

## Endothelial Dysfunction Biomarkers in Chronic Hypertension and Their Clinical : Penanda Biologis Disfungsi Endotel pada Hipertensi Kronis dan Aplikasinya Klinis

*Penanda Biologis Disfungsi Endotel pada Hipertensi Kronis dan Aplikasinya Klinis*

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### Abstract

**Background:** Endothelial dysfunction is a key factor linking hypertension, inflammation, and metabolic disturbances, yet its biomarker profile in chronic hypertension remains insufficiently clarified. **Specific Background:** The vascular endothelium regulates vascular tone and homeostasis, but persistent hypertension alters its function through inflammatory and oxidative pathways. **Knowledge Gap:** Although endothelial impairment is recognized in cardiovascular disease, comprehensive biomarker-based evidence in chronic hypertensive patients is limited, particularly in Middle Eastern populations. **Aim:** This study aimed to assess endothelial dysfunction biomarkers and their correlations with metabolic and inflammatory markers in patients with chronic hypertension. **Results:** A case-control study involving 100 hypertensive patients and 50 healthy controls revealed significantly elevated endothelin-1, VCAM-1, ICAM-1, E-selectin, CRP, IL-6, TNF- $\alpha$ , MDA, total cholesterol, LDL-C, triglycerides, and fasting glucose, alongside reduced NO, SOD, and HDL-C ( $p < 0.001$ ). Biomarker levels correlated positively with age, BMI, hypertension duration, and inflammatory indices. **Novelty:** This study provides integrative evidence linking vascular, inflammatory, and metabolic biomarkers with disease severity, emphasizing endothelial dysfunction as a multifactorial process in hypertension. **Implications:** The findings underscore the potential of biomarker profiling to improve risk stratification, early detection of complications, and the design of targeted therapeutic interventions in chronic hypertension.

#### Highlight :

Hypertensive patients show higher endothelial dysfunction biomarkers and lower nitric oxide.

Inflammation and oxidative stress are strongly associated with hypertension progression.

Lipid and glucose abnormalities increase cardiovascular complication risks.

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## Introduction

Vascular endothelium is an important part of cardiovascular (CV) function because it connects blood to nearby tissues and helps move nutrients and chemicals around. It also interacts with cells, hormones, and cytokines that are in the blood [1]. Endothelial cells control the tone of the blood vessels by making prostaglandins, nitric oxide (NO), and other factors that relax the cells. In addition, healthy endothelium helps keep vascular tone and controls blood pressure [2]. It does this by acting as a barrier for organ and tissue balance and reducing inflammation and thrombosis. Endothelial failure is when the endothelium stops widening blood vessels, stopping cells from multiplying, stopping platelets from sticking together and activating, and becoming more inflammatory and thrombotic. High blood pressure, high cholesterol, and insulin resistance are all things that can lead to endothelial failure and increase the chance of CVD. In conducting arteries, it leads to more lipoprotein oxidation, smooth muscle cell growth, extracellular matrix buildup, cell binding, and thrombus formation. In resistance arteries, it causes inflammation in the walls [3][4][5]. It's important to keep in mind that the signs of capillary failure may show up before hypertension [6]. Essential hypertension is marked by changes in the structure and function of resistance vessels, which cause peripheral arterial resistance to rise [7]. Endothelial dysfunction may cause higher peripheral resistance in a number of ways. This can lead to resistance arteries getting narrower and changing shape (structural, mechanical, and functional changes), which is linked to the development of high blood pressure and its complications [8]. There is a new idea that the endothelium and insulin signaling pathways talk to each other. It is very important for people with high blood pressure, fat, and diabetes to understand how endothelial function and insulin utilization are connected. Insulin resistance, which is a feature of metabolic syndrome, makes it harder for blood vessels to respond and raises the chance of heart disease. In these diseases, insulin resistance and endothelial failure make it harder for blood vessels to widen and cells to take in glucose. There is more inflammation and reactive stress because of this. Lastly, all of these places where damage happens cause atherosclerosis. A lot of people also know that insulin resistance is a sign of prediabetes, which can turn into type II diabetes. Endothelial failure gets worse when you have insulin resistance along with other artery risk factors like high blood pressure and high cholesterol. This makes metabolic syndrome happen [9]. Essential hypertension is marked by changes in the structure and function of resistance vessels, which cause peripheral vascular resistance to rise. The greater peripheral resistance may be caused by endothelial failure in a number of ways. This can lead to resistance arteries getting narrower and changing shape (structurally, mechanically, and functionally). This process has something to do with how high blood pressure starts and gets worse. The high myogenic tone of resistance arteries may be caused by endothelial failure, which turns on the renin-angiotensin system (RAS) and makes endothelin-1, catecholamines, and growth factors. Because of this process, vasoconstriction and changes in the arteries happen. This makes the blood pressure around the edges of the body higher and makes it harder for blood to flow. When inflammation starts in the vessel wall, resistant arteries may change shape even more. This may be linked to endothelial failure [10]. Blood vessel failure and SAH may impact each other in more than one way. At first, the damaged endothelial cells lead to a picture of thrombosis and inflammation that worsens the effects of high blood pressure in the arteries and hurts the organs that receive blood [11]. At this point, most people agree that the connection between high blood pressure and vascular failure is not a straight line. Instead, each factor can affect the other, creating a harmful cycle [12]. These substances include adenosine triphosphate (ATP), adenosine diphosphate (ADP), substance P, bradykinin, histamine, and thrombin. They have been used in original research to show that the tone of vascular smooth muscle is affected by how well endothelial cells work [13]. Also, endothelial cells regularly produce different molecules, including endothelins, cyclooxygenase-dependent vasoconstrictors, and endothelium-derived hyperpolarizing factors, which have an impact on how high blood pressure happens [14]. The goal of this study is to find out if there is a link between signs of endothelial failure and changes in the health of people with chronic high blood pressure. It also tries to figure out how important these factors are for predicting problems from disease and making the right treatment choices.

