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RESEARCH

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Investigating the association between blood oxidative stress markers and dementia in Egyptian elderly women

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Abstract

Background The predicted increase in the senior population will have a substantial impact on mental health and dementia development, emphasizing the need to study the biochemical components related to the pathogenesis of dementia. Oxidative stress is caused by an imbalance between the production of reactive oxygen species and the antioxidant balance of the body. The brain is particularly vulnerable to oxidative stress because of the relatively low levels of antioxidants in the brain, high levels of polyunsaturated fatty acids, and increased oxygen needs. The increase of reactive oxygen species leads to the accumulation of protein oxidation by-products which has a key role in dementia pathogenesis. The aim of the study is to investigate the link between oxidative stress and dementia in Egyptian older women and its possible effect on dementia severity and types. A case–control study was conducted involving 40 elderly women with dementia, and another 40 cognitively intact controls. All participants were subjected to a comprehensive geriatric evaluation, which included cognitive assessment, depression screening, and functional assessment. Blood levels of malondialdehyde (an oxidative stress marker), glutathione peroxidase enzyme and total antioxidant capacity (an antioxidant markers) were measured.

Results Malondialdehyde's blood level was significantly higher in dementia cases ($p < 0.001$), indicating a higher oxidative stress status in dementia cases. While blood levels of both glutathione peroxidase enzyme and total antioxidant capacity were significantly lower in dementia cases ($p < 0.001$), indicating a lower antioxidant activity in dementia cases. We found that glutathione peroxidase enzyme at a cutoff point ≤ 122 mu/ml, total antioxidant capacity at a cutoff point ≤ 39.1 mm/l, and malondialdehyde at a cutoff point > 95 nmol/ml had perfect diagnostic value for identifying patients with dementia.

Conclusion Oxidative stress showed a significant role in the pathogenesis of dementia, with the presence of higher levels of oxidative damage by-products and lower levels of antioxidant status. So, the role of oxidative stress in dementia should not be neglected, and more effort should be directed to prevent unnecessary exposure to oxidative stress in older adults to contribute towards dementia prevention.

Keywords Dementia, Oxidative stress markers, Elderly women

Background

By 2040, there will be 81 million dementia patients in developing nations [1]. Also, dementia is the world's seventh greatest cause of death among all diseases [2]. In Egypt, elderly individuals, 60 years of age and above, are predicted to rise from 6 to 11.5% by the year 2025 [3]. This anticipated rise in the elderly population will have

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a significant influence on mental health and dementia development [4].

Aging is defined by a loss of homeostasis produced by chronic oxidative stress, which affects the nervous, endocrine, and immune systems [5]. Reactive oxygen species (ROS)-producing enzymes such as nicotinamide adenine dinucleotide phosphate (NADP) oxidase and myeloperoxidase increase with aging, while antioxidant enzymes such as glutathione peroxidase and superoxide dismutase are downregulated [6]. As a result, oxidative stress is believed to be the principal cause of dementia, with accumulative oxidative damage being the primary driver of cognitive decline [7].

Oxidative stress is implicated in the pathophysiology of both Alzheimer's disease (AD) and vascular dementia (VaD), and it is probable that the two diseases are linked via oxidative stress [8]. Senile plaques wreak havoc on neurons by activating microglia, astrocytes, and the complementing system [9]. These pathways are associated with a high amount of free radical production, which hastens neuronal death [10].

Because malondialdehyde (MDA) is both cytotoxic and carcinogenic, it can be used as a biomarker for lipid peroxidation and oxidative stress [11]. MDA in blood samples is more accurate for assessing systemic oxidative stress [12].

Antioxidant molecules function on multiple levels including radiation damage healing, radical scavenging, and radical prevention [13].

Glutathione peroxidase enzyme (GPx) is the main enzyme responsible for reducing ROS and lipid peroxidation products [14]. It holds the status of a redox system glutathione/glutathione disulfide (GSH/GSSG) in the glutathione system to prevent oxidative damage of cellular constituents. As such, the GPx is the first line of defense against free radicals [15].

Total antioxidant capacity (TAC) is a biomarker that measures the antioxidant capacity of bodily fluids [16]. It indicates the serum's ability to protect the cell structure from the destructive effects of free radicals, and it indicates greater vulnerability to oxidative damage [17].

The purpose of this study was to examine the possible link between oxidative stress and dementia in Egyptian older women and its effect on dementia severity and types.

Methods

In our study, we tried to investigate the possible role of oxidative stress in the occurrence of dementia among Egyptian elderly women. So, a case–control study was conducted. Participants were recruited from older women who attended geriatrics clinics or were admitted to Ain Shams University Hospitals in Cairo, Egypt. The research was carried out between May and November of 2021. A total of 80 elderly ladies were recruited for the study. They were separated into two groups: a case group of 40 dementia patients and a control group of 40 cognitively intact participants. Age and educational level were matched in both groups. Patients with severe/critical medical illness, uncontrolled hypothyroidism, autoimmune disorders, sepsis, severely disrupted liver/kidney/lung function, delirium, psychiatric illness such as schizophrenia, an acute stroke, brain tumors, and positive smoking status were excluded.

