.01κ
DBP (mmHg)	91 (±14.02)	71.63 (±9.35)	t = 9.61; <0.01κ
Weight (kg)	84.45 (68.2-94.4)	71.6 (62.5-81.5)	z = 3.328; <0.01#
Height (cm)	168.25 (162.5-175)	173 (168 -179.5)	z = -2.682; <0.01#
BMI (kg/m^2)	28.85 (24.8-32.65)	23.98 (20.9-27.6)	z = 4.647; <0.01#

The significantly higher BMI and body weight observed among hypertensive participants align with evidence that excess adiposity is a primary driver of elevated blood pressure through mechanisms such as insulin resistance, chronic low-grade inflammation,

and activation of the sympathetic nervous system (Martín et al., 2021; Sena et al., 2022). These pathways collectively contribute to endothelial dysfunction and increased peripheral vascular resistance, which are key features of hypertension pathophysiology.

The absence of significant differences in age and pulse rate between hypertensive and control groups further reinforces the idea that traditional demographic and basic physiological markers may be less predictive of hypertension risk in this population. Instead, metabolic indicators appear to play a more dominant role. This observation is consistent with findings that BMI is a stronger predictor of hypertension than age in many contemporary populations, particularly in early-onset or community-based hypertension cohorts (Adegoke et al., 2021; Zuo et al., 2025).

Consequently, BMI emerges as a clinically valuable screening tool for identifying individuals at risk of hypertension, independent of age-related vascular changes (Fabi et al., 2023). Early identification of elevated BMI is especially important because progressive weight gain exacerbates hemodynamic load and disrupts normal blood pressure regulation over time (Alvi et al., 2024). Supporting this, obesity-related indices have been repeatedly identified as strong predictors of poor blood pressure control and cardiovascular complications (Kirema et al., 2025).

The significant reduction in height observed among hypertensive participants may reflect broader developmental and socioeconomic influences. Early-life nutritional deficits and disadvantaged socioeconomic conditions have been associated with altered growth trajectories and increased cardiovascular vulnerability in adulthood. This suggests that height differences may serve as a proxy marker for early developmental risk factors contributing to later hypertension susceptibility.

These findings emphasize that hypertension in this cohort is primarily metabolically driven rather than demographically determined. This is further supported by evidence advocating for targeted public health strategies focusing on weight reduction, dietary modification, and physical activity as primary preventive measures (Wang et al., 2023; Wu et al., 2022). Moreover, incorporating more refined anthropometric indicators such as waist-to-height ratio may improve risk stratification, as emerging evidence suggests superior predictive capacity over BMI alone in identifying visceral adiposity and cardiovascular risk (Taurio et al., 2023).

Future research should prioritize longitudinal designs to determine whether early metabolic changes can predict progression to overt hypertension, particularly using dynamic anthropometric markers (Corsi & Agbaje, 2025; Josipović et al., 2025). This is crucial because visceral fat accumulation is closely linked to renal sympathetic overactivity and increased systemic vascular resistance, which are central mechanisms in sustained hypertension (Abolhasani et al., 2021; Oseni et al., 2023).

The integration of metabolic and anthropometric risk assessment provides a more comprehensive understanding of hypertension pathogenesis than reliance on traditional demographic variables alone. This multifactorial perspective supports clinical and public health strategies that prioritize early metabolic intervention to reduce long-term cardiovascular burden (Gui et al., 2024; Zhang et al., 2023; Bhardwaj & Passey, 2025; Cai et al., 2023; Tan et al., 2023).

