Original Article

The Associations of Iron Accumulation and Cognitive Impairment in Alzheimer's Disease in Kerbala Governate, Iraq

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Abstract

Background: Recent research has revealed that ferroptosis plays an important part in the pathophysiological process of numerous body systems, including the nervous system. Ferroptosis may be linked to the onset and progression of Alzheimer's disease (AD). **Objective:** The goal of this study was to look at the serum levels of free iron, total iron-binding capacity (TIBC), ferritin, and divalent metal transporter 1 (DMT1) in Alzheimer's patients. **Materials and Methods:** A total of 80 blood samples were taken from 40 cases of Alzheimer's disease and 40 healthy controls for a case–control study. The following parameters' regarding serum biomarker levels were determined: The serum DMT1 was measured using the enzyme-linked immunosorbent assay technique. The colorimetric approach is used for serum-free iron and TIBC, and the spectrophotometric method is used for serum ferritin. The receiver operating characteristic (ROC) curve was used to assess the accuracy of the prediction value. **Results:** When compared to healthy control groups, patients with Alzheimer's disease had an increasing range level of TIBC, free iron, and ferritin, whereas the range level of DMT1 was lowered. ROC and area under curve analysis results for the ion forms were utilized as a feasible diagnostic parameter, and it was found that free iron and TIBC have an excellent diagnostic performance for Alzheimer's disease prediction when compared to the control group. **Conclusion:** Changes in iron levels in Alzheimer's disease patients should be addressed since homeostatic imbalance can have dual repercussions via iron induction. An imbalance in brain iron status can result in free radical production and oxidative damage, leading to neurodegenerative illness.

Keywords: Alzheimer's disease, divalent metal transporter 1, ferroptosis, iron deposition, iron storage protein

Introduction

Alzheimer's disease (AD) is the most common type of dementia, with a complex pathogenesis that is still unknown.[1] Ferroptosis is a unique type of controlled cell death that differs from conventional cell death forms such as apoptosis, necrosis, autophagy, and pyroptosis. The iron-dependent increase of lipid peroxides and reactive oxygen species (ROS) generation, glutathione depletion, and inactivation of glutathione peroxidase 4 (GPX4) in cells cause ferroptosis.[2] Some of the characteristics of ferroptosis reported in clinical AD samples include phospholipid peroxidation and iron overload. The presence of extracellular-amyloid (A) deposition in senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs) produced from tau protein hyperphosphorylation is the histological hallmark of AD. Neurocognitive deterioration is linked to synapse loss and neurotransmitter oxidation. These modifications are the result of an increase in oxidative stress, namely an increase in ROS and intra- and extracellular hydrogen peroxides.[3] Proteolytic cleavage of the -amyloid precursor protein (APP) to generate the -amyloid peptide (A) is linked to the etiology of Alzheimer's disease (AD) because APP mutations that impact this process induce familial AD or lower the risk of AD.[4] According to the amyloid cascade hypothesis, aggregation and development of A plaques in the brain would occur,