Cognitive function assessment: screening was initially performed using the Arabic version [18] of the Mini Mental State Examination (MMSE) [19], with a cut-off score of 26 out of 30 to diagnose dementia. It is also used to classify dementia phases as mild, moderate, or severe. The ranges for mild dementia were 21–25, 11–20 for moderate dementia, and 0–10 for severe dementia. The scores were also corrected for age and education. Dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria [20, 21]. Depression screening: In the control group, PHQ-2 (patient health questionnaire-2) [22] was used to screen for depression, whereas the Cornell scale [23] was used for the demented patients.

All the chosen participants underwent a history taking, a clinical examination, and a full geriatric assessment, which included the following:

The Activities of Daily Living scale (ADL) [24] and the Instrumental Activities of Daily Living scale (IADL) [25] were used for functional evaluation.

The Hachinski ischemia score (HIS) [26]: This is a basic clinical technique used to distinguish between dementia types (Alzheimer's, vascular or multi-infarct dementia, and mixed type).

Malondialdehyde (MDA), glutathione peroxidase enzyme (GPX), and total antioxidant capacity (TAC) were all measured in blood as oxidative stress markers. The blood samples were obtained without the use of an anticoagulant at a geriatric hospital and left to clot for 30 min at 25 °C. The top yellow serum layer is pipetted without disturbing the white buffy coat after centrifuging the blood at 2,000 xg for 15 min at 4 °C. Serum was kept on ice and frozen at − 80 °C.

Glutathione peroxidase enzyme (GPX)

Measurement technique principles: The assay is an indirect measurement of GPx activity. The enzyme glutathione reductase recycles oxidized glutathione (GSSG) to its reduced state when GPx reduces an organic peroxide.

The oxidation of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) to NADP + causes a

decrease in absorbance at 340 nm (A340), which provides a spectrophotometric technique for measuring the GPx enzyme activity. At 340 nm, NADPH has a molar extinction value of 6220 M^{-1} cm^{-1}. To measure GPx, a cell or tissue homogenate is mixed with glutathione, glutathione reductase, and NADPH. The enzymatic reaction was initiated by introducing hydrogen peroxide as a substrate, and then the A340 was measured. The rate of reduction of the A340 is directly related to the sample's GPx activity.

Total antioxidant capacity (TAC)

Measurement technique principles: The antioxidative capacity was determined by reacting antioxidants in the sample with a specific amount of exogenously supplied hydrogen peroxide (H2O2). The antioxidants in the sample eliminate a specific amount of the supplied hydrogen peroxide. An enzymatic procedure that converts 3,5, dichloro-2-hydroxy benzenesulfonate into a colored product determines the residual H2O2 colorimetrically.

Malondialdehyde (MDA)

Measurement technique principles: Thiobarbituric acid (TBA) combines with malondialdehyde (MDA) in an acidic media at 95 °C for 30 min to create thiobarbituric acid reactive product, the absorbance of which was measured at 534 nm.

On the 25th of July 2020, the FMASU REC (faculty of medicine at Ain Shams University Research Ethics Committee) granted ethical research approval.

The data were statistically analyzed with the Statistical Software Package for Social Science (SPSS) 20. (IBM, Chicago, USA, 2011).

Data were presented, and appropriate analysis was performed based on the type of data obtained for each parameter.

Statistics for descriptive purposes: Mean, standard deviation (SD), and range were used for parametric numerical data, whereas median and interquartile range (IQR) were used for nonparametric numerical data. Nonnumerical data were also represented using frequency and percentage.

A Student's T test was performed to examine the statistical significance difference between two study groups, which were utilized to assess the relationship between oxidative stress markers in the studied groups.

A Chi-square test was employed to assess the connection between two qualitative variables.

A one-way ANOVA test was performed to compare quantitative factors between more than two groups in order to investigate the relationship between oxidative stress and different forms of dementia.

The Mann–Whitney test was employed to compare nonparametric quantitative data between two groups.

A linear regression model was employed to determine the most important predictor of cognition.

$P < 0.05$ was regarded as a statistically significant value, P-value > 0.05 was considered as non-significant. Also, P-value < 0.01 was considered highly significant in our results.

Results

The study participants' average age was 74.53 ± 6.30, and the majority of them were widows and illiterate. The most common comorbidities were hypertension and diabetes mellitus; polypharmacy was widespread; the majority of dementia cases were in severe stages (72.2%); and vascular dementia was the most common type discovered (50.0%). Both the case and control groups were matched for age and educational level; the case group had a substantially higher history of cerebrovascular stroke and polypharmacy (p-values: 0.001 and < 0.001, respectively) (Table 1).

