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Original Article

The Correlation Between Oxidative Stress and Cognitive Decline in Egyptian Elderly with Mild Cognitive Impairment

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ABSTRACT

Background/Purpose: Plasma levels of non-enzymatic antioxidants and antioxidant enzyme activity looked to be lower in patients with mild cognitive impairment (MCI), which increased the rate of neuronal damage and increased the likelihood that MCI would quickly advance to dementia. To evaluate the correlation between oxidative stress and cognitive decline in elderly with mild cognitive impairment.

Methods: For this investigation, there were 40 senior patients with cognitive impairment who were 60 years or older, as well as 40 healthy controls who were the same age and sex. Serum malondialdehyde (MDA), superoxide dismutase and catalase used as oxidative stress indicators, and assessments of cognitive function, depression, nutrition, functional ability, and fall risk were performed on all individuals (superoxide dismutase and catalase).

Results: Serum Malondialdehyde were higher in MCI group (p <0.001) while superoxide dismutase and catalase were significantly lower in MCI group (p <0.001). Catalase ≤100.0 U/mL had perfect diagnostic value for MCI with sensitivity and specificity of 100%, followed by MDA ≥75.0 U/mL with sensitivity and specificity of 100% and 97.5% and SOD ≤61.0 U/mL with sensitivity and specificity of 100% and 75% (p <0.001).

Conclusion: Oxidative stress play a role in development of MCI with decrease level of antioxidant while increase level of oxidative damage products, comparing the efficacy of markers of oxidative damage as well as antioxidant in diagnosis of MCI and their cutoff point, the study concluded that Catalase (≤100.0 U/mL), followed by MDA (≥75u/ml) then SOD (≤61.0 u/ml).

1. INTRODUCTION

The fast rise in the average life expectancy has led to an increase in the number of old people globally. The World Health Organization predicts that by 2050, 1 in 6 of the world's population, up from 1 in 11 in 2019, will be over the age of 65. Even though a longer life expectancy is a sign of better human development, a new problem is emerging due to the elderly population's increased susceptibility to cognitive and biological degeneration, including physical frailty, psychological impairment, and cognitive decline. This vulnerability leads to the emergence of several age-related diseases, which

are one of the biggest health threats of the twenty-first century.[1,2]

The chance of developing a wide range of diseases, including diabetes mellitus, osteoarthritis, osteoporosis, cancer, cardiovascular diseases, and neurological disorders like dementia, is increased in aged people due to age-related changes.[3-5]

Mild cognitive impairment (MCI) is a condition (recently referred to as minor neurocognitive disorder) that encompasses cognitive disorders that occur outside of ageing and dementia in which the decline occurs but does not affect a person's activities of daily living, so it represents an important point on the pathway to developing dementia and is a target for early detection and intervention. The estimated rate of change from MCI to dementia is around 10-15% every year and that 50% of people with MCI will eventually develop dementia.[8-11]

While the prevalence of MCI worldwide ranges from 16 percent to 42 percent, the prevalence of MCI in Egypt is also debatable and varies from 1.7 percent to 39.9 percent according to various studies, there is controversy surrounding the number of MCI cases worldwide due to differences in diagnostic criteria, sample taking techniques, and neuropsychological tests used.[12-15]

The physiology of ageing remains controversial, but several theories link diminished redox state and weakened antioxidant system to increased oxidative stress, reactive oxygen and nitrogen species (ROS/RNS) imbalance, and ageing.[16]

Reactive oxygen species (ROS), which are produced in greater quantities during oxidative stress (OS), have been linked to the pathophysiology of both cardiovascular and neurological illnesses. Therefore, the buildup of oxidative stress byproducts such as glycated products, oxidized proteins, and lipid peroxidation causes neuronal degeneration and is typically seen in brain illnesses.[17]

The antioxidant pathways, which include enzymes like catalase, superoxide dismutase, glutathione peroxidase, and numerous non-enzymatic antioxidants like reduced glutathione (GSH) and vitamins A, C, and E and carotenoids, serve as a defensive mechanism to prevent oxidative damage to the human body.[18]

When compared to individuals with normal cognitive function, mild cognitive impairment (MCI) patients' plasma levels of non-enzymatic antioxidants and the activity of antioxidant enzymes appeared to be lower, and there was a higher amount of the byproduct of oxidative damage.[19]

So, the objective of the study was to evaluate the correlation between oxidative stress and cognitive decline in elderly with mild cognitive impairment.