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resulting in cell death. As part of the catalytic protease complex, presenilins 1 (PSEN1) and 2 (PSEN2) precisely cut the APP and other proteins.[5] Furthermore, in the presence of free iron, a plaques efficiently generate ROS, resulting in enhanced lipid peroxidation, protein oxidation, and DNA damage.[6] Iron is normally stored in reserve in the liable iron pool and ferritin via divalent metal transporter 1 (DMT1).[7] Ferritin, Tf, TfR1, DMT1, FPN1, and hepcidin are involved in the iron recycling process and carefully maintain iron homeostasis in cells. Ferritin retains excess iron in a redox inactive state and protects the cell and tissue from oxidative harm. During the creation, ferritin light chain 1 and ferritin heavy chain 1 unite to form a spherical shell cavity structure.[8] To avoid cell death caused by oxidative stress induced by Fe^{2+} mediated Fenton reactions. The heavy chain exhibits ferrous oxidase activities that oxidize Fe^{2+}, Fe^{3+}, which is then stored in ferritin. TfR1 is another ferroptotic protein that is abundant on the cell surface. TfR1 can not only expedite iron intake via importing iron from the extracellular environment into cells.[9] DMT1 is a critical metal transporter that aids iron uptake and is hence linked to cellular iron buildup. DMT1 is present on cellular and endosomal membranes and plays a significant role in the absorption of both transferrin-bound and non-transferrin-bound iron.[10] Iron accumulated in the brain in ferritin or hemosiderin is necessary for critical physiological processes. Iron overload, on the other hand, can stimulate free radical formation and oxidative damage. It has been consistently proven that an increase in stored iron with age can promote common medical problems such as diabetes and vascular disease, which are linked to an increased risk of AD development by magnifying the redox-active iron pool in brain cells.[11] Increased stored iron as a result of high iron load and defective iron storage/detoxification may increase Fenton reaction-mediated oxidative stress/free radical damage in susceptible neurons. A significant indicator of early change in Alzheimer's disease. Thus, elevated levels of brain iron have been linked to an increased risk of Alzheimer's disease. It is unclear whether iron deposition in the brain is a key cause of Alzheimer's disease.[12] There are around 10 million cases of dementia each year, and there are about 50 million individuals with dementia worldwide. Two in three people with dementia live in low- and middle-income countries.[13] In 2006, there were 26.6 million cases of AD in the world. By the year 2050, the worldwide prevalence of AD will grow fourfold to 106.8 million.[14] According to the most recent WHO data, 2429 fatalities in Iraq from Alzheimer's and dementia or 1.66% of all deaths occurred in 2020. Iraq is standing 66 in the world with an age-adjusted death rate of 19.16 per 100,000 people.[15] The aim of this study was concentrated on serum free iron, total iron-binding capacity (TIBC), ferritin, and DMT1 levels in AD patients from the Karbala governate in Iraq.

Materials and Methods

The study design

A case–control study was included in this investigation. A total of 80 blood samples were taken from 40 cases of AD which was diagnosed by a specialized psychiatric/neurological doctor and collected from outpatient clinic, as well as 40 healthy control subjects. The study's protocol was approved by the Ethical Committee, and all participants or their relatives provided written informed permission. A qualified psychiatric and neurological expert did the neurocognitive examination, which focused on attention, memory, and executive function. After 12 h of fasting, 5 mL of venous blood were collected, allowed to clot for one hour, centrifuged at 3000 rpm, serum was separated after 15 min of spinning, and finally stored at –80°C until biochemical testing of serum iron was done describes the colorimetric approach. The photometric determination of serum ferritin was based on the interaction of sample ferritin with latex covalently attached anti-ferritin antibodies. TIBC was determined by measuring the decrease in absorbance of the colored dye-iron complex, which was proportionate to the TIBC of the serum sample. It was spectrophotometrically detected at 660 nm. The serum DMT1 was measured using the enzyme-linked immunosorbent assay technique.[13,14,16,17]

Ethical approval

Written illustrative consent form was signed by all parents/caregivers of the participating patients. This study was performed according to the ethical rules for medical research involving human participants of the Declaration of Helsinki (1964). The study protocol and the subject information and consent form were reviewed and approved by the Medical Research Bioethical committee, College of Medicine, University of Karbala.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS, IBM Company, Chicago, IL 60606, USA). Descriptive statistics were used for the data distribution was evaluated using the Shapiro–Wilk test as a numerical method of determining normality. The relationship between the investigated components was assessed using odds ratios (ORs) and a 95% confidence interval (CI) range obtained by a non-conditional logistic regression. Analytical statistical analyses indicated significant variations in categorical variables among the parameters. All hypothesis tests with *P*-values less than 0.05 (two-sided) were judged statistically significant. Using receiver operating characteristic (ROC) analysis, the best threshold with high specificity and sensitivity for crucial instances was identified. It was discovered that all *P*-values were two-sided, and a $P \leq 0.05$ was regarded statistically significant.

Results

Demographic and clinical characteristics

A total of 80 samples were obtained from 40 cases of neurodegenerative disorders (Alzheimer's disease cases) (23 female and 17 male) patients aged (65–90) years, and 40 healthy control participants (34 female and 6 male) aged (65–87) years. Participants were (47.5%) between the ages of 65 and 73, (30%) between the ages of 74 and 82, and (22.5%) between the ages of 83 and 91. Patient groups were subdivided based on age, gender, risk factors, family history, disease duration, and smoking. Table 1 summarizes the clinical demographic features of the research groups. Furthermore, data analysis revealed that the majority of patients (42.5%) had an illness duration of less than one year, 20% had a disease duration of (1–2) years, and 37.5% had a disease duration of more than three years, as shown in Table 1.