There were statistically significant changes in blood levels of oxidative stress between the case and control groups. The case group exhibited significantly lower levels of GPX and TAC, while the case group had significantly higher levels of MDA (P-values: 0.001, 0.001, 0.001, respectively) (Table 2).

There were no significant differences in blood levels of oxidative stress indicators GPX, TAC, and MDA among dementia types (P-values: 0.183, 0.937, and 0.828, respectively) (Table 3).

Univariate logistic regression revealed that cerebrovascular stroke, polypharmacy, widowhood, and having a poor functional status were all risk factors of dementia (P-values: 0.000, 0.001, 0.004, 0.000, 0.000, respectively), whereas multivariate regression analysis revealed that both history of cerebrovascular stroke and polypharmacy had the strongest associations with dementia (P-values: 0.002 and 0.024, respectively) (Table 4).

Markers of oxidation were compared with regard to their specificity and sensitivity in diagnosing dementia, as well as their cutoff values for diagnosis and it was found that GPX at cutoff point 122 mu/ml, TAC at cutoff point 39.1 mm/l, and MDA at cutoff point > 95 nmol/ml exhibited significant specificity and sensitivity for dementia identification (Table 5).

As a summary of the results, blood levels of malondialdehyde were significantly higher in dementia cases, indicating a higher oxidative stress status in dementia patients, while both glutathione peroxidase enzyme and total antioxidant capacity showed significantly lower blood levels in dementia cases, which indicates a lower antioxidant activity in dementia cases. Glutathione

Table 1 Demographic characteristics and clinical data of the studied groups

Clinical characteristics		Control group	Case group	*P*-value
		n = 40	n = 40	
Age (years)				
Mean ± SD Range		73.38 ± 6.56 60–81	75.68 ± 5.88 65–85	0.103[a]
Marital status				
Single		4 (10.0%)	0 (0.0%)	0.040[b]
Married		21 (52.5%)	13 (32.5%)	0.070[b]
Widow		15 (37.5%)	27 (67.5%)	0.007**[b]
Education level				
Illiterate		26 (65.0%)	31(77.5%)	
< 5 years		9 (22.5%)	5 (12.5%)	
Primary/prep		3 (7.5%)	1 (2.5%)	0.333[b]
Secondary		1 (2.5%)	0 (0.0%)	
Highly educated		1 (2.5%)	3 (7.5%)	
Polypharmacy				
Median (IQR)		2 (1–3) 0–4	6 (3–9) 3–9	0.001 [c]**
Comorbidities				
DM	Yes	21 (52.5%)	21 (52.5%)	1.000 [b]
HTN	Yes	27 (67.5%)	30 (75.0%)	0.459 [b]
ISHD	Yes	4 (10.0%)	4 (10.0%)	1.000 [b]
CLD	Yes	7 (17.5%)	9 (22.5%)	0.576 [b]
CKD	Yes	4 (10.0%)	2 (5.0%)	0.396 [b]
CHD	Yes	2 (5.0%)	2 (5.0%)	1.000 [b]
Thyroid diseases	Yes	3 (7.5%)	9 (22.5%)	0.060 [b]
CVS	Yes	2 (5.0%)	19(47.5%)	< 0.001**[b]

IQR interquartile range, *SD* standard deviation, *DM* diabetes mellitus, *HTN* hypertension, *ISHD* ischemic heart diseases, *CLD* chronic liver disease, *CKD* chronic kidney disease, *CHD* chronic heart disease, and *CVS* cerebrovascular stroke

[a] Independent *t*-test; [b]Chi-square test; [c]Mann–Whitney test

P-value > 0.05: non-significant; ** *P*-value < 0.01: highly significant

Table 2 Oxidative stress markers blood levels of the studied groups

Oxidative stress markers		Control group	Case group	*P*-value
		n = 40	n = 40	
GPX (mu/ml)	Mean ± SD	222.51 ± 21.71	82.56 ± 25.64	< 0.001[a,**]
	Range	183.2–293	47–122	
TAC (mm/l)	Mean ± SD	95.16 ± 9.50	22.52 ± 9.47	< 0.001[a,**]
	Range	67–115.5	10.2–39.1	
MDA (nmol/ml)	Mean ± SD	45.36 ± 12.96	200.06 ± 51.47	< 0.001[a,**]
	Range	30–95	113–290	

GPX glutathione peroxidase, *TAC* total antioxidant capacity, *MDA* malondialdehyde, *nmol/ml* nanomole/milliliter, *mm/l* millimolar/liter, *mu/ml* milliunits/milliliter, *SD* standard deviation

[a] Independent *t*-test, ***P*-value < 0.01: highly significant

peroxidase enzyme at cutoff point ≤ 122 mu/ml, total antioxidant capacity at a cutoff point ≤ 39.1 mm/l, and malondialdehyde at cutoff point > 95 nmol/ml had perfect diagnostic values for identifying patients with dementia.