2. METHODS

A small scale preliminary study carried out from May 1, 2020 to October 1, 2021, at the Geriatric Outpatient Clinic of Ain Shams University Hospitals. In this study, there were 40 elderly patients (60 years or older) with cognitive impairment who underwent the Addenbrookes Cognitive Examination (ACE) and 40 healthy controls (40 people of similar age and sex). The ethics board at Ain Shams University approved the study, and subjected signed informed consent. We excluded patients who were taking multivitamins, smoked, had dementia, visual or hearing impairment, psychiatric conditions like schizophrenia, acute strokes, brain tumors, or had delirium were excluded from the study.

All participants subjected to history taking and clinical assessment. The following assessments were done:

- *Cognitive function assessment:* using Arabic version of Addenbrookes Cognitive examination ACE III in educated elderly.[20] Diagnostic criteria for mild cognitive impairment (MCI) was done according to DSM-5 criteria: [21]

DSM-5 criteria

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual–motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia).

- *Depression assessment:* Geriatric depression scale (GDS) to screen for depression in cognitively intact patients which is a 15-item scale with a cut-off of 5 for significant depression. The Arabic version was used.[22] if depressed by GDS, we done a DSM-5 diagnostic criterion for depression. GDS is screening scale for depression with cutoff point 5 out of 15 for diagnosis of depression, then we used a DSM-5 diagnostic criterion for depression which includes depressed mood or loss of interest over the last 2 weeks not due to medical condition.

- *Nutritional assessment:* using Mini-nutritional assessment.[23]
- *Functional assessment:* using activities of daily living (ADL)[24] and Instrumental activities of daily living (IADL).[25]
- *Assessment for fall risk:* by using Timed up and go test.[26]
- *Laboratory markers of oxidative stress:* included serum Malondialdehyde (MDA)[27], superoxide dismutase[28] and catalase.[29]

2.1. Oxidative Damage Biomarkers

2.1.1. Serum malondialdehyde (MDA)

▪ Principle

Thiobarbituric acid (TBA) reacts with malondialdehyde (MDA) in acidic medium at temperature of 95°C for 30 min to form thiobarbituric acid reactive product the absorbance of the resultant pink product can be measured at 534 nm.

▪ Reagents

1. **Standard**	10 nmol / mL
2. **Chromogen** Thiobarbituric acid Detergent Stabilizer	25 mmol / L

▪ Stability

Stable until the expiry date specified when stored at 4 to 8 °C.

▪ Procedure

To 0.5 ml of the serum, 0.5 ml of 30% Trichloroacetic acid (TCA) (Merck) was added and centrifuged at 3,000 rpm for 5 minutes and supernatant was collected. Thereafter, 0.5 ml of supernatant was added to 0.5 ml of 1% TBA (Merck) in a boiling water bath for 30 minutes following which tubes were kept in an ice-cold water bath for 10 minutes. The resulting chromogen absorbance was determined at the wavelength of 532 nm at room temperature against blank reference. The concentration of MDA was read from standard calibration curve plotted using 1, 1, 3, 3' tetra-ethoxy propane (TEP). The extent of lipid peroxidation was expressed as MDA (μM/L) using a molar extinction coefficient for MDA of $1.56 \times 105\ M^{-1}\ cm^{-1}$.[27]

2.2. Endogenous Antioxidant

2.2.1. Superoxide dismutase

▪ Principle

Superoxide dismutases (SODs) are metalloenzymes that catalyze the dismutation of the superoxide anion to molecular oxygen and hydrogen peroxide and thus form a crucial part of the cellular antioxidant defense mechanism.