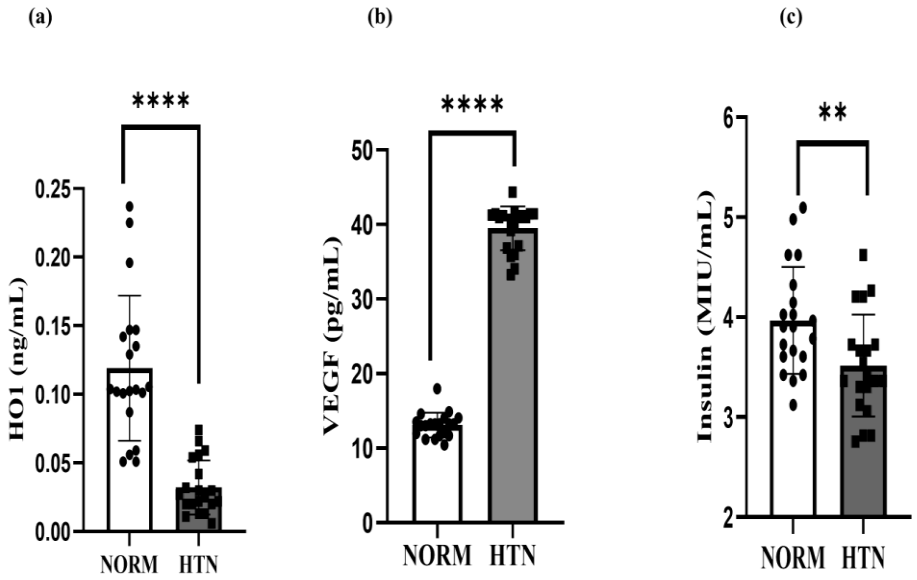

Figure 1: Shows HO1 (a), VEGF (b) and Insulin (c) in normotensive and HTN. Values are represented as median and analysed by Kruskal-Wallis. *P<0.05 vs. NORM. NORM (Normotensive); HTN (Hypertension); HO-1 (Heme Oxygenase-1); VEGF (Vascular endothelial growth factor).

The findings in fig 1 revealed that hypertensive participants exhibited significantly lower HO-1 levels, significantly higher vascular endothelial growth factor (VEGF) levels, and altered insulin concentrations compared with normotensive controls. These observations suggest that oxidative stress, endothelial dysfunction, and metabolic

disturbances play important roles in the development and progression of hypertension in young adults.

The marked reduction in HO-1 levels observed among hypertensive individuals ($P < 0.00001$) indicates impaired antioxidant and cytoprotective mechanisms. HO-1 is a stress-inducible enzyme that catalyzes the degradation of heme into biliverdin, carbon monoxide, and free iron, all of which exert antioxidant, anti-inflammatory, and vasodilatory effects. Reduced HO-1 expression weakens the body's ability to neutralize reactive oxygen species (ROS), thereby promoting oxidative stress and endothelial injury. Increased oxidative stress is a well-established contributor to hypertension through mechanisms involving reduced nitric oxide bioavailability, enhanced vascular smooth muscle contraction, and increased peripheral vascular resistance. Therefore, the significantly lower HO-1 levels observed in hypertensive participants support the hypothesis that impaired antioxidant defense plays a central role in hypertension pathogenesis among young adults.

The study also demonstrated significantly elevated VEGF levels in hypertensive subjects ($P < 0.00001$). VEGF is a potent angiogenic factor released in response to hypoxia, inflammation, and endothelial injury. Elevated VEGF levels may initially represent a compensatory response aimed at restoring vascular integrity following oxidative damage. However, sustained overexpression of VEGF can become maladaptive, promoting pathological angiogenesis, increased vascular permeability, and vascular remodeling, all of which are characteristic features of hypertension. The inverse relationship between HO-1 and VEGF suggests that reduced antioxidant protection may trigger endothelial stress signals that upregulate VEGF as a compensatory but potentially harmful vascular response. This aligns with evidence showing that VEGF elevation is associated with endothelial activation and progressive cardiovascular remodeling in hypertensive conditions.

Regarding metabolic status, insulin levels differed significantly between hypertensive and normotensive participants ($P < 0.01$), indicating metabolic dysregulation. Hypertension is frequently associated with insulin resistance, compensatory hyperinsulinemia, obesity, and impaired glucose handling. Insulin resistance contributes to hypertension through multiple mechanisms, including sympathetic nervous system activation, renal sodium retention, and vascular smooth muscle proliferation. Importantly, insulin resistance also reduces nitric oxide bioavailability and enhances systemic oxidative stress, thereby worsening endothelial dysfunction. These mechanisms suggest that

metabolic disturbances may act synergistically with oxidative stress and inflammation to accelerate vascular injury in young adults.