The difference in biomarker levels between the patient and control groups

In general, individuals with neurodegenerative illness had higher range levels of TIBC, Free iron, and Ferritin when compared to healthy control groups, although DMT1 had a lower range level when compared to healthy control groups. The results showed a substantial difference in TIBC, free iron, and ferritin levels between groups. Figure 1 depicts the means and standard deviations, patients had considerably higher mean values of TIBC, free iron, and ferritin (311.92), (60.96), and (201.26) than the control group (63.13), (21.25), and (78.8) ($P = 0.001$). Figure 1, also shows a non-significant difference in the mean level of DMT1 (1.04).

The difference in biomarker levels with age in the patient and control groups

Figure 2 depicts the mean level of biochemical in the patients and control groups based on age. The level of biomarkers (TBIC, free-iron, and ferritin) increased considerably in the patient group compared to the control, P-value ≤ 0.05, the mean levels in the patient were (318.11), (66.33), and (211.06), respectively. While the levels of biomarkers (TBIC, free iron, and ferritin) increased considerably in the patient group compared to the control, with P-value ≤0.05, the mean levels in the patient were (314.00), (1.41), and (195.21), respectively. Finally, the level of biomarkers (TBIC, DMA, and iron) increased considerably in the patient group compared to the control, with P value ≤ 0.05, the mean level in the patient was (301.17), (0.96), and (193.91), respectively.

The variation in biomarker levels between gender groups

Table 2 depicts the mean level of the biochemical in the patients and control groups based on gender. The levels of TIBC, free iron, and ferritin were significantly higher in the patient group, both male and female, when compared to the control, with a P value of 0.05.

Table 1: Described the demographic characteristics of the study population ($N = 80$)

Variable	Groups	Patient N=40	Control N=40
Age groups	65–73 years	19	33
	74–82 years	12	3
	83–91 years	9	4
BMI groups	Normal weight	7	6
	Over weight	14	13
	Obesity	19	21
Gender	Male	17	6
	Female	23	34
Risk factors	Yes	1	0
	No	39	40
Family history	Yes	18	0
	No	22	40
Duration of disease	Less than one years	17	40
	1–2 years	8	0
	More than three years	15	0
DM	Yes	21	12
	No	19	28
HT	Yes	35	20
	No	5	20
Smoking	Yes	12	0
	No	28	40

