

Evaluation of Serum Nitric Oxide Levels Across Ethnic Groups and Its Association with Hypertension in Aceh

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Abstract

Hypertension is a global health problem, affecting an estimated 1.4 billion people worldwide. The pathophysiology of hypertension is multifactorial and involves complex mechanisms, one of which is endothelial dysfunction, marked by disruption of NO production and its bioavailability. NO is a key modulator of vasodilation that takes part in controlling vascular homeostasis. This research aims to evaluate NO serum among three ethnicities in Aceh to assess its role in hypertension pathogenesis. This observational analytic research included 120 participants, comprising 90 hypertensive patients from three ethnic groups (Gayo, Aneuk Jamee, and Acehnese), with 30 participants in each ethnic group, and 30 normotensive individuals who served as the control group. The NO serum level among their ethnicities was analysed by the Kruskal-Wallis test, while the association between NO levels across three ethnicities and the control group (not hypertensive patients) was assessed by the Spearman test. The study found that the Gayo group had the highest NO level (51.79 pg/mL), followed by Aneuk Jamee (44.27 pg/mL) and the Acehnese group (31.87 pg/mL), with significant differences ($p < 0.001$). The correlation analysis showed a weak relation, both across the three ethnic groups and when compared to the control group ($p > 0.05$). Serum nitric oxide (NO) levels differ significantly among ethnic groups; however, no significant association was observed between ethnic groups and the incidence of hypertension.

Keywords: Ethnic, Hypertension, Nitric Oxide (NO).

1. INTRODUCTION

Hypertension is a medical condition characterized by increased blood pressure above normal levels ($\geq 140/90$ mmHg). Hypertension is estimated to affects 1.4 billion individuals aged 30–79 years worldwide (World Health Orgnaization, 2025). Among 54% of adults diagnosed with hypertension, only 42% receive treatment, and only 21% of patients achieve target blood pressure levels. The 2023 Indonesian Health Survey (SKI) documented a hypertension prevalence of 30.8% among individuals aged ≥ 18 years in Indonesia, with a prevalence of 22.6% in Aceh Province (Kementerian Kesehatan Republik Indonesia, 2023).

Much remains to be understood concerning the underlying mechanism of hypertension. Various physiological mechanisms are involved in blood pressure regulation, and disturbances in these may result in pathogenesis of essential hypertension. Multiple interconnected factors are likely involved in elevating blood pressure in hypertensive patients, with their relative contributions varying in individuals. The renin–angiotensin system, obesity, sodium consumption, sympathetic nervous system, and insulin resistance are among the most extensively studied factors. Other factors, including genetics, alterations in endothelin and nitric oxide, as well as neurovascular abnormalities, have also been studied over the years (Beevers et al., 2001; Hall et al., 2024).

The vascular endothelium plays a critical role in maintaining vascular homeostasis through various functions, including the modulation of haemostasis, vascular permeability, immune response, and vascular tone (Sturtzel, 2017). One of the key mechanisms underlying these functions is the nitric oxide (NO) signalling pathway (Incalza et al., 2018). Nitric oxide is a gaseous free radical with strong oxidative characteristics that is extremely reactive and diffusible. It is synthesised by three subtypes of the nitric oxide synthase (NOS) enzyme, each with distinct expression patterns and functions: neuronal NOS (nNOS/NOS1), inducible NOS (iNOS/NOS2), and endothelial NOS (eNOS/NOS3). In general, these enzymes catalyse the production of NO and L-citrulline from L-arginine and O₂, using electrons donated by nicotinamide adenine dinucleotide phosphate (NADPH) (Forstermann & Sessa, 2012; Gresele et al., 2019). NO generated by endothelial cells acts as a strong vasodilator with anti-inflammatory and antioxidant properties, making it essential for maintaining normal vascular function (Cyr et al., 2020).

Endothelial dysfunction, characterised by reduced production and responsiveness to nitric oxide (NO), leads to an imbalance in the vascular system and promotes pro-inflammatory and pro-thrombotic conditions, as well as decreased vascular elasticity. This condition represents an early stage in the pathogenesis of hypertension and may occur even before clinical hypertension develops. In hypertension, structural and functional changes in resistance arteries further increase peripheral vascular resistance, partly driven by reduced NO bioavailability and enhanced vasoconstriction (Gallo et al., 2022).