▪ Stability

The reagents are stable up to the expiry date specified when stored at the proper temperature indicated R1 Store at 2-8°C. R2, R3, R4 Store at - 20°C or below.

▪ Procedure

SOD activity was estimated using the method described by Akindukom et al.[28] This is a semi-automated spectrophotometric procedure which is based on the ability of SOD generated by the xanthine oxidase reaction to inhibit the auto-oxidation of adrenaline at pH of 10.2. The reaction leads to the formation of an adenochrome (which gives off a yellowish coloration) which is measured spectrophotometrically at a wavelength of 480 nm.

2.2.2. Catalase

▪ Procedure

Catalase was colorimetrically determined using a catalase assay kit containing a stopping solution based on Jeong et al.[30] The stop solution caused the complete stop of catalase activity. Catalase content of the samples reacted firstly with hydrogen peroxide to produce water and oxygen and the unconverted hydrogen peroxide reacted with OxiRed™ probe solution to produce a product which was measured at 570 nm. 12 μL 1 mM fresh hydrogen peroxide solution was added to 40 μL serum samples or high control serum samples (HC sample); stopping solution was firstly added to HC serum samples and then the catalase activity was assayed. All samples were incubated at 25°C for 30 min and then 10 μL stop solution was added into sample vials. HC and standard samples already contained the stop

1. Chromogen - buffer: Phosphate buffer, pH 7.0 DCHBS Detergent	 100 mM / L 1 mM / L
2. H_2O_2 (substrate and standard) (Dilute 1000 times before use)	0.5 mM / L
3. Catalase Inhibitor	
4. Enzyme : Peroxidase 4 – Aminoantipyrine Preservative	 > 2000 / L 2 mM / L

solution. OxiRed™ probe solution was added to the samples and incubated at 25°C for 10 min. Then, the absorbance at 570 nm was measured. A standard curve was prepared by adding 10 µL stop solution to 0, 2, 4, 6, 8 and 10 µL 1 mM hydrogen peroxide solution.

▪ Reagents

2.3. Statistical Analysis

The statistical software for social sciences (SPSS) version 22 was used to examine all data (SPSS Inc, Chicago, USA). Frequency and percent distributions were computed for qualitative data. The mean and standard deviation (SD) for quantitative data were computed. The threshold for significance was set at $p<0.05$. The Independent *t*-test, *Chi* square test, and Fisher's Exact test were all employed.

3. RESULTS

The study involved a total of 80 participants; 40 MCI patients (with scores ranging from 74 to 81) of ACE III and 40 healthy controls (with mean ages of 65.6±3.0 and 64.7±3.2 years, respectively). Age, sex, place of residence, family history, and co-morbidity did not substantially differ between the two groups (Table 1).

Fish, nuts, turmeric, and vegetables were substantially less common in the MCI group according to the pattern of dietary habits among the people under study ($p<0.05$), whereas dark chocolate consumption did not differ significantly between the two groups (Table 2).

The MCI group had a greater significant risk of malnutrition assessed by MNA ($p<0.001$) and risk of fall assessed by TUGT ($p=0.029$) in terms of nutritional, functional, and mood assessment among individuals. Additionally, depression was considerably more prevalent in the MCI group ($p<0.001$) but there was no difference between ADL and IADL (Table 3). Nutritional assessment as a part of comprehensive geriatric assessment showed risk of malnutrition as scores range from 17 to 23.5.

In addition, participants in the study were tested for Malondialdehyde and antioxidant indicators, such as superoxide dismutase and catalase. The results revealed that the MCI group had significantly lower levels of superoxide dismutase and catalase than the control group did ($p<0.001$) (Table 4).