Collectively, these findings highlight a complex and interrelated network linking oxidative stress, vascular dysfunction, and metabolic abnormalities in hypertension. Reduced HO-1 expression weakens antioxidant defenses, facilitating oxidative damage and endothelial injury. Consequently, VEGF is upregulated in response to vascular stress, contributing to remodeling and maladaptive angiogenesis. At the same time, metabolic disturbances reflected by altered insulin signaling further exacerbate vascular dysfunction by promoting oxidative stress and impairing endothelial relaxation. These interconnected processes ultimately contribute to sustained elevation of blood pressure and increased cardiovascular risk.

The study provides strong evidence that decreased HO-1 expression is closely associated with increased oxidative stress, elevated VEGF-mediated vascular responses, and metabolic dysregulation, thereby contributing significantly to the pathogenesis of hypertension among young adults. Furthermore, the observed insulin abnormalities may foster a pro-inflammatory and pro-oxidative environment that intensifies vascular injury. Insulin resistance has been positively associated with increased peripheral vascular resistance in young populations, suggesting a direct link between early metabolic dysfunction and cardiovascular risk development (Cao et al., 2010; Micieta et al., 2025). These findings support a reciprocal and self-reinforcing relationship in which oxidative stress and insulin resistance synergistically drive endothelial dysfunction and vascular impairment (Park et al., 2009; Rademacher et al., 2009; Tsai et al., 2024).

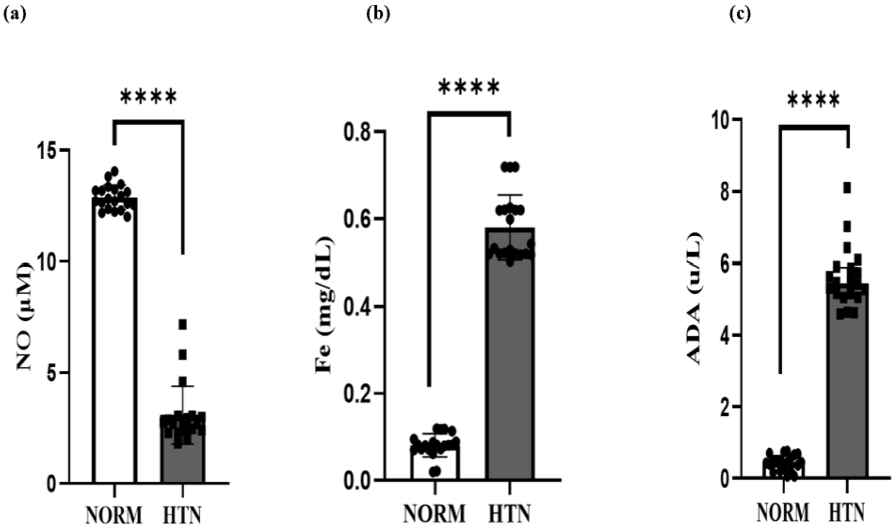

Figure 2: Shows NO (a), Fe (b) and ADA (c) in normotensive and HTN. Values are represented as median and analysed by Kruskal-Wallis. *P<0.05 vs. NORM. NORM (Normotensive); HTN (Hypertension); NO (Nitric oxide); Fe (Iron); ADA (Adenosine deaminase).

The results in fig 2 above demonstrated that hypertensive participants had significantly lower NO levels and significantly higher Fe and ADA concentrations compared with normotensive controls ($P < 0.00001$ for all parameters). These findings provide additional evidence that hypertension is characterized by impaired vascular homeostasis, enhanced oxidative stress, and chronic inflammatory activation.

