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Original Article

The Relationship of Cognitive Performance with Oxidative Stress in Alzheimer's Disease

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SUMMARY

Aims: Alzheimer's disease (AD) has a complex neurodegenerative etiology and pathogenesis. In addition to oxidative stress, inflammation also plays an important role in the development of AD. In this study, we aimed to determine the total antioxidant status (TAS), total oxidation status (TOS) and oxidative stress index (OSI) levels in AD patients. We also planned to evaluate the relationship of OSI with interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α).

Methods: A total of 33 subjects with AD (mean age 78.9 ± 7.8) and 33 subjects as control (mean age 72.3 ± 2.6) were enrolled in this cross-sectional study. TAS and TOS were assessed with commercial kits using an autoanalyzer. TNF-α and IL-1β were measured with commercial ELISA kits.

Results: The AD group demonstrated significantly higher TNF-α, IL-1β, and TOS levels compared to the control group (p = 0.001, p = 0.029, p = 0.005). The mean TAS level was significantly lower in the AD group than in the control group (p = 0.007). There was a statistically significant negative correlation between TNF-α and ADL, IADL, MMSE (p = 0.001, p = 0.003, p = 0.003). There was a statistically significant negative correlation between IL-1β and AIDL, as well as a positive correlation between IL-1β and GDS (p = 0.029, p = 0.016).

Conclusion: Our study contributes to the understanding of the situation by showing that the oxidative balance is impaired in favor of oxidants in AD. A negative correlation was found between functional capacity and TNF-α and IL-1β levels in AD patients. Different therapeutic interventions that reduce the oxidant load can be considered in the treatment of AD.

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly population and is characterized by progressive memory loss and other cognitive impairments.[1] Alzheimer's disease is has a multi-faceted neurodegenerative complex etiology and pathogenesis. Histopathologically, it is characterized by extracellular senile plaques and intracellular neurofibrillary tangles. Senile plaques are formed by the accumulation of amyloid b protein (Ab) and neurofibrillary tangles by the collection of the hyperphosphorylated tau protein. The accumulation of neurotoxic Ab proteins results in inflammation, oxidative stress, and hyperphosphorylation of the tau protein.[2]

Studies on AD cases show the presence of common reactive oxygen species (ROS) even in cerebral areas, confirming that the whole brain is exposed to oxidative stress.[3] Plasma concentrations of oxidants and antioxidants can be measured separately in the laboratory, but these measurements are time consuming, laborious and costly. The oxidative and antioxidant effects of the oxidative and antioxidant components of plasma are only additive in the measurement of total oxidant status (TOS) and total antioxidant status (TAS) may reflect the oxidative and antioxidative state of the plasma.[4,5] Evaluation of total oxidant-antioxidant capacity is necessary to investigate the specific relationship between AD and oxidative metabolism. It is possible to evaluate TOS and TAS, which are used to determine oxidative and antioxidative status, with new automatic colorimetric measurement methods. The oxidative stress index (OSI), a quantitative determinant of oxidative stress, is calculated by the ratio of TOS to TAS.[6]

Interleukin-1 (IL-1), a proinflammatory cytokine, is a member of a pleiotropic cytokine family that has numerous effects on the central nervous system (CNS). Interleukin-1 beta (IL-1β) elevation is a critical component of the brain's patterned response to insults termed "neuroinflammation" and of leukocyte recruitment into the CNS. After the discovery of neuroinflammation in the AD brain, increased IL-1β expression in the reactive microglia surrounding the amyloid plaques was found to be closely linked to the pathogenesis of AD.[7–9] Since then, IL-1β elevations have been detected in aging AD mouse models and plaque-associated microglia brains.[10]

One of the cytokines that cause inflammation in the pathophysiology of AD is tumor necrosis factor-alpha (TNF-α).[11] It is associated with the beta-amyloid collection and tau protein hyperphosphorylation of excess TNF-α expression in blood, cerebrospinal fluid (CSF), and brain tissue in AD patients.[12]

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Even though it has been shown that the current oxidant balance in AD changes towards oxidative stress, the uncertainty between cognitive performance, functional capacity, and oxidative stress in these patients remains.

In this study, we aimed to determine the TAS, TOS and OSI levels in AD patients. In addition, for the first time in the literature, we aimed to evaluate the relationship of OSI with inflammatory markers IL-1β and TNF-α in AD patients.

