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Research Article

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The Evaluation of Serum Total Tau, NFL, Neurogranin, YKL-40, and FABP-3 as Screening Biomarkers for Alzheimer's Disease

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Abstract

Objective: Alzheimer's disease (AD) is a neurodegenerative disorder that causes dementia and accounts for 50-75% of all cases. Since cerebrospinal fluid sampling (CSF) is an invasive procedure, there is a need for non- or less invasive alternatives to identify new biomarkers that reflect the underlying AD pathology.
Materials and Methods: Blood samples were obtained from 86 AD patients (33 mild, 29 moderate, and 24 severe AD) and 30 controls. Serum total tau, neurofilament light polypeptide (NFL), neurogranin, chitinase-3-like protein 1 (YKL-40), and fatty acid-binding protein 3 (FABP-3) were measured using enzyme-linked immunosorbent assay (ELISA).
Results: Serum total tau and NFL levels were higher in AD patients compared to controls, whereas neurogranin, YKL-40, and FABP-3 levels remained unchanged. In the receiver operating characteristic (ROC) curve analysis, the sensitivity and specificity for total tau alone (cut-off point: 71.5 pg/mL) were 79.1% and 76.7% (Area under the curve (AUC): 0.865; p<0.001), while the sensitivity and specificity for NFL alone (cut-off point: 1.835 pg/mL) were 66.3% and 66.7% (AUC: 0.693; p=0.002). When total tau and NFL were concomitantly evaluated, the AUC was 0.848 (p<0.001).
Conclusion: Alongside the established core AD biomarkers, serum total tau and NFL are promising biomarkers for AD, reflecting additional pathological changes during the disease.

Keywords Alzheimer's disease · Serum · Biomarker · Tau · NFL · YKL-40 · FABP-3

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INTRODUCTION

Dementia is a global health problem and one of the leading causes of death. Alzheimer's disease (AD) is a neurodegenerative disorder that causes dementia, accounting for 50-75% of all cases. With increasing average lifespan and an aging population, AD is expected to become one of the most serious health challenges in the future. Progressive memory loss and other cognitive impairments are the main clinical characteristics of AD. On the other hand, extracellular deposits of β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles, composed of clusters of hyperphosphorylated tau protein, are the primary pathological hallmarks of AD (1). Other pathological changes include microglial activation, neuronal degeneration, neuroinflammation, altered protein clearance, lipid metabolism disturbances, disrupted synaptic function, and impaired blood-brain barrier (BBB) integrity (2). Previously, cerebrospinal fluid (CSF) was the most preferred sample for studying AD biomarkers. However, CSF sampling is an invasive lumbar puncture procedure that carries a risk of infection and headaches. Alternatively, less invasive biological samples include peripheral blood and urine. Recently, new candidate biomarkers in blood samples that reflect the underlying AD pathology have been investigated for early diagnosis. Among these markers, neurofilament light polypeptide (NFL) is the most abundant component of myelinated axons and serves as a marker of axonal degeneration (2). Neurogranin is a postsynaptic protein that plays a crucial role in synaptic activity and plasticity, reflecting synaptic degeneration (2). Chitinase-3-like protein 1 (YKL-40) is synthesized by activated macrophages and microglia and serves as a marker of neuroinflammation. Fatty acid-binding protein 3 (FABP-3) is essential for membrane fluidity, synapse formation, and lipid transport, and it indicates lipid metabolism disorders (2).

Recent studies have clarified that AD neuropathology is associated with metabolic syndrome (MetS) and insulin resistance (IR). Moreover, AD has been classified as "Type 3 Diabetes" (3, 4). Components of MetS and IR, including hyperglycemia, dyslipidemia, and central obesity, adversely affect the pathogenesis of AD through various mechanisms, such as neuroinflammation, brain IR, oxidative stress with increased lipid peroxidation, and synaptic and axonal dysfunction (3, 4).

In the present study, we measured serum total tau, NFL, neurogranin, YKL-40, and FABP-3 levels in patients with mild, moderate, and severe AD, as well as in cognitively healthy controls, to assess whether these biomarkers provide relevant information for AD diagnosis. Additionally, we aimed to evaluate their potential for early diagnosis and disease monitoring. The second objective of this study was to investigate the relationship between these biomarkers and blood glucose and lipid profiles in AD patients.

MATERIALS AND METHODS

Study Population and Sample Collection

Eighty-six AD patients from the Department of Neurology at Bakirkoy Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, along with 30 cognitively normal individuals, were included in this case–control study. The characteristics of patients with AD and controls are presented in Table 1. Age and gender distributions were comparable between the patient and control groups.

