

Association of APOE E4 Genotype With Lipid Profile in Patients With Alzheimer's Disease

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which genetic susceptibility and disturbances in lipid metabolism contribute to disease onset and progression. The Apolipoprotein E (APOE) ε4 allele has been consistently implicated in late-onset AD, while alterations in circulating lipids, small dense low-density lipoprotein (sdLDL), and lipoprotein-associated phospholipase A₂ (Lp-PLA₂) may further influence neurodegenerative and vascular processes. However, evidence describing their combined relationship in postmenopausal women remains limited.

Objective: To investigate the association between APOE (rs429358) polymorphism, lipid profile, sdLDL, and Lp-PLA₂ in female patients with Alzheimer's disease and cognitively healthy women.

Methods: This hospital-based case-control study enrolled 100 postmenopausal women, including 50 clinically diagnosed Alzheimer's disease patients and 50 age-matched cognitively normal controls. Fasting serum lipid parameters were estimated using standard biochemical methods, plasma Lp-PLA₂ was quantified by ELISA, and sdLDL was calculated using the Sampson equation. APOE (rs429358) polymorphisms were determined by PCR-restriction fragment length polymorphism analysis. Genotype distribution, biochemical parameters, and their associations with Alzheimer's disease were statistically evaluated.

Results: Women with Alzheimer's disease demonstrated significantly higher concentrations of total cholesterol, triglycerides, LDL-C, non-HDL-C, VLDL-C, cholesterol/HDL ratio, sdLDL, and Lp-PLA₂, whereas HDL-C was significantly reduced compared with controls. The T allele and TT genotype of APOE (rs429358) occurred more frequently among Alzheimer's disease patients and showed a strong association with disease risk. Individuals carrying the TT genotype also exhibited a more atherogenic lipid profile, characterized by increased total cholesterol, triglycerides, LDL-C, non-HDL-C, VLDL-C, and sdLDL together with lower HDL-C. These findings indicate that APOE-related lipid dysregulation is closely linked with metabolic and vascular abnormalities in Alzheimer's disease.

Conclusion: The present study highlights a significant relationship between APOE polymorphism and adverse lipid alterations in female patients with Alzheimer's disease. The combined assessment of APOE genotype, lipid profile, sdLDL, and Lp-PLA₂ may improve identification of individuals at increased risk and provide clinically relevant biomarkers for early diagnosis and disease stratification. Larger prospective studies are warranted to validate these findings and clarify their prognostic value.

Keyword: APOE ε4, lipoprotein, Alzheimer's disease, Lp-PLA₂

Introduction:

Alzheimer's disease (AD) is the most common cause of dementia worldwide and is characterized by progressive cognitive decline, memory impairment and neurodegeneration. The pathological hallmarks of AD include extracellular deposition of amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, and neuronal loss (Querfurth et al, 2010). Although aging is the strongest risk factor for AD, increasing evidence suggests that genetic, metabolic, and vascular factors also play a crucial role in its pathogenesis. Dyslipidemia has emerged as an important metabolic risk factor associated with AD. Abnormal lipid profiles, including elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and reduced high-density lipoprotein cholesterol (HDL-C), have been linked to increased amyloidogenic processing of amyloid precursor protein and subsequent accumulation of Aβ in the brain (Pugliese et al, 2003). Cholesterol is an essential component of neuronal membranes and is vital for synapse formation, neurotransmitter release, and myelin maintenance. Disturbances in cholesterol homeostasis may therefore contribute to neuronal dysfunction and neurodegeneration observed in AD. Among the genetic factors, the Apolipoprotein ε4 allele is recognized as the strongest genetic risk factor for late-onset AD. ApoE exists in three major isoforms they are ε2, ε3 and ε4 and plays a central role in lipid transport and cholesterol metabolism in both the peripheral circulation and

