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Association between lipid profile, atherogenic index, and cognitive function in Alzheimer's disease: A retrospective cohort study

Alzheimer hastalığında lipid profili, aterojenik indeks ve bilişsel işlev arasındaki ilişki: Retrospektif kohort çalışması

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ABSTRACT

Aim: This study aimed to investigate the relationship between lipid profile parameters (including the atherogenic index of plasma (AIP)) and cognitive function in patients diagnosed with Alzheimer's disease (AD), based on Mini-Mental State Examination (MMSE) scores measured at the same visit and after a two-year follow-up period.

Material and Methods: This retrospective study included patients followed at the Dementia Outpatient Clinic of University Hospital between 2016 and 2025. A total of 84 AD patients with simultaneous lipid profile measurements (total cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides [TG]) and MMSE scores were included. Among them, 41 patients had a second MMSE recorded two years later. AIP was calculated using the logarithmic formula log(TG/HDL). Additional ratios including LDL/HDL, TC/HDL, non-HDL cholesterol, and TG/HDL were also analyzed. Correlation analyses were performed using Pearson or Spearman tests depending on data distribution, with statistical significance set at $p<0.05$.

Results: A significant negative correlation was found between MMSE scores and both TC ($r=-0.291$, $p=0.007$) and LDL levels ($r=-0.231$, $p=0.034$). No significant association was observed between AIP or other lipid ratios and cognitive performance. Likewise, no significant correlation was found between changes in MMSE scores over two years and any lipid parameter. Subgroup analysis revealed a significant negative correlation between TC and two-year MMSE score change only in female patients ($\rho=-0.537$, $p=0.022$).

Conclusion: TC and LDL levels were negatively associated with cognitive function in AD patients. The observed sex-specific effect suggests that lipid metabolism may play a more prominent role in cognitive aging among women. Further prospective studies are needed to validate these findings and explore the temporal dynamics of lipid levels.

Keywords: Alzheimer's disease, Lipid profile, Atherogenic index, Cognition, Mini-Mental State Examination

ÖZ

Amaç: Bu çalışmanın amacı, Alzheimer hastalığı (AH) tanısı almış bireylerde lipid profili parametreleri (plazmanın aterojenik indeksi (AIP) dahil) ile bilişsel işlev arasındaki ilişkiyi, aynı vizitte ve iki yıllık takip sonrasında ölçülen Mini Mental Test (MMT) skorlarına dayanarak araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, 2016–2025 yılları arasında Üniversite Hastanesi Demans Polikliniği'nde izlenen hastalar dahil edilmiştir. Lipid profili ölçümleri (total kolesterol [TC], düşük yoğunluklu lipoprotein [LDL], yüksek yoğunluklu lipoprotein [HDL], trigliserid [TG]) ile eş zamanlı MMT skorları bulunan toplam 84 AH hastası analize alınmıştır. Bu hastalardan 41'inin iki yıl sonraya ait ikinci bir MMT ölçümü mevcuttu. AIP, logaritmik formül [log(TG/HDL)] kullanılarak hesaplanmıştır. Ayrıca LDL/HDL, TC/HDL, non-HDL kolesterol ve TG/HDL oranları da analiz edilmiştir. Korelasyon analizleri, veri dağılımına bağlı olarak Pearson veya Spearman testleri ile yapılmış; istatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edilmiştir.

Bulgular: MMT skorları ile hem TC ($r=-0,291$, $p=0,007$) hem de LDL düzeyleri ($r=-0,231$, $p=0,034$) arasında anlamlı negatif korelasyon saptanmıştır. AIP veya diğer lipid oranları ile bilişsel performans arasında anlamlı bir ilişki saptanmamıştır. Aynı şekilde, iki yıllık süreçte MMT skorundaki değişim ile herhangi bir lipid parametresi arasında anlamlı korelasyon görülmemiştir. Alt grup analizinde, yalnızca kadın hastalarda TC ile iki yıllık MMT skor değişimi arasında anlamlı negatif korelasyon bulunmuştur ($\rho=-0,537$, $p=0,022$).