Each patient underwent a comprehensive clinical evaluation, including medical history, physical and neurological examination, laboratory screening tests, brain magnetic resonance imaging (MRI), and positron emission tomography (PET). All participants completed cognitive assessments, including the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). An MMSE score below 24 and a CDR-SB score above 4 indicated AD severity. Patients with mild cognitive impairment (MCI) were not included in the study. AD diagnosis was made according to the NINCDS-ADRDA criteria (5). The exclusion criteria included a history of neuropsychiatric disorders other than AD, metabolic disorders, cerebral infarction, subdural hematomas, hydrocephalus, intracranial tumors, infections, alcohol abuse, or substance abuse. This study was approved by the Local Ethics Committee at Istanbul Faculty of Medicine (18.01.2023-1582983). Written informed consent was obtained from all participants or their close relatives. Fasting venous blood samples were collected, centrifuged at 2500 rpm for 15 min within 20 to 60 min of collection, aliquoted, and stored at −80°C until use. Glucose and lipid profile parameters were measured using an autoanalyzer (Roche Cobas C6000, Switzerland).

Determining Serum Total Tau, NFL, Neurogranin, YKL-40, and FABP-3 Levels

Serum total tau, NFL, neurogranin, YKL-40, and FABP-3 levels were measured using enzyme-linked immunosorbent assay (ELISA) test kits (TAU, Elabscience E-EL-H0948, Houston, Texas; NFL, Elabscience E-EL-H0741, Houston, Texas, USA; Neurogranin, Mybiosource MBS167225, San Diego, CA, USA; YKL-40, Invitrogen BMS2322, Waltham, MA, USA; and FABP-3, Invitrogen BMS2263, Waltham, MA, USA). All measurements were performed in duplicate within the same run. The inter-run coefficients of variation (CV) for the studied parameters

Table 1. Characteristics of patients with Alzheimer's disease (AD) and controls

	AD (n= 86)	Control (n= 30)	p value
Age	71.73 (48-91)	72.63 (62-87)	0.377
Gender			
Male, n (%)	37 (43)	15 (50)	0.518
Female, n (%)	49 (57)	15 (50)	-
Disease onset		-	-
<65 years, n (%)	28 (32.5)		
>65 years, n (%)	58 (67.5)		
Family history, n (%)	39 (45)	-	-
Clinical dementia staging scale		-	-
Mild, n (%)	33 (38.4)		
Moderate, n (%)	29 (33.7)		
Severe, n (%)	24 (27.9)		
MMSE, median (range)	13.76 (0-24)	-	-
CDR-SB, median (range)	11.31 (4-18)	-	-
Glucose, (mg/dL) median (range)	120.29 (78 - 267)	100.34 (68 - 140)	**0.014**[a]
Total cholesterol, (mg/dL) median (range)	206.10 (96.2 - 292.8)	174 (101.3 - 243.2)	**0.001**[a]
Triglyceride, (mg/dL) median (range)	151.04 (48.3 - 437)	114.65 (50.7 –255.1)	**0.028**[a]
LDL-cholesterol, (mg/dL) median (range)	126.96 (35 - 190)	103.36 (46 - 172)	**0.003**[a]
HDL-cholesterol, (mg/dL) median (range)	50.63 (32.3 - 141.6)	54.52 (26.5 - 86.6)	0.248[a]
Total tau, (pg/mL) median (range)	208.97 (20.2 - 679.62)	48.33 (6.98 - 117.42)	**< 0.001**[a]
NFL, (pg/mL) median (range)	3.67 (0.11 - 13.23)	1.66 (0.32 - 7.08)	**< 0.001**[a]
Neurogranin, (ng/mL) median (range)	232.83 (58.01- 688.34)	216.17 (70 - 635.96)	0.612[a]
YKL-40, (pg/mL) median (range)	56441.1 (21094.22 - 93599.2)	64927.34 (19262.78 - 173242.26)	0.213[a]
FABP-3, (pg/mL) median (range)	2552.41 (1065.63 - 6182.5)	2459.9 (717.75 - 6285.03)	0.608[a]

Mann–Whitney U test, [a] Analysis of covariance and Bonferroni post hoc correction tests

Abbreviations: AD: Alzheimer's disease; MMSE: Mini-Mental State Examination; CDR-SB: Clinical dementia rating scale-sum of boxes; NFL: Neurofilament light polypeptide; YKL-40: chitinase-3-like protein 1; FABP-3: Fatty acid binding protein-3.