## Methodology

### A. Study area

A case control study conducted in A case study and monitoring were conducted at Al-Haboubi Hospital, Thi-Qar Province, Iraq. The study period extends from October 10, 2024, to March 10, 2025. A total of n=150 samples were collected from patients and n=100 samples from the control n= 50 group. A gender distribution of n= 52 males and n=48 females in the patient group, and n=26 males and n=24 females in the control group. Were smokers in the patient group n=38 and n=12 were smokers in the control group.

### B. Serological, Chemistry and Hematological Testing

The provided data pertains to laboratory measurements and analyses conducted using ELISA and spectrophotometry techniques. The analyses include the quantification of VCAM-1, ICAM-1, and E-selectin (ng/mL) via ELISA, as well as the measurement of NO ( $\mu\text{M}$ ) using spectrophotometry. The ELISA test was also used to measure CRP (mg/L), IL-6 (pg/mL), TNF- $\alpha$  (pg/mL), MDA (nmol/L), and SOD (U/mL). We also used spectrophotometry to measure metabolic factors like fasting glucose (mg/dL), total cholesterol, LDL-C, HDL-C, and lipids. The wavelength we used was 532 nm.

### C. Statistical analysis

It was SPSS version 26 that was used to look at the numbers. Rates and frequencies are used to show the outcomes. For factors that were spread out normally, two-tailed independent and dependent t-tests were used. It was possible to use the Mann-Whitney U test, the Wilcoxon test, and the Chi-square test on factors that were not spread out regularly. People used

to think that a p-value less than 0.05 was statistically important.

## D. Ethical approval

The study was okay with the Al-Habbobi Teaching Hospital human ethics committee. Everyone who took part in the study was told about it and asked to sign a permission form. The patient was also told that no one else would see his details.

## Results

### A. Sociodemographic and Clinical Characteristics of Hypertensive Patients and Healthy Controls.

There were statistically significant changes in some clinical and socioeconomic factors between the 100 people with high blood pressure in the study group and the 50 healthy people in the control group. The mean age of the patients was  $55.4 \pm 10.2$  years compared to  $50.1 \pm 9.5$  years in the control group, a statistically significant difference ( $p = 0.031$ ). It was the same for both groups in terms of gender distribution: 52% of the patients were men and 48% were women. There were no significant changes between the sexes ( $p = 1.000$  for both). The patient group showed a higher mean body mass index (BMI) of  $29.5 \pm 4.2$  kg/m<sup>2</sup> compared to  $25.1 \pm 3.8$  kg/m<sup>2</sup> in the control group, a highly significant difference ( $p < 0.001$ ), indicating an association between hypertension and overweight and obesity. The percentage of smokers among patients was also found to be higher (38%) compared to 24% in the control group, and the difference was statistically significant ( $p = 0.048$ ). The average duration of hypertension among patients was  $8.2 \pm 3.5$  years, a fact not available in the control group, given that they did not have the disease. Together, these findings indicate that hypertension is associated with increasing age, obesity, and smoking, reinforcing the importance of monitoring these factors for prevention and early intervention as shown in table 1.