Given the central part of NO in vascular regulation and hypertension, evaluating serum NO levels may provide important insights into the underlying mechanisms of this disease. In addition, potential variations in biological responses among different ethnic groups may influence NO levels and vascular function, which could lead to differing prevalence rates of hypertension among these groups. This study aims to evaluate serum nitric oxide levels in three ethnic groups in Aceh to better understand its role in hypertension.

2. RESEARCH METHODOLOGY

The research took place in Aceh Province between April 2022 and January 2023. It began with the collection of subjects' epidemiological data, followed by assessment of hypertension indicators and measurement of NO levels using the ELISA method at the RSUZA Laboratory in Banda Aceh. The study participants were hypertension patients referred from regional hospitals throughout Aceh Province, comprising three ethnic groups (Gayo, Aneuk Jamee, and Aceh), with 30 individuals in each group, and also 30 normotensive individuals serving as control group. The comparisons of NO level among the three ethnic groups were analysed using the Kruskal-Wallis test with a significance level of $p < 0.05$. The relationship of NO levels among hypertensive subjects across ethnic groups and with the control group (non-hypertensive subjects) was assessed using Spearman's rho correlation ($r = 1$).

2.1 Materials and Equipment

The equipment used in this study included a centrifuge, vortex mixer, ELISA reader (Biorad), micropipette (Finnipipette), guide tube, incubator, 98 well plate, and strip plate. The materials consisted of blood serum, sodium nitrite, reagent 1, reagent 2, chromogenic reagent, 96% ethanol, phosphate-buffered saline (PBS), and distilled water.

2.2 Research Procedures

Standard dilution was initiated by diluting a 2 mmol/L sodium nitrite solution as the standard, using distilled water to obtain a series of concentrations. The recommended dilutions were 300, 200, 150, 100, 40, 20, 10, and 0 $\mu\text{mol/L}$. Subsequently, sample preparation (pre-treatment) was performed by mixing reagents in both standard and sample tubes. An amount of 100–300 μL of sample was transferred into the corresponding standard and sample tube, followed by the addition of 200 μL of Reagent 1 and 100 μL of Reagent 2. The mixtures were incubated for 15 minutes at room temperature and centrifuged at 3100 g for 10 minutes. After centrifugation, 160 μL of the supernatant from each standard and sample tube was collected for further analysis.

The next stage was the NO assay reaction. In this step, the sample supernatant (160 μL) and chromogenic reagent (80 μL) were added to both standard and sample tubes and mixed thoroughly for 2 minutes. The mixtures were then incubated at room temperature for 15 minutes. Optical density (OD) was subsequently measured as soon as possible using a microplate reader at a wavelength of 550 nm.

3. RESULTS AND DISCUSSION

3.1. Results

Blood pressure and NO levels were measured in a total of 120 hypertensive patients from three ethnic groups (Gayo, Aneuk Jamee, and Aceh), with 30 patients from each group, and 30 normotensive controls. The characteristics of NO levels in hypertensive patients based on sex and ethnicity are presented in Table 1.

Table 1. The characteristic and distribution of NO serum level in hypertensive patient

Variable	N	Mean ($\mu\text{mol/L}$)	Standard Deviation	Minimum	Maximum	P value
Sex						
- Men	60	41.40	19.58	3.73	96.43	
- Women	60	43.89	27.76	9.21	167.53	
Ethnic						
- Gayo	30	51.79	30.01	18.42	167.53	<0.001
- Aneuk Jamee	30	44.27	18.04	23.56	128.02	
- Acehnese	30	31.87	16.67	3.73	77.52	

Table 1 shows that, based on sex, the mean NO level was higher in females (43.89 $\mu\text{mol/L}$) than in males (41.40 $\mu\text{mol/L}$). Based on ethnicity, the highest mean NO level was observed in the Gayo group (51.79 $\mu\text{mol/L}$), followed by Aneuk Jamee (44.27 $\mu\text{mol/L}$), and the lowest in the Aceh group (31.87 $\mu\text{mol/L}$). The Kruskal–Wallis test showed a statistically significant difference in serum NO levels among the three ethnic groups ($p < 0.001$).

