Impact of Serum Biomarkers Level of Fibroblast Growth Factor 23, Sialic Acids, and Albumin for Alzheimer's Disease

Hashim Abdul-Sattar J. Al-Bajalani [1*]

Abstract

Background: Alzheimer's disease (AD) is one of the dementias members, which is a critical health and societal burdens. Neurofibrillary tangle and senile plaques pathologically characterize it with no clear diagnostic markers. Fibroblast growth factor (FGF)23 and Sialic Acids (Sias) are in cell signaling and antioxidative defenses, and lipid peroxidation (LPO) connected with neurodegeneration. This article examined serum biomarkers of FGF23, Malondialdehyde (MDA) as lipid peroxidation markers, Sialic Acids (Sias), and albumin in AD people in terms of age-matched healthy people. Method: This case-control had 17 AD patients and 17 controls examined terms for serum biomarkers of FGF23, Sias, malondialdehyde (MDA), and albumin. Results: According to the Biochemical tests, serum FGF23 and MDA levels in AD patients were significantly higher in relation to the controls ($p < 0.05$). Also, in the AD patients, serum Sias and albumin were low. Also, in the patients, serum MDA levels negatively correlated with normalized global gray matter volume (GMV), adjusted for sex, age, and Child-Pugh class. Conclusion: The potential of FGF23, MDA, Sias, and albumin as biomarkers for AD was underscored. More studies are need to explain their roles in AD pathogenesis. Lowe FGF23 in AD requires regulating disrupted phosphates and neuroprotection mechanisms. Higher MDA indicated low lipid peroxidation which contributes to neuronal damages. Low Sias possibly damages antioxidative defenses, exacerbating oxidative stresses. Low albumin levels are in correlation with cognitive and oxidative damage in AD.

Keywords: Alzheimer's disease, Serum biomarkers, Fibroblast growth factor 23 (FGF23), Oxidative stress, Sialic acid (SA)

Significance | This study demonstrated a potential biomarkers and mechanisms underlying AD pathology for novel therapeutic strategies in future. Understanding serum biomarkers and oxidative stress in AD is critical for early treatment and interventions.

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Introduction

AD is a common type of dementia, posing a big risk to the health of the elderly and placing a substantial burden on families and society (Sarhat, 2015; Mahde et al., 2023). It has now affected 37 million people in the world and the number is tripling in 2050, making considerable social and economic challenges (Iyaswamy et al., 2022). AD is followed by cognitive impairment due to the advanced loss of basal forebrain cholinergic neurons because of two pathological hallmarks: neurofibrillary tangles of the hyperphosphorylated tau protein and senile plaque made frim amyloid-β protein (Aβ), as the defining characteristics of Alzheimer's diseases (Mori et al., 2021).

Clinically, AD is diagnosed by a comprehensive assessment neurological examination, mental status tests, and brain imaging techniques. Yet, due to pathological evidence, diagnosing AD needs big clinical experience in the current medical setting (Piubelli et al., 2021; Zhang et al., 2023).

Fibroblast growth factor (FGF)23, with FGF19 and FGF21, is an endocrine subfamily representing the newest member of a diverse

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family of FGF proteins. Primarily secreted by osteoblasts and osteocytes, FGF23 is involved in cell signaling and exhibits autocrine, paracrine, or hormonal activities (Liang et al., 2021; Anna et al., 2021; Imel et al., 2019).

Sialic acids (Sias) are commonly located at the glycan outmost end chains across all cell types. With a nine-carbon backbone, they adorn the surfaces of cells and are among the most released proteins in vertebrates and higher invertebrates. Sias play critical roles in mediating or modulating various normal and pathological processes and are major element impacting the half-life of glycoproteins in circulation (Guruaribam et al., 2020).

In the mammalian brain, the Sias majority is found on gangliosides, which carry approximately 75% of the total brain sialic acids. Although gangliosides share a lipid core structure, they are not similar in the Sias position and number linked to the lipid head group combined into the membrane bilayer (Huan et al., 2020).