The significant reduction in nitric oxide levels observed among hypertensive individuals suggests severe endothelial dysfunction. Nitric oxide is a key vasodilatory molecule synthesized by endothelial nitric oxide synthase (eNOS) and is essential for maintaining vascular tone, inhibiting platelet aggregation, and preventing vascular smooth muscle proliferation. Reduced NO bioavailability is a hallmark of hypertension and contributes directly to increased vascular resistance and elevated blood pressure. In the context of the present study, the decrease in NO may be linked to reduced HO-1 activity. HO-1-derived products, particularly carbon monoxide and bilirubin, exert strong antioxidant effects that preserve NO bioavailability by limiting oxidative degradation. Therefore, diminished HO-1 expression may enhance reactive oxygen species (ROS) accumulation, leading to excessive NO scavenging and endothelial dysfunction. This mechanism supports the hypothesis that reduced HO-1 expression contributes to hypertension through oxidative stress–mediated vascular impairment.

The significantly elevated iron levels in hypertensive participants further support the role of oxidative stress in disease progression. Although iron is an essential element for physiological processes, excess free iron can catalyze the Fenton reaction, generating highly reactive hydroxyl radicals that intensify lipid peroxidation, endothelial injury, and vascular inflammation. Importantly, circulating free iron not only promotes oxidative stress but can also interfere with the catalytic efficiency of HO-1, thereby impairing its ability to effectively detoxify pro-oxidant heme and maintain cellular redox balance. The coexistence of reduced HO-1 activity and elevated iron levels observed in this study therefore reflects a disrupted iron–antioxidant equilibrium, which accelerates oxidative vascular damage and contributes to hypertension development.

Another important finding was the significant elevation of adenosine deaminase (ADA) levels among hypertensive subjects. ADA is a key enzyme in purine metabolism and immune regulation that catalyzes the conversion of adenosine to inosine. Elevated ADA activity reflects increased T-lymphocyte activation and chronic immune stimulation, both of which are closely linked to systemic inflammation. Since adenosine exerts vasodilatory and anti-inflammatory effects, increased ADA activity reduces its protective availability, thereby worsening endothelial dysfunction. The elevated ADA levels observed in this study therefore indicate a persistent inflammatory state that likely antagonizes the protective effects of the HO-1/CO/bilirubin axis. In addition, chronic inflammation may suppress or overwhelm the compensatory antioxidant responses mediated by HO-1, further contributing to vascular injury.

Furthermore, the observed interplay between reduced HO-1 activity, elevated iron, and increased ADA levels suggests a self-perpetuating cycle of oxidative stress and inflammation. Excess iron enhances ROS production, which in turn depletes NO and damages endothelial cells. Concurrently, inflammatory activation reflected by elevated ADA exacerbates vascular dysfunction and interferes with protective antioxidant pathways. These processes collectively amplify endothelial injury and impair vascular homeostasis.

When considered alongside the earlier findings of reduced HO-1 and NO levels and elevated VEGF, iron, and ADA concentrations, these results provide a comprehensive explanation of hypertension pathogenesis in young adults. Reduced HO-1 expression disrupts antioxidant defense mechanisms and iron regulation, while increased oxidative stress diminishes NO bioavailability, leading to endothelial dysfunction. Simultaneously, inflammatory activation (ADA elevation) and vascular remodeling responses (VEGF elevation) further aggravate vascular damage and contribute to sustained hypertension.

The findings strengthen the evidence that HO-1 plays a central protective role in vascular homeostasis. Its reduction is associated with increased oxidative stress, iron-mediated radical formation, decreased nitric oxide availability, and enhanced inflammatory activity, all of which contribute to the development and progression of hypertension in young adults. These results support therapeutic strategies aimed at enhancing HO-1 activity, restoring endothelial NO signaling, reducing iron-driven oxidative stress, and suppressing chronic inflammation as potential approaches for managing hypertension and

preventing cardiovascular complications (Martínez-Casales et al., 2021; Jacobs et al., 2025; Aluia et al., 2025; Viana et al., 2025).