Table 2. The Relationship between NO level in hypertensive patients and control group across 3 ethnics

Variable		N	Coefficient Correlation (r)	p-value
Gayo	Aneuk Jamee	30	-0,004	0,983
	Acehnese	30	-0,003	0,989
	Control	30	0,070	0,714
Aneuk Jamee	Acehnese	30	-0,178	0,347
	Control	30	0,083	0,663
Acehnese	Control	30	-0,026	0,893

Table 2 shows the relationship between hypertension incidence and ethnic groups in Aceh based on NO titres, including comparisons with a non-hypertensive control group. In the Gayo group, correlations with Aneuk Jamee ($r = -0.004$; $p = 0.983$), Acehnese ($r = -0.003$; $p = 0.989$), and the control group ($r = 0.070$; $p = 0.714$) were very weak and not statistically significant. Similarly, in the Aneuk Jamee group, no significant correlations were found with the Acehnese group ($r = -0.178$; $p = 0.347$) or the control group ($r = 0.083$; $p = 0.663$). In the Acehnese group, comparison with the control group also showed no significant correlation ($r = -0.026$; $p = 0.893$). Overall, these findings indicate that NO levels did not demonstrate a significant correlation with the incidence of hypertension across the ethnic groups in this study.

3.2. Discussion

Nitric oxide has been suggested to have a role in the complex pathways that lead to hypertension. Endothelial cells generate NO from L-arginine using the eNOS enzyme, which is found in the caveolae structure. Caveolin-1 binds to calmodulin and prevents eNOS from being activated. But when calcium attaches to calmodulin, caveolin-1 is pushed out of the way, and eNOS can start functioning and produce NO. Subsequently, NO migrates into vascular smooth muscle cells and relaxes them by activating the enzyme guanylate cyclase. This leads to an increase in cyclic guanosine monophosphate (cGMP) levels, which causes vasodilation (Bolad & Delafontaine, 2005). NO plays an important role in controlling blood pressure by dilating blood vessels and enhancing blood flow throughout the body. Reduced NO levels result in vasoconstriction and increased vascular tension, which contribute to elevated blood pressure. Low NO levels have been associated with the development of hypertension (Ahmad et al., 2018).

This study evaluated the NO levels of 90 hypertensive patients from three distinct ethnic groups. The Gayo group had the highest NO levels, followed by the Aneuk Jamee group, while the Acehnese group had the lowest. Overall, NO levels in all subjects exceeded the normal reference range. The typical range of serum NO can differ based on the laboratory and measuring techniques; nonetheless, it is commonly reported to be between 0 and 50 μM (micromolar) or 0 and 3 $\mu\text{mol/L}$ in healthy adults (Ghasemi et al., 2010). Another study reported a median serum NO level of 25.0 $\mu\text{mol/L}$ (19.0–37.0), with an optimal cutoff value of 30.5 $\mu\text{mol/L}$ for predicting cardiovascular disease (Bahadoran et al., 2019).

Elevated NO levels can affect multiple organ systems. Excessively high NO concentrations in the blood may lead to excessive vasodilation, resulting in a marked decrease in blood pressure and symptoms such as dizziness and syncope. In addition, increased NO levels can influence cardiac function by reducing myocardial contractility and potentially triggering arrhythmias. Elevated NO in the neurological system correlates with symptoms like headaches, migraines, and disorientation. On the other hand, although NO possesses antimicrobial properties, imbalances in its levels may disrupt immune regulation and potentially affect the body's response to infections, leading to an increased susceptibility to various pathogens and a diminished ability to fight off illness (Forstermann & Sessa, 2012; Puzserova & Bernatova, 2016).

The nitric oxide (NO) plays an important role in sustaining vascular homeostasis through mechanisms such as vasodilation. As a result, high NO levels rarely contribute to the development of hypertension but rather have the opposite impact. Within specific limits, higher NO levels are more closely associated with vasodilatory effects than an increased risk of hypertension (Dinh et al., 2014). In addition, elevated serum NO levels may be influenced by multiple sources, including endogenous production (e.g., iNOS activation), impaired renal function, and exogenous exposure to nitrates (NO_3^-) and nitrites (NO_2^-). Limitations in measurement methods, which are not yet able to

simultaneously assess $\text{NO}_3^-/\text{NO}_2^-$ levels in serum, urine, and dietary intake, may contribute to inconsistencies in research findings. Generally, under fasting conditions, NO metabolites reflect systemic NO production, whereas under normal dietary conditions, serum NO levels more accurately represent total exposure to nitrates and nitrites from both endogenous and exogenous sources (Gilchrist & Shore, 2017).