Sonuç: TC ve LDL düzeylerinin, AH hastalarında bilişsel işlev ile negatif yönde ilişkili olduğu belirlenmiştir. Gözlenen cinsiyete özgü etki, lipid metabolizmasının kadınlarda bilişsel yaşlanma üzerinde daha belirgin bir rol oynayabileceğini düşündürmektedir. Bu bulguların doğrulanması ve lipid düzeylerinin zamansal dinamiklerinin incelenmesi için ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Alzheimer hastalığı, Lipid profili, Aterojenik indeks, Biliş, Mini Mental Test

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Highlights

- TC and LDL levels negatively correlated with concurrent MMSE scores in Alzheimer's patients.
- AIP and other lipid ratios showed no significant association with cognitive performance.
- TC predicted two-year cognitive decline specifically in female patients (ρ=–0.537).

INTRODUCTION

Cognitive impairment associated with Alzheimer's disease (AD) and other types of dementia represents a substantial public health concern within aging demographics. Numerous research investigations have shown that elevated total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels throughout midlife may enhance the risk of Alzheimer's disease in later years (1).

Likewise, it has been noted that both extremely low and extremely high high-density lipoprotein (HDL) cholesterol levels increase the risk of dementia (2). Moreover, the impact of lipid profiles on cognitive functions is assessed not only through static levels but also by ratio-based indicators such as the atherogenic index of plasma (AIP). Higher AIP levels have been associated with cognitive decline and the development of dementia (3, 4). The AIP, calculated particularly according to the logarithmic ratio of triglycerides (TG) to HDL-C, allows for the assessment of both vascular and metabolic risk.

The clinical relevance of dyslipidemia to dementia prevention has gained further attention, with the 2024 Lancet Commission identifying high LDL cholesterol as a potentially modifiable dementia risk factor (5). However, the relationship between circulating lipids and cognition is complex and may vary according to age at lipid measurement, duration of follow-up, lipid fraction, and stage of cognitive impairment (6). Large population-based data also suggest that the direction and magnitude of lipid-dementia associations may differ across individual lipid traits and age groups (7).

Longitudinal lipid patterns may therefore provide information that is not captured by a single measurement. Recent evidence indicates that lipid trajectories and variability during the years preceding cognitive symptoms may improve risk models for mild cognitive impairment and AD beyond conventional clinical and genetic factors (8). These findings support evaluating both conventional lipid measures and composite atherogenic indices in relation to current cognition and subsequent cognitive change.

Therefore, this study aimed to investigate the association between lipid parameters, particularly atherogenic indices, and cognitive function in patients with Alzheimer's disease.

MATERIAL and METHODS

Within the scope of this retrospective study, the medical records of patients who attended the Dementia Clinic affiliated with the Department of Neurology at University Hospital between 2016 and 2025 were reviewed. Ethical approval for this retrospective study was obtained from the relevant institutional Clinical Research Ethics Committee. Patients included in the study were those who had undergone the Mini-Mental State Examination (MMSE) at the dementia clinic and were followed with a diagnosis of AD. Lipid parameters (TC, LDL, HDL, TG) measured at the visit when the MMSE was delivered, along with the MMSE scores recorded on that day, were retrieved from hospital archive records. Additionally, MMSE scores from follow-up visits at least two years later for these same patients were also collected retrospectively from the medical records.

Among the total 547 patient records screened, 84 patients with lipid parameters measured concurrently with the MMSE were identified. Of these, 41 patients with available MMSE scores at follow-up visits two years later were included in the study to evaluate longitudinal cognitive changes.

AIP was calculated using the log (TG/HDL) formula. Additionally, other cardiometabolic risk indicators based on lipid profiles (such as the LDL/HDL ratio, TC/HDL ratio, non-HDL cholesterol, and TG/HDL ratio) were also calculated and evaluated alongside AIP.

The statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Following the evaluation of distribution normality, Pearson correlation analysis was utilized for parametric variables, whilst Spearman rank correlation coefficients were employed for non-parametric variables to examine the associations between MMSE scores and lipid parameters. A significance level of $p<0.05$ was deemed statistically significant.