the central nervous system. Individuals carrying one or two $\epsilon 4$ alleles have a significantly increased risk of developing AD and tend to exhibit an earlier onset of the disease (Corder EH et al, 1993). ApoE4 has been shown to impair cholesterol transport, reduce neuronal repair mechanisms, and decrease the clearance of A β peptides; thereby promoting amyloid deposition and neurodegeneration (Liu CC et al, 2013). Small dense low-density lipoprotein (sdLDL) is a highly atherogenic sub fraction of LDL characterized by its smaller size, greater susceptibility to oxidation, and prolonged circulation time. Elevated sdLDL levels are associated with endothelial dysfunction, oxidative stress, and vascular inflammation, all of which are implicated in the development of cerebrovascular disease and AD (Berneis KK et al, 2002). Recent studies suggest that sdLDL may contribute to AD pathogenesis by enhancing oxidative damage and promoting vascular injury, thereby facilitating neuroinflammatory processes and cognitive decline.

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), also known as platelet-activating factor acetyl hydrolase, is an inflammatory enzyme primarily bound to LDL particles, particularly sdLDL. Lp-PLA₂ hydrolyzes oxidized phospholipids, generating pro-inflammatory mediators such as lysophosphatidylcholine and oxidized fatty acids, which can induce endothelial dysfunction and vascular inflammation (Macphee CH et al, 2005). Elevated circulating levels of Lp-PLA₂ have been associated with an increased risk of cardiovascular disease and have been implicated in cognitive impairment and AD (Fitzpatrick AL et al, 2014). Since Lp-PLA₂ is closely linked to oxidized LDL and sdLDL particles, it may serve as a biomarker reflecting the interplay between lipid abnormalities, vascular inflammation, and neurodegeneration. The interaction between ApoE4 genotype, dyslipidemia, sdLDL, and Lp-PLA₂ may represent a critical mechanistic pathway in AD pathogenesis. ApoE4 carriers often exhibit altered lipid metabolism and increased susceptibility to oxidative stress and vascular dysfunction, which may enhance the atherogenic and inflammatory effects of sdLDL and Lp-PLA₂ (Mahley RW et al, 2000). Therefore, evaluating the association between lipid profile, Lp-PLA₂, sdLDL, and ApoE4 in patients with AD is of considerable clinical importance. Understanding this relationship may provide valuable insights into the metabolic and vascular mechanisms underlying AD and help identify potential biomarkers and therapeutic targets for early diagnosis, prevention, and management of the disease. Therefore, the present study aims to investigate the association between lipid profile, Lp-PLA₂, sdLDL, and ApoE4 in patients with Alzheimer's disease, with the objective of elucidating potential metabolic and inflammatory biomarkers that may contribute to early diagnosis, risk stratification, and therapeutic targeting in AD.

Materials and methodology:

Total subjects include 50 controls and 50 cases belongs to age above 65 years of Indian origin attending SRMC & RI with evidence of AD will be selected as cases and age matched non demented healthy female individuals will be included as controls. The study subjects were recruited based on inclusion and exclusion criteria. The control group belongs to aged matched non-demented healthy individuals. These individuals did not have any family histories, symptoms or signs of psychiatric or neurological disease, malignant disease or systemic disorders (e.g. collagenosis, rheumatoid arthritis or infectious disease). None of the controls were receiving pharmacological therapy for neurological or psychiatric disorders. Their cognitive status was examined using the MMSE (Folstein et al., 1975). Subjects with the history of brain disorders, psychiatric problems, cardiovascular disease and other co morbidities (Diabetes, thyroid disorder and abnormal lipid profile) were excluded from the study. In this study, we included only postmenopausal women. Institutional ethical clearance were obtained for data collection. Informed consent was obtained from the patients. Data collection were comprised of age-specific standardized questionnaires, physical examination and CT/MRI report & detailed information on past medical history. Blood samples were collected from healthy age matched controls and AD patients for the analysis of lipid profile and Lp PLA₂.

