KESANS: International Journal of Health and Science
2808-7178 / 2808-7380
http://kesans.rifainstitute.com/index.php/kesans/index

Peripheral Blood GPX1 mRNA Expression in Adults Aged 50–60 Years with Hypertension and Normotension: A Cross-Sectional Comparative Study

[1]Yohana*, [2]Meiyanti, [3]Eveline Margo, [4]Meutia Atika Faradilla
[1]Department Biochemistry, Universitas Trisakti, Indonesia*; email: dryohana@trisakti.ac.id
[2]Department Pharmacology and Pharmacy, Universitas Trisakti, Indonesia; email: meiyanti@trisakti.ac.id
[3]Department Physiology, Universitas Trisakti, Indonesia; email: evelinemargo@trisakti.ac.id
[4]Department Biochemistry, Universitas Trisakti, Indonesia; email: meutia.atika@trisakti.ac.id
*Correspondence

Article Information
Submitted: **24 August 2026**
Accepted: **07 September 2026**
Publish: **16 September 2026**

Keyword: mRNA; GPX; Hypertension;

Abstract
Introduction: *Glutathione peroxidase 1 (GPX1) is an important intracellular antioxidant that protects vascular tissue by reducing hydrogen peroxide and lipid hydroperoxides. Impaired GPX1 regulation may contribute to oxidative stress, endothelial dysfunction, and hypertension.* ***Objective:*** *This study evaluated peripheral blood GPX1 mRNA expression in hypertensive subjects compared with normotensive controls aged 50–60 years.* ***Methods:*** *A cross-sectional study included 60 participants, consisting of 30 hypertensive and 30 normotensive subjects selected purposively according to JNC VIII criteria. GPX1 mRNA expression was measured from venous blood using two-step RT-qPCR with GAPDH as the reference gene. Relative expression was calculated using the Livak method and compared using the Mann–Whitney test.* ***Results and Discussion:*** *PX1 expression was approximately 2.65-fold lower in hypertensive subjects, although the difference was not statistically significant ($p = 0.165$).* ***Conclusion:*** *Although GPX1 mRNA expression exhibited a marked decline in hypertensive subjects, establishing its diagnostic utility warrants further investigations quantifying total protein abundance and functional enzymatic activity.*

How to Cite **Yohana, Meiyanti, Eveline Margo, Meutia Atika Faradilla/Peripheral Blood GPX1 mRNA Expression in Adults Aged 50–60 Years with Hypertension and Normotension: A Cross-Sectional Comparative Study/Vol. 5, No. 12, 2026**
DOI https://doi.org/10.54543/kesans.v5i12.728
e-ISSN/p-ISSN **2808-7178 / 2808-7380**
Published by **CV. Rifainstitut/KESANS: International Journal of Health and Science**

Introduction

Glutathione peroxidase (GPX) is an antioxidant enzyme which could transform hydrogen peroxide into oxygen and water. It contains selenium cysteine as catalytic component and related to selenium level. GPX enzyme was divided into few subclasses which are GPX1, GPX2, GPX3 and GPX4. GPX1 was found almost in mammals cell body included in cytoplasm and mitochondria. GPX2 was found in gastrointestinal cell such as esophagus, intestinal an colon epithel, GPX3 located in plasm and also detected in kidney. GPX4 has a function to demolish lipid hydroperoxide, hydrogen peroxide and lipid peroxide It could modify reduced glutathione (GSH) to oxidized glutathione (GSSG) and reducing lipid peroxidase to alcohol or hydrogen peroxide to water. (Pei et al., 2023) GPX1 enzyme could neutralize H2O2 become harmless. Hydrogen peroxide and lipid peroxide were one of kind reactive oxygen species (ROS). When there is imbalance between ROS and antioxidant enzyme, there might have tissue damage such as protein, lipid and DNA.(Handy & Loscalzo, 2022) Accumulation ROS in vascular might lead to endothel disfunction, increasing contractility and vascular remodelling so ability to normalize blood pressure is decreasing. (Kirana et al., 2020) GPX1 disfunction in vascular such as depleting nitrit oxide which lead to decrease vasoconstriction from smooth muscle in endothel.

An age-dependent increase in blood pressure is largely driven by structural vascular aging, specifically through calcification of the tunica media and fibrosis of vascular connective tissues. The prevalence of hypertension increased by 8% from 2018 to 2023, causing this disease to become a silent killer that needs to be addressed.(Mugi Wahidin et al., 2025) Previous studies indicate that plasma glutathione peroxidase activity decreases non-significantly with advancing age. Gluthation peroxidase activity in individuals over the age of 70 is lower than in younger age groups. (Kirana et al., 2020) Contrasting results were observed in low-grade gliomas, where higher GPX1 expression was associated with a poor prognosis. High GPX1 expression was also found in acute myeloid leukemia, where it was linked to an unfavorable prognosis. (Wei et al., 2020)

Several factors may contribute to variation in GPX1 expression among individuals with hypertension. Antihypertensive treatment can influence vascular oxidative stress and endothelial function, whereas diet and physical activity may modify systemic redox balance (Higashi et al., 2012). Selenium is also relevant because GPX1 is a selenium-dependent antioxidant enzyme, and its expression can be affected by selenium availability. (Lee et al., 2020) Previous research in older adults has also examined the relationship between blood selenium levels and glutathione peroxidase activity.(Kirana et al., 2020) Because these factors were not assessed in the present study, their possible contribution to differences in GPX1 expression cannot be excluded. Therefore, this study aimed to compare peripheral blood GPX1 mRNA expression between hypertension and normotension adults aged 50–60 years.