RESULTS

Pearson correlation analysis between lipid parameters and concurrent MMSE scores revealed that TC (r=-0.291, p=0.007) and LDL (r=-0.231, p=0.034) values showed a negative and statistically significant correlation with MMSE scores. No significant correlation was found between MMSE scores and other lipid parameters (AIP, HDL, TG,

Table 1: Correlation between lipid values and concurrent MMSE scores

Lipid Parameters	Pearson Correlation Coefficient (r)	p
AIP	-0.014	0.899
LDL	**-0.231**	**0.034**
HDL	-0.164	0.136
TC	**-0.291**	**0.007**
TG	-0.092	0.404
LDL/HDL	-0.059	0.595
TC/HDL	-0.047	0.669
non-HDL Cholesterol	-0.047	0.669
TG/HDL	-0.018	0.871

AIP: Atherogenic Index of Plasma **LDL:** Low-Density Lipoprotein **HDL:** High-Density Lipoprotein **TC:** Total Cholesterol **TG:** Triglyceride.

LDL/HDL, TC/HDL, non-HDL cholesterol, TG/HDL) ($p > 0.05$) (Table 1).

Correlation analysis between the difference in MMSE scores over two years and lipid parameters showed no significant results for either Pearson or Spearman coefficients. In Pearson correlation analysis, no significant relationship was observed between the MMSE score difference and TC (r=-0.200, p=0.210), TC/HDL ratio (r=0.107, p=0.515), non-HDL cholesterol (r=0.107, p=0.515), or AIP (r=0.155, p=0.347).

Similarly, Spearman correlation analysis revealed no statistically significant correlation between the MMSE score difference and LDL (ρ=-0.255, p=0.107), HDL (ρ=-0.284, p=0.072), TG (ρ=0.112, p=0.486), LDL/HDL ratio (ρ=-0.152, p=0.355), or TG/HDL ratio (ρ=0.127, p=0.441) (Table 2).

Correlation analyses between changes in MMSE scores over two years and lipid parameters by gender subgroups are summarized in Table 3. In female patients, a negative and statistically significant correlation was found between

Table 2: Correlations between the Difference in MMSE Scores over Two Years and Lipid Parameters

Lipid Parameters	Pearson r	p (Pearson)	Spearman ρ	p (Spearman)
TC	-0.200	0.210	—	—
TC /HDL	0.107	0.515	—	—
non-HDL Cholesterol	0.107	0.515	—	—
AIP	0.155	0.347	—	—
LDL	—	—	-0.255	0.107
HDL	—	—	-0.284	0.072
TG	—	—	0.112	0.486
LDL/HDL	—	—	-0.152	0.355
TG/HDL	—	—	0.127	0.441

AIP: Atherogenic Index of Plasma **LDL:** Low-Density Lipoprotein **HDL:** High-Density Lipoprotein **TC:** Total Cholesterol **TG:** Triglyceride

Table 3: Spearman Correlations between MMSE Score Changes and Lipid Parameters by Gender

Lipid Parameters	Female - Correlation Coefficient (ρ)	Female - p-value	Male - Correlation Coefficient (ρ)	Male - p-value
LDL	-0.351	0.153	-0.188	0.390
HDL	-0.428	0.077	-0.267	0.217
TC	**-0.537**	**0.022**	-0.042	0.849
TG	0.011	0.967	0.113	0.608
LDL/HDL	-0.082	0.747	-0.030	0.892
TC/HDL	0.215	0.392	0.145	0.508
non-HDL Cholesterol	0.215	0.392	0.145	0.508
TG/HDL	0.203	0.419	0.155	0.480
AIP	0.203	0.419	0.155	0.480

AIP: Atherogenic Index of Plasma **LDL:** Low-Density Lipoprotein **HDL:** High-Density Lipoprotein **TC:** Total Cholesterol **TG:** Triglyceride

two-year MMSE score change and TC level (ρ=-0.537, p=0.022). Correlation coefficients for other lipid parameters did not reach significance. In male patients, no statistically significant correlation was observed between two-year MMSE score change and any lipid parameter (p > 0.05).

DISCUSSION

In this study, the relationships between lipid profile levels and concurrent MMSE scores as well as cognitive changes over two years were retrospectively evaluated in individuals diagnosed with Alzheimer's disease. According to our findings, significant negative correlations were identified between TC and LDL levels and concurrent MMSE scores (TC: r=–0.291, p=0.007; LDL: r=–0.231, p=0.034), while no significant associations were found with other lipid parameters or AIP. Furthermore, no significant correlations were observed in either Pearson or Spearman analyses for changes in MMSE scores after two years.

