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Integrated Dynamics of Oxidative Stress, Atherogenic Lipids, and Vascular Inflammation in Early-Stage Hypertensive Patients

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Abstract

Background: Hypertension (HTN) in young adults is increasingly prevalent and frequently accompanied by subclinical metabolic and vascular abnormalities that predispose affected individuals to future cardiovascular disease. Oxidative stress, dyslipidemia, endothelial dysfunction, and low-grade inflammation are central to early hypertensive (HTN) pathophysiology, yet their interactions remain incompletely characterized. Methods: This cross-sectional case-control study included 110 HTN and 60 normotensive (NORM) participants aged 20-45 years recruited from tertiary hospitals in Ekiti State, Nigeria. Sociodemographic, anthropometric, and clinical data were collected. Circulating biomarkers of oxidative stress, antioxidant defense, endothelial function, inflammation, purine metabolism, insulin regulation, and lipid profile were measured using colorimetric and ELISA methods. Appropriate parametric and non-parametric statistical analyses were applied. Results: HTN participants exhibited significantly higher systolic and diastolic blood pressure (DBP), body weight, and body mass index (BMI) compared with controls ($P<0.01$). They showed marked oxidative stress and endothelial dysfunction, evidenced by reduced heme oxygenase-1 (HO-1), nuclear factor erythroid 2-related factor 2 (Nrf2), nitric oxide (NO), and endothelial nitric oxide synthase (eNOS), alongside elevated xanthine oxidase (XO), uric acid, iron, adenosine deaminase (ADA), vascular endothelial growth factor (VEGF), and plasminogen activator inhibitor-1 ($P<0.00001$). An atherogenic lipid profile was observed, including higher total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and TC/HDL ratio, with reduced high-density lipoprotein (HDL) ($P<0.00001$). Circulating insulin levels were higher in HTN participants compared with NORM controls, consistent with insulin resistance. Correlation analyses revealed predominantly weak and non-significant associations between HO-1 and individual biomarkers. Conclusions: Early-stage HTN in young adults is characterized by coexisting oxidative stress, dyslipidemia, endothelial dysfunction, elevated insulin, metabolic dysregulation, and vascular inflammation, underscoring the need for early, integrative preventive strategies.

Keywords

Hypertension, Adolescents, Metabolic profile, Dyslipidemia, Inflammatory markers

Article History

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1. Introduction

Hypertension (HTN), defined according to established international guidelines as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, is a major global health concern and a significant independent risk factor for cardiovascular diseases and cognitive impairment [1,2]. Early-stage HTN in this study refers to individuals with mildly elevated or recently diagnosed HTN, including those receiving antihypertensive therapy, without known target-organ damage based on clinical history. Its prevalence has risen dramatically over the past three decades, doubling from 650 million in 1990 to approximately 1.3 billion adults in 2019, largely due to urbanization, dietary shifts, sedentary lifestyles, and the increasing aging population [3]. HTN is often asymptomatic until advanced stages, earning it the label "silent killer," and is currently responsible for 12.8% of global deaths, amounting to approximately 7.5 million annually [4]. Even modest elevations in blood pressure significantly increase cardiovascular risk; for example, a 20 mmHg rise in systolic pressure nearly doubles the likelihood of developing cardiovascular disease [5].

Despite its high prevalence, awareness, treatment, and control of HTN remain suboptimal worldwide. Only 54% of HTN adults are diagnosed, 42% receive treatment, and merely 21% achieve adequate blood pressure control [6]. Moreover, approximately one in four patients exhibits resistance to standard pharmacological therapies, suggesting that additional pathophysiological mechanisms, including oxidative stress and inflammatory signaling, contribute to disease development and progression beyond hemodynamic factors alone [7,8].

HTN's pathophysiology is multifactorial. Genetic predisposition, environmental influences, and lifestyle factors such as poor diet, physical inactivity, and obesity converge to increase vascular resistance and impair blood pressure regulation [9,10]. Oxidative stress defined as an imbalance between reactive oxygen species (ROS) production and antioxidant defenses plays a central role in vascular injury, endothelial dysfunction, and inflammatory activation [11]. These interrelated processes form the so-called "vascular health triad" of oxidative stress, inflammation, and endothelial dysfunction, which underlies the onset and progression of HTN [12,13].

The disease disproportionately affects adults in low-and middle-income countries, where unhealthy dietary patterns and limited access to healthcare amplify both prevalence and complication rates [14,15]. Early identification of modifiable risk factors, including obesity, sedentary behavior, and dyslipidemia, is therefore critical for timely intervention and effective disease management [16,17]. Although approximately 1.3 billion adults worldwide are HTN, only a small proportion achieve adequate blood pressure control, underscoring persistent gaps in prevention, diagnosis, and treatment strategies [18].

Understanding the interactions between oxidative stress, atherogenic lipids, and vascular inflammation is particularly important in the context of early-stage HTN, defined here as newly diagnosed or mildly elevated HTN corresponding to guideline-based thresholds, prior to the development of clinically apparent complications. Elucidating these interactions is essential for clarifying disease mechanisms, identifying novel therapeutic targets, and improving patient outcomes [19-21]. Addressing these molecular and immune-mediated pathways may also facilitate the identification of individuals at increased risk of pharmacological resistance, enabling more personalized and targeted management strategies [22,23].

This study investigates the interplay between oxidative stress, atherogenic lipids, and vascular inflammation in early-stage HTN, defined as newly diagnosed or mildly elevated blood pressure according to guideline-based thresholds. Blood pressure was measured in participants who were not receiving antihypertensive therapy at the time of assessment. Participants were classified as having no known target-organ damage based on clinical history, physical examination, and basic laboratory tests; advanced imaging or specialized cardiovascular assessments were not systematically performed. The study aims to identify early biomarkers and mechanistic pathways relevant to disease initiation and risk stratification.

2. Literature Review

Early-stage HTN involves subclinical vascular and molecular changes that precede overt increases in blood pressure. Central to these changes are oxidative stress, lipid dysregulation, and vascular inflammation, which collectively drive endothelial dysfunction and microvascular remodeling [24-26]. Oxidative stress arises when ROS production exceeds endogenous antioxidant capacity, reducing nitric oxide (NO) availability, impairing endothelial function, and activating inflammatory signaling cascades [27,28].

Atherogenic lipids, particularly oxidized low-density lipoprotein (LDL), contribute to vascular inflammation by attracting monocytes and macrophages, forming foam cells, and releasing cytokines such as IL-6, TNF-α, and MCP-1 [29,30]. This lipid-driven inflammatory microenvironment promotes endothelial dysfunction, vascular stiffening, and increased peripheral resistance, key events in early HTN development [31].

The immune system mediates the interaction between oxidative and lipid-induced vascular damage. Innate immune cells, including neutrophils and macrophages, initiate early vascular injury through ROS production and chemokine release, while adaptive $CD4^+$ T cells respond to neoantigens generated by oxidative modification of vascular proteins.

These T cells infiltrate perivascular fat and vessel walls, releasing pro-inflammatory cytokines that further amplify oxidative stress and endothelial dysfunction [32,33]. The resulting feed-forward loop links immune dysregulation directly to blood pressure elevation.

Target organs such as the kidney and brain are especially susceptible to oxidative-inflammatory injury. In the kidney, immune cell infiltration and ROS production drive tubular injury, fibrosis, and glomerulosclerosis, with angiotensin II-mediated stimulation further exacerbating damage [32,33]. Cerebral microvascular dysfunction impairs the blood-brain barrier, increasing stroke risk and vulnerability to ischemic injury [32,33].

Given the complex interplay of oxidative stress, lipid dysregulation, and inflammation, combining biomarkers from these pathways can improve early risk stratification. Emerging predictive tools, including machine learning models that integrate inflammatory, lipid, and hemodynamic variables, offer superior early detection compared to conventional risk factors [32,33].

Although the roles of oxidative stress, atherogenic lipids, and inflammation are well-established individually, there is limited research on their combined predictive value in early-stage HTN, particularly in low-and middle-income populations. This study addresses this gap by evaluating interactions among oxidative stress markers, lipid profiles, and inflammatory cytokines, providing insights for early detection and targeted preventive interventions [32,34].

3. Materials and Methods

3.1 Study Centers

The following centers in Ado-Ekiti, Nigeria, were used to collect the data: cardiology units. ABUAD Multisystem Hospital, Ado-Ekiti. Ado-Ekiti, Ekiti State University Teaching Hospital. Federal Teaching Hospital, Ido-Ekiti.

