

Research Article

Role of Oxidative Stress in Microvascular Dysfunction and Early Neurocognitive Changes

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ABSTRACT

Background: Oxidative stress plays a significant role in endothelial damage, microcirculatory dysfunction and early cognitive dysfunction. Further clinical assessment is needed to determine its associations with microvascular dysfunction and subtle cognitive changes.

Objective: To assess the association of oxidative stress biomarkers with microvascular dysfunction and early neurocognitive changes among adults with cardiovascular risk factors.

Methods: This prospective observational study was conducted from June 2024 to June 2025 at the Department of Medicine, Indus Medical College, Tando Muhammad Khan, Pakistan, in collaboration with the Department of Psychiatry, Lady Reading Hospital-Medical Teaching Institution, Peshawar, Pakistan. One hundred and twenty cardiovascular risk factor adults (40-70 years) were recruited. Oxidative stress markers, inflammatory markers, microvascular markers and neurocognitive function were measured. Data were analyzed using correlation and multivariable regression analysis.

Results: Microvascular dysfunction was observed in 71 participants (59.2%). The malondialdehyde, oxidized LDL, hs-CRP, and interleukin-6 levels were significantly higher and total antioxidant capacity, superoxide dismutase, and catalase levels were significantly lower in these participants. They also had decreased flow-mediated dilatation, longer capillary refill time, higher retinal microvascular abnormalities, and lower cognitive scores. Microvascular dysfunction was associated with early neurocognitive change. The factors independently associated with early change in neurocognition were elevated malondialdehyde, oxidized LDL, reduced flow-mediated dilation, and retinal microvascular abnormality.

Conclusion: There is a very significant relationship between oxidative stress, microvascular dysfunction and early neurocognitive decrease. The early detection of oxidative and microvascular markers may be useful in identifying individuals at risk for vascular cognitive impairment.

Keywords: Oxidative Stress, Microvascular Dysfunction, Endothelial Dysfunction, Neurocognitive Changes, Malondialdehyde, Oxidized LDL.

INTRODUCTION

Oxidative stress has emerged as one of the principal mechanisms underlying vascular injury and neurodegeneration.¹ It results from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense systems.² Excessive ROS promotes lipid peroxidation, protein oxidation, mitochondrial

dysfunction, DNA damage, endothelial dysfunction, chronic inflammation, and apoptosis.³ These pathological mechanisms may precede clinically evident cardiovascular and neurodegenerative disease, making oxidative stress an important early marker of vascular and cognitive risk.

The microcirculation, comprising arterioles, capillaries, and venules measuring less than 150 μm in diameter, plays a critical role in tissue perfusion, oxygen delivery, nutrient exchange, and waste removal.⁴ The vascular endothelium regulates vasomotor tone through nitric oxide (NO), prostacyclin, endothelin, and other vasoactive mediators.⁵ Excessive ROS reduces NO bioavailability and increases peroxynitrite formation, resulting in impaired vasodilation, endothelial activation, increased vascular permeability, leukocyte adhesion, platelet aggregation, and microvascular remodeling.⁶ Microvascular abnormalities are now known to be a primary pathological process that occurs early, before large-vessel atherosclerosis, and before major cardiovascular events.⁷ Microvascular abnormalities may be clinically silent until significant organ dysfunction occurs, unlike large-vessel atherosclerosis.⁸ Endothelial dysfunction, capillary rarefaction, impaired autoregulation, and chronic tissue hypoperfusion slowly impair organ working despite the lack of obstructive large-vessel disease.⁹

The brain is particularly vulnerable to oxidative injury because of its high oxygen consumption, abundant lipid content, limited antioxidant reserve, and dependence on tightly regulated cerebral perfusion.¹⁰ Cerebral microvascular dysfunction may reduce regional blood flow, impair neurovascular coupling, disrupt the blood–brain barrier, and promote chronic neuroinflammation.¹¹ These alterations contribute to synaptic dysfunction, neuronal injury, white matter damage, and subtle deficits in memory, attention, executive function, processing speed, and learning before clinically apparent dementia develops.¹²