Variable	Patients (n=100)	Controls (n=50)	p-value
Age (years)	$55.4 \pm 10.2$	$50.1 \pm 9.5$	0.031
Male (%)	52 (52%)	26 (52%)	1.000
Female (%)	48 (48%)	24 (48%)	1.000
BMI (kg/m <sup>2</sup> )	$29.5 \pm 4.2$	$25.1 \pm 3.8$	<0.001
Smoking (%)	38 (38%)	12 (24%)	0.048
Hypertension Duration (years)	$8.2 \pm 3.5$	-	-

Table 1. Sociodemographic Characteristics of Study Participants.

### B. Endothelial Dysfunction Biomarkers in Hypertensive Patients and Healthy Controls.

In the table 2, biochemical analysis results showed significant differences between hypertensive patients ( $n = 100$ ) and healthy controls ( $n = 50$ ) in the levels of several biomarkers associated with endothelial function. Hypertensive patients recorded significantly higher levels of endothelin-1 (ENDO1), with an average of  $3.5 \pm 1.2$  pg/ml, compared to  $1.8 \pm 0.6$  pg/ml in the control group ( $p < 0.001$ ), reflecting an increase in their vasoconstriction. Levels of the vascular adhesion molecules VCAM-1 and ICAM-1 were also significantly higher in patients, with VCAM-1 averaging  $850 \pm 120$  ng/ml versus  $600 \pm 90$  ng/ml in healthy controls, and ICAM-1 averaging  $320 \pm 50$  ng/ml versus  $220 \pm 40$  ng/ml ( $p < 0.001$  for both), indicating chronic endothelial inflammation. Patients also had elevated E-selectin levels, averaging  $45 \pm 10$  ng/ml versus  $28 \pm 7$  ng/ml in the control group ( $p < 0.001$ ), reflecting increased inflammatory activity. In contrast, nitric oxide (NO) levels, an indicator of vasodilation and healthy endothelial function, were significantly lower in the patient group ( $15.2 \pm 3.4$  μmol/L) compared to healthy controls ( $25.7 \pm 5.1$  μmol/L) ( $p < 0.001$ ), suggesting endothelial dysfunction in hypertensive patients (Table 2).

Biomarker	Patients (n=100)	Controls (n=50)	p-value
Endothelin-1 (pg/mL)	$3.5 \pm 1.2$	$1.8 \pm 0.6$	<0.001
VCAM-1 (ng/mL)	$850 \pm 120$	$600 \pm 90$	<0.001
ICAM-1 (ng/mL)	$320 \pm 50$	$220 \pm 40$	<0.001
E-selectin (ng/mL)	$45 \pm 10$	$28 \pm 7$	<0.001
NO (μM)	$15.2 \pm 3.4$	$25.7 \pm 5.1$	<0.001

Table 2. Endothelial Dysfunction Biomarkers

### C. Inflammatory and Oxidative Stress Markers in Hypertensive Patients and Healthy Controls.

The study found big changes in oxidative stress and inflammatory markers between healthy people ( $n = 50$ ) and people with high blood pressure ( $n = 100$ ). C-reactive protein (CRP) levels, which show general inflammation, were significantly higher in the patients (mean  $5.8 \pm 2.1$  mg/L vs.  $2.3 \pm 1.0$  mg/L in the control group;  $p < 0.001$ ). Also, levels of interleukin-6 (IL-6) rose to  $18.5 \pm 5.2$  pg/ml in cases, compared to  $7.6 \pm 2.4$  pg/ml in healthy controls. The amount of tumor necrosis factor alpha (TNF-α) also went up to  $22.1 \pm 4.8$  pg/ml, compared to  $9.5 \pm 3.2$  pg/ml in the control group ( $p < 0.001$  for both), showing that there was active, long-lasting inflammation linked to high blood pressure. Oxidative stress markers showed similar results, with malondialdehyde (MDA) levels, a byproduct of free radical damage, elevated in patients by an average of  $3.2 \pm 0.7$  nmol/L, compared to  $1.8 \pm 0.5$  nmol/L in the control group ( $p < 0.001$ ). In contrast, levels of superoxide dismutase (SOD), a protective antioxidant, were significantly lower in patients ( $98 \pm 15$  U/ml) compared to healthy controls ( $130 \pm 18$  U/ml) ( $p < 0.001$ ), indicating a weakened antioxidant capacity in hypertensive patients. These findings reflect a

pronounced inflammatory and oxidative state that may contribute to the development of vascular complications in this patient population as shown in the table 3.