were as follows: total tau: 4.8%; NFL: 4.9%; neurogranin: <10%; YKL-40: 7.2% and FABP-3: 6.2%.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., SPSS Inc., Chicago, IL, USA) and GraphPad Prism 10 (GraphPad Software, La Jolla, CA, USA). Data distribution and homogeneity were assessed using the Kolmogorov-Smirnov and Levene tests. Since obtained data were non-homogeneous and non-normally distributed, Kruskal-Wallis and Mann–Whitney U tests were applied. Serum total tau, NFL, neurogranin, YKL-40, and FABP-3 levels of the mild, moderate, severe AD patients and control groups were compared with the Analysis of covariance (ANCOVA) test. Age, which is thought to affect biochemical parameters, was used as covariate. Bonferroni correction was used as a post hoc test. Gender distribution between the study and control groups was analyzed using the chi-square test. The correlation between continuous variables was assessed using Spearman's rank correlation analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of candidate biomarkers to discriminate between Alzheimer's patients and control groups. For biomarkers with an area under the curve (AUC)>0.6 in ROC analysis, sensitivity and specificity were calculated. Statistical significance was set at $p<0.05$. The study population was determined as 116 with G-power program by taking impact size 0.36 , $\alpha=0.05$, power $(1-\beta)=0.95$ at a confidence level of 95%.

RESULTS

The characteristics of patients with AD and controls are presented in Table 1. AD patients had higher serum glucose, total cholesterol, triglyceride, and low density lipoprotein (LDL) levels compared to controls. As expected, significant correlations were observed between glucose and lipid profile parameters including positive correlations between glucose and triglyceride, total cholesterol and triglyceride, and total cholesterol and LDL. Conversely, a negative correlation was found between glucose and high density lipoprotein (HDL) (data not shown). MMSE scores gradually decreased, while

CDR-SB scores increased across mild, moderate, and severe AD (data not shown).

Serum total tau and NFL levels were significantly higher in AD patients compared to controls (p<0.001), whereas neurogranin, YKL-40, and FABP-3 levels remained unchanged (Figure 1A, B, C, D, E). Total tau levels were elevated in all AD subgroups compared to controls (Figure 1A).

Serum NFL levels were significantly higher in moderate and severe AD patients compared to controls (p<0.001), whereas no significant change was observed in mild AD. Additionally, NFL levels were significantly increased in severe AD compared to mild AD and in moderate AD compared to mild AD (p<0.001, p=0.001, respectively) (Figure 1B).