3.2 Study Design

The study was a cross-sectional comparative study involving HTN and age-matched normotensive (NORM) participants aged 20-45 years who provided written informed consent. This design allowed for the assessment and comparison of blood pressure, anthropometric parameters, and plasma biomarkers including oxidative stress markers, atherogenic lipids, and inflammatory cytokines between the two groups to investigate early mechanistic changes associated with HTN.

3.3 Population Sampling

HTN and NORM people were recruited to give a total of 187 participants. Fisher's exact formula was used to determine the sample size.

$$\frac{n=Z^2(1-P)}{d^2}$$

Where:

(n)=sample size, (Z)=1.96 (for 95% confidence interval), (d)=0.05 (margin of error), (P)=12.7% prevalence of HTN among adolescents in Ekiti. An attrition rate of 10% was considered for non-responders [28].

3.4 Ethical Clearance

Ethical consent was taken out in: Ethics and Research Committee of ABUAD (ABUADHRE/06/01/2025/535). Ekiti state university teaching hospital (EKSUTH/A67/2023/11/005). Ido-Ekiti (ERC/2024/01/15/1066B) Federal Teaching Hospital. ABUAD Multisystem Hospital (AMSH/REC/BOO/184). All the participants were informed and provided informed consent and all their personal information remained confidential.

3.5 Materials

3.5.1 Reagents and Kits

Adenosine, DCIP, nucleoside phosphorylase (NP), xanthine oxidase (XO), and phosphate buffer were of analytical grade. The HO-1 activity assay kit was obtained from Elabscience Biotechnology Inc., Houston, TX, USA. The XO assay kit and Human eNOS ELISA kit were purchased from Abcam, Cambridge, United Kingdom. The Human Nrf2 ELISA kit (ELH-Nrf2) was sourced from RayBiotech Life Inc., Peachtree Corners, GA, USA. The colorimetric assay kit for iron (UIBC) and the PA-I-1 ELISA kit (E-EL-H2104) were obtained from Elabscience Biotechnology Inc., Houston, TX, USA.

NO reagents included vanadium (III) chloride and Griess reagents (analytical grade). The insulin ELISA kit (96-well microplate pre-coated with anti-insulin antibodies) was commercially obtained (manufacturer specifications followed).

Colorimetric assay reagents included kits for the determination of triglycerides (TG) in samples according to the manufacturer's instructions.

3.5.2 Colorimetric Assays of TG

Colorimetric assay kit (Fortress Diagnostics, BXC0271) The colorimetric assays are conducted to ascertain the amount of TG in the sample.

3.5.3 Equipment

Cobas Mira analyzer or a double-beam spectrophotometer; microplate reader (450-540 nm); centrifuge; micropipettes and microtiter plates; and a temperature-controlled incubator.

3.6 Methods

3.6.1 Questionnaire Administration

A structured questionnaire was administered to collect socio-demographic and clinical information from all participants, including age, gender, weight, height, and body mass index (BMI); age at diagnosis of HTN; family history of HTN in first-degree relatives; and lifestyle factors such as alcohol consumption and cigarette smoking. Information on current use of antihypertensive medications, including ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, β-blockers, and calcium channel blockers, was recorded and accounted for in the analysis. Both treated and untreated HTN participants were included in the study, and blood pressure was measured under usual conditions without altering ongoing therapy.

3.6.2 Collection and Storage of Samples

Blood samples (5 mL) were collected from the cubital fossa using non-heparinized tubes. The samples were immediately centrifuged at 3500 rpm for 15 minutes to separate plasma. The plasma was carefully aliquoted into labeled polypropylene tubes and stored at -80°C until analysis to preserve the stability of oxidative stress, lipid, and inflammatory biomarkers. All samples were analyzed within three months of collection to minimize degradation and ensure reliability of results.

3.6.3 Biochemical Analyses

3.6.3.1 Adenosine Deaminase (ADA)

Principle Kinetic method DCIP, adenosine, NP, and XO coupled enzymatic reaction. Technique: The substrate and enzyme reagents were placed in phosphate buffer, 100 µL of serum was added to the reaction mixture and absorbance decrease was recorded at 600 nm (or 606 nm to optimise) in 200 seconds.

3.6.3.2 Heme Oxygenase-1 (HO-1)

Principle: HO-1 activity quantified through biliverdin production. Procedure: The plasma samples were prepared and incubated using the assay reagents. Spectrophotometrically, absorbance was used to measure the activity of HO-1 in units/mg protein.

3.6.3.3 XO

Concept: XO changes xanthine into uric acid; the increase of the absorbance at 290 nm will be observed. Method: xanthine substrate was incubated with serum homogenates and the enzyme activity was determined using absorbance change/mg protein.

3.6.3.4 Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)

Principle ELISA-based quantitative serum Nrf2 analysis. Procedure: Pre-coated microplate was added with samples and standards, biotinylated antibody, HRP-streptavidin and TMB substrate was added and the absorbance at 450 nm was measured.

3.6.3.5 Iron (Colorimetric, UIBC)

Principle: The reaction of chromogenic reagent with free iron was observed; spectrophotometry. Procedure: samples of serum added to the ferrous ion solution and chromogen; the analysis of UIBC levels was performed using a standard curve.

3.6.3.6 Plasminogen Activator Inhibitor-1 (PAI-1)

Principle: Sandwich ELISA. Procedure: Adding of samples to pre-coated wells with PAI-1 antibody, incubation and washing of the samples, addition of detection antibody and subsequent addition of HRP conjugate, TMB substrate and finally the absorbance at 450 nm was detected.

3.6.3.7 NO

Principle: Spectrophotometric determination of nitrate/ nitrite based on the reduction of vanadium (III) by Griess reaction. Procedure Vanadium (III) chloride was used to reduce plasma samples and Griess reagents were added followed by an absorbance reading at 540 nm.

3.6.3.8 Insulin

Principle ELISA-based sandwich immunoassay. Procedure: Raw plasma was incubated in pre-coated wells, adsorbent antibody and HRP conjugate measured, colorimetric reaction, in 450 nm, and insulin concentration determined by comparing the sample with the standard curve.

3.6.3.9 Endothelial Nitric oxide Synthase (eNOS)

Principle: Sandwich ELISA. Procedure Samples were added to pre-coat wells, biotinylated detection antibody and HRP-streptavidin were added, TMB substrate added, colour change at 450 nm measured and a standard curve used to calculate concentration.

3.6.3.10 Lipid Profile (TG)

Principle Colorimetric enzyme assay. Lipase hydrolyzed TG to glycerol, oxidised to form hydrogen peroxide, formed coloured product with chromogenic substrate. Procedure: The samples were incubated in the presence of reagents and the absorbance recorded at 540 nm. Results obtained using standard curve.

3.7 Statistical Analysis

Categorical variables: Pearson Chi-square test, which is in form of frequencies and %ages. Continuous variables Shapiro-Wilk test of normality; parametric data median, SDM, non-parametric data median, IQR. Comparisons Student t-test on normally distributed two-group data Mann Whitney U test on non-parametric, two-group data Kruskal-Wallis test-three or more groups. Correlation analysis: Visualised with a scatter plot and line of best fit, the analysis of correlation is a Spearman rank correlation. Statistical significance: $P<0.05$.

4. Results

4.1 Sociodemographic Characteristics of the Study Population

The sociodemographic profile of the study participants is summarized in Table 1. The study included 110 HTN patients and 60 control participants, with a balanced representation of sexes and varying educational and marital statuses. Analysis of the data shows that the majority of participants had tertiary education, and most were married among the HTN group, while the control group had a higher proportion of single individuals. Statistical comparisons using Chi-square (χ^2) and likelihood ratio (LR) tests were performed to assess significant differences between the hypertensive and control groups.

Table 1. Sociodemographic characteristics of the study population.

Variables	HTN	NORM	Statistical indices
Sex			
Male	61 (55.5%)	40 (66.7%)	χ^2=2.024; P=0.191
Female	49 (44.5%)	20 (33.3%)	
Educational Status			
No formal education	2 (1.8%)	0 (0.0%)	LR=3.26; P=0.354
Primary	3 (2.7%)	1 (1.7%)	
Secondary	8 (7.3%)	2 (3.3%)	
Tertiary	97 (88.2%)	57 (95.0%)	
Marital Status			
Single	48 (43.6%)	41 (68.3)	LR=10.21; P=0.006*
Married	61 (55.5%)	19 (31.7)	
Divorced	1 (0.9%)	0 (0.0)	

Note: Values are presented as frequency (%age). χ^2=Chi-square test; LR=Likelihood ratio test. $P<0.05$ considered statistically significant.