Biochemical analysis:

All the samples were collected from the study participants in fasting and Serum concentrations of total cholesterol, HDL-cholesterol, LDL cholesterol and triglycerides were determined by photometric method. We determined the Lp PLA₂ in plasma by ELISA (Elabscience-E-EL-H2286). we investigated the level of sdLDL using the formula proposed by Sampson sdLDL equation calculator:

$$VLDL-C = \frac{TG}{8.59} + \frac{TG \times nonHDL-C}{2,250} - \frac{TG^2}{16,500}$$

$$LDL-C = \frac{TC}{0.948} - \frac{HDL-C}{0.971} - \left(\frac{TG}{8.56} + \frac{TG \times nonHDL-C}{2,140} - \frac{TG^2}{16,100} \right) - 9.44$$

$$lbLDL-C = 1.43 \times LDL-C - (0.14 \times (\ln(TG) \times LDL-C)) - 8.99$$

$$sdLDL-C = LDL-C - lbLDL-C$$

Single nucleotide polymorphism Study:

The protocol for polymorphism study was taken based on Jie Zhen et al, 2017. ApoE Polymorphism (rs429358 and rs7412) were analysed using peripheral blood sample. Genomic DNA was extracted from EDTA blood sample using a kit method (QUIAGEN). We performed polymorphism of ApoE rs429358 by Polymerase Chain Reaction - Restriction Fragment Length Polymorphism (PCR-RFLP) using specific primers for rs429358 are: forward 5' AGGGCGCTGATGGACGAGAC -3'; Reverse 5'GCCCCGGCCTGGTACACT 3'. PCR reaction mixtures composed of 200 ng of DNA, 1xPCR Master Mix (Takara master mix) and 10p moles of each specific primer. Annealing temperatures of 55.0°C for rs429358 were used for amplification. The amplification cycles were processed at 95°C for 5 min, followed by 35 cycles of 95°C for 30 s, for annealing: 60° C - 62° C for 30 s and 72°C for 30 s and a final elongation time of 72°C for 5 min. Then PCR products were allowed to digest by restriction endonucleases – HaeII for rs429358 for 3 hr. Restriction endonuclease fragments were blended with gel red and then agarose gel electrophoresis (2-2.5 %) were done which was detected by visualization on an ultraviolet light transilluminator as shown in fig 1. We have done gene sequencing using snackvar software and ensures the site of polymorphism.

Result:

Table 1. Baseline characteristics of the study cohort (N=100) by ApoE (rs429358) genotype

Characteristic	Homozygous Dominant (n=28)	Heterozygous (n=17)	Homozygous Recessive (n=55)	P value
Age, years (mean ± SD)	66.89 ± 13.4	62.53 ± 8.16	65.96 ± 10.73	0.168
Female sex, n (%)	27 (96.4)	17 (100.0)	55 (100.0)	0.273
Diabetic, n (%)	0 (0.0)	1 (5.9)	17 (30.9)	<0.001*
Hypothyroidism, n (%)	0 (0.0)	2 (11.8)	20 (36.4)	<0.001*

*p < 0.05 are assumed to be statistically significant. Age compared using Kruskal-Wallis test; sex, diabetic status, and hypothyroidism compared using chi-square test.

Table 2: Lipid profile in case and control:

Lipid profile (mg/dl)	Mean ± SD		P Value
	Case	Control	
Cholesterol	252.7± 44.7	202.4 ± 39.6	< 0.00**
TGL	209.96± 69.4	122.02 ±42.4	< 0.00 **
HDL	43.44± 8.2	48.86 ± 7.5	< 0.001 **
LDL	182.36± 57.8	130.9 ± 28.2	< 0.00 **
NON HDL	209.3 ± 46.8	152.4 ± 38.9	< 0.00 **
VLDL	41.9 ± 13.9	24.4 ± 8.4	< 0.00 **

Chol /HDL	5.76 ± 1.7	4.2 ± 0.95	<0.00 **
sdLDL	4809.2 ± 2147.2	2217.7 ± 1179.1	<0.00 **
PLP A2	123.35± 44	67.5 ± 21	< 0.002 *
MMSE Score	12.2 ± 3.4	27.1 ± 2	< 0.03 *

Values indicate Mean ± SD ** (p<0.01)-Statistically highly Significant and P < 0.05

Table 3. Lipid profile parameters (mean ± SD) by ApoE genotype (rs429358).