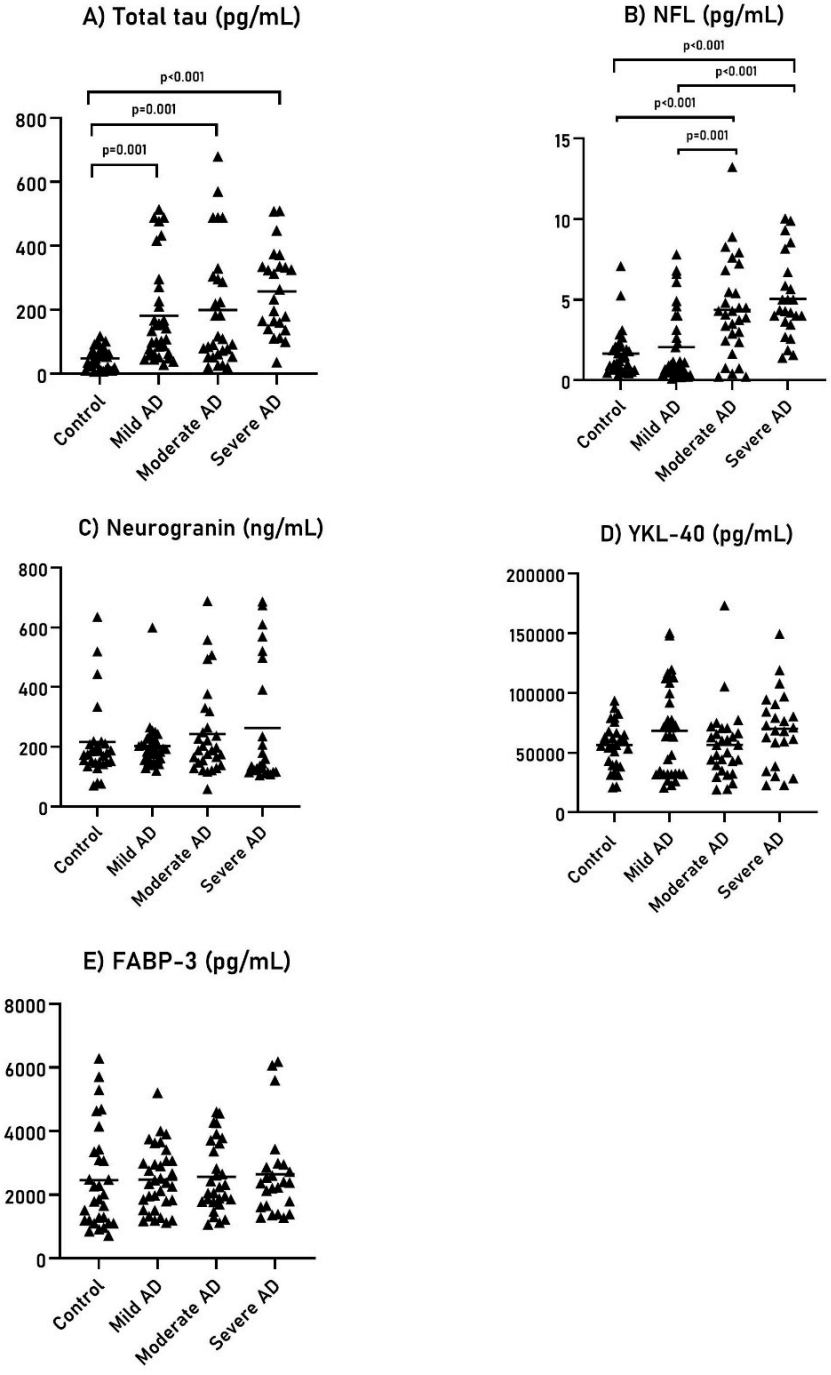

Figure 1. Serum total tau (A), NFL (B), neurogranin (C), YKL-40 (D), and FABP-3 (E) in controls and mild AD, moderate AD, and severe AD. Analysis of covariance and Bonferroni post hoc correction tests. Abbreviations: AD: Alzheimer's disease; NFL: Neurofilament light polypeptide; YKL-40: Chitinase-3-like protein 1; FABP-3: Fatty acid binding protein-3.

In addition, to assess the diagnostic potential of total tau and NFL as biomarkers for AD, ROC curves were generated. With a cut-off point of 71.5 pg/mL for total tau, sensitivity was 79.1% and specificity was 76.7% (AUC: 0.865, p<0.001). For the NFL, with a cut-off point of 1.835 pg/mL, sensitivity was 66.3% and specificity was 66.7% (AUC: 0.693, p=0.002). When total tau and NFL were concomitantly evaluated (total tau*NFL), the AUC was 0.848 (p<0.001; Figure 2).

Serum NFL levels were negatively correlated with the MMSE score (p<0.001; Figure 3A). Both total tau and NFL levels showed a positive correlation with CDR-SB (p=0.017 and p<0.001, respectively; Figure 3B, C). A positive correlation was also observed between total tau and NFL levels (p=0.002; Figure 3D). FABP-3 levels were significantly correlated with age (p=0.006; Figure 3E). Additionally, both NFL and total tau

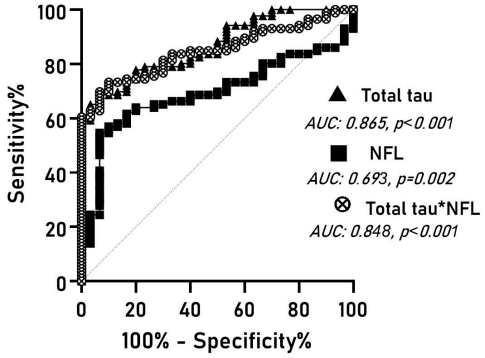

Figure 2. ROC curves for total tau, NFL and total tau * NFL for the discrimination between AD patients and controls. Abbreviations: ROC: Receiver operating characteristics; AUC: Area under the curve; AD: Alzheimer's disease; NFL: Neurofilament light polypeptide.