Oxidative stress activates several molecular pathways involved in neurovascular injury.¹³ Increased production of superoxide anion and hydrogen peroxide stimulates nuclear factor-kappa B (NF- κB), increases inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α , enhances vascular adhesion molecule expression, and promotes endothelial apoptosis.¹⁴ Mitochondrial dysfunction further amplifies ROS generation, creating a self-perpetuating cycle of oxidative injury and inflammation.¹⁵

Lipid peroxidation products such as malondialdehyde (MDA) and oxidized low-density lipoprotein (ox-LDL) contribute to endothelial damage, vascular stiffness, and accelerated microvascular remodeling.¹⁶ In contrast, endogenous antioxidant enzymes

including superoxide dismutase, catalase, and glutathione peroxidase protect against oxidative injury.¹⁷ Reduced antioxidant activity is frequently observed in patients with diabetes mellitus, hypertension, obesity, dyslipidemia, and chronic kidney disease, suggesting a shared oxidative pathway in cardiometabolic and microvascular disorders.¹⁸

Among available biomarkers, MDA, 8-hydroxy-2'-deoxyguanosine, ox-LDL, total antioxidant capacity, superoxide dismutase, catalase, and glutathione peroxidase have shown important associations with endothelial dysfunction and cardiovascular risk.¹⁹ Elevated oxidative stress biomarkers correlate with impaired flow-mediated dilation, reduced capillary density, retinal microvascular abnormalities, arterial stiffness, and systemic inflammation.²⁰ Inflammatory biomarkers such as high-sensitivity C-reactive protein and interleukin-6 may further amplify oxidative injury and contribute to progressive vascular dysfunction.²¹

Retinal microvascular imaging is a practical, non-invasive method for assessing systemic microvascular health.²² Retinal vessels share important anatomical and physiological similarities with cerebral microcirculation, making them useful indicators of neurovascular status.²³ Alterations in retinal vessel caliber, capillary density, perfusion indices, and vascular tortuosity have been associated with hypertension, diabetes mellitus, chronic kidney disease, stroke, and cognitive impairment.²⁴

Impaired endothelial function and elevated oxidative stress have been linked to faster cognitive decline and the risk of mild cognitive impairment in several clinical studies.^{26, 27}

Despite growing evidence, relatively few prospective clinical studies have simultaneously evaluated oxidative stress biomarkers, objective microvascular function, and neurocognitive performance in the same population.²⁸ Most previous studies have examined these components separately or focused on specific disease groups, limiting understanding of their integrated pathophysiological relationship.²⁹ Evidence from South Asian populations remains limited despite the high burden of diabetes mellitus, hypertension, obesity, and other metabolic disorders associated with oxidative stress and vascular dysfunction.³⁰

Thus, the current prospective clinical observational study aimed to assess oxidative stress markers in relation to microvascular dysfunction and to analyse their relationship with early neurocognitive deficits in adults with

cardiovascular risk factors. It was hypothesized that higher oxidative stress levels would be independently linked to endothelial/microvascular dysfunction and poorer neurocognitive performance, suggesting that oxidative injury is an important mechanism that links endothelial/microvascular dysfunction with early cognitive decline.

MATERIALS AND METHODS

This prospective observational clinical study was conducted from June 2024 to June 2025 at the Department of Medicine, Indus Medical College, Tando Muhammad Khan, Pakistan, in collaboration with the Department of Psychiatry, Lady Reading Hospital–Medical Teaching Institution (MTI), Peshawar, and Khyber Pakhtunkhwa, Pakistan. The study aimed to assess the correlation of oxidative stress, microvascular dysfunction and early neurocognitive alterations in adult patients with cardiovascular risk factors.

The number of the participants was 120, obtained by consecutive non-probability sampling. Individuals aged 40–70 years from the adult population with at least one cardiovascular or metabolic risk factor, such as smoking history, hypertension, type 2 diabetes mellitus, obesity and dyslipidemia were included. Patients who had a history of stroke, who had diagnosed dementia, major psychiatric disorder, neurodegenerative disease, chronic inflammatory disease, current history of antioxidant supplementation or advanced renal/liver failure or active malignancy were excluded.