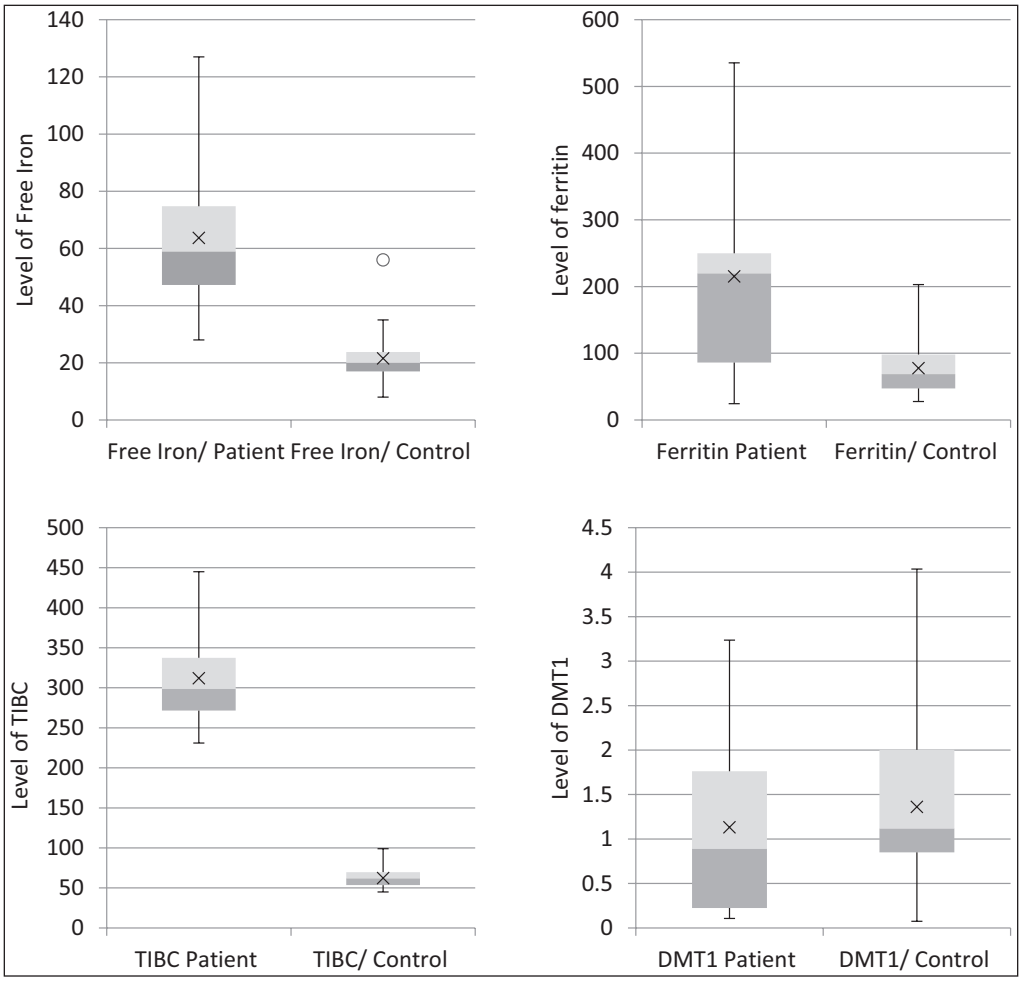

Figure 1: The boxplot distribution of biomarker levels in Alzheimer's disease patients compared to the control group

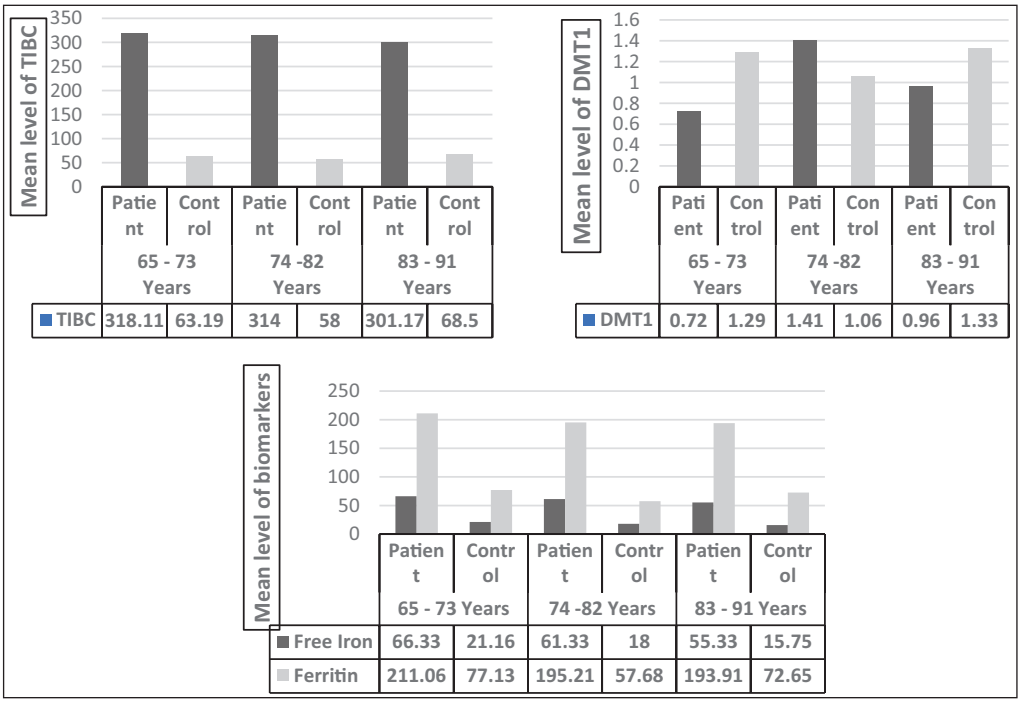

Figure 2: The impact of age groupings years on biochemical markers in patients and control groups

Table 2: The mean differences in biochemical parameters between the patient and control groups based on gender

Biomarker	Male			Female		
	Patients $N = 16$	Control $N = 6$	P value	Patients $N = 24$	Control $N = 34$	P value
TIBC	317.78 ± 65.66	69.50 ± 23.27	<0.001	308.40 ± 50.77	62.00 ± 9.17	<0.001
DMT1	1.04 ± 0.71	1.11 ± 0.63	0.860	1.04 ± 0.86	1.31 ± 0.76	0.28
Free iron	67.13 ± 22.64	25.00 ± 7.82	<0.001	57.67 ± 20.30	20.59 ± 8.20	<0.001
Ferritin	208.67 ± 112.07	80.14 ± 27.03	0.017	196.50 ± 142.75	77.83 ± 46.0	0.009