The elevated serum NO levels in hypertensive study participants should not necessarily be associated with preserved endothelial function. In hypertension, there is increased oxidative stress, which promotes the production of reactive oxygen species (ROS) such as superoxide anions. Nitric oxide reacts with superoxide anions and forms peroxynitrite (ONOO^-). This interaction ultimately leads to a decrease in vasodilatory NO and an increase in inactive NO metabolite production. Furthermore, profound oxidative stress can lead to eNOS uncoupling, a condition in which eNOS generates superoxide rather than NO, further impairing endothelial function. Therefore, in hypertensive patients, an elevation in serum NO levels can be observed in the presence of endothelial dysfunction and impaired vascular function. Since NO in this study was assessed as its metabolites, elevated metabolites should be interpreted as dysfunctional NO, rather than the functional bioavailability of NO (Janaszak-Jasiecka et al., 2023; Li et al., 2015).

In this study, female subjects exhibited higher NO levels compared to males. This finding contradicts with previous studies reporting that mean NO levels in males aged 20–29 years were significantly higher than in females (25.1 $\mu\text{mol/L}$ vs 22.7 $\mu\text{mol/L}$) and that higher serum NO levels in females were associated with greater body mass index and higher fasting glucose levels (Ghasemi et al., 2008). Another study involving 263 subjects aged 20–69 years showed that NO levels increased significantly with age in females but not in males. In younger individuals (<40 years), females had significantly lower NO levels than males, whereas in those aged ≥ 40 years, no significant difference was observed between sexes (Watanabe et al., 2000).

The correlation analysis in this study revealed no significant link between NO levels and hypertension across ethnic groups, nor when compared to the control group (non-hypertensive subjects). Prior research has demonstrated a negative correlation between serum NO levels and systolic blood pressure ≥ 160 mmHg in males ($r = -0.523$; $p = 0.002$), alongside elevated NO levels in males with grade 1 hypertension, followed by a significant drop in NO levels in grade 2 hypertension (Ghasemi et al., 2011). Another study also found that NO levels decrease as blood pressure increases (Sharma et al., 2024). Under physiological conditions, endothelial-derived NO induces vasodilatory effects and inhibits platelet aggregation and leukocyte adhesion. However, in hypertension, increased oxidative stress reduces NO bioavailability through several mechanisms, including inactivation of ROS, decreased eNOS, and disruption of NO signalling pathways. Consequently, reduced NO-mediated vasodilation and increased vasoconstriction contribute to elevated blood pressure and endothelial dysfunction (Goch et al., 2009).

Current study reported that there is no scientific evidence confirming a direct influence of ethnicity (race) on the incidence of hypertension (Norris, 2009). A meta-analysis study, however, found that racial differences may affect NO bioavailability, as shown by nitrite/nitrate (NO_x) levels in plasma. NO_x levels are influenced by endothelial production, oxidative stress, renal function, and dietary factors. The meta-analysis indicated that African Americans tend to have lower vasodilatory responses compared to European Americans, which is thought to be associated with reduced NO production. In addition, the differences were observed in sodium excretion regulation and responses to stimuli such as weight loss, mental stress, and hormone therapy. Overall, basal NO_x levels

are relatively similar across racial groups under controlled dietary conditions; however, NO-dependent responses to various stimuli show significant racial differences (Mata-Greenwood & Chen, 2008).

Hypertension is a multifactorial condition, influenced by complex interactions among biological, environmental, and behavioural factors. In Aceh, various determinants contribute to the incidence of hypertension, including the potential role of ethnicity in modulating individual risk. There has been no specific study evaluating the relationship between ethnic variation in Aceh and hypertension, particularly in relation to nitric oxide (NO) bioavailability. Most ethnic groups in Aceh strongly stick to traditional ways of eating that are closely linked to cultural ceremonies. Social events such as weddings, funerals, religious celebrations, communal feasts, and family visits commonly involve the consumption of large quantities and varieties of traditional foods. These foods are generally high in carbohydrates, saturated fats, protein, and salt, while relatively low in fibre. In a cultural context, these kinds of eating habits may raise the risk of high blood pressure. Risk factors contributing to the condition include unhealthy lifestyles such as poor diet, physical inactivity, and smoking, as well as other factors including genetic predisposition, obesity, psychological stress, and environmental pollution exposure (Masyudi et al., 2022).