Biomarker	Patients (n=100)	Controls (n=50)	p-value
CRP (mg/L)	5.8 ± 2.1	2.3 ± 1.0	<0.001
IL-6 (pg/mL)	18.5 ± 5.2	7.6 ± 2.4	<0.001
TNF-α (pg/mL)	22.1 ± 4.8	9.5 ± 3.2	<0.001
MDA (nmol/L)	3.2 ± 0.7	1.8 ± 0.5	<0.001
SOD (U/mL)	98 ± 15	130 ± 18	<0.001

Table 3. Inflammatory and Oxidative Stress Markers.

## D. Lipid Profile and Fasting Glucose Levels in Hypertensive Patients and Healthy Controls.

The lipid and glucose studies in Table 4 showed that there were important changes between the control group (n=50) and the hypertensive patients (n=100). Total cholesterol levels were much higher in people with high blood pressure (p < 0.001), average 220 ± 35 mg/dL compared to 180 ± 28 mg/dL in the control group. A patient's low-density lipoprotein cholesterol (LDL-C) level rose to 140 ± 30 mg/dL, compared to 110 ± 22 mg/dL in healthy controls (p < 0.001). On the other hand, their HDL-C level fell, averaging 38 ± 6 mg/dL compared to 50 ± 7 mg/dL in the control group (p < 0.001). Triglyceride levels were also higher in people with high blood pressure (180 mg/dL on average vs. 120 mg/dL in healthy controls; p < 0.001). Hypertensive patients had significantly higher fasting blood sugar levels than the control group, with an average of 108 ± 12 mg/dL vs. 92 ± 10 mg/dL (p < 0.001). These results make it clear that metabolic problems are present in people with high blood pressure, which may raise the risk of heart disease (Table 4).

Biomarker	Patients (n=100)	Controls (n=50)	p-value
Total Cholesterol (mg/dL)	220 ± 35	180 ± 28	<0.001
LDL-C (mg/dL)	140 ± 30	110 ± 22	<0.001
HDL-C (mg/dL)	38 ± 6	50 ± 7	<0.001
Triglycerides (mg/dL)	180 ± 40	120 ± 25	<0.001
Fasting Glucose (mg/dL)	108 ± 12	92 ± 10	<0.001

Table 4. Lipid Profile and Metabolic Parameters.

## E. Correlation of Endothelial Dysfunction Biomarkers with Clinical Parameters in Hypertensive Patients.

Correlational analysis results revealed strong, statistically significant relationships between biomarker variables and endothelial function with various risk factors. Levels of endothelin-1, VCAM-1, ICAM-1, and E-selectin were significantly and positively correlated with age, body mass index (BMI), duration of hypertension, and levels of inflammation (CRP, IL-6, TNF-α), as well as total lipids, LDL, and triglycerides, while they were negatively correlated with HDL. A significant negative correlation was also observed between nitric oxide (NO) levels and these parameters, reflecting the role of NO in improving endothelial function. All correlations were significant at p < 0.01, confirming a close relationship between endothelial dysfunction and metabolic and inflammatory factors associated with hypertension as shown in table 5.

Variable	Endothelin-1 (pg/mL)	VCAM-1 (ng/mL)	ICAM-1 (ng/mL)	E-selectin (ng/mL)	NO (µM)	p-value
Age (years)	0.42**	0.38**	0.34*	0.30*	-0.29*	<0.01
BMI (kg/m <sup>2</sup> )	0.50**	0.45**	0.40**	0.37**	-0.41**	<0.001
Hypertension	0.56**	0.48**	0.43**	0.39**	-0.44**	<0.001
Duration (years)						
CRP (mg/L)	0.60**	0.53**	0.50**	0.46**	-0.49**	<0.001
IL-6 (pg/mL)	0.55**	0.50**	0.47**	0.42**	-0.45**	<0.001
TNF-α (pg/mL)	0.58**	0.52**	0.49**	0.44**	-0.47**	<0.001
Total Cholesterol (mg/dL)	0.40**	0.38**	0.36**	0.32*	-0.35**	<0.01
LDL-C (mg/dL)	0.45**	0.42**	0.38**	0.35**	-0.38**	<0.01
HDL-C (mg/dL)	-0.38**	-0.35**	-0.32*	-0.30*	0.34**	<0.01
Triglycerides (mg/dL)	0.48**	0.44**	0.41**	0.38**	-0.40**	<0.001

Table 5. Pearson Correlation Between Endothelial Dysfunction Biomarkers and Clinical Parameters.