N = number of cases, SD = standard deviation, S = significant, NS = non-significant

T test was: *significant at $P \leq 0.05$

Table 3: The multinomial logistic regression of neurodegenerative disease with biomarker values

Groups	OR (Lower–upper)	P-value
TIBC	1.291 (1.275-1.308)	<0.001 [S]
DMT1	1.537 (0.753–3.135)	0.238 [NS]
Free iron	1.228 (1.102–1.368)	<0.001 [S]
Ferritin	1.019 (1.010–1.029)	<0.001 [S]

[S] = Significant; [NS] = non-significant; 1[a]: reference category is control

$P < 0.05$ considered significantly different

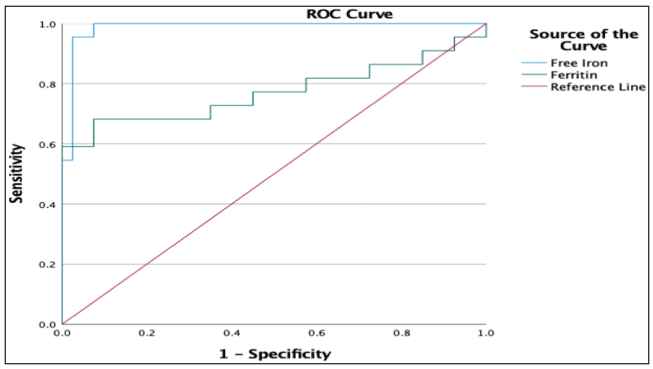

Figure 3: Receiver operating characteristics (ROC) curve analysis of iron and ferritin levels in patients

The relationship between biomarkers and patient groupings

The biomarkers' associations with Alzheimer's disease were investigated using binary logistic regression. As indicated in Table 3, TIBC, free iron, and ferritin were found to be highly significant related with Alzheimer's cases and represented as a risk factor.

Analysis of receiver operating characteristics

The ROC curve and area under curve (AUC) analysis for free iron and ferritin as a possible diagnostic measure were done. The biomarkers demonstrated superior diagnostic capability for Alzheimer's disease when compared to the control group; findings are provided in Figure 3 and Table 4. For ferritin levels, (sensitivity = 68.2%, specificity = 92.5%) at a level = 122.595, (sensitivity = 95.5%, specificity = 97.5%) at a level = 36.5. As a result, Table 4 shows the distribution of patients based on free iron and ferritin cut-off values. The AUC P value ≤ 0.05, and statistically significant.

Table 4: AUC, optimal threshold, sensitivity, and specificity of proposed marker obtained from ROC curves in Alzheimer's disease patients

Test result variable(s)	Free-iron	Ferritin
AUC	98.6%	77.2%
Sensitivity %	95.5%	68.2%
Specificity %	97.5%	92.5%
Youden index	0.93	0.607
Cut-off points	36.5	122.595
CI (95%)	(0.962–1.000)	(0.623–0.920)
PPV	85%	90.6%
NPV	91%	67.2%
Accuracy	86%	65.2%
P value	<0.001[S]	<0.001[S]

Discussion

Iron buildup in the brain is thought to contribute to neurodegenerative illnesses such as Alzheimer's. While an imbalance in brain iron status may produce free radical production and oxidative damage, it is also possible that such iron is insoluble and unavailable for cellular usage.[15] When compared to the healthy control groups, patients with neurodegenerative disease had higher range levels of TIBC, Free Iron, and Ferritin, while DMT1 had a lower range level. When iron overload in the brain has a neurotoxic effect, it disrupts the brain's regular physiological functioning. The iron concentration of the brain increases with age. Interestingly, it was shown that the iron level in the brains of Alzheimer's disease patients was dramatically elevated; these findings were consistent with ours.[16] Iron is not only involved in the formation of myelin and neurotransmitter synthesis and metabolism in the brain, but it also plays a crucial function in maintaining neurons' high metabolic capacity.[17] Under normal physiological settings, iron metabolism maintains brain homeostasis. When iron metabolism is out of equilibrium, it has a variety of impacts on brain function.[18] Iron deposition in persons with AD is more severe in these locations when compared to healthy people of the same age.[19] So yet, no evidence has been found linking DMT1 to mitochondrial metabolism activation. DMT1 was recently shown to be situated in the outer mitochondrial membrane and to perform functions in mitochondrial iron import and other metal transport.[20]