2. Materials and methods

2.1. Study design

The study was conducted in a cross-sectional design. All participants gave written individual informed consent to participate. Experimental analyzes were carried out in Gaziantep University Biochemistry. The study protocol was approved by the Local Ethics Committee at Gaziantep University Medical Faculty (IRB number: 2017/431; Date: 25.12.2017).

2.2. Participants

Patients aged 65 and over 48 diagnosed with Alzheimer's disease who applied for medical care to Gaziantep University Hospital Internal Diseases Department Geriatric Medicine Department outpatient clinic between July 2017 and January 2019 were included in the study.

Those under 65 years of age, with infection, acute condition, end-stage chronic liver and kidney disease, malignancy, diabetes mellitus, hypothyroidism, severe malnutrition, history of trauma or infection, and those using corticosteroids, methotrexate, nonsteroidal anti-inflammatory drugs or other immunomodulatory agents were excluded from the study. In addition, a total of 15 patients included in the study were excluded from the study for various reasons [failure to fill in the study questionnaire (n = 8), active psychosis (n = 2), recent hospitalization (n = 2) = 3), history of malignancy (n = 2))].

Data could be collected from 33 patients out of the 48 patients under treatment (Figure 1). A control group of 33 people with age matched with the patient group was formed. All patients under follow up were invited to join the study without sampling. All participants underwent a comprehensive medical history and frailty measurement by trained staff. Socioeconomic and demographic data on age, sex, and educational level were collected.

2.3. Comprehensive geriatric assessment tests

All participants underwent a standardized and comprehensive geriatric assessment. Investigators collected detailed patient history using several clinical testing modalities, including the geriatric depression scale (GDS) with 15 questions,[13] the mini-mental state examination (MMSE),[14] Katz index of activities of daily living (ADL),[15] Lawton Brody index of the instrumental activities of daily living (IADL),[16] the short form of the Mini Nutritional Assessment Tool (MNA-SF),[17] and Tinetti Balance-Gait Evaluation Scale.[18]

GDS scores of 5 and over indicate depression. The MMSE assesses six different areas in cognitive function: orientation: registration, attention, calculation, recall, and language. MMSE scores of 24 and below were considered as impaired, suggesting dementia.

Katz's index of ADL was used for evaluating the physical disability of the subjects. This scale includes dressing, bathing, using the toilet, eating, transferring, and incontinence. Scores can range from 0 to 6, higher scores indicating increased independence. The Lawton Brody index was used to evaluate the disability in IADL. This scale aims to assess performance in the following activities: doing laundry, shopping, taking medicine, housekeeping, food preparation, using the telephone, using transportation, and managing money. Increased scores indicate higher independence.

The nutritional status of participants was determined with the MNA-SF, which is a simple and validated screening tool for nutritional risk assessment. An MNA-SF score of ≤ 7 is accepted as malnutrition.

2.4. Blood samples

After 8 hours of fasting, 5 cc venous blood samples were taken from patients and controls. Specimens were centrifuged at 4000 rpm for 10 minutes, and serums were separated. After separation, the serum samples were frozen and stored at -80 °C until analyzed for TNF-α, IL-1β, TAS, and TOS. TAS and TOS were assessed with commercial kits (Rel Assay, Turkey) using an autoanalyzer (Beckman Coulter AU 4800, USA). TNF-α and IL-1β were measured with commercial ELISA kits (USCNK, USA) by an ELISA reader (BioTek EL*800, USA).

2.5. TAS assay principle

A standardized solution of Fe^{2+}–o-dianisidine complex reacts with a standardized solution of hydrogen peroxide by a Fenton-type reaction, producing OH. These potent ROS oxidize the reduced colorless o-dianisidine molecules to yellow-brown colored dianisidyl radicals at low pH. The oxidation reactions progress among dianisidyl radicals and further oxidation reactions develop. The color formation is increased with further oxidation reactions. Antioxidants in the sample suppress the oxidation reactions and color formation. This reaction can be monitored by spectrophotometry. The suppression