Discussion

Dementia is a disabling brain disorder that is associated with severe disability, increased demands for medical and personal care, and premature death [27].

The brain is particularly vulnerable to oxidative stress due to its excessive usage of glucose for energy production [28]. ROS are important in both normal brain function and the pathophysiology of neurological diseases [29, 30].

Oxidative stress is involved in several acute and chronic pathological processes, such as cerebrovascular diseases (CVDs), acute and chronic kidney disease (CKD), neurodegenerative diseases (NDs), macular degeneration (MD), biliary diseases, and cancer. Furthermore, cardiovascular (CV) risk factors (ie, obesity, diabetes, hypertension, and atherosclerosis) are associated with the inflammatory pathway mediated by interleukin IL-1α, IL-6, IL-8, and increased cellular senescence [31, 32].

As a result, serum oxidative stress markers are likely to be higher in patients suffering from neurodegenerative diseases and cognitive impairment [30].

The aim of our study was to investigate the association between dementia and oxidative stress status in elderly women.

A case–control study has been conducted, included 80 elderly women, 40 participants had dementia, and another 40 cognitively intact participants as a control group. Comprehensive geriatric assessment was done for all participants including cognitive assessment, screening for depression and functional assessment.

Age and educational level were matched in both groups. Patients with severe/critical medical illness, uncontrolled hypothyroidism, autoimmune disorders, sepsis, severely disrupted liver/kidney/lung function, delirium, psychiatric illness such as schizophrenia, an acute stroke, brain tumors, and a positive smoking status were excluded.

Blood levels of a three of oxidative stress markers were measured, namely glutathione peroxidase enzyme (GPX), total antioxidant capacity (TAC), and malondialdehyde (MDA).

Age [33] and educational level [34] continue to be important risk factors for dementia development worldwide. On the other hand, Tripathi and colleagues [35], who investigated the risk and preventive variables for dementia in North India, did not find significant relationship between age and educational levels in relation

Table 3 Comparison between types of dementia regarding oxidative stress markers blood levels

		Types of dementia (HIS)			*P*-value
		Mixed dementia	AD	VaD	
		n = 13	n = 7	n = 20	
GPX (mu/ml)	Mean ± SD	72.71 ± 25.86	93.66 ± 26.48	85.07 ± 24.23	0.183[a]
	Range	47–122	55.2–114	47.5–121	
TAC (mm/l)	Mean ± SD	22.12 ± 9.96	23.7 ± 10.11	22.36 ± 9.41	0.937[a]
	Range	12.8–38	12.3–35.7	10.2–39.1	
MDA (nmol/ml)	Mean ± SD	195.7 ± 52.71	210.66 ± 60.12	199.17 ± 49.87	0.828[a]
	Range	119.5–290	119.5–263	113–290	

AD Alzheimer's dementia, *VaD* vascular dementia, *GPX* glutathione peroxidase, *TAC* total antioxidant capacity, *MDA* malondialdehyde, *HIS* Hachinski ischemic score, *P*-value > 0.05: non-significant; a: one-way ANOVA test. nmol/ml: nanomole/milliliter, mm/l: millimolar/liter, mu/ml: milliunits/milliliter

Table 4 Analysis of dementia-related variables using univariate and multivariate logistic regression

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		*P*-value	OR	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Widow status	0.004**	3.519	1.507	8.215	–	–	–	–
History of CVS	0.000**	17.190	3.643	81.108	0.002*	12.914	2.646	63.031
Polypharmacy (> 5)	0.001**	4.846	1.882	12.482	0.024*	3.328	1.172	9.449
ADL score ≤ 3	0.000**	741.000	64.478	8515.777	–	–	–	–
IADL score ≤ 2	0.000**	741.000	64.478	8515.777	–	–	–	–

CI confidence interval, *ADL* Activities of Daily Living Scale; *IADL* Instrumental Activities of Daily Living Scale; *OR* odds ratio; *CVS* cerebrovascular stroke

**P*-value < 0.05: significant; ** *P*-value < 0.01: highly significant

Table 5 The receiver-operating curve (ROC) analysis of oxidative stress blood markers in the studied groups

Variables	Cutoff point	AUC	Sensitivity	Specificity	PPV	NPV
GPX (mu/ml)	≤ 122	1.000	100.00	100.00	100.0	100.0
TAC(mm/L)	≤ 39.1	1.000	100.00	100.00	100.0	100.0
MDA(nmol/ml)	> 95	1.000	100.00	100.00	100.0	100.0

ROC the receiver-operating curve, *GPX* glutathione peroxidase, *TAC* total antioxidant capacity, *MDA* malondialdehyde, *AUC* area under the curve, *PPV* positive predictive value, *NPV* negative predictive value. nmol/ml nanomole/milliliter, mm/L millimolar/liter, mu/ml milliunits/milliliter

to dementia. In our study, both case and control groups were matched in age and educational level.