Sialic acids possess antioxidant properties, acting as scavengers for hydrogen peroxide (H2O2) and serving as defense molecules against increased oxidative stress in brain cells (Saurav et al., 2022). Cell membranes consist of various lipid types and membrane-bound proteins/receptors that facilitate interactions between cellular organelles, cells, and their setting. These membrane lipids play a crucial role in maintaining cellular functions. Lipid peroxidation disrupts the structural integrity of the cell membrane, given that lipids are its major constituents. Due to their high reactivity, lipid peroxides is able of accelerating the chain reaction of reactive oxygen species (ROS) formation, contributing to cellular damage. This process can lead to non-apoptotic cell death. Lipid peroxides are eventually degraded into two: hydroxyl acids and aldehydes. These degradation products, being highly reactive themselves, are commonly used as important tools for quantifying lipid peroxidation (Rao et al., 2022).

The aim of this research was to evaluate the levels of FGF23 (Fibroblast Growth Factor 23), MDA (Malondialdehyde) as a marker for fat cells, Sias, and albumin in AD patients, regarding similar healthy controls of similar age. By performing case-study research with 17 AD patients, and 17 healthy subjects, we explored the biochemical services to recognize indicators of this brain-degenerating disease. Furthermore, we wanted to assess the relationship between these above-mentioned biomarkers and the patients' brain images, looking at significant areas including the gray matter volume in the cerebrum to better understand the disease, hopefully helping in finding a cure.

Materials and methods

Study Design

This work which is case-control was conducted at the Department of Biochemistry, Kirkuk Teaching Hospital, Department of Internal Medicine, in Kirkuk Governorate, Iraq. The study spanned from December 2020 to March 2021. The study comprised seventeen patients clinically diagnosed with Alzheimer's disease (AD) by specialist physicians, including eight males and nine females, with a mean age of 81.42 ± 11.35 years. Additionally, seventeen apparently healthy control subjects, consisting of five males and twelve females, with a mean age of 80.93 ± 12.37 years, were included. We obtained an informed consent was from all participants, with approved protocol by the medical ethics committee of the hospital.

ELISA

The study sampled blood from all subjects in vacutainer tubes and we allowed the samples to clot at room temperature for half an hour prior to centrifugation at 3000 g for 10 minutes at 4°C. The human FGF23 ELISA Kit (My BioSource, USA) was used for the quantitative human FGF23 analysis in serum. The sandwich enzyme immunoassay technique was employed, where standards and samples were pipetted into wells, allowing FGF23 in the sample to bind to immobilized antibodies. Upon washing away unbound biotinylated antibody, we added an HRP-conjugated streptavidin to the wells. Following another wash, we added a TMB substrate solution, and measured color development at 450 nm, with the intensity of the color indicating the amount of bound FGF23. The reaction was stopped using a Stop Solution, which changed the color from blue to yellow.

Sialic acid creates a purplish-red complex with methyl resorcinol in an oxidant, as an absorbance after Lambert-Beer's law. The sialic acid is calculated by the OD value at 560 nm. The detection of the tissue and cell samples helps in the detection of the protein concentration of the sample (recommended kits: E-BC-K165, E-BC-K168, E-BC-K318).

NWK-MDA01 assay

The North West Kit NWK-MDA01 is according to the reacting malondialdehyde with thiobarbituric acid (TBA), which forms MDA-TBA2 adducts absorbing strongly at 532 nm. BHT and EDTA put in the sample and reaction mixture for minimizing oxidating lipids contributing artifactually when processing the sample and the TBA reaction. The low temperature of the reaction mixture minimizes decomposing lipid hydroperoxides. As most the MDA is protein-bound, mostly as Schiff base, the reaction pH is optimized for the facilitation of MDA hydrolysis. Also, derivative spectrophotometric analysis application helps in resolving the issue of the variable and nonlinear baseline in the attempt for A532 absorbance calculation.

Albumin analysis

The Albumin Assay Kit (Colorimetric) follows the selective interacting n Bromocresol Green (BCG) and albumi which, forms a chromophore detectable at 620 nm. The signal is in a direct proportion with the amount of albumin t in the serum. BCG makes

Table 1. Basic characteristics of study groups.

Parameters		Control group	Patients group
No. of subjects		17	17
Sex	Male	5	8
	Female	12	9
Age (years)		80.93 ±12.37	81.42 ±11.35

Table 2. Descriptive characteristics of serum FGF23, SA, albumin, and MDA level (Pg/ml) between between studied groups. (**N**=number, **St.Dev**= Standard Deviation)

Groups	Control	Patients	P-Value
FGF23 (Pg/mL)	37.51±2.60	241.00±20.08	P< 0.05
MDA (μ mol/L)	1.22±0.04	5.61±0.38	p < 0.05
SA (mM)	2.38±0.16	3.44±0.38	p < 0.05
Albmin (g/dl)	4.46±0.27	3.25±0.05	p < 0.05

no reaction with other abundant plasma proteins like IgG (Grant G.).