The sociodemographic analyses of the study population indicated that the HTN group included slightly more males (55.5%) than females (44.5%), while the control group had a higher proportion of males (66.7%) than females (33.3%). The chi-square test (χ^2=2.024; P=0.191) showed that sex distribution did not differ significantly between HTN and control participants, suggesting that sex may not be a major determinant of early-stage HTN in this cohort. Similarly, there were no significant differences in educational levels between HTN patients (88.2% with tertiary education) and controls (95.0%), indicating that educational attainment might not significantly impact the risk of early-stage HTN (LR=3.26; P=0.354).

In contrast, marital status was significantly associated with HTN (LR=10.21; P=0.006). Among hypertensives, 55.5% were married versus 31.7% of controls, whereas single individuals were more prevalent in the control group (68.3%) than among hypertensives (43.6%). Divorce was rare in both groups (0.9% in hypertensives; 0% in controls). This observation suggests that marital status may influence early-stage HTN, potentially reflecting differences in psychosocial stress, lifestyle, and household responsibilities [34,35]. Overall, these findings indicate that while sex and educational level do not significantly differ between groups, marital status may interplay with psychosocial or behavioral factors, including oxidative stress, in the early development of HTN. These results highlight the potential value of socio-environmental interventions, such as stress reduction or social support, in mitigating cardiovascular risk [34,35].

4.2 Clinical Characteristics of All the Study Population

The clinical parameters of HTN and control participants are summarized in Table 2. Continuous variables, including age, pulse rate, blood pressure, weight, height, and BMI, were compared between the two groups using independent t-tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed variables.

The results indicate that HTN participants had significantly higher systolic and DBP compared to controls (P<0.01). Weight and BMI were also significantly higher in the HTN group (P<0.01), while height was significantly lower (P<0.01). Age and pulse rate did not differ significantly between groups, suggesting that the observed differences in blood pressure and anthropometric measures were independent of age or resting heart rate.

Table 2. Clinical characteristics of all the study population.

Variables	HTN	NORM	Statistical indices
Age (years)	34 (23-42)	29 (25-38)	Z=1.234; P=0.217
Pulse rate	83 (72-94)	79.5 (72-87)	Z=1.601; P=0.109
SBP (mmHg)	146±18.7	121.15±11.22	t=9.29; P<0.01
DBP (mmHg)	91±14.02	71.63±9.35	t=9.61; P<0.01
Weight (kg)	84.45 (68.2-94.4)	71.6 (62.5-81.5)	Z=3.328; P<0.01
Height (cm)	168.25 (162.5-175)	173 (168-179.5)	Z=−2.682; P<0.01
BMI (kg/m²)	28.85 (24.8-32.65)	23.98 (20.9-27.6)	Z=4.647; P<0.01

Note: Values are presented as mean±SD or median (range). P<0.05 was considered statistically significant.

The current research was aimed at assessing the interaction of oxidative stress and atherogenic lipids and vascular inflammation in the early HTN patients. The HTN and control groups had a similar age (34 *vs*. 29 years, P=0.217), which minimized the possibility of age confounding the oxidative stress and lipid metabolism. The hypertensives had a slightly elevated pulse rate (83 *vs*. 79.5 bpm, P=0.109), which was not found to be significant, indicating that early-stage HTN had no significant changes in heart rate when the hemodynamic changes were impaired.

Important increases in systolic and diastolic blood pressures were also observed in patients with HTN (SBP: 146±18.7 mmHg *vs*. 121.15±11.22 mmHg; DBP: 91±14.02 mmHg *vs*. 71.63±9.35 mmHg; P<0.01), which proves the existence of hemodynamic overload. This heightened vascular pressure has been known to cause endothelial dysfunction and activate oxidative stress pathways capable of triggering the formation of ROS and inflammatory cascades in the vascular endothelium.

The anthropometric results showed that HTN patients were found to be having a lot more body weight and BMI (84.45 kg and 28.85 kg/m², respectively) than the controls (71.6 kg and 23.98 kg/m², respectively). Higher adiposity is a proven candidate risk factor of systemic oxidative stress and long-term low-grade inflammation, both of which enable the dysregulation of lipid metabolism and augment atherogenic potential. Interestingly, HTN patients were meanwhile a bit shorter (168.25 cm *vs*. 173 cm, P<0.01), which could affect BMI values and indicate the tendency to central adiposity, only serving to increase vascular risks.

These findings taken together suggest that a cascade of interconnected physiological and metabolic alterations, including high blood pressure, excess body weight, and initial signs of oxidative stress, is manifested in the HTN patients and contributes to the onset of vascular inflammation and atherogenesis in a synergistic manner. The absence of the important change in age and pulse rate proves the idea that these changes happen before the development of the overt cardiovascular complications, with the focus on the important period of intervention. These findings support the hypothesis that hemodynamic stress, excessive adiposity, and early metabolic imbalance are jointly contributing factors to oxidative stress and abnormal lipids, leading to progressive vascular malpractice in HTN patients. This cluster of alterations may be a factor in the increased cardiovascular risk in HTN groups, and this fact makes early intervention and multi-parametric evaluation significant to comprehend pathological development, involving physiological and biochemical indicators [36].

Table 3. Antihypertensive medication use among HTN participants (n=110).

Medication Type	Number of Participants (n)	Percentage (%)
ACE inhibitors	32	29.1
ARBs	26	23.6
Diuretics	22	20.0
β-blockers	15	13.6
Calcium channel blockers	10	9.1
Combination therapy	5	4.6
Total	110	100

Among the 110 HTN participants, 85% (n=94) were receiving at least one antihypertensive medication, while 15% (n=16) were untreated at recruitment. The distribution of antihypertensive therapies is summarized in Table 3: ACE inhibitors (29.1%), ARBs (23.6%), diuretics (20.0%), β-blockers (13.6%), calcium channel blockers (9.1%), and combination therapy (4.6%). All participants were free of major comorbidities, ensuring that the study population reflected early-stage, uncomplicated HTN, minimizing confounding effects on oxidative stress, metabolic, and vascular markers. The observed distribution, with ACE inhibitors and ARBs being most frequently prescribed followed by diuretics, β-blockers, and calcium channel blockers, aligns with contemporary patterns reported in recent clinical and observational studies of antihypertensive prescription trends. Real-world data from primary care settings have shown that prescription of calcium channel blockers and renin-angiotensin system blockers (ACE inhibitors and ARBs) remains high as first-or second-line therapies, reflecting their effectiveness, tolerability, and guideline support for reducing blood pressure and cardiovascular risk across diverse patient populations . In a large retrospective analysis, calcium channel blockers were the most commonly prescribed class, followed by ARBs and diuretics, highlighting the sustained relevance of these agents in clinical practice. Population studies also document shifts in prescribing, with increased utilization of ARBs and calcium channel blockers over time, while diuretic use has declined in some settings, suggesting evolving clinician preferences and adaptation to guideline updates [37]. These patterns are clinically important because different antihypertensive classes may have distinct effects on vascular biology beyond blood pressure lowering, including modulation of oxidative stress and inflammation, which are central to the pathophysiology of HTN and cardiovascular outcomes.

4.3 Determination of HO-1, Vascular Endothelial Growth Factor (VEGF) and Insulin Levels

Figure 1 presents comparative data on circulating levels of three key biomarkers HO-1 in panel (a), VEGF in panel (b), and Insulin in panel (c) between NORM individuals and patients with HTN. Data are expressed as medians with interquartile ranges, reflecting non-parametric distribution, and statistical differences were evaluated using the Kruskal-Wallis test, with significance indicated as *P<0.05, P<0.01, or P<0.001 versus NORM.