Except for cerebrovascular stroke, the current investigation found no statistically significant differences between the case and control groups in comorbidities among the examined population. Cerebrovascular stroke was substantially more common in the dementia group. This was consistent with the findings of Kuźma and colleagues, who sought to investigate the effect of stroke on incident dementia and discovered that stroke was a well-established risk factor for dementia [36].

Corraini and colleagues found that the 30-year absolute risk of dementia among stroke survivors was 11.5% higher than in the general population [37] when they investigated the long-term risk of dementia among survivors of ischemic or hemorrhagic stroke. Furthermore, published meta-analyses demonstrate that ischemic stroke nearly doubles the incidence of dementia in older persons and that a stroke patient has a 59% greater chance of acquiring AD when compared to controls [38].

This was explained by the fact that vascular risk factors cause cerebrovascular damage, which directly causes vascular dementia, and that vascular risk factors enhance the chance of neurodegenerative Alzheimer's disease [39]. Furthermore, cerebrovascular diseases (CVDs) are distinguished by insulin resistance, a pro-oxidative and

pro-inflammatory state, as well as a dysregulation of the expression of various factors involved in redox homeostasis and an inflammatory environment that impairs cognitive function [40].

In addition to the recognized risk factors for dementia in the elderly, our study emphasized the importance of blood levels of oxidative stress markers in dementia pathogenesis and progression. The primary findings of this study were that the pattern of oxidative stress identified in the population surveyed was linked to dementia. Lower antioxidant activity was discovered to be a predictor of dementia.

In our investigation, MDA levels were much greater in the case group, whereas TAC and GPX levels, which reflect antioxidant status, were significantly lower. Furthermore, there was no significant difference in blood levels of oxidative stress indicators between dementia types, indicating that oxidative stress is one of the elements that play a role in dementia regardless of its kind.

Excessive proinflammatory cytokines, vascular problems, and altered mitochondrial activity, which is followed by overproduction of ROS and oxidized molecules, all contribute to dementia pathogenesis [41].

Our findings were consistent with those of Poildori and colleagues, who examined oxidative stress in Alzheimer's disease (AD), vascular dementia (VaD), and controls and found that all antioxidants were reduced in demented patients compared to controls. However, identical plasma antioxidant and MDA levels were identified in vascular and Alzheimer dementia [42].

Similarly, Cherbuin and colleagues' study, which examined the impact of oxidative stress, inflammation, and dementia, discovered that low TAC and high MDA were associated with cognitive decline and neurodegeneration and that higher antioxidant activity appeared to be more protective [43].

Also, Qi and colleagues' study which assessed the role of antioxidant molecules such as TAC and GPX in their case–control study found that vascular dementia patients show lower levels of antioxidant molecules than the normal population [44].

It was in line with the study of Vogrinc and colleagues, which discovered that genetic variation linked to inflammation and oxidative stress may influence an individual's susceptibility to AD and MCI, supporting the critical role that neuroinflammation and oxidative stress play in the pathophysiology of AD [45].

In contrast to our findings, one study reported no statistically significant change in plasma levels of oxidative stress (OS) indicators when participants with cognitive decline were compared to the control group. This gap could be explained by the fact that their study only included people with mild cognitive impairment (MCI) and mild dementia, whereas 72% of the case group in our study had severe dementia [46].

In contrast to our findings, Casado and colleagues found that GPx activity was reduced in VaD and AD patients compared to controls, with a statistically significant difference only in AD (P 0.005) [47]. The differences between our findings and those of this study could be explained by the fact that this study measured GPX in red blood cells (RBCs) rather than plasma. Furthermore, their study included both men and women, whereas our study only included women.

Furthermore, Gustaw-Rothenberg and colleagues found that MDA levels were considerably greater in the VaD group only, as compared to both AD patients and controls [48]. This could be explained by a number of variables, including the fact that the study population with vascular dementia had higher levels of vascular risk factors such as hypertension and smoking than other groups. Furthermore, the dementia group only had mild to moderate dementia. Finally, both men and women were recruited for this study.

Many earlier research have found correlations between oxidative stress indicators and different kinds of dementia. This could be attributed to a variety of factors. The sample size is a crucial consideration in determining the statistical significance of the differences observed. The use of different assays may also have a role in the variances. Another explanation for the disparities in results between studies on MDA levels, antioxidant enzymes, and ageing could be heredity or dietary habits, which make it much more difficult to disentangle their influence from enzyme expression and activity [49].