Polymorphisms of the eNOS gene are associated with variations in eNOS expression and the production of NO. Several studies have proposed that these polymorphisms are related to cardiovascular diseases. For instance, the polymorphisms NOS3-786T>C and 894G>T are associated with hypertension, myocardial infarction, and other cardiovascular disorders (Tran et al., 2022). Many studies have also shown that the eNOS polymorphisms are not the same across ethnicity. There are reported differences, for example, between Caucasians and African Americans and between White, Black, and mixed Colombian populations (Serrano et al., 2010; Tanus-Santos et al., 2001). A study performed in Italy found another novel eNOS allele that highlights the genetic diversity of eNOS (Bolli et al., 2007). Such ethnic variation in eNOS polymorphisms may contribute to differences in circulating NO levels between populations. However, genetic variation in eNOS was not evaluated in the present study.

Nitrate intake from daily food consumption may affect the production of nitric oxide (NO). Ethnic dietary variations of Aceh may cause differences in nitrate intake and consequently endogenous NO production. Vegetables are the major dietary source of plant-based nitrates, which are associated with positive health effects. Unlike plant-based nitrates and nitrites, consumption of processed and red meats is linked to a greater likelihood of developing cardiovascular disease (Zhong et al., 2025). The highland populations of the Gayo and Aneuk Jamee ethnic groups consume locally grown fruits and vegetables (Syamsuardi et al., 2022). In contrast, meat-based cuisine, such as *sie reuboh*, the signature dish of Aceh Besar, is one of the cultural foods of most Acehnese (Arprassinta et al., 2024). These differences in dietary patterns among ethnicities may contribute to variation in circulating NO levels. The NO levels of different Acehnese groups were determined in the present study, without consideration of their diets.

This study suggests that ethnic variables alone cannot account for elevated NO levels. Changes in serum NO levels are more likely indicative of intricate interactions with other factors, including dietary habits and the existence of metabolic disorders that may aggravate hypertension, rather than being influenced by ethnic variables alone. However, this study has several limitations. The intake of dietary nitrate and nitrite as well as the eNOS genetic variations were not directly assessed in the study participants. Thus, the influence of diet patterns and genetics on the differences in serum NO levels are hypothetical at best and should be interpreted with great care.

4. CONCLUSION

The study results indicate that NO levels in hypertensive patients in Aceh differ among ethnic groups, with statistically significant variations in mean levels and titre quantities. The Gayo group demonstrated the highest values in comparison to the Aneuk Jamee and Acehnese groups. However, no significant association was found between NO levels and the incidence of hypertension across ethnic groups. These findings suggest that although there are indications of endothelial dysfunction among ethnic groups, this factor does not play a direct role in the occurrence of hypertension.