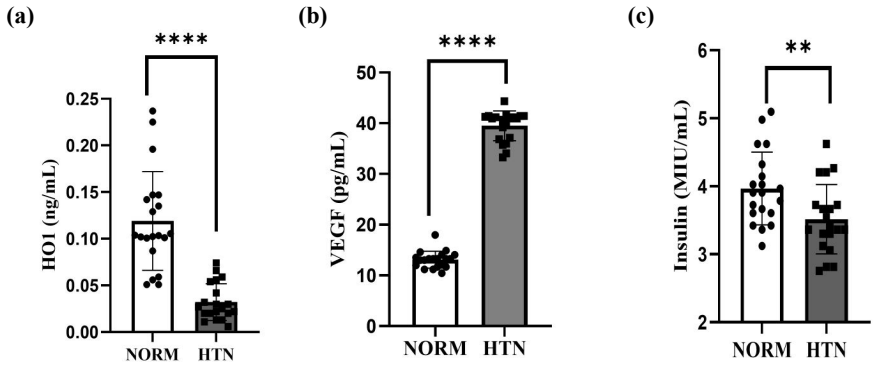

Figure 1. Circulating levels of HO-1 (a), VEGF (b), and insulin (c) in normotensive (NORM) and HTN participants. Values are expressed as medians with interquartile ranges and analyzed using the Mann-Whitney U test. *P<0.05 *vs*. NORM.

The HTN individuals in this study had significantly lower HO-1 levels (P<0.00001) and significantly higher VEGF and insulin levels (P<0.01) compared with NORM controls (Figure 1a-c). Lower HO-1 levels, an enzyme with anti-inflammatory and antioxidative properties, may reflect a reduced capacity to counteract oxidative stress in HTN participants, thereby contributing to endothelial dysfunction. The upregulation of VEGF suggests enhanced angiogenic signaling, potentially associated with early vascular remodeling. Elevated insulin levels (P<0.01) are indicative of insulin resistance, a metabolic disturbance closely linked with HTN, obesity, and increased cardiovascular risk [37-39]. Collectively, these findings highlight coordinated alterations in oxidative stress regulation, angiogenic activity, and metabolic control in early-stage HTN.

4.4 Determination of NO, Iron and ADA Levels

Figure 2 below illustrates comparative data on circulating levels of three additional biomarkers NO in panel (a), Iron (Fe) in panel (b), and ADA activity in panel (c) between NORM individuals and patients with HTN. Data are presented

as medians with interquartile ranges, consistent with non-parametric distribution, and statistical significance was assessed using the Kruskal-Wallis test, denoted as P<0.001 versus NORM.

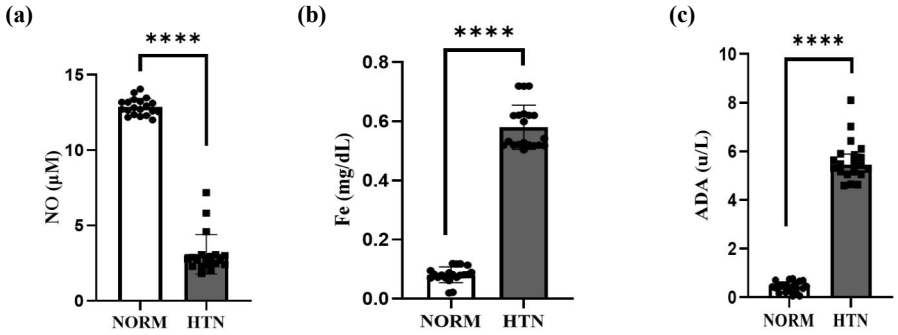

Figure 2. Levels of NO, Fe and ADA in NORM and HTN groups. (a) NO levels; (b) Fe levels; (c) ADA levels. Values are represented as median and analysed by Mann-Whitney U test. *P<0.05 *vs*. NORM. NORM: Normotensive; HTN: Hypertension; NO: Nitric oxide; Iron: Fe; ADA: Adenosine deaminase.

The findings as shown in Figure 2 (a-c) demonstrate that the NO level in HTN subjects is much lower (P<0.00001), and that the level of iron (Fe) and ADA are higher (P<0.00001). The reduced NO bioavailability in hypertensives implies the failure of the endothelial-dependent vasodilation, which is a hallmark of the vascular dysfunction in early HTN. This impairment disturbs the regulation of vascular tone, the non-thrombogenic integrity of the endothelium, and the adhesion of platelets and monocytes, and it supports pro-inflammatory conditions [40,41].

High Fe indicates the increased oxidative stress, because free iron is able to catalyze the formation of ROS, which further impairs the endothelial performance. At the same time, heightened ADA activity suppresses the protective action of adenosine, which has anti-inflammatory, vasodilatory, and anti-atherogenic actions. Taken together, these changes emphasize a trinity of endothelial dysfunction, oxidative stress, and inflammation as some of the drivers of HTN pathophysiology. The significance of these findings is that antioxidant treatments and interventions to reestablish NO bioavailability can be useful in the management of HTN at an early stage [40,41].

4.5 Determination XO, Adenosine, Uric Acid and Nrf2

Figure 3 displays comparative circulating levels of four biomarkers involved in oxidative stress and purine metabolism XO activity in panel (a), Adenosine in panel (b), Uric Acid in panel (c), and Nrf2 in panel (d) between NORM individuals and patients with HTN. Values are shown as medians with interquartile ranges, indicative of non-parametric data, and statistical comparisons were performed using the Kruskal-Wallis test, with P<0.001 versus NORM across all panels.

These markers reflect key aspects of HTN pathophysiology, including ROS generation via xanthine oxidoreductase, purinergic signaling, hyperuricemia-mediated vascular damage, and impaired antioxidant defenses.

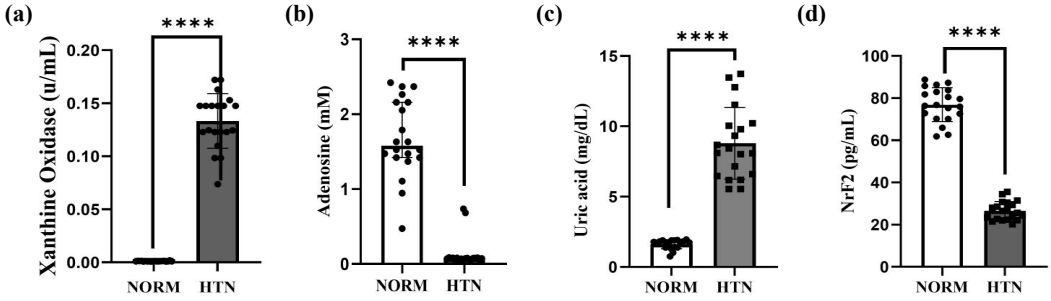

Figure 3. Levels of XO, adenosine, uric acid, and Nrf2 in NORM and HTN groups. (a) XO levels; (b) Adenosine levels; (c) Uric acid levels; (d) Nrf2 levels. Values are represented as median and analysed by Mann-Whitney U test. *P<0.05 *vs*. NORM. NORM: Normotensive; HTN: Hypertension; Nrf2: Nuclear factor erythroid 2-related factor 2.

The HTN group had a significantly higher level of XO and uric acid (P<0.00001) and a significantly lower level of adenosine and Nrf2 (P<0.00001) in comparison with NORM controls (Figure 3a-d). The high XO activity is an indication of more ROS formation, whereas higher levels of uric acid, a by-product of the purine metabolism catalyzed by XO, indicate additional oxidative stress load. The low levels of adenosine and Nrf2 denote the weakened antioxidant and anti-inflammatory defense system and the weakened ability to overcome the vascular oxidative damage.

The results emphasize the importance of oxidative stress in HTN at the early stages and the possible therapy, such as XO inhibition and Nrf2 expression, to reduce ROS formation and enhance the endogenous antioxidant protective mechanisms. Markedly, uric acid has been repeatedly linked to the pathogenesis of HTN in humans and animals and is again substantiated to be relevant as a risk factor that can be modified in the treatment of HTN [42,43].

4.6 Determination of Plasminogen Activator Inhibitor 1, eNOS and TC/HDL

Figure 4 depicts comparative data on three biomarkers related to fibrinolysis, endothelial function, and cardiovascular risk plasminogen activator inhibitor-1 (PAI-1) in panel (a), eNOS in panel (b), and TC to HDL Cholesterol ratio (TC/HDL) in panel (c) between NORM individuals and patients with HTN. Values are represented as medians (or means where applicable) with interquartile ranges, and statistical significance was determined using appropriate tests (t-test or Kruskal-Wallis), indicated as P<0.001 versus NORM across all panels.