The significance of our research is to understand exactly one of the potential causes of dementia, which is one of the most hazardous diseases in the world. It also paves the way for a lot of future studies trying to detect cognitive impairment in preclinical stages and compare many oxidative stress markers to detect which one has the highest specificity and sensitivity to dementia.

Our study has some points of strength as the exclusion of patients with psychiatric illnesses, delirium, and acute medical diseases, which can all affect the results of cognitive evaluation results as well as oxidative stress markers in blood levels. Also, both case and control groups were matched in age, as age difference could affect the results. Furthermore, we measured three different oxidative stress markers. Lastly, to the best of our knowledge, this was the first study in Egypt that looked at the relationship between dementia and blood levels of oxidative stress indicators in older females.

Conclusion

Our results demonstrated the role of oxidative stress (OS) in dementia pathogenesis, confirmed by significantly lower blood levels of antioxidant markers together with a higher accumulative oxidative damage in demented women patients.

Also, there were no significant differences in blood levels of oxidative stress indicators GPX, TAC, and MDA among dementia types.

Limitations and future directions: It is critical to avoid exposure of older adults to unnecessary oxidative stress. This may contribute to dementia prevention programs.

More research is needed to evaluate the role of trace elements and certain vitamins as cofactors for the antioxidant system, and their possible role in both preventing and delaying the progression of dementia.

Also, future research is needed to assess the role of oxidative stress in the early detection of mild cognitive impairment (MCI) and mild dementia patients.

The generalizability of our study to other populations is limited, as all study patients were older adult ladies who attended Ain Shams University's geriatric hospital. Individuals with mild dementia were also underrepresented in our study.

Abbreviations

GPX	Glutathione peroxidase enzyme
MDA	Malondialdehyde
TAC	Total antioxidant capacity
OS	Oxidative stress
GSSG	Glutathione disulfide (oxidized glutathione)
ROS	Reactive oxygen species
AD	Alzheimer dementia
VaD	Vascular dementia
HTN	Hypertension
ISHD	Ischemic heart disease
CLD	Chronic liver disease
CKD	Chronic kidney disease
CHD	Chronic heart disease
CVS	Cerebrovascular stroke
H2O2	Hydrogen peroxide
GSH/GSSG	Glutathione/glutathione disulfide
MMSE	The mini mental state examination
TBA	Thiobarbituric acid
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
PHQ-2	Patient Health Questionnaire-2
ADL scale	The Activities of Daily Living scale
IADL scale	The Instrumental Activities of Daily Living scale
HIS	The Hachinski ischemic score
SD	Standard deviation
SPSS	Statistical Software Package for Social Science
IQR	Interquartile range
FMASU REC	Faculty of medicine at Ain Shams University research ethics committee
nmol/ml	Nanomole/milliliter
mm/l	Millimolar/liter
mu/ml	Milliunits/milliliter
AUC	Area under the curve
CI	Confidence interval
OR	Odds ratio
PPV	Positive predictive value
NPV	Negative predictive value
ROC	Receiver-operating curve
CVDs	Cerebrovascular diseases
CV	Cardiovascular
RBCs	Red blood cells
DM	Diabetes mellitus
IL	Interleukin
NDs	Neurodegenerative diseases
MD	Macular degeneration
NADP +	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
MCI	Mild cognitive impairment

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Author contributions

LK: The practical part, collection of references, writing manuscript, data entry and analysis. SH: Study design and methodology, revision of manuscript. SA: Laboratory work, revision of manuscript. MA: Study design and methodology, analysis of data, revision of manuscript. SM: Study design and methodology, analysis of data, revision of manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in the manuscript.

Declarations

Ethics approval and consent to participate

Date of ethical committee approval: 25/7/2020. Approval was obtained from the FMASU REC (faculty of medicine at Ain Shams University research ethics committee), which was organized and operated according to guidelines of the International Council on Harmonization (ICH) Anesthesiology, the Islamic Organization for Medical Sciences (IOMS), the United States Office for Human Research Protections, and the United States Code of Federal Regulations, and operates under Federal Wide Assurance No. FWA 000017585. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American stroke association. Stroke. 2011;42(9):2672–713. https://doi.org/10.1161/str.0b013e3182299496.
2. World health report 2021: Global status report on the public health response to dementia. https://iris.who.int/bitstream/handle/10665/344701/9789240033245.
3. Radwan DN, Ali HD, Elmissiry AA, Elbanouby MM. Cognitive and functional impairment in Egyptian patients with late-onset schizophrenia versus elderly healthy controls. Middle East Curr Psychiatr. 2014;21(1):28–37. https://doi.org/10.1097/01.xme.0000438434.30383.69.
4. El-Banouby MH. Health and aging in the Eastern Mediterranean region. In: Robinson M, Novelli W, Pearson C, editors. Global health and global aging. Hoboken: Wiley; 2007. p. 215–26.

5. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. Clin Interv Aging. 2018;13:757–72. https://doi.org/10.2147/cia.s158513.
6. Violi F, Loffredo L, Carnevale R, Pignatelli P, Pastori D. Atherothrombosis and oxidative stress: mechanisms and management in elderly. Antioxid Redox Signal. 2017;27(14):1083–124. https://doi.org/10.1089/ars.2016.6963.
7. Islam MT. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. Neurol Res. 2017;39(1):73–82. https://doi.org/10.1080/01616412.2016.1251711.
8. Bennett S, Grant MM, Aldred S. Oxidative stress in vascular dementia and Alzheimer's disease: a common pathology. J Alzheimers Dis. 2009;17(2):245–57. https://doi.org/10.3233/JAD-2009-1041.
9. Grodzicki W, Dziendzikowska K. The role of selected bioactive compounds in the prevention of Alzheimer's disease. Antioxidants (Basel). 2020;9(3):229. https://doi.org/10.3390/antiox9030229.
10. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease Alzheimer's and Dementia. Transl Res Clin Interven. 2018;4:575–90. https://doi.org/10.1016/j.trci.2018.06.014.
11. Verma MK, Jaiswal A, Sharma P, Kumar P, Singh AN. Oxidative stress and biomarker of TNF-α, MDA and FRAP in hypertension. J Med Life. 2019;12(3):253–9. https://doi.org/10.25122/jml-2019-0031.
12. Farouk A, Hassan MH, Nady MA, AbdelHafez MF. Role of oxidative stress and outcome of various surgical approaches among patients with bullous lung disease candidate for surgical interference. J Thorac Dis. 2016;8(10):2936–41. https://doi.org/10.21037/jtd.2016.10.41.
13. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. Molecules. 2019;24(8):1583. https://doi.org/10.3390/molecules24081583.
14. Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med. 2009;30(1–2):1–12. https://doi.org/10.1016/j.mam.2008.08.006.
15. Fundu TM, Kapepula PM, Esimo JM. Subcellular localization of glutathione peroxidase, change in glutathione system during ageing and effects on cardiometabolic risks and associated diseases. In: Remacle J, Ngombe NK, editors. Glutathione system and oxidative stress in health and disease. 2019. P 29–48.
16. Niki E. Assessment of antioxidant capacity in vitro and in vivo. Free Radic Biol Med. 2010;49(4):503–15. https://doi.org/10.1016/j.freeradbiomed.2010.04.016.
17. Koracevic D, Koracevic G, Djordjevic V, Andrejevic S, Cosic V. Method for the measurement of antioxidant activity in human fluids. J Clin Pathol. 2001;54(5):356–61. https://doi.org/10.1136/jcp.54.5.356.
18. El Okl MA, Banouby E, Etrebi ME. Prevalence of Alzheimer dementia and other causes of dementia in Egyptian elderly. MD thesis, faculty of medicine, ain shams university. 2002.
19. Folstein MF, Folstein SE, Mchugh PR. Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
20. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5 (R)). 5th ed. Arlington, VA: American Psychiatric Association Publishing; 2013.
21. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med. 2014;30(3):421–42. https://doi.org/10.1016/j.cger.2014.04.001.
22. Spitzer RL, Kroenke K, Williams JB, Patient Health Questionnaire Primary Care Study Group & Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. 1999;282(18):1737–44.
23. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. Biol Psychiatry. 1988;23(3):271–84. https://doi.org/10.1016/0006-3223(88)90038-8.
24. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. studies of illness in the aged the index of adl: a standardized measure of biological and psychosocial function. JAMA. 1963;185:914–9.
25. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3 part 1):179–86. https://doi.org/10.1093/geront/9.3_part_1.179.
26. Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia. A cause of mental deterioration in the elderly. Lancet. 1974;2(7874):207–10.
27. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017;177(1):51–8. https://doi.org/10.1001/jamainternmed.2016.6807.
28. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab. 2011;14(6):724–38.
29. Bhatt S, Nagappa AN, Patil CR. Role of oxidative stress in depression. Drug Discov Today. 2020;25(7):1270–6. https://doi.org/10.1016/j.drudis.2020.05.001.
30. Peña-Bautista C, Baquero M, Vento M, Cháfer-Pericás C. Free radicals in Alzheimer's disease: lipid peroxidation biomarkers. Clin Chim Acta. 2019;491:85–90. https://doi.org/10.1016/j.cca.2019.01.021.