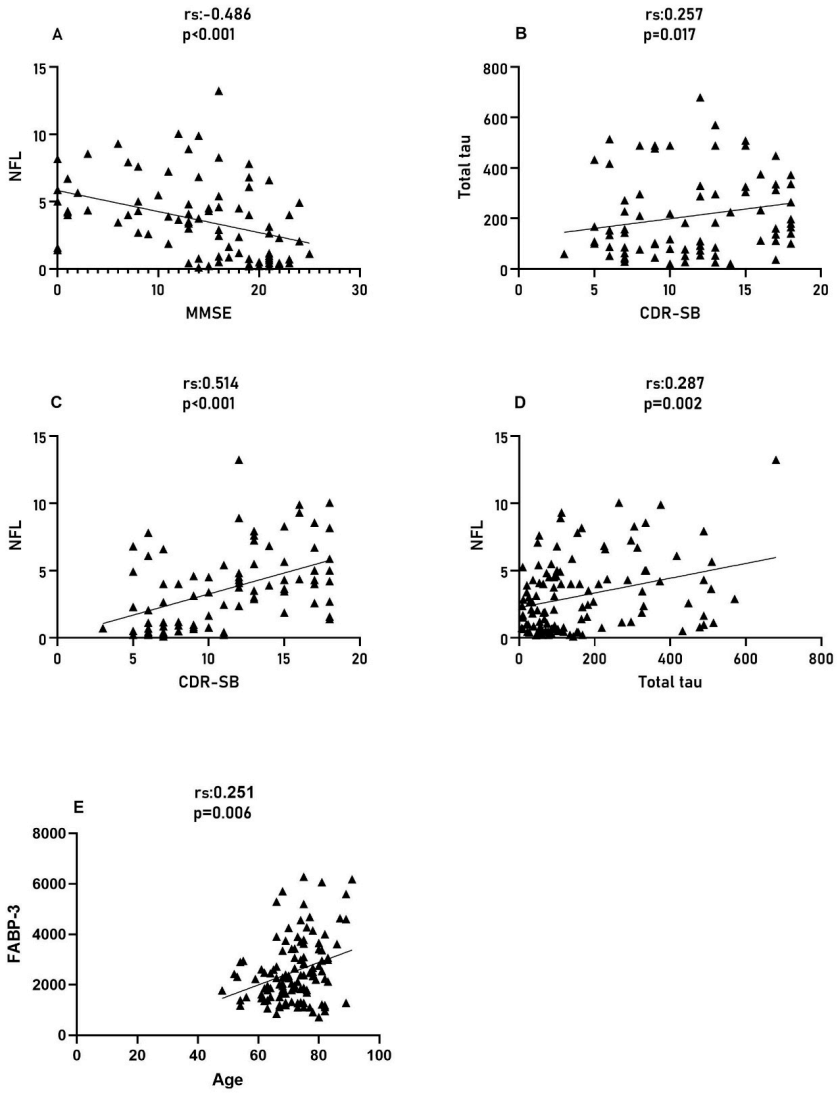

Figure 3. Correlation between NFL – MMSE (A); total tau – CDR-SB (B); NFL – CDR-SB (C); NFL – total tau (D); FABP-3 – age (E). Abbreviations: NFL: Neurofilament light polypeptide; MMSE: Mini-Mental State Examination; CDR-SB Clinical dementia rating scale-sum of boxes; FABP-3: Fatty acid binding protein-3.

showed a strong relationship with lipid profile parameters (Table 2).

Table 2. Correlations between serum total tau, NFL levels with total cholesterol, triglyceride, LDL-cholesterol and glucose levels

	Total tau r (p value)	NFL r (p value)
Total cholesterol	0.299 (**0.001**)	0.247 (**0.008**)
Triglyceride	0.210 (**0.024**)	0.196 (**0.035**)
LDL-cholesterol	0.287 (**0.002**)	0.199 (**0.032**)
Glucose	0.127 (0.175)	0.127 (0.174)

Spearman correlation test was used for analyses. Abbreviations: NFL: Neurofilament light polypeptide; LDL: Low density lipoprotein.

DISCUSSION

In the present study, we aimed to evaluate the relationship between the serum total tau, NFL, neurogranin, YKL-40, and FABP-3 concentrations and cognitive impairment, as well as the diagnostic performance of these potential biomarkers for the early detection of AD.

AD is a neurodegenerative disease and a significant public health concern with an increasing incidence. Laboratory medicine plays a crucial role in the effective monitoring of AD. The primary goal is to improve patients' quality of life while reducing economic costs. Notably, most biomarkers are assessed in CSF, which is the preferred biological sample for reflecting neuropathological alterations. However, obtaining CSF is a challenging procedure because of its invasive nature and the requirement for highly skilled personnel. In contrast, blood collection is far less invasive than lumbar puncture and is routinely performed. Therefore, using serum or plasma for biomarker assessment offers several advantages.

Among the main characteristics of AD are tau and Aβ pathologies (1,6). Tau protein plays a crucial role in maintaining the structural integrity of the neuronal cytoskeleton and regulating axonal transport. Abnormal posttranslational phosphorylation of tau protein disrupts its binding to microtubules, leading to the formation of insoluble double-stranded neurofilaments and intraneuronal tangles, ultimately resulting in neuronal death. Both phosphorylated and total tau are secreted into the CSF and peripheral blood. Several studies have demonstrated a correlation between peripheral blood total tau levels and brain total tau levels, as assessed by PET scan (7, 8). In our study, serum total tau concentrations were significantly elevated in AD patients. Moreover, there was a gradual increase in serum total tau levels from the mild to severe AD. Our findings align with studies that report increasing total tau levels in Alzheimer's patients (9, 10) yet differ from other studies that found no clear relationship between serum total tau and AD (11, 12). Since peripheral blood total tau levels reflect axonal degeneration and neuronal death, they may also serve as an indicator of cognitive decline (13). Therefore, serum total tau measurement could be valuable not only for the early diagnosis of AD but also for monitoring the dynamic process of neurodegeneration as the disease progresses. We observed that with the determined cut-off value, 79.1% sensitivity, 76.7% specificity, and 0.865 AUC value, together with established core AD markers, serum total tau could be a valuable parameter in discriminating between healthy individuals and Alzheimer's patients. Our findings agree with many studies on the same subject (9, 10).