Parameter	Homozygous Dominant (n=28)	Heterozygous (n=17)	Homozygous Recessive (n=55)	P value
Total Cholesterol (mg/dL)	197.11 ± 34.12	230.53 ± 39.3	242.13 ± 51.7	<0.001*
Triglycerides (mg/dL)	123.46 ± 36.98	130.06 ± 55.51	198.75 ± 74.52	<0.001*
HDL-C (mg/dL)	47.46 ± 7.55	49.71 ± 5.89	44.38 ± 8.84	0.040*
LDL-C (mg/dL)	139.54 ± 27.45	131.24 ± 29.45	173.2 ± 60.9	0.004*
Non-HDL-C (mg/dL)	147.33 ± 32.86	180.82 ± 39.96	197.75 ± 54.57	<0.001*
VLDL-C (mg/dL)	24.69 ± 7.4	26.01 ± 11.1	39.75 ± 14.9	<0.001*
Chol/HDL ratio	4.22 ± 0.87	4.69 ± 1.01	5.44 ± 1.8	0.005*
sdLDL (particle no.)	2198.82 ± 1026.87	2776.72 ± 1556.08	4410.45 ± 2328.76	<0.001*

*p < 0.05 are assumed to be statistically significant. Non-HDL comparison based on n=27 for CC (1 missing value).

Table 4. Association of the ApoE (rs429358) gene polymorphism with case and control.

Cases vs control	Cases N=18 (%)	Control N=82 (%)	Odds ratio	95% confidence interval	p value
Allele					
C	1 (2.78)	72 (43.9)	Reference	-	-
T	35 (97.22)	92 (56.1)	27.39	3.66-204.75	<0.001*
Genotype					
CC	0 (0.0)	28 (34.15)	Reference	-	-
CT	1 (5.56)	16 (19.51)	5.18	0.2-134.66	0.378
TT	17 (94.44)	38 (46.34)	25.91	1.49-449.07	<0.001*

*p < 0.05 are assumed to be statistically significant. OR = odds ratio vs reference category; overall genotype distribution p = <0.001.

Figure 1:Gel electrophoresis for ApoE genotype (rs429358).

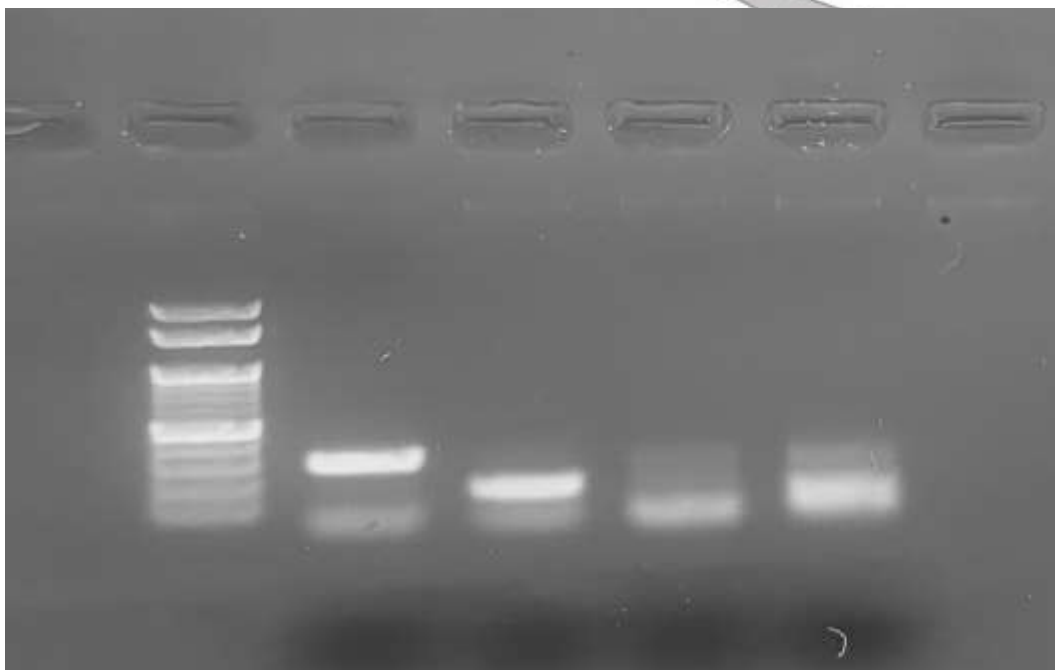


Figure 2. ApoE genotype (CC/CT/TT) frequency distribution in Case vs Control.