REFERENCES

- Ahmad, A., Dempsey, S. K., Daneva, Z., Azam, M., Li, N., Li, P.-L., & Ritter, J. K. (2018). Role of Nitric Oxide in the Cardiovascular and Renal Systems. *International Journal of Molecular Sciences*, 19(9), 2605. <https://doi.org/10.3390/ijms19092605>
- Arprassinta, A. P., Khasanah, D. M., Stefanie, D., Finatsiyatull, & Rosida, D. (2024). Makanan Tradisional Wilayah Aceh. *Food Science and Technology*, 9, 60–68.
- Bahadoran, Z., Mirmiran, P., Tahmasebinejad, Z., Azizi, F., & Ghasemi, A. (2019). Serum nitric oxide metabolites and hard clinical endpoints: a population-based prospective study. *Scandinavian Cardiovascular Journal*, 53(4), 176–182. <https://doi.org/10.1080/14017431.2019.1618493>
- Beevers, G., Lip, G. Y. H., & O'Brien, E. (2001). The pathophysiology of hypertension. *BMJ*, 322(7291), 912.1-916. <https://doi.org/10.1136/bmj.322.7291.912>
- Bolad, I., & Delafontaine, P. (2005). Endothelial dysfunction: its role in hypertensive coronary disease. *Current Opinion in Cardiology*, 20(4), 270–274. <https://doi.org/10.1097/01.hco.0000167719.37700.1d>
- Bolli, P., Sticchi, E., Abbate, R., & Fatini, C. (2007). A novel allele of eNOS gene in the Italian population: The actual essence of intron 4 polymorphism. *Nitric Oxide*, 16(3), 392–394. <https://doi.org/10.1016/j.niox.2006.12.005>
- Cyr, A. R., Huckaby, L. V., Shiva, S. S., & Zuckerbraun, B. S. (2020). Nitric Oxide and Endothelial Dysfunction. *Critical Care Clinics*, 36(2), 307–321. <https://doi.org/10.1016/j.ccc.2019.12.009>
- Dinh, Q. N., Drummond, G. R., Sobey, C. G., & Chrissobolis, S. (2014). Roles of Inflammation, Oxidative Stress, and Vascular Dysfunction in Hypertension. *BioMed Research International*, 2014, 1–11. <https://doi.org/10.1155/2014/406960>
- Forstermann, U., & Sessa, W. C. (2012). Nitric oxide synthases: regulation and function. *European Heart Journal*, 33(7), 829–837. <https://doi.org/10.1093/eurheartj/ehr304>
- Gallo, G., Volpe, M., & Savoia, C. (2022). Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Frontiers in Medicine*, 8, 798958. <https://doi.org/10.3389/fmed.2021.798958>
- Ghasemi, A., Zahedi Asl, S., Mehrabi, Y., Saadat, N., & Azizi, F. (2008). Serum nitric oxide metabolite levels in a general healthy population: Relation to sex and age. *Life Sciences*, 83(9–10), 326–331. <https://doi.org/10.1016/j.lfs.2008.06.010>
- Ghasemi, A., Zahediasl, S., & Azizi, F. (2010). Reference values for serum nitric oxide metabolites in an adult population. *Clinical Biochemistry*, 43(1–2), 89–94. <https://doi.org/10.1016/j.clinbiochem.2009.09.011>
- Ghasemi, A., Zahediasl, S., Syedmoradi, L., & Azizi, F. (2011). Association between serum nitric oxide metabolites and hypertension in a general population. *International Angiology: A Journal of the International Union of Angiology*, 30(4), 380–387.
- Gilchrist, M., & Shore, A. (2017). Inorganic Nitrate: Marker or Mediator of Mortality? *Journal of the American Heart Association*, 6(11), 007782. <https://doi.org/10.1161/JAHA.117.007782>