In the spectrum of AD pathologies, neurofilaments are molecules that reflect axonal degeneration and provide prognostic information. Neurofilaments are critical for the growth and stability of axons. NFL is the smallest unit among neurofilaments, consisting of light, medium, and heavy chains, as well as α-internexin and peripherin. In various neurodegenerative, vascular, traumatic, and inflammatory diseases, NFL is secreted in high amounts into the CSF and plasma. Although plasma NFL levels are 50 times lower than in CSF, it has been shown that CSF and plasma concentrations are well correlated (14). In our study, NFL levels were elevated in the AD group compared to the control group. When evaluated according to the CDR, there were significant increases from the mild to the severe stage. However, no significant difference was detected between the control group and the mild AD group. Accordingly, NFL seems to be a suitable parameter for follow-up rather than for the early diagnosis of the disease and may be associated with the progression of cognitive decline. Similar to our findings, various studies have reported increased NFL levels in AD, linked to brain hypometabolism, brain atrophy, and cognitive decline (14, 15). In addition, it is seen from the results that both tau and NFL were correlated with clinical dementia score, reflecting cognitive decline. When total tau and NFL were concomitantly evaluated (total tau*NFL), the accuracy of disease diagnosis increased, with an AUC value of 0.848. A similar correlation was found by Mattsson et al. (14).

It is well known that the degree of cognitive dysfunction is closely related to the number of synapses, and synapse loss in AD is the strongest pathological finding correlated with cognitive decline (16). Therefore, we decided to measure serum neurogranin levels as a marker reflecting synaptic degeneration; however, no significant change was detected. Previous studies have reported elevated CSF neurogranin levels in patients with AD and mild cognitive impairment compared to controls (17). Additionally, it has been shown that the neurogranin 48-76 peptide is dominant in CSF and brain

tissue but is not found in plasma (17). Because neurogranin is enzymatically cleaved, it is expected that neurogranin fragments in brain tissue, CSF, and peripheral blood will vary in length. Another reason for the differing results may be the different sample matrices used in our study.

Neuroinflammation is a prominent feature of AD pathology, and many studies have demonstrated a reduced risk and slower progression of AD following long-term treatment with nonsteroidal anti-inflammatory drugs (18). YKL-40 is a marker of microglial differentiation and activation and is considered an indicator of inflammation (17). Increased CSF levels of YKL-40 have been found in various infectious and non-infectious disorders of the CNS. Additionally, while elevated CSF YKL-40 levels have been reported in AD, conflicting data also exist (19). In our study, although YKL-40 levels showed an increasing pattern, particularly in patients with severe AD, this increase was not statistically significant. This pattern may suggest that the inflammatory process and pro-inflammatory signals are more pronounced in patients with severe AD. Excessive inflammation and microglial activation contribute to the exacerbation of neurodegeneration, impairment of synaptic plasticity, and cognitive decline (20). However, in our study, no correlation was found between YKL-40 levels and clinical dementia score. The most significant limitation of using YKL-40 as a marker appears to be its lack of specificity. Comorbidities such as inflammatory and oncologic diseases, which are highly prevalent among older adults, may lead to increased YKL-40 concentrations. Therefore, when evaluating YKL-40 as a marker, it is essential to take a thorough medical history, considering comorbidities and medications, to avoid misinterpretation.

FABP-3 is a marker reflecting neuronal membrane damage related to lipid metabolism, and its usability for the diagnosis of AD is currently being investigated. FABP-3 was initially isolated from heart muscle and has a widespread tissue distribution. Clinically, FABP-3 may be used as a supplementary serum marker in myocardial infarction. Many studies have suggested that CSF levels of FABP-3 may have diagnostic significance in the early stages of AD (21). It has been reported that high CSF FABP-3 levels positively correlate with brain Aβ burden and are associated with brain atrophy in individuals with Aβ pathology (19). In contrast, Vidal-Pinerio et al. (22) showed that CSF FABP-3 levels predicted brain atrophy in cognitively healthy elderly individuals, independent of amyloidopathy and tauopathy biomarkers. Based on these findings, it is thought that all measured FABP-3 levels originate from the brain rather than from the serum. However, in our study, we did not observe any difference in serum FABP-3 levels between groups. This may be due to the use of serum instead of CSF or the presence of additional diseases, such as cardiovascular disease, in the control group. Our results also revealed a significant correlation between age and FABP-3 concentrations. It is possible that, with aging, the disintegration of lipids and fatty acids in the brain increases, leading to higher serum FABP-3 levels (23).

Recently, many studies have shown that disorders such as diabetes mellitus, obesity, and hypercholesterolemia play an important role in the development of AD (24). Indeed, in our study, serum glucose, total cholesterol, and LDL levels were found to be higher in AD patients. The brain's glucose requirement is met by insulin-independent glucose transporters (GLUT-1, GLUT-3) (25). Increased blood glucose levels lead to causes of abnormally high glucose transfer to neurons, triggering gluconeurotoxicity (26). Glucose exerts neurotoxic effects through various mechanisms, including the polyol pathway, the formation of advanced glycation end products (AGE), and the activation of MAP kinases (27). Studies have reported that high AGE levels induce Aβ accumulation and are associated with cognitive decline in AD (28).