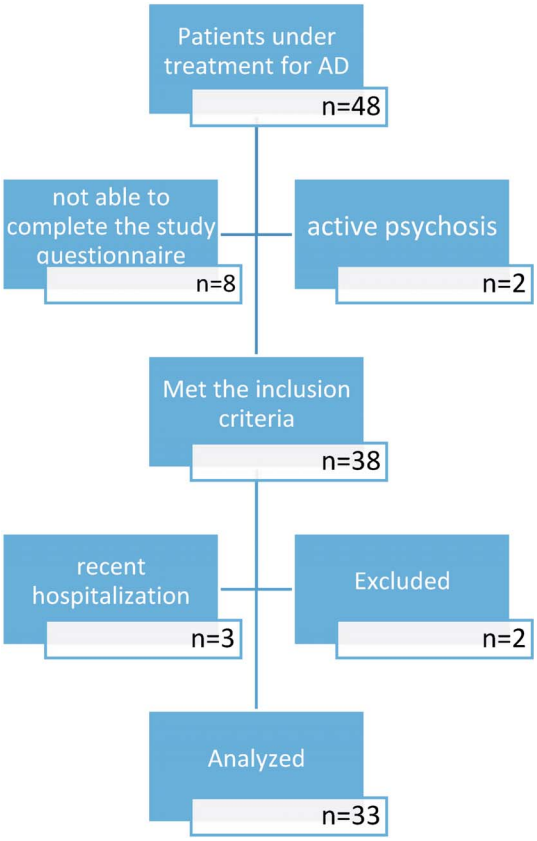

Figure 1. Study AD group flow diagram. AD, Alzheimer's disease.

of the color formation is calibrated with Trolox, which is widely used as a traditional standard for TAR measurement assays, so the results in this assay are expressed as in terms of millimolar Trolox equivalent per liter.[4]

2.6. TOS assay principle

Oxidants in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2Equiv/L).[19]

The following formula was used to calculate the OSI, which is an indicator of the degree of oxidative stress;

OSI = [(TOS, μmol/L)/(TAS, mmol Trolox equiv/L) × 100].[20]

2.7. Statistical analysis

The IBM SPSS Statistics 21 software program was used for data analysis. The normality of continuous variables were tested using the Shapiro-Wilk test. Descriptive statistics [mean ± standard deviation (SD)] were given for continuous variables. Sex distribution was expressed as frequencies and percentages. The oxidative stress variables were presented as mean ± SD.

Continuous variables of both groups were compared using the independent samples t-test. Univariate analysis of covariance was performed to investigate the effects of potential confounders [age, sex, and body mass index (BMI)]. The relationship between the levels of the oxidative stress parameters of the patient group, total illness duration, and the scores of the PHQ-15 and SSAS scales were examined using Spearman correlation analysis. The statistical significance level was determined as $p < 0.05$.

3. Results

Participants of the study were 33 patients with AD (15 males and 18 females) and 33 healthy controls (22 males and 11 females). The sociodemographic and clinical characteristics of the participants are shown in Table 1. The mean age was 78.92 ± 7.84 years for the AD group and 72.26 ± 2.60 years for the control group. There was no significant difference between AD and control groups concerning age ($p = 0.528$). There was no significant difference between the groups regarding sex, educational status, and BMI ($p > 0.05$). There was a statistically significant difference between the two groups for ADL, IADL, MMSE, and MNA-SF ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.022$, respectively) (Table 1).

Comparison of TNF-α, IL-1β, TAS, TOS, and OSI levels between the healthy control and AD groups are summarized in Table 2. The AD group demonstrated significantly higher TNF-α, IL-1β, and TOS levels compared to the control group ($p = 0.001$, $p = 0.029$, and $p = 0.005$, respectively). The mean TAS level was significantly lower in the AD group than the control group ($p = 0.007$).

Correlations between TNF-α, IL-1β, TAS, TOS, OSI, and other variables are given in Table 3. Age and educational level showed no significant associations with TNF-α, IL-1β, TAS, and TOS levels. There was a statistically significant negative correlation between TNF-α and ADL ($r = -0.396$, $p = 0.001$), AIDL ($r = -0.360$, $p = 0.003$), and MMSE ($r = -0.364$, $p = 0.003$), (Table 3). There was a statistically significant negative correlation between IL-1β and AIDL ($r = -0.269$, $p = 0.029$), as well as a positive correlation between IL-1β and GDS ($r = 0.295$, $p = 0.016$) (Table 3). Also, TAS was positively correlated with ADL ($r = 0.324$, $p = 0.009$), AIDL ($r = 0.335$, $p = 0.066$), and MMSE ($r = 0.319$, $p = 0.009$). There was a statistically significant negative correlation between TOS and AIDL ($r = -0.266$, $p = 0.031$), as well as MMSE ($r = -0.300$, $p = 0.014$). While OSI showed a negative correlation with ADL ($r = -0.516$, $p = 0.001$), AIDL ($r = -0.500$, $p = 0.001$), and MMSE ($r = -0.541$, $p = 0.001$), it was positively correlated with age ($r = 0.391$, $p = 0.001$). While a significant negative correlation was found

Table 2
Comparison of the mean inflammatory cytokine levels between the AD and control groups.