31. Cervellati C, Cremonini E, Bosi C, Magon S, Zurlo A, Bergamini CM, et al. Systemic oxidative stress in older patients with mild cognitive impairment or late onset Alzheimer's disease. Curr Alzheimer Res. 2013;10(4):365–72. https://doi.org/10.2174/1567205011310040003.
32. Chandrasekaran A, Idelchik MDPS, Melendez JA. Redox control of senescence and age-related disease. Redox Biol. 2017;11:91–102. https://doi.org/10.1016/j.redox.2016.11.005.
33. Mecocci P, Boccardi V. The impact of aging in dementia: it is time to refocus attention on the main risk factor of dementia. Ageing Res Rev. 2021;65(101210): 101210. https://doi.org/10.1016/j.arr.2020.101210.
34. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology. 1999;52(1):78–84. https://doi.org/10.1212/wnl.52.1.78.
35. Tripathi M, Vibha D, Gupta P, Bhatia R, Srivastava MVP, Vivekanandhan S, et al. Risk factors of dementia in North India: a case-control study. Aging Ment Health. 2012;16(2):228–35. https://doi.org/10.1080/13607863.2011.583632.
36. Kuźma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: a systematic review and meta-analysis. Alzheimers Dement. 2018;14(11):1416–26. https://doi.org/10.1016/j.jalz.2018.06.3061.
37. Corraini P, Henderson VW, Ording AG, Pedersen L, Horváth-Puhó E, Sørensen HT. Long-term risk of dementia among survivors of ischemic or hemorrhagic stroke. Stroke. 2017;48(1):180–6. https://doi.org/10.1161/STROKEAHA.116.015242.
38. Zhou J, Yu J-T, Wang H-F, Meng X-F, Tan C-C, Wang J, et al. Association between stroke and Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis. 2015;43(2):479–89. https://doi.org/10.3233/JAD-140666.
39. Lo Coco D, Lopez G, Corrao S. Cognitive impairment and stroke in elderly patients. Vasc Health Risk Manag. 2016;12:105–16. https://doi.org/10.2147/VHRM.S75306.
40. Faraco G, Park L, Zhou P, Luo W, Paul SM, Anrather J. Hypertension enhances A β-induced neurovascular dysfunction, promotes β-secretase activity, and leads to amyloidogenic processing of APP. J Cereb Blood Flow Metab. 2016;36(1):241–52.
41. Kubis-Kubiak AM, Rorbach-Dolata A, Piwowar A. Crucial players in Alzheimer's disease and diabetes mellitus: friends or foes? Mech Ageing Dev. 2019;181:7–21. https://doi.org/10.1016/j.mad.2019.03.008.
42. Polidori MC, Mattioli P, Aldred S, Cecchetti R, Stahl W, Griffiths H, et al. Plasma antioxidant status, immunoglobulin g oxidation and lipid peroxidation in demented patients: relevance to Alzheimer disease and vascular dementia. Dement Geriatr Cogn Disord. 2004;18(3–4):265–70. https://doi.org/10.1159/000080027.
43. Cherbuin N, Walsh E, Baune BT, Anstey KJ. Oxidative stress, inflammation and risk of neurodegeneration in a population sample. Eur J Neurol. 2019;26(11):1347–54.
44. Qi FX, Hu Y, Li YW, Gao J. Levels of anti-oxidative molecules and inflammatory factors in patients with vascular dementia and their clinical significance. Pak J Med Sci. 2021;37(5):1509–13. https://doi.org/10.12669/pjms.37.5.3854.
45. Vogrinc D, Gregorič Kramberger M, Emeršič A, Čučnik S, Goričar K, Dolžan V. Genetic polymorphisms in oxidative stress and inflammatory pathways as potential biomarkers in Alzheimer's disease and dementia. Antioxidants (Basel). 2023;12(2):316.

46. Baldeiras I, Santana I, Proença MT, Garrucho MH, Pascoal R, Rodrigues A, et al. Peripheral oxidative damage in mild cognitive impairment and mild Alzheimer's disease. J Alzheimer's Dis. 2008;15(1):117–28.
47. Casado A, Encarnación López-Fernández M, Concepción Casado M, de La Torre R. Lipid peroxidation and antioxidant enzyme activities in vascular and Alzheimer dementias. Neurochem Res. 2008;33(3):450–8. https://doi.org/10.1007/s11064-007-9453-3.
48. Gustaw-Rothenberg K, Kowalczuk K, Stryjecka-Zimmer M. Lipids' peroxidation markers in Alzheimer's disease and vascular dementia. Geriatr Gerontol Int. 2010;10(2):161–6. https://doi.org/10.1111/j.1447-0594.2009.00571.x.
49. Mariani E, Cornacchiola V, Polidori MC, Mangialasche F, Malavolta M, Cecchetti R, et al. Antioxidant enzyme activities in healthy old subjects: influence of age, gender and zinc status: results from the Zincage Project: 2006;7(5–6):391–8. https://doi.org/10.1007/s10522-006-9054-6.

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