On the other hand, even subtle changes in lipid metabolism can have profound effects on cognitive function. The human brain produces approximately 30% of the body's cholesterol, which plays a crucial role in regulating the membrane fluidity of neurons and astrocytes. Cholesterol is also essential for the formation of myelin, which provides insulation around axons and increases the speed of signal transmission throughout the nervous system. Demyelination is used as a biomarker for dementia pathology. Moreover, cholesterol is a key component of lipid rafts, which are involved in signal transmission, cell-to-cell adhesion, and cell division. Therefore, alterations in cholesterol metabolism may contribute to various diseases, including AD. Another link between cholesterol and AD is 24-hydroxycholesterol, an oxidation product of cholesterol that occurs exclusively in the brain. This oxysterol can cross the blood-brain barrier, and its increased plasma levels in AD likely reflect neuronal death and disrupted membrane cholesterol turnover (29). Additionally, high LDL levels induce vascular changes similar to atherosclerotic inflammatory lesions and impair blood-brain barrier permeability (30). Tau and Aβ pathologies have been observed in patients with metabolic syndrome (3, 4). Since AD shares many biochemical features with insulin resistance and metabolic syndrome, the elevated serum glucose, total cholesterol, and LDL cholesterol levels observed in AD patients in our study are not surprising. Moreover, the strong correlations between both serum total tau and NFL with lipid profile parameters further support the hypothesis that dyslipidemia is likely a predisposing factor for AD.

CONCLUSION

This study demonstrated increased serum total tau and NFL levels in AD. For the first time, we evaluated the concomitantly use of serum total tau and NFL as biomarkers for the early diagnosis of AD and assessed whether the created ROC curves enhanced the predictive power of these parameters.

Our findings showed that serum total tau alone had the highest sensitivity and specificity. Moreover, when NFL and total tau were concomitantly used, both sensitivity and specificity were higher compared to their individual values. This suggests that, alongside the established core AD biomarkers, serum total tau and NFL are promising biomarkers that reflect additional pathological changes in the progression of AD. Additionally, the significant correlations between both total tau and NFL with lipid profile parameters in AD support a possible relationship between AD and metabolic syndrome. Although lifestyle changes such as dietary modifications and increased physical activity cannot fully prevent AD, they may positively influence disease progression by reducing modifiable risk factors.

Ethics Committee Approval	This study was approved by the Local Ethics Committee of Istanbul Faculty of Medicine (18.01.2023-1582983).
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of study: P.V., S.D.A.; Data Acquisition: G.C., N.K.S., H.E.I.; Data Analysis/Interpretation: G.C., C.B.K., P.V.; Drafting Manuscript: P.V., G.C.; Critical Revision of Manuscript: S.D.A.; Final Approval and Accountability: P.V., S.D.A., G.C., N.K.S., H.E.I., C.B.K.
Conflict of Interest	The authors declare no conflict of interest.
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REFERENCES

1. Guo T, Zhang D, Zeng Y, Huang TY , Xu H , Zhao Y. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol Neurodegener 2020; 15: 1-37.
2. Park SA, Han SM, Kim CE. New fluid biomarkers tracking non-amyloid-β and non-tau pathology in Alzheimer's disease. Exp Mol Med 2020; 52: 556-68.
3. Fahed G, Aoun L, Zerdan MB, Allam S, Zerdan MB, Bouferraa Y. Metabolic syndrome: updates on pathophysiology and management in 2021. Y Int J Mol Sci 2022; 23: 786.
4. Al-Kuraishy HM, Majid S. Jabir MS, Albuhadily AK, Al-Gareeb AI, Rafeeq MF. The link between metabolic syndrome and Alzheimer disease: A mutual relationship and long rigorous investigation. Ageing Res Rev 2023; 91: 102084.
5. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et.al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018; 14: 535-62.
6. Pais M, Martinez L, Ribeiro O, Loureiro J, Fernandez R, Valiengo L, et al. Early diagnosis and treatment of Alzheimer's disease: new definitions and challenges. Braz J Psychiatry 2020; 42: 431-41.
7. Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, et al. Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. Alzheimers Dement 2018; 14: 989-97.
8. Park JC, Han SH, Yi D, Byun MS, Lee JH, Jang S, et al. Plasma tau/amyloid-β1-42 ratio predicts brain tau deposition and neurodegeneration in Alzheimer's disease. Brain 2019; 142: 771-86.
9. Tsai CL, Liang CS, Lee JT, Su MW, Lin CC, Chu HT, et al. Associations between plasma biomarkers and cognition in patients with Alzheimer's disease and amnestic mild cognitive impairment: a cross-sectional and longitudinal study. J Clin Med 2019; 8: 1893.
10. Jiang T, Gong PY, Tan MS, Xue X, Huang S, Zhou JS, et al. Soluble TREM1 concentrations are increased and positively correlated with total tau levels in the plasma of patients with Alzheimer's disease. Aging Clin Exp Res 2019; 31: 1801-5.
11. Verberk IMW, Slot RE, Verfaillie SCJ, Heijst H, Prins ND, van Berckel BNM, et al. Plasma amyloid as prescreener for the earliest alzheimer pathological changes. Ann Neurol 2018; 84: 648-58.
12. De Wolf F, Ghanbari M, Licher S, McRae-McKee K, Gras L, Weverling GJ, et al. Plasma tau, neurofilament light chain and amyloid-β levels and risk of dementia; a population-based cohort study. Brain 2020; 143: 1220-32.
13. Chiu MJ, Chen YF, Chen TF, Yang SY, Yang FP, Tseng TW, et al. Plasma tau as a window to the brain-negative associations with brain volume and memory function in mild cognitive impairment and early Alzheimer's disease. Hum Brain Mapp 2014; 35: 3132-42.
14. Mattsson N, Andreasson U, Zetterberg H, Blennow K. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. JAMA Neurol 2017; 74: 557-66.
15. Lewczuk P, Ermann N, Andreasson U, Schultheis C, Podhorna J, Spitzer P, et al. Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease. Alzheimers Res Ther 2018; 10: 71.