Method

This study used cross sectional analysis method. Purposive Sampling method was used. Sixty subject which aged from 50-60 years old was chosen and divided into two groups. They divided each thirty subjects into hypertension and normotension according JNC VIII. Inclusion criteria was subject who willing participate into research while exclusion criteria were subject who has cancer, diabetes mellitus, autoimmune and liver disease. Blood pressure measurements were taken using a digital blood pressure monitor and performed twice. All subject is agreed to give 2 ml blood sample. Vein blood was

taken with EDTA and isolate into RNA. This study was conducted with ethics from Fakultas Kedokteran Universitas Trisakti. Ethics number is 001/KER/FK/2024.

RNA Isolation

RNA isolation was performed using a 2 ml venous blood sample. The ZYMORESEARCH Quick-RNA Miniprep Kit was used for this procedure. A 400 µl blood sample was mixed with 400 µl of RNA cell lysis buffer in a 1.5 ml microtube. Subsequently, 16 µl of Proteinase K was added, and the mixture was incubated for 30 minutes at a temperature of 20–30°C. Isopropanol was then added at a 1:1 ratio, and the mixture was homogenized. The sample was transferred to a Zymo-Spin column and centrifuged at 16,000 x g for 30 seconds. The sample was washed with 200 µl of RNA Wash Buffer and centrifuged at 15,000 x g for 30 seconds. The flow-through was discarded, and 5 µl of DNase and 75 µl of DNA Digestion Buffer were added to the column and mixed until homogeneous. The process continued with incubation at room temperature (20–30°C) for 15 minutes. Following incubation, 400 µl of RNA Prep Buffer was added to the sample, and it was centrifuged. The flow-through was discarded, and 700 µl of RNA Wash Buffer was added to the column, followed by centrifugation. After centrifugation, another 400 µl of RNA Wash Buffer was added, and the sample was centrifuged for 1 minute. Finally, 100 µl of RNase-free water was added to the column, and the sample was centrifuged for 1 minute. (Yohana et al., 2024)Following the total RNA purification stage, the RNA concentration was measured using a spectrophotometer at a wavelength of 260 nm. The sample was stored at -80°C. (Hardiany et al., 2021)

Quatitative real time PCR

PCR primers were selected by searching a primer database. qRT-PCR was performed in two steps: cDNA synthesis and expression quantification. Purified RNA was converted into cDNA via PCR using the SensiFAST cDNA Synthesis kit. cDNA synthesis involved adding 4 µl of buffer, 1 µl of reverse transcriptase enzyme, RNase-free water, and 200 ng of RNA. The product was amplified through a process consisting of denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 60 seconds, repeated for 40 cycles.(Yohana et al., 2024)

Quantitative measurement of the target genes GPX-1 was performed using the housekeeping gene GAPDH. The cDNA was combined with SensiFAST SYBR Green No-ROX master mix, forward and reverse gene-specific primers, and RNase-free water. Primer annealing temperatures are listed in the primer table. Expression levels were measured using the software of the RotorGene 6000 (Qiagen Q-series) instrument. The measured output was the Ct value of the target genes. Expression results were calculated using the Livak method (mean $2^{-}\Delta Ct$).(Yohana et al., 2025)

Primers sequences:(Gharib et al., 2021)

GADPH	F: GTC TCC TCT GAC TTC AAC AGC G
	G: ACC ACC CTG TTG CTG TAG CCA A
GPX-1	F: GTG CTC GGC TTC CCG TGC AAC
	G: CTC GAA GAG CAT GAA GTT GGG C

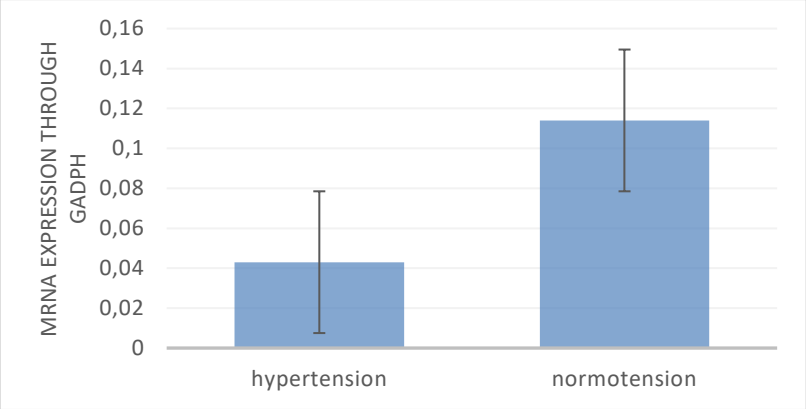
Statistical analyses

Data analysis using GraphPad software. Data distribution was assessed using the Shapiro-Wilk test. Differences between the two groups were evaluated using the Mann-Whitney test, with a significance level of $p<0.05$.