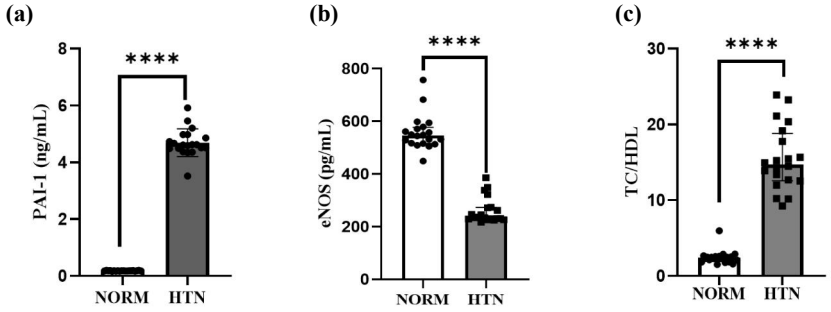

Figure 4. Levels of PAI-1, eNOS, and TC/HDL ratio in NORM and HTN groups. (a) PAI-1 levels; (b) eNOS levels; (c) TC/HDL ratio. Values are represented as median or median and analyzed by the Mann-Whitney U test *P<0.05.

Figure 4 Analysis indicates that the HTN group had a high level of PAI-1 (P<0.00001) and TC to high-density lipoprotein (HDL) (TC/HDL) (P<0.00001) and low levels of eNOS (P<0.00001). High levels of PAI-1 are a sign of a prothrombotic condition, which implies poor fibrinolysis and susceptibility to thrombotic cardiovascular occurrences among HTN individuals [44]. Less than normal eNOS, necessary in the production of NO and vasodilation, points to significant endothelial impairment, factors that lead to lasting HTN and risk of cardiovascular disease [45].

The much greater TC/HDL ratio in HTN patients is an additional symptom of the unbalanced state of TC and protective HDL cholesterol, showing an increased atherogenic potential despite the absence of blatant cardiovascular complications. Together, these results highlight endothelial dysfunction, prothrombotic activity, and dyslipidemia as a complex of factors in early HTN, and the interventions on cardiovascular risks and their specific treatment options should be applied in a complex manner [44,45].

4.7 Determination of TC, TG High/low Density Lipoprorein

Figure 5 presents comparative lipid profile data TC in panel (a), HDL in panel (b), TG in panel (c), and low-density lipoprotein cholesterol (LDLc) in panel (d) between NORM individuals and patients with HTN. Values are shown as medians (or means where appropriate) with interquartile ranges, and statistical differences were assessed using t-test or Kruskal-Wallis test, with *P<0.001 versus NORM in all panels.

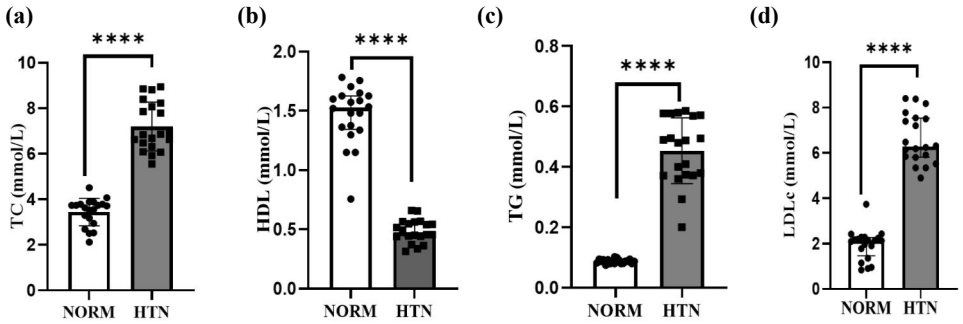

Figure 5. Levels of TC, HDL, TG, and LDL in NORM and HTN groups. (a) TC levels; (b) HDL levels; (c) TG levels; (d) LDL levels. Values are represented as median and analysed by Mann-Whitney U test. *P<0.05 *vs*. NORM. NORM: Normotensive; HTN: Hypertension; TC: Total cholesterol; HDL: High-density lipoprotein; TG: Triglyceride; LDLc: Low-density lipoprotein.

As Figure 5 shows, the HTN individuals had much higher levels of the TC (P<0.00001), TG (P<0.00001), and LDL levels (P<0.00001) as compared to the NORM controls, and significantly lower levels of HDL (P<0.00001). High levels of TC and LDL are well-known risk factors of atherosclerosis and cardiovascular disease because they enhance the deposits of cholesterol in the artery walls. The loss of HDL, which aids in the reverse cholesterol transport, also increases the risk of the formation of the vascular plaque. Higher levels of TG are also indicative of an atherogenic lipid profile that is often related to HTN, obesity, and metabolic syndrome [46,47].

The identified dyslipidemia, which is characterized by the increase in TC, TG, and LDL and the reduction of HDL, indicates that HTN people are at a high risk of experiencing cardiovascular events. The findings highlight the necessity of extensive lipid profile measurements and specific treatments such as lifestyle change and drug therapy to reduce cardiovascular risk in HTN populations [47,48].

4.8 Correlation between HO-1 and VEGF, NO and Iron

Figure 6 presents Spearman correlation scatter plots examining the relationships between circulating HO-1 levels and three key biomarkersVEGF in panel (a), NO in panel (b), and Iron (Fe) in panel (c) exclusively in the HTN group. Each panel includes individual data points, a linear regression line for visual trend, Spearman correlation coefficient (r), and corresponding P-value. Non-significant trends are indicated.

These correlations explore potential mechanistic links between the protective antioxidant enzyme HO-1 and markers of angiogenesis, endothelial function, and iron homeostasis in the context of HTN pathophysiology.

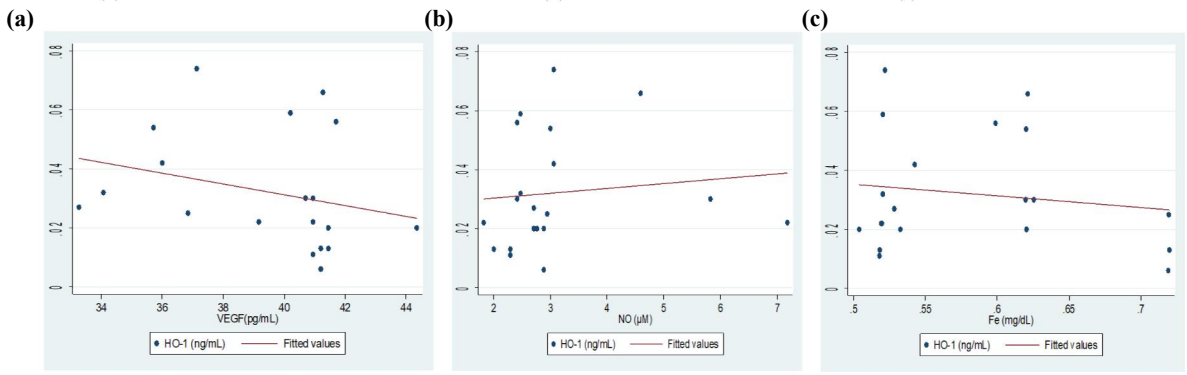

Figure 6. Correlation of HO-1 with VEGF, NO, and Fe in HTN participants. (a) HO-1 *vs*. VEGF; (b) HO-1 *vs*. NO; (c) HO-1 *vs*. Fe. Correlation coefficients and P-values were as follows: VEGF (r=0.404, P=0.078), NO (r=0.383, P=0.090), and Fe (r=0.092, P=0.699). Correlations were analyzed using Spearman's rank correlation. VEGF: Vascular endothelial growth factor; NO: Nitric oxide; Fe: Iron; HTN: Hypertension; HO-1: Heme oxygenase-1.

The correlations between VEGF, NO, Fe, and HO-1 in HTN individuals are shown in Figure 6. A moderate positive correlation was observed between VEGF and HO-1 (r=0.4036, P=0.0777), approaching statistical significance (Figure 6a), suggesting a possible relationship between increased VEGF levels and HO-1 expression. However, the correlations between NO and HO-1 (r=-0.383, p=0.09; Figure 6b) and between Fe and HO-1 (r=0.092, P=0.699; Figure 6c) were weak and not statistically significant. Overall, these findings indicate that while VEGF may be modestly associated with HO-1, most relationships between HO-1 and the measured biomarkers were not significant. This pattern reflects the complexity of interactions among angiogenic, oxidative, and cytoprotective pathways in early-stage HTN. The weak association between VEGF and HO-1 may suggest that even small changes in angiogenic factors could influence antioxidant and immunomodulatory responses, potentially contributing to vascular homeostasis during early HTN stages [49].