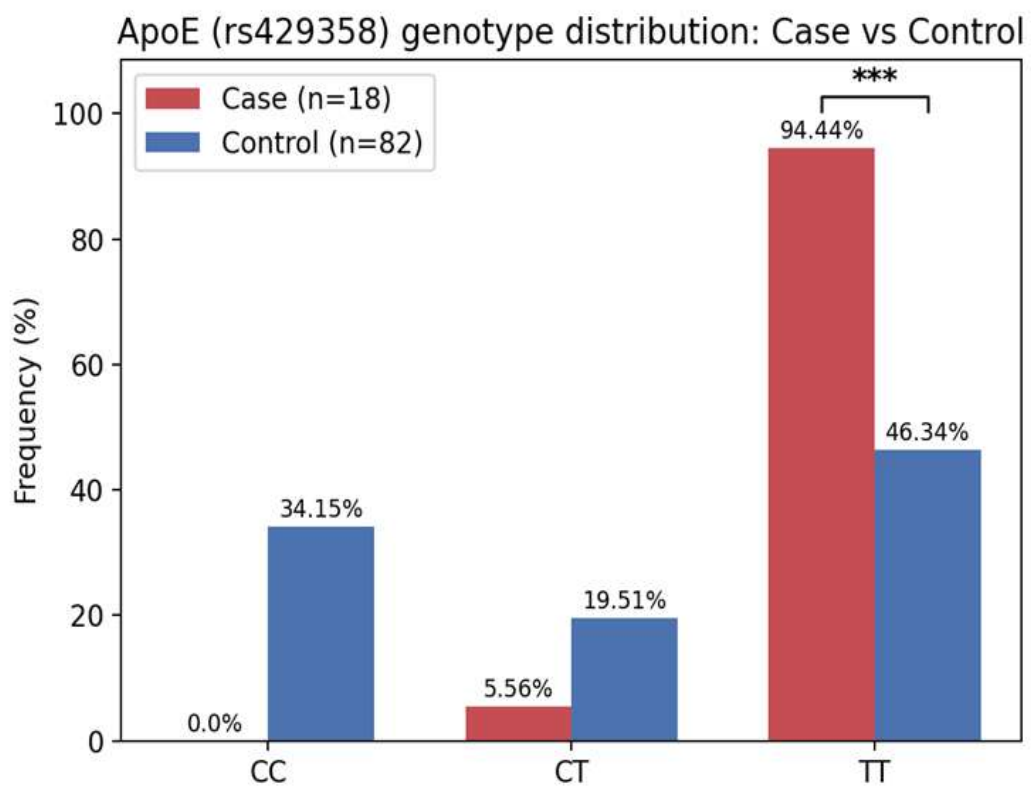
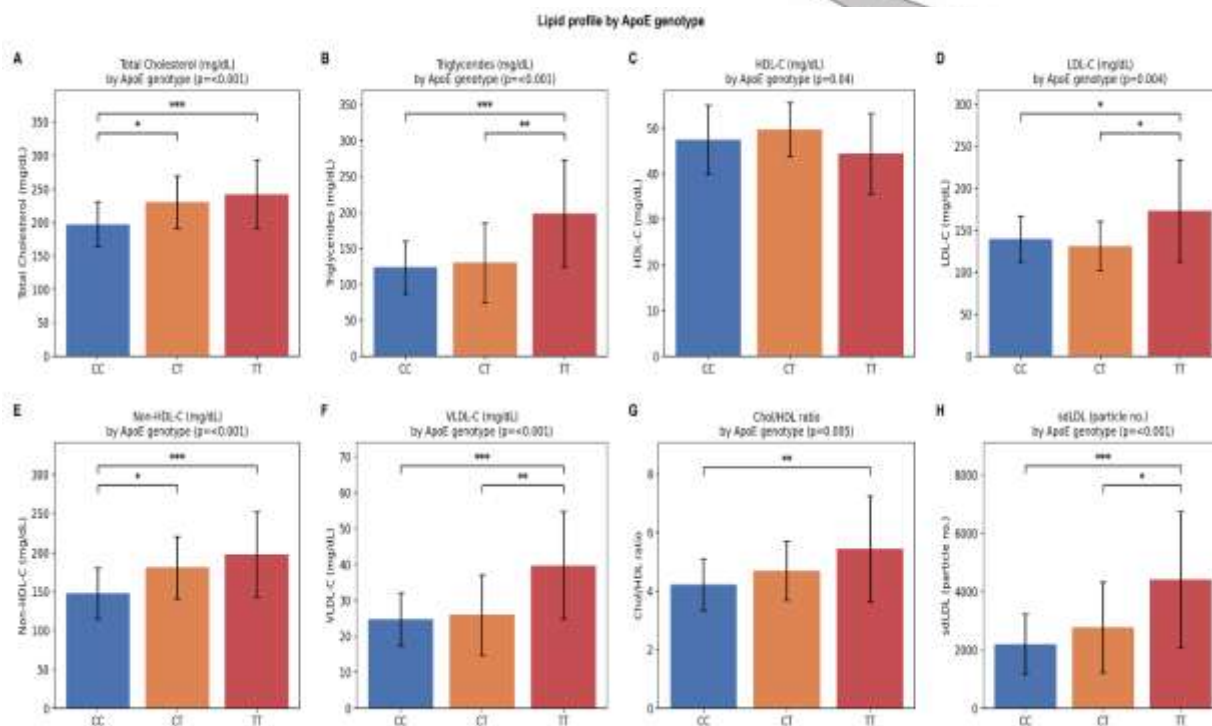