16. Jessen F, Amariglio RE, Buckley RF, van der Flier WM, Han Y, Molinuevo JL, et al. The characterisation of subjective cognitive decline. Lancet Neurol 2020; 19: 271-8.
17. Hellwig K, Kvartsberg H, Portelius E, Andreasson U, Oberstein TJ, Lewczuk P, et al. Neurogranin and YKL-40: independent markers of synaptic degeneration and neuroinflammation in Alzheimer's disease. Alzheimers Res Ther 2015; 7: 74.
18. McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta Neuropathol 2013; 126: 479-97.
19. Mattsson N, Tabatabaei S, Johansson P, Hansson O, Andreasson U, Månsson JE, et al. Cerebrospinal fluid microglial markers in Alzheimer's disease: elevated chitotriosidase activity but lack of diagnostic utility. Neuromolecular Med 2011; 13: 151-9.
20. Norden DM, Muccigrosso MM, Godbout JP. Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, andneurodegenerative disease Neuropharmacology 2015; 96: 29-41.
21. Chiasserini D, Parnetti L, Andreasson U, Zetterberg H, Giannandrea D, Calabresi P, et al. CSF levels of heart fatty acid binding protein are altered during early phases of Alzheimer's disease. J Alzheimer's Dis 2010; 22: 1281-8.
22. Vidal-Piñeiro D, Sorensen Q, Blennow K, Capogna E, Halaas NB, Idland AV, et al. Relationship between cerebrospinal fluid neurodegeneration biomarkers and temporal brain atrophy in cognitively healthy older adults. Neurobiol Aging 2022; 116: 80-91.
23. Shioda N, Yabuki Y, Kobayashi Y, Onozato M, Owada Y, Fukunaga K. FABP3 protein promotes α-synuclein oligomerization associated with 1-Methyl-1,2,3,6 tetrahydropiridine- induced neurotoxicity. J Biol Chem 2014; 289: 18957-65.
24. Armstrong RA. Risk factors for Alzheimer's disease. Folia Neuropathol 2019; 57:87-105.
25. Simpson IA, Carruthers A, Vannucci SJ. Supply and demand in cerebral energy metabolism: The role of nutrient transporters. J Cereb Blood Flow Meta 2007; 27: 1766-91.
26. Jacob RJ, Fan X, Evans ML, Dziura J, Sherwin RS. Brain glucose levels are elevated in chronically hyperglycemic diabetic rats: No evidence for protective adaptation by the blood brain barrier. Metabolism 2002; 51: 1522-4.
27. Tomlinson DR, Gardiner NJ. Glucose neurotoxicity. Nat Rev Neurosci 2008; 9:36-45.
28. Li S, Jin M, Zhang D, Yang T, Koeglsperger T, Fu H, et al. Environmental novelty activates beta2-adrenergic signaling to prevent the impairment of hippocampal LTP by Abeta oligomers. Neuron 2013; 77: 929-41.
29. Vega GL, Weiner MF, Lipton AM, Von Bergmann K, Lutjohann D, Moore C, et al. Reduction in levels of 24S-hydroxycholesterol by statin treatment in patients with Alzheimer disease. Arch Neurol 2003; 60: 510-5.
30. Chakraborty A, de Wit NM, van der Flier WM, de Vries HE. The blood brain barrier in Alzheimer's disease. Vascul Pharmacol 2017; 89: 12-8.