	AD (n = 33)	Control (n = 33)	p
TNF-α (pg/ml)	4.00 ± 1.34	2.88 ± 1.24	0.001*
IL-1β (pg/ml)	21.50 ± 12.29	15.72 ± 5.97	0.029*
TAS (mmol Trolox equiv/L)	2.29 ± 0.81	2.91 ± 0.88	0.007*
TOS (μmol/L)	7.35 ± 1.78	6.22 ± 1.24	0.005*
OSI UA	1.30 ± 0.67	0.87 ± 0.62	< 0.001*

IL-1β, Interleukin-1 beta; OSI, oxidative stress index; TAS, total antioxidant status; TNF-α, tumor necrosis factor-alpha; TOS, total oxidant status.
Values are presented as mean ± SD. * $p < 0.05$ was considered significant.

Table 1
Demographic characteristics of the two groups.

	AD	Control	p
Sex			
Female (%)	18 (27.3)	11 (16.7)	0.830
Male (%)	15 (22.7)	22 (33.3)	0.829
Age (years)	78.92 ± 7.84	72.26 ± 2.60	0.528
Educational level (years)	3.95 ± 3.67	4.46 ± 4.16	0.602
BMI (kg/m^2)	24.89 ± 3.96	25.11 ± 3.59	0.454
Comprehensive Geriatric Assessment Tests			
ADL disability	1.25 ± 1.54	5.80 ± 0.49	< 0.001*
IADL disability	0.52 ± 0.93	6.88 ± 1.24	< 0.001*
Cognition (MMSE, points)	9.80 ± 4.69	27.461 ± 1.47	< 0.001*
Depression (GDS, points)	2.87 ± 3.22	2.7692 ± 2.12	0.883
MNA-SF (points)	5.02 ± 2.81	3.53 ± 1.98	0.022*

ADL, activities of daily living; BMI, body mass index; GDS-SF, Geriatric Depression Scale Short Form; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MNA-SF, Mini Nutritional Assessment Tool Short Form.
Data are presented as n (%) or mean ± standard deviations.
* $p < 0.05$ was considered significant.

between MNA-SF, which evaluates nutritional status, and TAS, no significant correlation was found between TOS, TNF-α and IL-1β (p = 0.048, p = 0.192, p = 0.147, p = 0.617, respectively) (Table 3).

Corelations between TNF-α, IL-1β, TAS, TOS, OSI are given in Table 4. There was a positive correlation between OSI and TNF-α (r = 0.294, p = 0.016), IL-1β (r = 0.381, p = 0.002), TOS (r = 0.599, p = 0.001), and a negative correlation with TAS (r = -0.610, p = 0.001).

4. Discussion

This is a cross-sectional study that examines the relationship between inflammatory markers TNF-α and IL-1β, as well as evaluating oxidative stress index and cognitive and functional capacity in AD patients. In the study, TNF-α, IL-1β, OSI, and TOS levels were found to be significantly higher in AD patients compared to the control group, while TAS was found to be significantly lower. In the correlation analysis, OSI was positively correlated with both TNF-α and IL-1β. TNF-α, TAS, and OSI were correlated with functional capacity and MMSE in AD patients.

Neuroinflammation is a common feature in neurodegenerative diseases, but it is unclear whether this process is protective and when it begins during neurodegenerative progression.[21] Our results support the hypothesis that inflammation is a pathological part of cognitive impairment. We found higher levels of proinflammatory cytokine TNF-α in individuals with low MMSE scores. Moreover, there was a negative correlation between TNF-α and ADL, as well as IADL. We determined that increased TNF-α levels had adverse effects on cognition and functional capacity.