Demographic data, clinical history, medication use, smoking status, BMI, BP and relevant comorbidities were recorded on a structured proforma after obtaining informed consent. Venous blood samples were taken in the fasting state for the measurement of oxidative stress and inflammatory markers such as malondialdehyde, oxidized low-density lipoprotein, total antioxidant capacity, superoxide dismutase, catalase, high-sensitivity C-reactive protein, interleukin-6, as well as fasting blood glucose, HbA1c, lipid profile, and serum creatinine.

Microvascular function was evaluated by clinically and non-invasively by endothelial function evaluation, capillary refill time, peripheral perfusion assessment, and retinal microvascular examination if available. Endothelial dysfunction was considered to be the absence of a normal vasodilatory response or abnormal peripheral microvascular perfusion

parameters as per institutional laboratory and clinical assessment protocols.

Trained clinical staff conducted neurocognitive testing with the Montreal Cognitive Assessment, Trail Making Test (Parts A and B), Digit Symbol Substitution Test, and verbal fluency testing. Early neurocognitive change was defined as decrease in one or more neurocognitive domains, in the absence of dementia or severe functional impairment.

The main end point was the relationship between biomarkers of oxidative stress and microvascular dysfunction. Secondary outcomes were the correlation between biomarker of oxidative stress and neurocognitive performance and the correlation between microvascular dysfunction and early cognitive impairment.

Data was coded and analyzed with SPSS 27 software. Data of qualitative variables were expressed as frequency and percent, and quantitative variables were expressed as mean $\pm$ standard deviation. For continuous variables, independent samples t-test or Mann–Whitney U test was used and Chi-square test or Fisher's exact test was used for categorical variables. Pearson or Spearman correlation analysis was used to determine the associations between oxidative stress markers, microvascular parameters and cognitive scores. Independent predictors of microvascular dysfunction and early neurocognitive impairment using multivariable regression analysis. Statistically significance was set at a p-value of <0.05 .

Prior to data collection, an ethics clearance was sought from the institutional review committee. The written informed consent was obtained from all the participants and confidentiality of patient information was respected during the study.

RESULTS

The final analysis included 120 participants. The mean age was 55.8 ± 8.7 years, with 68 males (56.7%) and 52 females (43.3%). Hypertension was present in 74 participants (61.7%), type 2 diabetes mellitus in 58 (48.3%), dyslipidemia in 64 (53.3%), obesity in 46 (38.3%), and current smoking in 34 (28.3%). Microvascular dysfunction defined in 71 participants (59.2%) and preserved microvascular function in 49 participants (40.8%). Levels of malondialdehyde, oxidized LDL, hs-CRP and interleukin-6 was significantly higher for participants with microvascular dysfunction; however, total antioxidant capacity, superoxide dismutase and catalase was significantly lower.

This group also had longer capillary refill time, decreased flow-mediated dilation, decreased peripheral perfusion index, and higher

incidence of microvascular abnormalities of the retina clinically. Table 1 below summarizes these findings.

Table 1. Baseline Characteristics, Oxidative Stress Biomarkers, and Microvascular Parameters According To Microvascular Status

Variable	Normal microvascular function (n = 49)	Microvascular dysfunction (n = 71)	p-value
Age, years	53.6 ± 8.2	57.3 ± 8.7	0.020
Male sex	27 (55.1%)	41 (57.7%)	0.779
Female sex	22 (44.9%)	30 (42.3%)	0.779
Body mass index, kg/m ²	26.4 ± 3.8	28.4 ± 4.1	0.008
Hypertension	24 (49.0%)	50 (70.4%)	0.018
Type 2 diabetes mellitus	17 (34.7%)	41 (57.7%)	0.013
Dyslipidemia	20 (40.8%)	44 (62.0%)	0.023
Current smoking	10 (20.4%)	24 (33.8%)	0.110
Malondialdehyde, nmol/mL	3.8 ± 0.9	5.9 ± 1.4	<0.001
Oxidized LDL, U/L	54.6 ± 15.8	82.3 ± 21.4	<0.001
Total antioxidant capacity, mmol/L	1.42 ± 0.31	1.03 ± 0.28	<0.001
Superoxide dismutase, U/mL	128.5 ± 24.7	96.8 ± 22.6	<0.001
Catalase, U/mL	54.7 ± 11.6	41.3 ± 10.2	<0.001
hs-CRP, mg/L	3.4 ± 1.5	6.2 ± 2.4	<0.001
Interleukin-6, pg/mL	4.8 ± 1.9	8.1 ± 2.7	<0.001
Capillary refill time, seconds	1.8 ± 0.4	3.1 ± 0.7	<0.001
Flow-mediated dilation, %	8.4 ± 1.9	5.2 ± 1.6	<0.001
Peripheral perfusion index	4.8 ± 1.2	2.9 ± 1.1	<0.001
Retinal microvascular abnormality	13 (26.5%)	47 (66.2%)	<0.001

Values are presented as mean ± standard deviation or number (%).