Table 1. Demographic characteristics among the studied groups

Variables		MCI (*N*=40)	Non-MCI (*N*=40)	*p*-value
Age (years)	Mean±*SD*	65.6±3.0	64.7±3.2	^0.21
	Range	60.0–75.0	60.0–74.0	
Sex	Male	20 (50.0%)	18 (45.0%)	#0.654
	Female	20 (50.0%)	22 (55.0%)	
Residence	Urban	30 (72.5%)	27 (67.5%)	#0.459
	Rural	10 (27.5%)	13 (32.5%)	
Family history	Yes	15 (37.5%)	10 (25.0%)	#0.228
Co morbidity	Diabetes mellitus	19 (47.5%)	17 (42.5%)	#0.742
	Hypertension	27 (67.5%)	30 (75.0%)	
	Cardiova scular	9 (22.5%)	4 (10.0%)	
	Hepatic	3 (7.5%)	8 (20.0%)	
	Renal	3 (7.5%)	3 (7.5%)	
	Chest	5 (12.5%)	1 (2.5%)	
	Osteoart hritis	12 (30.0%)	12 (30.0%)	

Data presented as n (%) unless mentioned otherwise. ^: Independent t-test, #: Chi square test, §: Fisher's Exact test, *: Significant

Table 2. Dietary habits among the studied groups

Food	MCI (*N*=40)	Non-MCI (*N*=40)	*p*-value
Healthy food	4 (10.0%)	17 (42.5%)	#0.001*
Fish (twice per week)	2 (5.0%)	16 (40.0%)	#<0.001*
Nuts (30gm daily)	0 (0.0%)	6 (15.0%)	§0.026
Turmeric (Twice per week)	1 (2.5%)	8 (20.0%)	§0.029*
Dark chocolate (20 gm daily)	0 (0.0%)	1 (2.5%)	§0.99
Coconut oil (60ml divided daily)	2 (5.0%)	11 (27.5%)	#0.006

Data presented as n (%) unless mentioned otherwise.
^: Independent t-test, #: Chi square test, §: Fisher's Exact test. *: Significant

Table 3. Geriatric assessment tools findings among the studied groups

Tools		MCI (*N*=40)	Non-MCI (*N*=40)	*p*-value
ADL	6	40 (100.0%)	40 (100.0%)	NA
IADL	6	3 (7.5%)	3 (7.5%)	§0.397
	7	19 (47.5%)	13 (32.5%)	
	8	18 (45.0%)	24 (60.0%)	
MNA	Normal	1 (2.5%)	37 (92.5%)	#<0.001*
	Risk	20 (50.0%)	2 (5.0%)	
	Malnourished	19 (47.5%)	1 (2.5%)	
Depression		25 (62.5%)	4 (10.0%)	#<0.001*

Data presented as n (%) unless mentioned otherwise.
NA: Not applicable, ^: Independent t-test, #: Chi square test

Table 4. Oxidant markers among the studied groups

Variables		MCI (*N*=40)	Non-MCI (*N*=40)	^*p*-value
MDA (U/mL)	Mean±*SD*	152.0±36.0	45.6±12.9	<0.001*
	Range	89.2–216.5	30.6–95.0	
SOD (U/mL)	Mean±*SD*	39.5±13.3	69.0±12.0	<0.001*
	Range	19.4–60.0	51.3–89.2	
Catalase (U/mL)	Mean±*SD*	66.5±19.9	128.8±20.9	<0.001*
	Range	33.5–100.0	101.6–183.3	

MDA: Malondialdehyde, SOD: superoxide dismutase,
^: Independent t-test, *: Significant

Markers of oxidation were compared with regard to their sensitivity and specificity in diagnosing MCI cases as well as their cutoff value for diagnosis, and it was found that Catalase (100.0 U/mL) had the perfect diagnostic value for MCI with 100% sensitivity and specificity, followed by (MDA 75.0 U/mL) with 100% sensitivity and 97.5 percent specificity, and SOD (61.0 U/mL) with 100% sensitivity and 75% specificity (Table 5 & Figure 1).