4.9 Correlation between HO-1 and Adenosine, ADA, XO and Uric Acid

Figure 7 displays Spearman correlation scatter plots assessing the relationships between circulating HO-1 levels and four biomarkers involved in purine metabolism and oxidative stress Adenosine in panel (a), ADA activity in panel (b), XO activity in panel (c), and Uric Acid in panel (d) specifically in the HTN group. Each panel shows individual data points with a fitted linear regression line for trend visualization, along with the Spearman correlation coefficient (r) and p-value. All associations are non-significant.

These analyses probe potential interconnections between the protective HO-1 system and the purinergic/xanthine oxidoreductase pathway, which is frequently dysregulated in HTN.

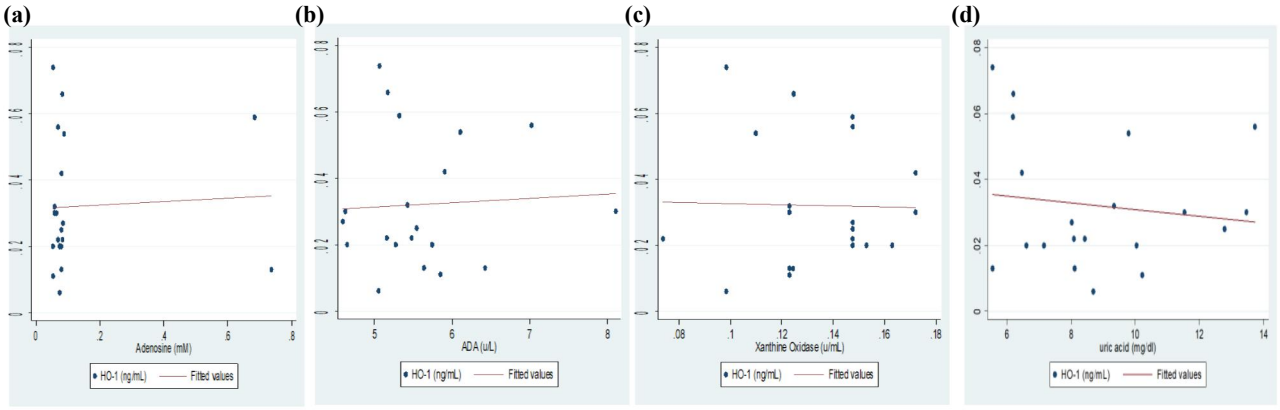

Figure 7. Correlation of HO-1 with adenosine, ADA, XO, and uric acid in HTN participants. (a) HO-1 *vs*. adenosine; (b) HO-1 *vs*. ADA; (c) HO-1 *vs*. XO; (d) HO-1 *vs*. uric acid. Adenosine (r=0.0779, P=0.744)[#]; ADA (r=0.012, P=0.959)[#]; Fe (r=0.048, P=0.839); Uric acid ((r=-0.126, P=0.595); ADA: Adenosine deaminase; HTN: Hypertension; HO-1: Heme Oxygenase-1. [#]Spearman correlation.

Figure 7 illustrates the associations between HO-1 and the main purinergic and oxidative stress-related biomarkers adenosine, ADA, and XO in HTN patients. The correlation between adenosine and HO-1 was weak and not statistically significant (r=0.0779, P=0.744; Figure 7a), suggesting no clear relationship between adenosine availability and HO-1 expression in this cohort. Similarly, the correlation between ADA and HO-1 was negligible and non-significant (r=0.012, p=0.959; Figure 7b), indicating that variations in ADA activity are not closely associated with HO-1 levels. The correlation between XO and HO-1 was also weak and non-significant (r=0.048, P=0.839; Figure 7c), suggesting that oxidative stress generated by XO activity does not directly correspond to compensatory HO-1 expression in early-stage HTN.

These observations highlight the complex and multifactorial regulation of HO-1, which likely depends on cumulative oxidative stress, inflammatory signaling, and transcriptional control rather than individual purine metabolic pathways. While purinergic dysregulation and uric acid accumulation, the end product of XO activity, are recognized contributors to HTN and vascular dysfunction [50,51], their effects on HO-1 may be indirect or delayed rather than immediate. Overall, these findings emphasize the importance of integrative and longitudinal studies to better understand the regulatory mechanisms of antioxidant defense in HTN, particularly in relation to HO-1 and purine metabolism.

4.10 Correlation between HO-1 and PAI-1, eNOS and Nrf2

Figure 8 displays Spearman correlation scatter plots assessing the relationships between circulating HO-1 levels and three biomarkers involved in oxidative stress regulation and endothelial function Nrf2 in panel (a), PAI-1 in panel (b), and eNOS in panel (c) specifically in the HTN group. Each panel shows individual data points with a fitted linear regression line for trend visualization, along with the Spearman correlation coefficient (r) and P-value. All associations are non-significant (Nrf2: r=-0.160, P=0.499; PAI-1: r=0.155, P=0.512; eNOS: r=-0.258, P=0.270). These analyses probe potential interconnections between the protective HO-1 system and key Nrf2-driven antioxidant responses as well as endothelial dysfunction markers, which are frequently dysregulated in HTN.

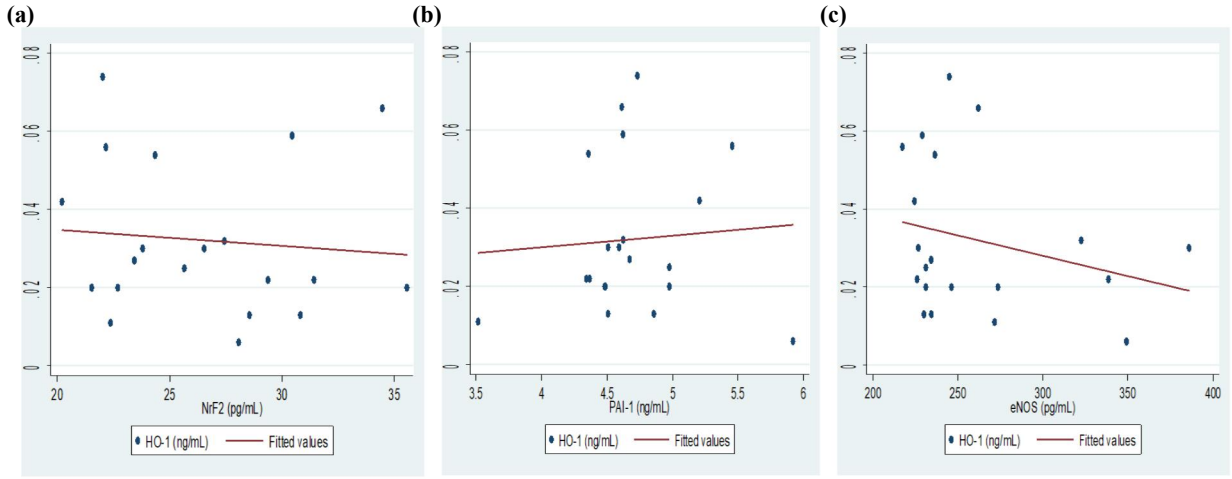

Figure 8. Correlation of HO-1 with Nrf2, PAI-1, and eNOS in HTN participants. (a) HO-1 *vs*. Nrf2; (b) HO-1 *vs*. PAI-1; (c) HO-1 *vs*. eNOS. Nrf2 (r=-0.160, P=0.499)· PAI-1 (r=0.155, P=0.512)· eNOS (r=-0.258, P=0.270)#; HTN: Hypertension; PAI-1: Plasminogen activator inhibitor-1; eNOS: Endothelial nitric oxide synthase; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1: Heme Oxygenase-1. #Spearman correlation.

Figure 8 describes the correlations between HO-1 and selected biomarkers of oxidative stress regulation, endothelial function, and fibrinolysis, including Nrf2, PAI-1, and eNOS in HTN patients. The correlation between Nrf2 and HO-1 was weakly negative and not significant (r=-0.160, P=0.499; Figure 8a), suggesting that Nrf2-mediated antioxidant signaling may not directly correspond to HO-1 levels in this cohort. PAI-1 and HO-1 showed a weak positive but non-significant correlation (r=0.155, P=0.512; Figure 8b), indicating that fibrinolytic imbalance does not appear to strongly influence HO-1 expression. Similarly, eNOS and HO-1 exhibited a modest positive relationship (r=0.258, P=0.270; Figure 8c), which, although slightly stronger than the other associations, remained statistically non-significant, suggesting that endothelial NO bioavailability is not a primary determinant of HO-1 expression in early-stage HTN.