The inverse associations of TC and LDL with concurrent MMSE in our cohort should be considered within the broader and heterogeneous literature on cholesterol and cognition. Evidence linking hypercholesterolemia to AD appears particularly strong when exposure occurs in midlife, whereas associations measured later in life are less consistent (6, 9). Long-term cohort data further suggest that lipid concentrations may change during the years preceding dementia diagnosis, raising the possibility that the timing of measurement partly explains apparently discordant findings between studies (10). In addition, associations may differ according to the specific lipid fraction and age group examined (7). Thus, a single lipid measurement obtained after AD has become clinically manifest may not reflect the cumulative lipid exposure relevant to disease development.

The sex-specific finding in our study is also consistent with evidence that the relationship between lipid metabolism and dementia may differ between women and men. In the Whitehall II cohort, several unfavorable lipid measures, including TC, LDL-C, non-HDL-C and lipid ratios, were higher in midlife among women who subsequently developed dementia and then declined progressively before diagnosis, whereas comparable long-term associations were not observed in men (10). Studies focusing on postmenopausal women have also linked less favorable lipid profiles to subsequent dementia or cognitive impairment, with evidence that these relationships may be modified by APOE genotype (11). Moreover, circulating cholesterol metabolites such as oxysterols have been associated with dementia risk in older women, providing a potential biological link between peripheral lipid metabolism and neurodegenerative processes (12). Nevertheless, given the limited size of our sex-stratified sample, the present female-specific association should be regarded as exploratory rather than definitive.

The absence of a significant association between AIP and cognitive performance in our study warrants further consideration. Prior population-based studies by Zhou et al. and Zhang et al. have reported associations between higher AIP and cognitive impairment (3, 4). Several factors may explain the discrepancy between these findings and ours. First, our cohort comprised patients who had already received an established diagnosis of Alzheimer's disease; AIP may exert its influence on cognitive function earlier in the disease course, particularly during the prodromal or mild cognitive impairment stages, rather than in clinically manifest AD. Second, the relatively small sample size (n = 84 for cross-sectional analyses; n = 41 for longitudinal analyses) may have limited the statistical power to detect moderate associations. Third, the absence of data on statin use and other lipid-lowering therapies represents a potential confounder, as these treatments may influence circulating lipid parameters independently of cognitive status.

Future studies should prospectively examine AIP in earlier stages of cognitive decline and stratify analyses by pharmacological treatment to better delineate its role.

The distinction between static and longitudinal lipid measurements may help explain why we observed significant cross-sectional associations but no relationship with two-year MMSE change. Although cognitive performance was assessed longitudinally in 41 patients, lipid parameters were measured only at baseline; therefore, our analysis could evaluate the association of baseline lipid status with subsequent cognitive change, but not the relationship between longitudinal changes in lipid levels and cognitive trajectories.

However, the limitations of our study include its retrospective design, small sample size, and reliance on lipid measurements at a single time point. Furthermore, important potential confounders such as APOE genotype, vascular comorbidities, and medication use were not controlled. Therefore, in future prospective studies, the impact of longitudinal changes in lipid levels on cognitive trajectories should be investigated using larger datasets.

Conclusion

The relationship between lipid metabolism and cognitive function is complex, and evaluating dynamic changes in lipid profiles over time may provide more accurate clinical insights for predicting cognitive decline than relying on single static measurements.

Author Contributions

The author(s) confirm(s) contribution to the paper as follows: Study conception and design: **Burcu Karpuz Seren;** data collection: **Filiz Dïlek, Aysun Ünal, Bengü Altuna;** analysis and interpretation of results: **Burcu Karpuz Seren, Bengü Altunan;** draft manuscript preparation: **Burcu Karpuz Seren, Aysun Ünal.** The author(s) reviewed the results and approved the final version of the article.

Conflicts of Interest

The authors declare that there is no conflict of interest to disclose.

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Ethical Approval

Ethics committee approval: Approved by the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University. (Date: 25/11/2025 Number: 2025.228.11.25)

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