It is assess functional status using ADL & IADL to assess functional status in participants for MCI diagnosis in which there is no affection of functional status. Also physical inactivity is one of modifiable risk factors for dementia according the 2020 lancet.[31]

4. DISCUSSION

According to the "free radical theory of aging", an elevation in reactive oxygen and nitrogen species damages neuronal membranes and induces oxidative and nitrosative stress. So, it plays a role in development of neurodegeneration and cognitive decline.[32]

The current study aimed to investigate cognitive impairment among elderly participants and its association with cellular oxidative stress, as regard demographic data of participants there were no statistically significant differences between the MCI patients' group and controls regarding Age and Sex, this was similar to study done by Horvat et al.[33] where increased derivative of reactive oxygen metabolites (d-ROM) levels were inversely associated with verbal fluency and global cognition, both cross-sectionally and at 3-year follow-up, but the protective biological antioxidant potential (BAP) was not related to cognitive function. Also Our results is convenient with study done by Al-Rawaf et al.[34] where the plasma levels of oxidative damage markers like MDA, nitric oxide (NO), and dipeptidyl peptidase 4 (DPP4) activity significantly increased, and the levels of protective antioxidant markers like SOD, CAT, brain derived neurotrophic factor (BDNF), and sirtuin 1 (SIRT1) significantly reduced in MCI subjects compared to controls.

Regarding food habits among the studied groups, we found that Healthy food in general is more among the control group than participant with MCI and by revising different type of food and its relation with risk of MCI, the current study found that fish, nuts, turmeric, vegetables were more consumed by control group than MCI group so this indicates significant relation between consumption of these food and protection of cognitive function.

Diet has been linked to significant cognitive decline and dementia progression, particularly when it comes to protecting against the negative effects of neuro-inflammation and oxidative stress. Antioxidants found in meals like fruit and vegetables are thought to help lower levels of oxidative stress in the brain, while n-3 PUFA poly unsaturated fatty acid , found in foods like oily fish, are also associated to decreased inflammation.[35]

We discussed in our study the correlation between healthy brain food and cognitive impairment where we found that healthy brain food usage is associated with less cognitive impairment.

The results of current study were similar to results by Khater & Abouelezz[36], That also linked risk of development of MCI with dietary habits among participant.

Figure 1. ROC curve for the studied markers in diagnosing MCI

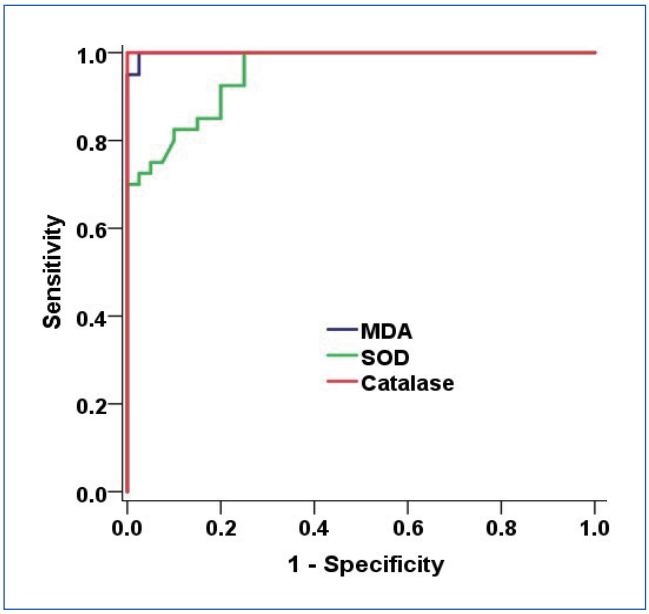

Table 5. Oxidant markers cutoff points as well as sensitivity and specificity in diagnosing MCI