Overall, these results indicate that HO-1 regulation in HTN is unlikely to be driven by any single biomarker or pathway. Instead, the data support the concept of a multifactorial vascular health triad, encompassing oxidative stress, inflammation, and endothelial dysfunction, in which HO-1 participates as part of a broader network rather than as a central mediator [52,53]. Independent oxidative stress markers, such as malondialdehyde, have been shown to correlate with HTN risk even without direct HO-1 modulation, highlighting the complexity and heterogeneity of redox regulation in HTN disease [54]. Collectively, these findings suggest that therapeutic strategies targeting HTN may benefit from broad modulation of oxidative and inflammatory pathways.

4.11 Correlation between HO-1 and Insulin, TC/HDL and LDLc

Figure 9 displays Spearman correlation scatter plots assessing the relationships between circulating HO-1 levels and three cardiometabolic risk markers Insulin in panel (a), TC/HDL ratio in panel (b), and LDLc in panel (c) specifically in the HTN group. Each panel shows individual data points with a fitted linear regression line for trend visualization, along with the Spearman correlation coefficient (r) and p-value. The associations show positive trends of varying strength but remain non-significant (Insulin: r=0.440, P=0.052; TC/HDL: r=0.236, P=0.316; LDLc: r=0.348, P=0.132). These analyses explore potential links between the protective HO-1 system and markers of insulin resistance and atherogenic dyslipidemia, which are commonly altered in HTN and associated cardiovascular risk.

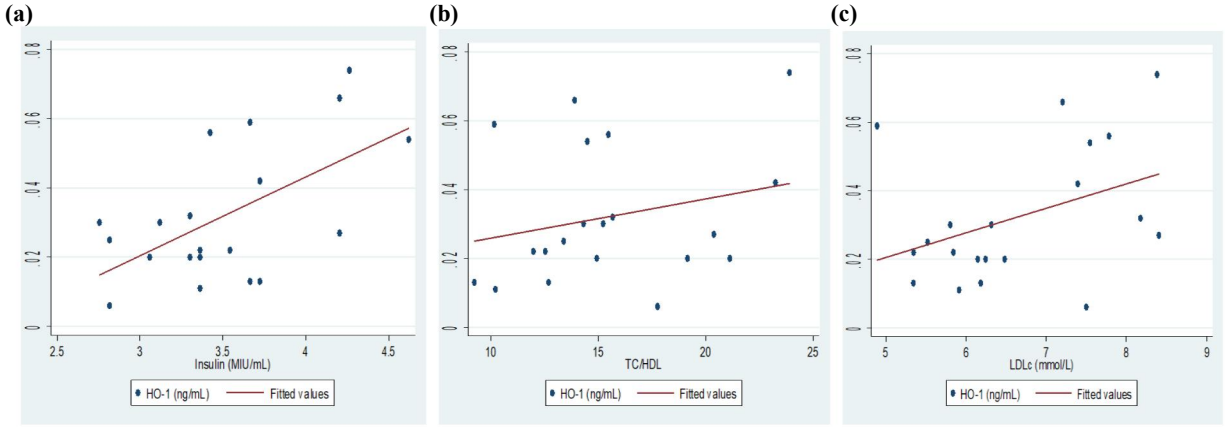

Figure 9. Correlation of HO-1 with insulin, TC/HDL ratio, and LDL in HTN participants. (a) HO-1 *vs*. insulin; (b) HO-1 *vs*. TC/HDL ratio; (c) HO-1 *vs*. LDL. Insulin (r=0.440, P=0.052)$^{\#}$, TC/HDL (r=0.236, P=0.316), LDL (r=0.348, P=0.132)$^{\#}$; HTN: Hypertension; TC: Total cholesterol; HDL: High-Density Lipoprotein; LDLc: Low-Density Lipoprotein. $^{\#}$Spearman correlation.

Figure 9 assesses the correlations among HO-1 and some metabolic parameters, such as insulin, TC/HDL ratio, and LDL in HTN people. These biomarkers are indicators of metabolic and lipid imbalance that are usually linked to high blood pressure and heart disease.

A moderately positive correlation was observed between insulin and HO-1 levels (r=0.440); however, this relationship did not reach statistical significance (P=0.052). Although slightly below the conventional threshold for significance, this trend suggests a potential association between hyperinsulinemia and elevated HO-1 expression in hypertensive (HTN) patients. This pattern may reflect a compensatory upregulation of HO-1 in response to insulin-induced oxidative stress and inflammation, supporting its role as a stress-responsive, cytoprotective enzyme under metabolically dysregulated conditions (Figure 9a).

The correlation between the total cholesterol to HDL ratio (TC/HDL) and HO-1 levels was weak and not statistically significant (r=0.236, P=0.316), indicating that global lipid imbalance, as assessed by TC/HDL, does not markedly influence HO-1 expression in this cohort (Figure 9b). Similarly, the correlation between LDL cholesterol and HO-1 was moderate but statistically insignificant (r=0.348, P=0.132), suggesting a possible trend without reaching statistical significance (Figure 9c).

These findings suggest that insulin may exert a stronger influence on HO-1 expression than traditional lipid parameters in HTN patients. The marginal correlation between insulin and HO-1 underscores the potential involvement of insulin signaling in the regulation of antioxidant defense mechanisms, warranting further investigation through mechanistic and longitudinal studies. In contrast, the absence of significant associations with TC/HDL and LDL implies that conventional lipid markers are not primary determinants of HO-1 expression. Instead, metabolic stress and inflammatory signaling are likely more critical drivers of HO-1 induction, consistent with evidence that HO-1 expression is predominantly regulated by oxidative and inflammatory stimuli rather than individual dyslipidemic parameters [55]. Furthermore, emerging data indicate that novel inflammatory biomarkers, such as C-reactive protein and homocysteine, may indirectly influence cardiovascular pathology and redox regulation, providing additional mechanisms through which HO-1 expression can be modulated [56].

4.12 Correlation between HO-1 and TC, TG and HDL

Figure 10 displays Spearman correlation scatter plots assessing the relationships between circulating HO-1 levels and three lipid profile parameters TC in panel (a), TG in panel (b), and HDL in panel (c) specifically in the HTN group. Each panel shows individual data points with a fitted linear regression line for trend visualization, along with the Spearman correlation coefficient (r) and p-value. The associations are weak and non-significant (TC: r=0.132, P=0.167; TG: r=-0.229, P=0.330; HDL: r=-0.01, P=0.9648), with mild positive trend for TC, mild inverse trend for TG, and essentially no trend for HDL. These analyses investigate potential interconnections between the protective HO-1 system and dyslipidemia components, which are frequently altered in HTN and contribute to atherosclerotic risk.

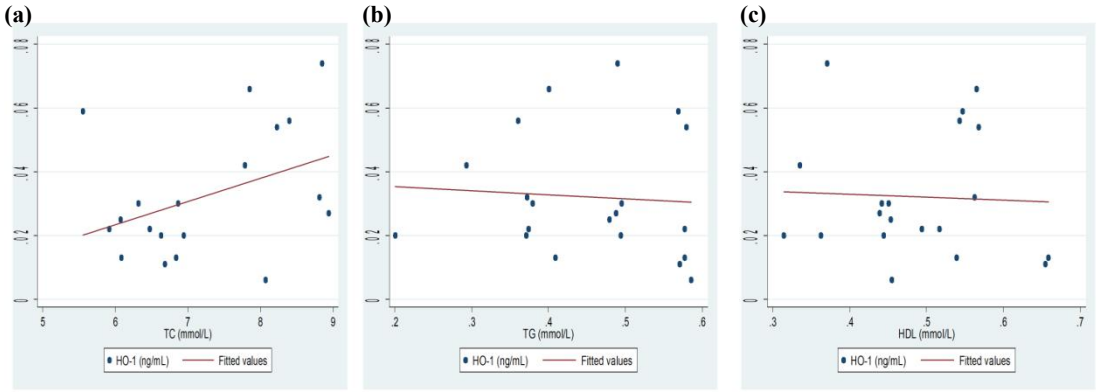

Figure 10. Correlation of HO-1 with TC, TG, and HDL in HTN participants. (a) HO-1 *vs*. TC; (b) HO-1 *vs*. TG; (c) HO-1 *vs*. HDL. TC (r=0.132, P=0.167), TG (r=-0.229, P=0.330), HDL (r=-0.01, P=0.9648)[#]; HTN: Hypertension; TC: Total cholesterol; TG: Triglyceride; HDL: High-Density Lipoprotein. [#]Spearman correlation.