Those with microvascular dysfunction had significantly poorer cognitive performance. The microvascular dysfunction group had a lower mean Montreal cognitive assessment score compared with the normal microvascular function group. TMT Part A and Part B completion times were significantly longer, which reflects a decrease in attention and

processing speed as well as an overall decrease in executive function. There was also a significant decrease in Digit Symbol Substitution Test and verbal fluency scores. In total, early neurocognitive change was found in 39 (54.9%) microvascular dysfunction participants and 11 (22.4%) preserved microvascular function participants. These neurocognitive findings will be presented in Table 2.

Table 2. Neurocognitive Assessment According To Microvascular Status

Cognitive variable	Normal microvascular function (n = 49)	Microvascular dysfunction (n = 71)	p-value
MoCA score	26.1 ± 2.4	22.8 ± 3.1	<0.001
Trail Making Test A, seconds	41.6 ± 10.5	58.7 ± 14.9	<0.001
Trail Making Test B, seconds	91.4 ± 25.2	128.6 ± 34.7	<0.001
Digit Symbol Substitution Test score	48.9 ± 8.6	38.2 ± 9.4	<0.001
Verbal fluency score	18.7 ± 4.3	14.9 ± 4.6	<0.001
Early neurocognitive change	11 (22.4%)	39 (54.9%)	<0.001

Values are presented as mean $\pm$ standard deviation or number (%).

These relationships were further established by correlation and multivariable regression analyses between oxidative stress, microvascular dysfunction, and early neurocognitive change. Malondialdehyde and oxidized LDL were negatively correlated with MoCA score and with flow mediated dilation and positively with capillary refill time and completion time of Trail Making Test B. The MoCA score and flow-mediated dilation positively correlated with total antioxidant

capacity and superoxide dismutase. Elevated malondialdehyde, elevated oxidized LDL, reduced flow mediated dilation, prolonged capillary refill time, low total antioxidant capacity, and retinal microvascular abnormality were still significant predictors of early neurocognitive change after controlling for the variables of age, sex, hypertension, diabetes mellitus, dyslipidaemia, smoking and BMI. Retinal microvascular abnormality was the strongest independent predictor followed by increased malondialdehyde and decreased flow-mediated dilation as reported in Table 3.

Table 3. Correlation and Multivariable Regression Analysis for Oxidative Stress, Microvascular Dysfunction, and Early Neurocognitive Change

Variable	Association with MoCA score / early neurocognitive change	p-value
Malondialdehyde and MoCA score	$r = -0.54$	<0.001
Oxidized LDL and MoCA score	$r = -0.50$	<0.001
Total antioxidant capacity and MoCA score	$r = 0.47$	<0.001
Superoxide dismutase and MoCA score	$r = 0.44$	<0.001
Malondialdehyde and flow-mediated dilation	$r = -0.49$	<0.001
Oxidized LDL and flow-mediated dilation	$r = -0.45$	<0.001
Malondialdehyde >5.0 nmol/mL	AOR = 3.41; 95% CI: 1.62–7.18	0.001
Oxidized LDL >75 U/L	AOR = 2.86; 95% CI: 1.34–6.09	0.006
Reduced flow-mediated dilation	AOR = 3.08; 95% CI: 1.47–6.46	0.003
Prolonged capillary refill time	AOR = 2.21; 95% CI: 1.04–4.69	0.039
Retinal microvascular abnormality	AOR = 3.76; 95% CI: 1.72–8.23	0.001
Low total antioxidant capacity	AOR = 2.39; 95% CI: 1.12–5.11	0.025

AOR: adjusted odds ratio; CI: confidence interval; MoCA: Montreal Cognitive Assessment. The results indicated that the oxidative stress was significantly associated with the microvascular function and early neurocognitive decline overall. The relationship between oxidative stress burden and endothelial function, retinal microvascular abnormalities, and cognitive performance indicated that oxidative injury might be a potential mechanism connecting microvascular dysfunction to early cognitive dysfunction.