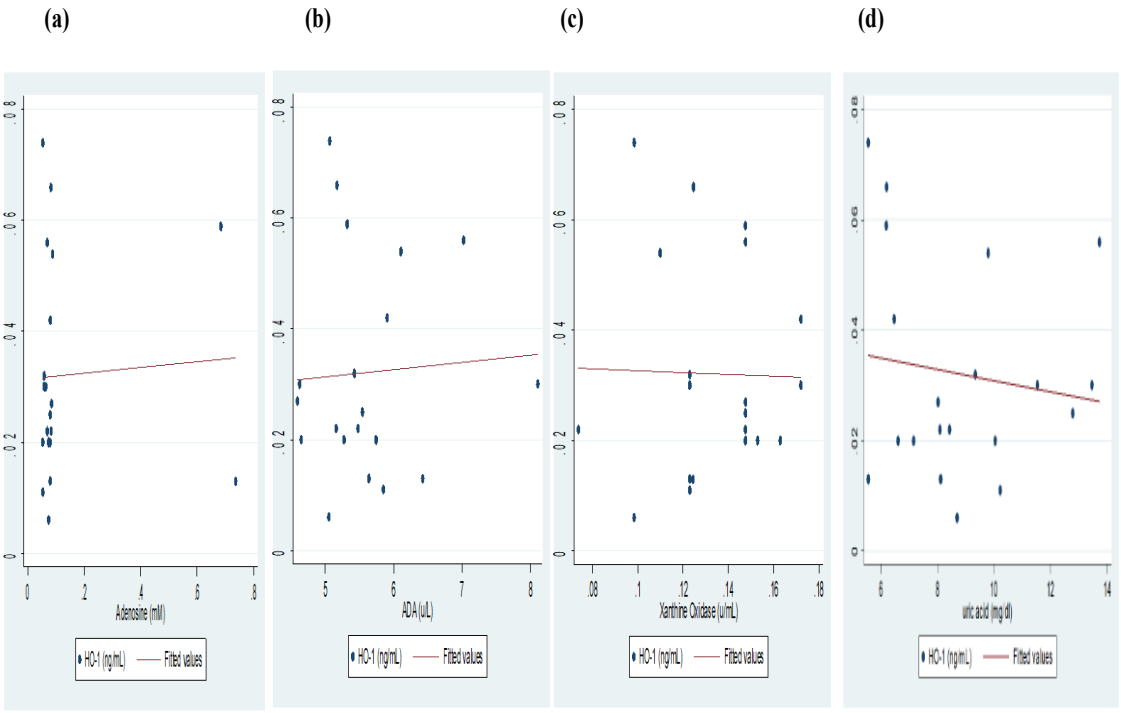

Figure 3**.** Shows a correlation between Adenosine (a), ADA (b), Xanthine Oxidase (c), Uric acid (d) and HO-1 in HTN. Adenosine (r=0.0779, p= 0.744) [#]; ADA (r= 0.012, p= 0.959) [#]; Fe (r = 0.048, p = 0.839); Uric acid ((r = -0.126, p= 0.595); ADA (Adenosine deaminase); HTN (Hypertension); HO-1 (Heme Oxygenase-1). [#] Spearman correlation.

The present study evaluated the relationship between heme oxygenase-1 (HO-1) and key purine metabolism biomarkers, including adenosine, adenosine deaminase (ADA), xanthine oxidase (XO), and uric acid, among hypertensive young adults. HO-1 is recognized as an important cytoprotective enzyme that mitigates oxidative stress and inflammation, both of which are central to the pathogenesis of hypertension. Understanding the association between HO-1 and these metabolic markers provides deeper insight into the complex and multifactorial mechanisms underlying hypertensive vascular injury.

The correlation analysis revealed a weak positive but statistically insignificant relationship between HO-1 and adenosine (r = 0.0779, p = 0.744). Adenosine is an

endogenous nucleoside with potent vasodilatory, anti-inflammatory, and cardioprotective effects. Under conditions of hypoxia, oxidative stress, or vascular injury, adenosine production generally increases as a compensatory mechanism to maintain vascular homeostasis. Although both adenosine and HO-1 possess protective properties against oxidative damage, the absence of a significant association suggests that their regulatory pathways may operate independently in hypertensive individuals. This finding indicates that alterations in HO-1 expression are not directly reflected by circulating adenosine levels and that adenosine metabolism is likely regulated by additional enzymatic and inflammatory factors during hypertension.