Figure 10 examines the relationships between HO-1 and selected lipid profile parameters TC, TG, and HDL in HTN individuals. The analysis reveals no statistically significant correlations between HO-1 and HDL (r=0.010, P=0.9648), TG (r=−0.229, P=0.330), or total cholesterol (r=0.132, P=0.167).

Overall, these findings indicate the absence of a discernible association between HO-1 expression and classical lipid indices in this HTN population. Despite the established role of HO-1 as a cytoprotective enzyme involved in redox regulation and inflammatory modulation, the present results suggest that HO-1 does not directly influence conventional lipid parameters such as TC, TG, and HDL in HTN. This observation contrasts with theoretical expectations that antioxidant pathways might substantially affect lipid metabolism, particularly under conditions of chronic oxidative stress[52].

The lack of significant associations implies that HO-1 mediated protective mechanisms in HTN may operate independently of bulk lipid concentrations, instead targeting oxidative damage, endothelial function, or immune-inflammatory pathways. It is also plausible that HO-1 influences more specific lipid subclasses, such as oxidized LDL, lipoprotein particle size, or lipid peroxidation products, which were not evaluated in the present study. Consequently, further investigations incorporating advanced lipid profiling and metabolic flux analyses are warranted to elucidate the indirect or context-dependent roles of HO-1 in lipid homeostasis under HTN conditions [53,52].

4.13 Correlation between HO-1 and SBP, DBP

Figure 11 displays Pearson correlation scatter plots assessing the relationships between circulating HO-1 levels and blood pressure parameters SBP in panel (a) and DBP in panel (b) specifically in the HTN group. Each panel shows individual data points with a fitted linear regression line for trend visualization, along with the Pearson correlation coefficient (r) and P-value. Both associations exhibit inverse trends but remain non-significant (SBP: r=-0.314, P=0.177; DBP: r=-0.163, P=0.491). These analyses examine potential links between the protective HO-1 system and blood pressure control, where higher HO-1 levels might theoretically associate with lower pressures due to its vasoprotective and antioxidant effects, though no statistically significant relationships were observed in this HTN cohort.

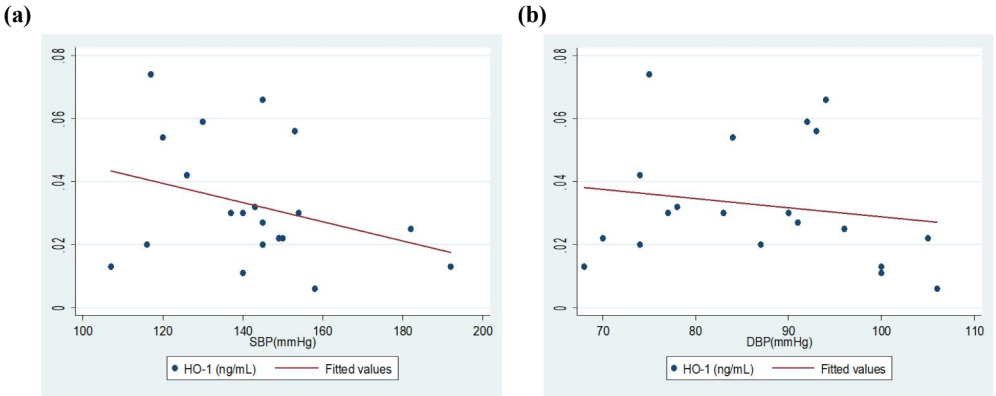

Figure 11. Correlation of HO-1 with SBP and DBP in HTN participants. (a) HO-1 *vs*. SBP; (b) HO-1 *vs*. DBP. SBP (r=-0.314, P=0.177), DBP (r=-0.163, P=0.491)[*]; HTN: Hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. [*]Pearsons correlation.

Figure 11 illustrates the relationship between HO-1 levels and SBP and diastolic blood pressure (DBP) in HTN patients. The analysis reveals weak negative correlations between HO-1 and SBP (r=−0.314, P=0.177) as well as DBP (r=−0.163, P=0.491); however, neither association reaches statistical significance. These findings indicate that HO-1 levels are not significantly associated with resting blood pressure values in this HTN cohort.

The absence of statistically significant correlations, despite the observed inverse trends, suggests that the relationship between HO-1 and blood pressure regulation is likely complex and not adequately captured through simple linear analyses. Given the dynamic nature of blood pressure and the multifaceted biological functions of HO-1 including its anti-inflammatory, antioxidative, and cytoprotective roles its influence may be more evident in long-term vascular remodeling or endothelial protection rather than direct modulation of systolic or diastolic pressure at a single time point [52].

Moreover, HO-1 derived metabolites such as bilirubin and carbon monoxide have been shown to confer vascular protection by reducing oxidative stress and preserving endothelial function, mechanisms that may not translate directly into measurable reductions in blood pressure in individuals with established HTN. It is therefore plausible that HO-1 exerts a modulatory effect on blood pressure variability, vascular compliance, or responsiveness to vasoactive stimuli rather than absolute blood pressure values.

Future studies incorporating longitudinal designs, blood pressure variability indices, or genetic polymorphisms influencing HO-1 expression may provide deeper insight into its role in cardiovascular regulation [55,56]. Collectively, these findings underscore that while HO-1 contributes to vascular homeostasis, its protective effects in HTN may be mediated through indirect pathways that mitigate oxidative stress and inflammation rather than direct blood pressure reduction.

5. Conclusion

This study demonstrates that early-stage HTN in young adults is associated with a convergence of oxidative stress, dyslipidemia, endothelial dysfunction, metabolic dysregulation, and low-grade vascular inflammation prior to overt cardiovascular complications. Although HTN and NORM participants were comparable in age, sex, and educational level, significant differences in anthropometric indices, blood pressure parameters, and multiple biochemical markers suggest that metabolic and psychosocial factors, including adiposity, may contribute to early HTN pathology.

HTN individuals exhibited increased oxidative stress, reflected by elevated XO activity, uric acid, iron, and ADA levels, alongside reduced antioxidant and cytoprotective defenses such as HO-1 and Nrf2. Impaired NO bioavailability and reduced eNOS further indicate endothelial dysfunction, accompanied by heightened angiogenic signaling and a prothrombotic vascular milieu.

In parallel, HTN participants displayed an atherogenic lipid profile, characterized by elevated TC, TG, LDL, and TC/HDL ratio, together with reduced HDL. Circulating insulin levels were higher in HTN participants compared with NORM controls, consistent with insulin resistance, reinforcing the presence of early metabolic impairment. Given that formal analyses controlling for BMI were not conducted, these findings should be interpreted as associative rather than independent of adiposity. Correlation analyses suggest that HO-1 regulation reflects cumulative oxidative, inflammatory, and metabolic stress rather than isolated biomarker effects.

Collectively, these findings support the concept of a vascular health triad in early HTN, involving oxidative stress, lipid dysregulation, and inflammation, with contributory roles of metabolic dysfunction. Future studies incorporating BMI-adjusted and longitudinal analyses are warranted to clarify independent mechanisms and to guide early, integrated preventive strategies in young HTN populations.

6. Study Limitations

The limitations of this study are as follows:

(1). Sample size: The study included a relatively modest number of participants, which may limit the statistical power to detect subtle associations. (2). Single-center design: Conducted at a single site, which may restrict the generalizability of the findings to other populations or geographic regions. (3). Cross-sectional design: The study design does not allow for causal inferences or assessment of temporal changes in oxidative stress, lipid, or inflammatory markers. (4). Lack of follow-up data: The absence of longitudinal monitoring limits insights into the progression of HTN and the predictive value of the biomarkers over time. (5). Limited clinical data: While biochemical analyses were extensive, additional clinical information such as lifestyle factors, comorbidities, and medication use was limited, which may influence interpretation. In particular, information on concurrent medications that could affect metabolic or lipid markers (e.g., lipid-lowering therapy) was not systematically collected.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The author declares that no Gen AI was used in the creation of this manuscript.

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