Result and Discussion

1. Result

Level expression mRNA GPX1 in hypertension was lower in hypertension groups than normotension (p=0.165).



Graph 1. Expression mRNA GPX1 in hypertension and normotension through GADPH

2. Discussion

Glutathione peroxidase is an antioxidant enzyme located in the cytoplasm and mitochondria. GPX1 plays a protective role in blood vessels by modulating the activation of proinflammatory factors. Our study found lower GPX1 mRNA expression in subjects with hypertension compared to those with normotension. Similarly, a study by Chrissobolis et al. demonstrated that GPX1 deletion leads to aortic and mesenteric artery endothelial dysfunction in mice; this deletion renders glutathione enzyme activity undetectable, thereby causing endothelial dysfunction. The absence of glutathione peroxidase activity leads to an upregulation of other antioxidant enzymes, such as SOD and catalase.(Chrissobolis et al., 2008) Another finding is that GPX1 deficiency can increase Angiotensin II levels, thereby causing endothelial dysfunction. Angiotensin II can induce an increase in reactive oxygen species (ROS), leading to endothelial dysfunction and also H2O2 also plays a role in this process. Plasma homocysteine levels contribute to the downregulation of GPX1 expression. Elevated homocysteine levels lead to reduced nitric oxide, thereby preventing vasodilation. In vitro studies using human umbilical vein cell cultures have shown that high homocysteine concentrations induce endoplasmic reticulum (ER) stress. This ER stress results in the downregulation of antioxidant genes, such as superoxide dismutase and glutathione peroxidase, and also alters protein folding. Similar results were observed in in vivo experiments, where moderate homocysteine concentrations caused changes in protein folding due to ER stress.(Esse et al., 2019)

These findings align with research by Azar B et al., which reported reduced activity of the enzymes superoxide dismutase and glutathione peroxidase at the time of initial hypertension diagnosis; hydrogen peroxide—a byproduct of oxidative stress—was also found to be elevated in patients with early-stage hypertension. It was further concluded that antioxidants play a role in mitigating oxidant-induced vascular damage.(Baradaran

et al., 2014) Vladimir et al. demonstrated that reduced activity of catalase and glutathione peroxidase in schizophrenia patients leads to impaired degradation of H2O2 into oxygen and water. Under physiological conditions, ROS levels play roles in cellular processes such as gene expression, growth, cell differentiation, and cell death. Cardiovascular disease can result from the overproduction of ROS, with mitochondria serving as the primary source.(Djordjević et al., 2022) This excessive production leads to permanent mitochondrial damage associated with heart disease. A study involving mice subjected to a model of myocardial heart disease—induced by coronary artery ligation for four weeks revealed elevated mitochondrial ROS levels and a consequent reduction in mitochondrial DNA transcription. Mitochondrial ROS oxidize complex proteins, thereby disrupting the respiratory chain.(Madamanchi & Runge, 2013)

Decreasing relative expression GPX1 observed in this study may be attributed to mechanisms involving Nrf2/ARE signalling pathway. GPX1 expression depends on the stability of Nrf2 as a transcription factor. A study in renal mouse showed silencing dopamine 2 receptor could decrease activity Nrf2 and increasing ROS product so blood pressure still very high. Chronic vascular disease is associated with increased Nrf2 degradation via the ubiquitin-proteasome pathway. When Nrf2 fails to translocate to the cell nucleus, GPX1 gene expression is inhibited. (Jerotic et al., 2019) It has also been shown that ROS levels must reach a specific threshold to trigger the release of the Keap1 protein and the subsequent activation of the antioxidant response element (ARE). Under chronic conditions, the NF-κB transcription factor promotes pro-inflammatory pathways; consequently, transcription factor signaling in hypertension can interfere with the Nrf2/ARE pathway, leading to an imbalance in GPX1 expression. (Macedo-da-Silva et al., 2021)

Conclusion

GPX1 mRNA expression was lower in hypertension than in normotension participants but the difference was not statistically significant ($p = 0.165$). Therefore, the present findings do not establish a significant association between GPX1 expression and hypertension. A limitation of this study is that the relationship between GPX1 mRNA expression and continuous systolic and diastolic blood pressure values was not assessed. Further studies with larger sample sizes, correlation analyses of blood pressure parameters, and additional measurements of GPX1 protein levels and enzymatic activity are required to clarify the role of GPX1 in hypertension

Acknowledgment

This research received an internal grant from the DRPMF of the Faculty of Medicine, Universitas Trisakti.

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