TNF-α and IL-1β are proinflammatory cytokines that play a role in the pathogenesis of systemic inflammatory and neurodegenerative diseases.[22] Microglia tend to release large amounts of TNF-α in pathological conditions. Concerning the role of TNF-α in the pathophysiology of AD, high TNF-α levels in CSF and sera of AD patients have been demonstrated by numerous studies.[23,24] TNF-α has both cytotoxic and excitotoxic effects and leads to a neuroinflammatory state. Excitotoxicity refers to excessive and/or prolonged activation of stimulating pathways leading to cell death. This process is associated with several diseases such as ischemia, AD, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis.[25] In the study of Gezen et al., serum TNF-α levels were significantly higher in the early and late-onset AD cases compared to controls in the same age group.[26] In addition, many studies suggest that increased serum TNF-α levels are associated with an AD-type pathology.[27] However, the opposite results have also been observed.[28] In another study, no correlation was found between cognitive scores and plasma cytokine and chemokine levels.[29] Our study showed that serum TNF levels in AD patients increased significantly compared to age-matched controls. We found that the decrease in functional capacity in the disease was negatively correlated with the increase of TNF-α levels.

Neuroinflammation with oxidative stress contributes significantly to the pathogenesis of AD.[30] Although many studies have shown high serum IL-1β levels in AD, studies are reporting no change in IL-1β levels compared to healthy controls.[31] In our research, we found an increased inflammatory response concerning high IL-1β levels in AD patients compared to those without AD. Besides, we determined that there was a negative correlation between IL-1β levels and functional capacity and a positive relationship with GDS. However, we did not find an association between IL-1β levels and MMSE. Forlenza et al. emphasized that serum IL-1β levels of AD patients were significantly higher compared to the control group, and differences in serum IL-1β levels between these groups remained statistically significant after controlling for age, education level, and the APOE 4 genotype.[32] In parallel with our study, the efficiency of proinflammatory cytokine levels of Khemka et al., such as IL-1 and TNF-α in peripheral circulation, was evaluated, and serum IL-1β levels were higher in patients with and without depression compared to controls. However, it has shown that there is no relationship between IL-1β and MMSE in AD patients with or without depression.[33] As to Yasutake et al., there was no correlation between IL-1β levels and MMSE scores in AD; however, there was a negative correlation in these variables in patients with vascular dementia.[34]

Antioxidants in the plasma interact with each other, and the collective antioxidant effect produced by the combination of anti-

Table 4
Correlation analysis of TAS, TOS, OSI, IL-1β and TNF-α.

		TNF-α	IL-1β	TAS	TOS	OSI
TNF-α	r	1	0.569**	-0.121	0.608**	0.294*
	p		0.001	0.335	0.001	0.016
IL-1β	r	0.569**	1	-0.337**	0.509	0.381**
	p	0.001		0.001	0.001	0.002
TAS	r	-0.121	-0.337**	1	-0.435**	-0.610**
	p	0.335	0.001		0.001	0.001
TOS	r	0.608**	0.509	-0.435**	1	0.599*
	p	0.001	0.001	0.001		0.001
OSI	r	0.294*	0.381**	-0.610**	0.599*	1
	p	0.016	0.002	0.001	0.001	

TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index; IL-1β, Interleukin-1 beta; TNF-α, tumor necrosis factor-alpha.
* p < 0.05 was considered significant. ** p < 0.005 was considered significant.

Table 3
Correlations of TNF-α, IL-1β, TAS, TOS, and OSI with the other variables.

Parameter		Age	Education	ADL	IADL	MMSE	GDS-SF	MNA-SF
TNF-α	r	0.225	0.033	-0.396**	-0.360**	-0.364**	-0.081	0.180
	p	0.070	0.794	0.001	0.003	0.003	0.518	0.147
IL-1β	r	0.075	-0.077	-0.225	-0.269*	-0.152	0.295*	0.063
	p	0.549	0.541	0.070	0.029	0.223	0.016	0.617
TAS	r	-0.119	0.115	0.324*	0.335**	0.319**	0.076	-0.160*
	p	0.943	0.359	0.009	0.006	0.009	0.054	0.048
TOS	r	0.198	-0.110	-0.209	-0.266*	-0.300*	-0.003	0.162
	p	0.112	0.379	0.092	0.031	0.014	0.982	0.192
OSI	r	0.391**	-0.070	-0.516**	-0.500**	-0.541**	-0.209	0.073
	p	0.001	0.579	0.001	0.001	0.001	0.092	0.561

ADL, activities of daily living; BMI, body mass index; GDS-SF, Geriatric Depression Scale Short Form; HGS, handgrip strength; IADL, instrumental activities of daily living; IL-1β, Interleukin-1 beta; MMSE, Mini-Mental State Examination; MNA-SF, Mini Nutritional Assessment Tool Short Form; OSI, oxidative stress index; TAS, total antioxidant status; TNF-α, tumor necrosis factor-alpha; TOS, total oxidant status.
* p < 0.05 was considered significant. ** p < 0.005 was considered significant.