Statistical analysis

Data, expressed as mean±SD, were statistically examined by means of the independent samples *t*-test. The significance levels were at *P* values (*P*) <0.05.

Results

In this case-control research at the Department of Biochemistry, Kirkuk Teaching Hospital, Department of Internal Medicine, Kirkuk Governorate, Iraq, spanning from December 2020 to March 2021, serum samples from 17 AD patients (8M/9F) and 17 controls (5M/12F) were analyzed (Table 1). The mean age in controls was 80.93 ± 12.37 years and in AD patients was 81.42 ± 11.35 years.

Table 2 displays significantly higher levels of FGF23 and MDA in AD people in comparison with the controls (241.00 ± 20.08 pg/mL vs. 37.51 ± 2.60 pg/mL and 5.61 ± 0.38 vs. 1.22 ± 0.04 μmol/L, in respect; $p < 0.05$). Conversely, the levels of SA and albumin were significantly lower in AD patients compared to controls (2.38 ± 0.16 mM vs. 3.44 ± 0.38 mM and 4.46 ± 0.27 vs. 3.25 ± 0.05 g/dL, respectively; $p < 0.05$).

ELISA was conducted using the human FGF23 ELISA Kit (My BioSource, USA) for quantifying serum FGF23 levels. Sialic acid levels were determined by forming a purplish-red complex with methyl resorcinol in an oxidant, measuring absorbance at 560 nm. The NWK-MDA01 assay detected malondialdehyde (MDA) according to its reaction with thiobarbituric acid (TBA), with absorbance measured at 532 nm. Albumin analysis relied on the interaction between Bromocresol Green (BCG) and albumin, detectable at 620 nm.

Statistical analysis, employing independent samples t-test, showed a big difference ($p < 0.05$) between the AD patients and control subjects.

Discussion

This work witnessed a significant decrease in serum FGF23 levels among AD patients in references to healthy individuals. Various mechanisms have been set for the elucidation of the serum FGF23 impact on AD risk. Although there is an FGF23 expression in bone, it is also high in the brain and cerebrospinal fluid, with production occurring in the ventrolateral nucleus of the thalamus. FGF23 receptors are in the kidney and the parathyroid gland. The mechanism which is mediated by FGF23 interacts with classical calcium/phosphates which is regulation which parathyroid hormone and calcitriol dervies. Phosphate absorption through the intestine, storage in bone, and urinary excretion constitute key aspects of phosphate homeostasis maintenance in mammals. FGF23 plays a role in inhibiting renal phosphate reabsorption by internalization of the phosphate co-transporters NPT2A and NPT2C which depends on sodium- (Takeshita et al., 2018; Cararo-Lopes et al., 2017).

Higher FGF23 levels have been linked to many vascular problems such as smoking, waist circumference, cardiovascular problem history, and serum glucose levels. Also, elevated FGF23 level correlates with vascular calcification and left ventricular hypertrophy (Mirza et al., 2009). Furthermore, FGF23 prevents 1-alpha hydroxylase activities in the kidneys, reducing vitamin D levels, and concurrently working as phosphaturic factors which lowers serum phosphate levels. Vitamin D deficiency is caused by cognitive failure in older adults, which possibly explain the link between higher FGF23 levels and dementia (Sirikul et al., 2022).

Higher levels of FGF23 could exacerbate negative remodeling by the inhibition of forming bones(Sirikul et al., 2022). FGF23 has been found in affecting neuronal morphologies and synaptic densities. In the kidneys, FGF receptors FGF23-mediated activation needs the co-receptor klotho. In addition, Klotho happens in the choroid plexus and brain parenchyma, possibly influence FGF23 function in the brain. In addition, klotho seems to have shown neuroprotective impacts in vitro and in vivo which shield primary neurons from oligomeric amyloid beta (Cararo et al., 2017; McGrath et al., 2019). Because of the brain's vulnerability to oxidative stress—because of its high oxygen uses, higher iron contents, and peroxidizable lipids—neurons exhibiting relatively decreased endogenous antioxidants to counterbalance their heightened metabolic activities (Liu et al., 2017; Chew et al., 2020).