- Goch, A., Banach, M., Mikhailidis, D. P., Rysz, J., & Henryk Goch, J. (2009). Endothelial Dysfunction in Patients with Noncomplicated and Complicated Hypertension. *Clinical and Experimental Hypertension*, 31(1), 20–30. <https://doi.org/10.1080/10641960802409846>
- Gresele, P., Momi, S., & Guglielmini, G. (2019). Nitric oxide-enhancing or -releasing agents as antithrombotic drugs. *Biochemical Pharmacology*, 166, 300–312. <https://doi.org/10.1016/j.bcp.2019.05.030>
- Hall, J. E., Omoto, A. C. M., Wang, Z., Mouton, A., Li, X., & Hall, M. E. (2024). Pathophysiology of Hypertension. In *Hypertension* (pp. 71–86). Elsevier. <https://doi.org/10.1016/B978-0-323-88369-6.00005-0>
- Incalza, M. A., D’Oria, R., Natalicchio, A., Perrini, S., Laviola, L., & Giorgino, F. (2018). Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascular Pharmacology*, 100, 1–19. <https://doi.org/10.1016/j.vph.2017.05.005>
- Janaszak-Jasiecka, A., Płoska, A., Wierońska, J. M., Dobrucki, L. W., & Kalinowski, L. (2023). Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. *Cellular & Molecular Biology Letters*, 28(1), 21. <https://doi.org/10.1186/s11658-023-00423-2>
- Kementerian Kesehatan Republik Indonesia. (2023). *Survei Kesehatan Indonesia (SKI)*.
- Li, Q., Youn, J.-Y., & Cai, H. (2015). Mechanisms and consequences of endothelial nitric oxide synthase dysfunction in hypertension. *Journal of Hypertension*, 33(6), 1128–1136. <https://doi.org/10.1097/HJH.0000000000000587>
- Masyudi, M., Yani, E. D., Ridhwan, M., Husna, H., & Rafsanjan, T. M. (2022). The Influence Risk Factors of Hypertension at the Community Coverage with the 35-54 years old: A mini study in the Meuraxa Health Community Center, Banda Aceh, Indonesia 2022. 199-208. *Proceedings of International Conference on Multidiciplinary Research*, 199–208.
- Mata-Greenwood, E., & Chen, D.-B. (2008). Racial Differences in Nitric Oxide—Dependent Vasorelaxation. *Reproductive Sciences*, 15(1), 9–25. <https://doi.org/10.1177/1933719107312160>
- Norris, M. (2009). *Curing the blood and balancing life: understanding, impact and health seeking behaviour following stroke in Central Aceh, Indonesia*. Brunel University School of Health Sciences and Social Care.
- Puzserova, A., & Bernatova, I. (2016). Blood Pressure Regulation in Stress: Focus on Nitric Oxide-Dependent Mechanisms. *Physiological Research*, 65, 309–342. <https://doi.org/10.33549/physiolres.933442>
- Serrano, N. C., Díaz, L. A., Casas, J. P., Hingorani, A. D., Moreno-De-Luca, D., & Páez, M. C. (2010). Frequency of eNOS polymorphisms in the Colombian general population. *BMC Genetics*, 11(1), 54. <https://doi.org/10.1186/1471-2156-11-54>
- Sharma, A., Patil, S. M., Dasgupta, A., Podder, A., Kumar, J., Sindwani, P., & Karumuri, P. (2024). Unravelling the Intricate Relationship Between Oxidative Stress and Endothelial Dysfunction in Hypertension. *Cureus*, 16(5), e61245. <https://doi.org/10.7759/cureus.61245>
- Sturtzel, C. (2017). Endothelial Cells. In *The Immunology of Cardiovascular Homeostasis and Pathology* (pp. 71–91). Springer, Cham. https://doi.org/10.1007/978-3-319-57613-8_4
- Syamsuardi, S., Nurainas, N., Taufiq, A., Harmawan, T., & Suwardi, A. B. (2022). Aneuk Jamee traditional foods in the South Aceh District, Indonesia. *Biodiversitas Journal of Biological Diversity*, 23(1), 443–454. <https://doi.org/10.13057/biodiv/d230146>
- Tanus-Santos, J. E., Desai, M., & Flockhart, D. A. (2001). Effects of ethnicity on the distribution of clinically relevant endothelial nitric oxide variants. *Pharmacogenetics*, 11(8), 719–725. <https://doi.org/10.1097/00008571-200111000-00011>
- Tran, N., Garcia, T., Anika, M., Ali, S., Ally, A., & Nauli, S. M. (2022). Endothelial Nitric Oxide Synthase (eNOS) and the Cardiovascular System: in Physiology and in Disease States. *American Journal of Biomedical Science & Research*, 15(2), 153–177.

- Watanabe, T., Akishita, M., Toba, K., Kozaki, K., Eto, M., Sugimoto, N., Kiuchi, T., Hashimoto, M., Shirakawa, W., & Ouchi, Y. (2000). Influence of sex and age on serum nitrite/nitrate concentration in healthy subjects. *Clinica Chimica Acta*, 301(1–2), 169–179. [https://doi.org/10.1016/S0009-8981\(00\)00340-5](https://doi.org/10.1016/S0009-8981(00)00340-5)
- World Health Organization. (2025). *Hypertension*. WHO Fact Sheets. <https://www.who.int/news-room/fact-sheets/detail/hypertension?>
- Zhong, L., Hodgson, J. M., Lewis, J. R., Blekkenhorst, L. C., Bondonno, N. P., Sim, M., Woodman, R. J., & Bondonno, C. P. (2025). Nitrate and nitrite food composition database: an update and extensive deep dive. *The American Journal of Clinical Nutrition*, 121(5), 1124–1136. <https://doi.org/10.1016/j.ajcnut.2025.01.031>