oxidants is more effective than individual antioxidants. Therefore, evaluating only TAS instead of measuring each antioxidant individually is more useful in assessing the oxidant-antioxidant balance in the human body.[6] Total oxidant status values can be used as a marker of all free radicals synthesized. The most apparent finding of this study is that TOS and OSI levels were significantly higher in patients with somatic disorders compared to the control group. In many studies, besides showing the role of oxidative stress in the development of AD, the relatively limited success achieved with antioxidant treatments emphasizes that the molecular mechanisms associated with the different stages of AD development should be better understood.[35] The increase in oxidative load leads to oxidative damage in many molecules, such as DNA and proteins, with a decrease in antioxidant molecules.[36] In the study of Guidi et al., TAS levels were lower in the AD group than in the healthy group, but no relationship was found between TAS and the level of cognitive impairment graded by MMSE.[37] In our study, we detected a negative correlation between MMSE and TOS and a positive correlation between MMSE and TAS. These results support the relationship between low cognitive performance and increased oxidant/antioxidant balance. In the study of Socha et al., AD (n = 110) and control (n = 60) groups were evaluated and TAS levels of the AD group were found to be significantly lower than the healthy group. In addition, TAS levels were found to be significantly higher ($p < 0.003$) in early stage ADs of the disease compared to middle stage ADs. Similar to our study, a positive correlation was found between TAS and MMSE.[38] In another study examining the oxidative stress status in AD patients, TAS levels were found to be significantly lower in the AD group compared to the healthy group.[39] So far, studies on AD have focused on pharmacological management of the disease process rather than prevention and repair mechanisms. However, it is understood that the effects of treatments aimed at increasing the antioxidant level in the early stages of AD will be beneficial by understanding the oxidative stress mechanisms that emerge from the early stages of AD.

Oxidative stress is an important pathological feature in AD. However, how and where oxidative stress originates in AD are unclear questions.[40] According to the researches, the basic mechanisms underlying oxidative stress induction are; metal accumulation, hyperphosphorylated tau, mitochondrial dysfunction, inflammation and β-amyloid (Aβ) accumulation.[41–47] Deficiency or destruction of antioxidant system components such as superoxide dismutase (SOD) and cytosol (Cu-Zn-SOD or SOD1), glutathione peroxidases and catalase in mitochondria, which are especially involved in scavenging free radicals, also play an important role in inducing oxidative stress.[48] Oxidative stress is a major contributor to Aβ accumulation and tau hyperphosphorylation, which plays an important role in the basic pathogenesis of AD and is thought to be a biomarker and therapeutic target for AD.[49] In our study, we found a decrease in antioxidant levels and an increase in oxidative stress index. however, it may contribute to the development of effective treatment models in AD, which is a multifactorial degenerative disease.

There are some limitations to our study. The first is that the study was conducted in a single center and with a relatively limited number of subjects. Furthermore, our research is a cross-sectional one. In addition, our findings may be insufficient to fully reflect the oxidative balance of the central cirrhosis system because oxidative stress parameters were studied for serum samples only. Depending on the studies carried out with CSF or oxidative parameters, changes in the receptor can give more precise results. Finally, if the MCI group had been taken as a third group of the study, it would be useful for interpreting the signal changes of the neurodegenerative process in the brain of the early stage.

In conclusion, AD etiology has many unknown factors related to diagnosis and treatment. Our study contributes to the understanding of the situation by showing that the oxidative balance is impaired in favor of oxidants in AD. In our study, it has been shown that increased oxidative stress level has a negative effect on cognitive and functional losses by causing neuronal cell damage in Alzheimer's disease. In addition, increased TNF-α, a marker of inflammation, was also found to be associated with decreased cognitive and functional capacity in AD. Our results should be supported by further studies with larger samples to investigate the potential effects of oxidative stress and inflammation on AD.

Conflict of interest

The authors have no conflict of interest in this study.

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Data sharing statement

Please contact the corresponding author for data availability.

Author contributions

F.D.Y and Z.A.Ö contributed to the design of the questionnaire. H.U and M.T. contributed to the data collection. F.D.Y and H.U contributed to the data analysis, interpretation, and manuscript preparation of this study. F.D.Y, H.U., Z.A.Ö and M.T contributed to the concept, design, data analysis, interpretation, and manuscript preparation and supervision of this study. All authors have read and approved the final manuscript.

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