Characteristics	MDA ≥75.0 U/mL		SOD ≤61.0 U/mL		Catalase ≤100.0U/mL	
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	100%	91.2%–100%	100%	91.2%–100%	100%	100%–91.2%
Specificity	97.5%	86.8%–99.9%	75.0%	58.8%–87.3%	100%	100%–91.2%
DA	98.8%	93.2%–100%	87.5%	78.2%–93.8%	100%	100%–95.5%
YI	97.5%	92.7%–100%	75.0%	61.6%–88.4%	100%	100%–100%
PPV	97.6%	87.1%–99.9%	80.0%	66.3%–90.0%	100%	100%–91.2%
NPV	100%	91.0%–100%	100%	88.4%–100%	100%	100%–91.2%
LR+	40.00	5.78–277.05	4.00	2.34–6.84	>100	>100–>100
LR-	0.00	0.00–0.00	0.00	0.00–0.00	0.00	0.00–0.00
DOR	>100.0	>100–>100	>100	>100–>100	>100	>100–>100

CI: Confidence interval, DA: Diagnostic accuracy, PPV: Positive Predictive value, NPV: Negative Predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, DOR: Diagnostic odd ratio

Regarding comprehensive assessment of participants, we found that MCI group had higher risk of malnutrition detected by MNA. Also depression was statistically significant among MCI group. In agreement with our results [33,36,37] reported that depression and anxiety was significantly more frequent in MCI group.

As depression is one of modifiable risk factors for cognitive impairment according to the 2020 lancet commission on dementia prevention, intervention and care.

We found that the MDA oxidative stress marker was statistically substantially greater in the MCI group among the examined groups. The antioxidant markers SOD and catalase were statistically significantly lower in the MCI group. So it follows that one of the variables contributing to cognitive impairment is oxidative stress as MCI groups have higher MDA levels and lower SOD and Catalase levels. These findings corroborated those of studies by Al-Rawaf et al.[34] and Balmuş et al.[38], which found a negative correlation between MDA and cognitive parameters due to the lower levels of antioxidant defense products (SOD and CAT) in MCI participants. The results showed that low cognitive performance was associated with both elevated MDA and NO levels and decreased SOD and CAT activity in subjects with MCI. MDA as lipid peroxide product was significantly reported in the serum of subjects with brain disorders such as MCI.[38] Also, it was reported that MDA and related lipid peroxides considered promising peripheral biomarkers during brain cases with white matter abnormalities. This may be related to higher lipid contents in both the axonal membranes and myelin sheaths of the brain.

Also, Umur et al.[39] supported the same result as it found that the level of MDA correlated with MMSE scores.

Markers of oxidation where compared as regard sensitivity and specificity in diagnoses of MCI cases as well as their cut-off value for diagnosis and showed that Catalase (with cutoff value ≤100.0 U/mL) had perfect diagnostic value for MCI followed by (MDA ≥75.0 U/mL and SOD (≤61.0 U/mL) with (p <0.001)

5. CONCLUSION

Oxidative stress plays a role in development of MCI with decrease level of antioxidant while increase level of oxidative damage products causing neuronal damage.

Markers used to measure oxidative stress and antioxidant activity could be a method for early diagnosis of MCI patients so providing early interventional measures for MCI patients and so better quality of life.

CONFLICTS OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or this article.

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ETHICAL APPROVAL

This study was approved by the Ethical Committee of Ain Shams University Hospitals (13/8/2020) (FWA 000017585) before conduction of the study.

LIMITATIONS OF STUDY

A small-scale preliminary study carried out from May 1, 2020 to October 1, 2021, at the Geriatric Outpatient Clinic of Ain Shams University Hospitals. In this study, there were 40 elderly patients (60 years or older) with cognitive impairment who underwent the Addenbrookes Cognitive Examination (ACE) and 40 healthy controls (40 people of similar age and sex).

These are new markers for generalization of that results, large study should be done. A study had been collected from one area, so it is recommended to be collected from different areas to be more representative and accurate.

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