Similarly, the relationship between HO-1 and ADA was extremely weak and statistically insignificant ($r = 0.012$, $p = 0.959$). ADA plays a crucial role in purine metabolism and immune regulation by catalyzing the deamination of adenosine to inosine. Elevated ADA activity is commonly regarded as a marker of inflammation and immune activation. Although increased ADA levels were observed in hypertensive participants in the present study, the lack of a significant correlation with HO-1 suggests that inflammatory processes mediated through adenosine degradation do not directly influence HO-1 expression. This supports the concept that HO-1 and ADA act through separate biological pathways, with HO-1 primarily involved in antioxidant defense and cytoprotection, while ADA reflects immune activation and purine catabolism.

The correlation between HO-1 and xanthine oxidase was also weak and statistically insignificant ($r = 0.048$, $p = 0.839$). Xanthine oxidase is a major enzymatic source of reactive oxygen species (ROS) during purine metabolism and is strongly implicated in endothelial dysfunction and hypertension. Despite the expectation of an inverse relationship due to the antioxidant role of HO-1, the absence of a significant correlation suggests that HO-1 expression does not directly mirror XO activity in this population. This indicates that oxidative stress in hypertension is driven by multiple parallel pathways, and HO-1 represents only one component of a broader antioxidant defense system rather than a direct regulator of XO-mediated ROS production.

Furthermore, the relationship between HO-1 and uric acid demonstrated a weak negative correlation that was also statistically insignificant ($r = –0.126$, $p = 0.595$). Uric acid, the final product of purine metabolism, has been extensively associated with hypertension, endothelial dysfunction, and oxidative stress. Although the negative trend

suggests that reduced HO-1 levels may be associated with increased uric acid concentrations, the lack of statistical significance indicates that this association is not strong in the present cohort.

The findings indicate that HO-1 does not exhibit significant correlations with adenosine, ADA, xanthine oxidase, or uric acid among hypertensive young adults. Despite the well-established involvement of these biomarkers in oxidative stress, inflammation, endothelial dysfunction, and purine metabolism, their variations appear to be independent of HO-1 expression in this study population. This suggests that the protective effects of HO-1 in hypertension may be mediated through alternative mechanisms such as carbon monoxide–induced vasodilation, bilirubin-associated antioxidant activity, nitric oxide preservation, and iron homeostasis regulation rather than direct modulation of purine metabolic pathways.

Moreover, the lack of significant association with xanthine oxidase activity and uric acid concentrations further implies that HO-1's vascular protective effects may operate through distinct signaling mechanisms, including carbon monoxide–mediated vasodilation and bilirubin-driven antioxidant activity, rather than direct involvement in purine metabolism regulation (Dirajlal-Fargo et al., 2021). Consequently, HO-1 may exert its cytoprotective influence more prominently through modulation of renal sodium handling and signaling pathways such as Na^+/K^+-ATPase activity rather than systemic purine degradation pathways (Cai et al., 2025). This mechanistic divergence highlights that although both HO-1 and purine-related enzymes respond to hypertensive stress, their functional roles in vascular protection appear largely uncoupled (Aluia et al., 2022). Therefore, future longitudinal studies are required to determine whether these biomarkers represent independent compensatory responses or are regulated by distinct upstream physiological triggers activated by different vascular stressors (Borghi et al., 2022; Miah et al., 2022).

CONCLUSION

This study demonstrates that hypertension in young adults is strongly associated with reduced HO-1 expression, increased oxidative stress, and significant endothelial dysfunction. The marked elevation of VEGF, iron, ADA, and insulin levels, alongside reduced nitric oxide, highlights a complex interaction between vascular injury,

inflammation, and metabolic disturbance in hypertensive pathology. The absence of significant correlations between HO-1 and other purine metabolism markers suggests that HO-1 may act independently rather than within a tightly linked enzymatic network in this condition. These findings indicate that HO-1 deficiency, coupled with oxidative and metabolic imbalance, plays a central role in the development and progression of hypertension, emphasizing its potential as a therapeutic and diagnostic biomarker in early-onset hypertension.

Acknowledgement

Funding – This study was supported by TETFund through the institution-based research (IBR) grant (TETF/DR&D/CE/UNI/AZARE/IBR/2023/VOL.I) from the Federal University of Health Sciences, Azare.

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