## Discussion

Endothelial cells make prostaglandins, nitric oxide (NO), and other factors that relax blood vessels. These cells control the tone of the blood vessels. In addition, good endothelium helps keep organs and tissues in balance and blood pressure under control. It also helps keep vascular tone and has anti-inflammatory, antithrombotic, and antioxidant effects. This study shows the social, behavioral, and clinical traits of people with high blood pressure and healthy subjects. They were older (55.4 ± 10.2 years vs. 50.1 ± 9.5 years, P=0.031) and had a higher BMI (29.5 ± 4.2 vs. 25.1 ± 3.8, P<0.001). Patients were more likely to smoke (38% vs. 24%), which showed that the disease was long-lasting. The average length of time someone had hypertension was 8.2 ± 3.5 years. So, high levels of apoptotic microparticles can predict serious endothelial failure, even if other risk factors like high blood pressure, high cholesterol, smoking, diabetes, age, or sex are not present [15]. Look into it Endothelin-1, VCAM-1, ICAM-1, and E-selectin levels were significantly higher in people with high blood pressure (P<0.001), which suggests that endothelial function is impaired. On the other hand, NO levels were much lower (P<0.001), which

means that vasodilation was not working as well. These results stress the circulatory problems caused by high blood pressure. Researchers looked at 16 healthy people, 272 people with carotid artery atherosclerosis, and 204 people who had developed coronary heart disease. It was discovered that people with coronary heart disease and carotid artery atherosclerosis had more E-selectin and ICAM-1 in their bodies. In the control group, there was also a clear link between the amount of E-selectin and the amount of HDL cholesterol. In the early stages of atherosclerosis, E-selectin may help white blood cells move along the endothelium if these results are right. High amounts of ICAM-1 in the blood are also linked to atherosclerosis. This is because ICAM-1 helps white blood cells stick to and move through arterial cells. That's the reason Hwang [16]. Soluble E-selectin and ICAM-1 could be used as biomarkers for endothelial activity in coronary heart disease and atherosclerosis of the arteries, but this hasn't been shown in live tests yet. A cohort study was done on a group of people by Tzoulaki. They were interested in how ICAM-1, sVCAM-1, and sE-selectin, which show how well blood channels work, are linked to the development of peripheral atherosclerosis. sICAM-1, IL-6, and CRP all strongly suggested that atherosclerosis would happen in the lower limbs. These genes ICAM-1, IL-6, and CRP are thought to show how much worse atherosclerosis is getting [17]. In the blood, E-selectin is only found on active endothelium, so its presence is thought to show that endothelial activation has occurred. In the past, higher levels of ICAM-1 and VCAM-1 were thought to be a sign of endothelial activation [18][19]. Hypertensive patients had significantly higher levels of CRP, IL-6, TNF- $\alpha$ , and MDA, indicating increased inflammation and oxidative stress. SOD levels were lower in patients, suggesting reduced antioxidant activity. These findings suggest an inflammatory and oxidative imbalance in hypertension. Different cytokines are known to show that endothelial cells aren't working properly in dysmetabolic situations and may play a part in the atherosclerosis process. There are certain chemicals in the body called inflammation cytokines that make endothelial adhesion molecules (E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1)) come out. These chemicals make it possible for white blood cells to cross over vascular cells. Total cholesterol, LDL-C, triglycerides, and fasting glucose levels were higher in hypertension patients than in controls. HDL-C levels were lower in these patients. These results show that people with high blood pressure have problems with how their bodies use sugars and fats. When you have high triglyceridemia, the protective high-density lipoproteins (HDL) levels drop. This makes the cholesteryl ester amount in the lipoprotein core go down [20]. Also, the production of low-density lipoproteins (LDL) is sped up by the lack of unesterified and esterified cholesterol and phospholipids, which are thick and small and have stronger effects on atherosclerosis. Endothelial and capillary failure may or may not cause high blood pressure [21]. This is still being debated. In spite of this, the close link between the two conditions means that improving capillary function might be a good treatment goal soon [22].

## Conclusion

The study found that people with high blood pressure were older, had a higher body mass index (BMI), and were more likely to smoke than healthy controls. Endothelial failure biomarkers like Endothelin-1, VCAM-1, ICAM-1, and E-selectin levels were much higher in patients than in controls. NO levels were also lower. Also, levels of inflammation markers like CRP, IL-6, and TNF- $\alpha$  were high, as well as total cholesterol, LDL-C, and triglycerides. HDL-C levels went down, and blood glucose levels were higher when the person woke up. Researchers discovered that these measurements were positively related to age, BMI, and the length of time that a person has had high blood pressure. This suggests that endothelial failure in people with high blood pressure is connected to increased inflammation, oxidative stress, and lipid problems.

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