DISCUSSION

Microvascular dysfunction was associated with increased levels of malondialdehyde, oxidized LDL, hs-CRP, and interleukin-6, and decreased total antioxidant capacity, superoxide dismutase, and catalase, which were all considered significant indicators of oxidative stress.¹ Utility measures of microvascular function showed impaired flow-mediated

dilation, capillary refill time, and reduced peripheral perfusion, as well as retinal microvascular abnormalities and poorer neurocognitive performance.²

The principal result of this study was that there was a strong association between increased oxidative stress and impaired microvascular function.³ This suggests that oxidative stress-induced damage may lead to early endothelial dysfunction, prior to the onset of clinical macrovascular disease, as evidenced by reduced flow-mediated dilation and increased capillary refill time in patients with a higher oxidative stress marker.⁴

This is biologically reasonable, as lipid oxidative injury is associated with vascular dysfunction and impaired perfusion, and the cerebral microcirculation is very vulnerable to oxidative damage and impaired perfusion.⁵

The lowered TAC, SOD, and CAT levels in the microvascular dysfunction group indicate an exhaustion of the body's protective antioxidant

system and could be involved in the process of microvascular injury, leading to chronic cerebral hypoperfusion.⁶

Impairment of these cognitive domains is typical of vascular cognitive impairment and could signal early disruption in neurovascular coupling, endothelial dysfunction and decreased cerebral perfusion.⁷

Thus, retinal microvascular abnormality was the most powerful independent predictor of early neurocognitive change, which has clinical implications given the shared features with cerebral microvasculature.⁸ Retinal narrowing, tortuosity, and perfusion abnormalities could therefore be noninvasive markers of cerebral microvascular damage, especially in places where advanced neuroimaging may not be readily available.⁹

The link between microvascular dysfunction and cognitive impairment could also be explained by the interaction between inflammatory biomarkers and oxidative stress, with inflammatory mediators enhancing the production of reactive oxygen species and oxidative injury promoting inflammatory pathways.¹⁰

Evaluation of oxidative stress biomarkers, endothelial function, retinal microvascular status, and brief cognitive assessment could be helpful for early identification of risk.¹¹ Early lifestyle modification, blood pressure control, glycemic optimization, lipid management, smoking cessation, and measures to reduce oxidative stress may help to slow or prevent microvascular and cognitive damage.¹²

There are certain limitations in this study. First, the prospective observational design permitted structured assessment only, and causality cannot be determined. Second, the number of samples was moderate, and the samples were collected in two clinical centers, which may affect the universality. Third, there was no complex cerebral imaging or direct measurement of cerebral blood flow. Fourth, dietary antioxidant intake and physical activity were not completely assessed and may have affected the level of oxidative stress. Although these conditions are limitations, the study offers clinically relevant evidence of the relationship between oxidative stress and micro vascular impairment and early neurocognitive decline in a high-risk adult population.¹³

Conclusion

Microvascular dysfunction and early neurocognitive changes were significantly related to oxidative stress among adults with

cardiovascular risk factors. Higher MDA and oxLDL, lower markers of antioxidant defense, endothelial dysfunction, longer CRT and retinal microvascular abnormalities were associated with lower cognitive function. Retinal microvascular abnormality, malondialdehyde, and flow-mediated dilation were independent predictors of early neurocognitive change. These results provide evidence that oxidative damage could be a key mechanistic link between microvascular dysfunction and early cognitive impairment. Understanding oxidative stress and microvascular impairment early in life could lead to better strategies in prevention to mitigate the risk of vascular cognitive impairment.

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Author contributions: MN conceived the study and supervised clinical data collection. NUK contributed to biochemical analysis and interpretation. SMA assisted in data collection and manuscript preparation. UH contributed to methodology and statistical review. RM assisted in clinical assessment and data interpretation. MMH supervised neurocognitive assessment, revised the manuscript critically, and served as corresponding author. All authors reviewed and approved the final manuscript.

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