The notion that iron is essential for mitochondrial energy metabolism in oxidative phosphorylation as electron carriers contradicts our findings that reduced DMT1 expression is related with gene enrichment in mitochondrial function. Because our study compared oxidative phosphorylation in high and low DMT1 expression, we cannot compare DMT1 expression in normal liver. The low DMT expression does not always indicate a lack of DMT1 and Iron. Other metals may be involved in the link between DMT1 deficiency and increased mitochondrial respiration.[21] Changes in iron levels in Alzheimer's disease should be addressed since homeostasis imbalance might have dual repercussions via iron induction. On the one hand, Iron overload causes oxidative stress and cell death around SPs and NFTs; on the other hand, iron deficiency causes impaired neuronal function in other sections of the brain.[22] The amount of Iron in the brain correlates with the severity of AD lesions and the rate of cognitive decline.[23] Ferritin, a protein that stores iron in the body, has been related to Alzheimer's disease. Elevated ferritin levels in the cerebrospinal fluid have been associated to poor cognitive function and an increased risk of mild cognitive impairment leading to Alzheimer's disease.[24] According to one study,[25] ferritin has the potential to contribute to a blood biomarker panel for preclinical Alzheimer's disease. Excessive iron deposition in the central nervous system has been linked to Alzheimer's disease. Although there is extensive evidence linking Iron homeostasis dysregulation in such circumstances, it has largely been linked to increased age and may involve iron absorption and release, storage, and intracellular metabolism.[26] Evidence suggests that dyshomeostasis of brain Iron metabolism is one of the first events in neurodegenerative diseases.[27] Age stimulate iron buildup caused by redistribution of Iron containing molecules in different brain locations has been linked to Alzheimer's disease. This has been seen most prominently in the cerebral cortex, cerebellum, SN, and hippocampus, which are involved inflammation of neuro seen in neurodegenerative diseases. Several explanations have been proposed to explain the intracellular buildup of iron in the brain. According to one such theory, blood brain barrier disruption may result in serum component exudation, including iron. Another theory posits that intracellular iron buildup is caused by protein dysregulation.[28] Increased total iron concentrations with age may be produced by a variety of causes, including increased blood-brain barrier permeability, inflammation, iron redistribution within the brain, and changes in iron homoeostasis.[29] The iron homoeostatic system may be compromised by aging processes, resulting in an excess of iron that is not properly chelated by storage proteins or other molecules.[30] The buildup of iron in neurons may cause apoptosis. Glial iron buildup can potentially cause inflammation by increasing the release of pro-inflammatory cytokines, resulting in a self-sustaining loop of neuroinflammation and neurodegeneration.[31,32] The diagnostic performance of the measured biomarkers for neurodegenerative disease was evaluated in comparison to the control group. The receiver operating curve (ROC) curve performed well in terms of predicting Alzheimer's disease. Iron levels were found to have a high diagnostic performance in neurodegenerative illness. Defective iron homoeostasis is likely to contribute to the neuropathology of Alzheimer's disease. Iron concentrations are high in the insoluble amyloid plaques and neurofibrillary tangles that characterize Alzheimer's disease. Focal iron buildup may deplete other brain tissues of these necessary metals, resulting in abnormal neuronal activity. Iron metal ions have been linked to the misfolding process associated with the generation of amyloid β (Aβ) from amyloid precursor protein (APP), as well as contributing to neuronal oxidative stress.[33-36]

Conclusions

When compared to healthy control groups, patients with Alzheimer's disease had a growing range level of TIBC, free iron, and ferritin, while the range level of DMT1 was lowered. The findings of ROC and AUC analysis for the iron forms were utilized as a possible diagnostic parameter, and it was found that free iron and TIBC have an excellent diagnostic performance for Alzheimer's disease prediction when compared to the control group.

Consent for publication

Informed written consent was obtained from all the study participants.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZNA and RMH were designed the experiments, wrote the manuscript; ZNA, RMH, AHO performed experiments and collected data, editing and prepare the manuscript for journal submission. ZNA, RMH, AHO and AFA were checking the final approved of the version to be published. All authors read and approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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