Lipid peroxidation (LPO) role in Alzheimer's disease (AD) pathology is still not clear. Yet, higher production of β-amyloid peptide generates free radicals outside neurotoxic neurons to synaptosomal membrane and hippocampal cells. Also, as a metal-chelating antioxidant, LPO contributes to pathological aggregating amyloid by the interaction with metal ions, thus exacerbating oxidative stress and lipid oxidation, which finally enhances neurotoxicity (Rani et al., 2017). Malondialdehyde (MDA), a reactive aldehyde and a final product of lipid peroxidation showed lower activity in the patients in in references to the controls(Entedhar et al., 2022; Washeel et al., 2019), confirming studies (Gustaw-Rothenberg et al., 2010; Mohammed et al., 2021; Aysel et al., 2020). The Aβ to sialic acid binding on gangliosides in neuronal membranes promotes amyloidosis and induces cytotoxicity in AD (Rao et al., 2021; Zhao et al., 2022).

The study has shown a significantly lower Sias in AD patients relative to this controls. This drop in Sias levels is due to a drop in sialyltransferase activity, reduces regenerative potential and the sialic acid release due damaged cells into the bloodstream (Entedhar et al., 2018). The results confirm Yadav et al. (2020), reporting higher total Sia in the plasma of Alzheimer's patients in relation to the controls (0.7133±0.0201 ng L−1 vs. 0.5972±0.01866 ng L−1).

Albumin, synthesized exclusively in the liver, serves as the most abundant serum protein with a half-life of approximately 3 weeks. It is crucial in keeping plasma oncotic pressure, controlling fluid distribution between body sections, facilitating metabolic material transport, and supporting nutrition. Additionally, albumin exhibits anti-inflammatory, antioxidant, and primary negative secretory acute phase protein properties (Entedhar et al., 2022; Hu et al., 2021).

Moreover, the derived neutrophil to lymphocyte ratio (dNLR), calculated as neutrophils divided by leukocytes minus neutrophils, has been investigated in various contexts, including cardiovascular disease and inflammation (Xiu et al., 2022; Zhao et al., 2022; Sarhat et al., 2022; Goro et al., 2021).

In terms of Aβ, approximately 90% of circulating Aβ is linked with albumin under physiological conduction which dynamically makes peripheral and central Aβ equal. This equilibrium hinders plasma and cerebrospinal fluid (CSF) Aβ aggregation maintaining a constant free-Aβ in the blood which balances its shift from the brain. There have been low albumin-bound Aβ in plasma (Sarhat et al., 2020; Mercè et al., 2021).

The cognitive damage relation to the serum albumin levels is clarified by many pathophysiological mechanisms. Albumin is an antioxidant, possibly reducing excessive oxidative stress which inflammation induces in aging neuronal cells. The inflammatory in dementia pathogenesis includes AD, low serum albumin levels pose dangers to cognitive drops in AD (Jia-Jyun et al., 2020).

Many mechanisms clarify the serum albumin effect on AD risk. Firstly, serum albumin levels are because of the nutritional status in the elderly, insistent malnutrition as an important factor to cognitive damage. So, lower albumin levels could show malnutrition, thus promote the AD. Secondly, albumin is crucial in keeping colloid osmotic pressure and blood in cognitive functions. Lower albumin levels are in interferences suitable to blood supplies to the central nervous systems, impairing cognitive abilities. Thirdly, the injury of the oxidative stress is a pathogenic element in cognitive drops. Albumin acts is effective in non-enzymatic antioxidant which contains sulfahydret (SH-) groups neutralizing free radicals. Also, albumin keeps unsaturated fatty acids safe in low-density lipoproteins from oxidation which earn it the moniker of "sacrificial antioxidant."

Conclusion

Taken together, this work has supplied compelling evidence to associate circulating concentrations of FGF23, MDA, SA, albumin, and AD. Yet, more studies are needed for elucidating the precise cellular mechanisms which underly the lower AD incidence in individuals with high FGF23 and MDA concentrations, so FGF23 and MDA serve as a plausible indicator of vulnerability to AD in the elderly.

Author contribution

H.A.J.A. conceptualized, conducted the experiment, analyzed data, prepared the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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