Figure 3: Lipid profile between case and control



The study included 100 participants, comprising of 50 Alzheimer's disease (AD) cases and 50 cognitively healthy controls. The distribution of the ApoE (rs429358) genotypes was Homozygous dominant CC (n=28), Heterozygous CT (n=17), and Homozygous Recessive TT (n=55).

There was no statistically significant difference in age among the three genotype groups (CC 66.89 ± 13.4 years, CT: 62.53 ± 8.16 years, TT: 65.96 ± 10.73 years; $p = 0.168$). Similarly, the proportion of females did not differ significantly across genotypes ($p = 0.273$). However, the prevalence of diabetes mellitus and hypothyroidism increased significantly among individuals carrying the TT genotype. Diabetes was observed in 30.9% of TT carriers compared with 5.9% of CT carriers and none of the CC carriers ($p < 0.001$). Likewise, hypothyroidism was present in 36.4% of TT carriers compared with 11.8% of CT carriers and none of the CC carriers ($p < 0.001$), indicating a significant association between the TT genotype and metabolic comorbidities. A significant association was observed between the ApoE (rs429358) polymorphism and Alzheimer's disease. The T allele was markedly more frequent among AD cases (97.2%) than controls (56.1%) and was associated with a 27.39-fold increased odds of Alzheimer's disease (OR = 27.39; 95% CI: 3.66–204.75; $p < 0.001$). Genotype analysis demonstrated that the TT genotype was present in 94.4% of AD cases compared with 46.3% of controls and conferred a 25.91-fold increased risk of disease (OR = 25.91; 95% CI: 1.49–449.07; $p < 0.001$). In contrast, the CT genotype did not show a statistically significant association with Alzheimer's disease (OR = 5.18; 95% CI: 0.20–134.66; $p = 0.378$).

Comparison of lipid profile between Alzheimer's disease cases and controls

Patients with Alzheimer's disease exhibits altered lipid parameters significantly compared with healthy controls. Mean total cholesterol was found to be (252.7 ± 44.7 vs. 202.4 ± 39.6 mg/dL), triglycerides (209.96 ± 69.4 vs. 122.02 ± 42.4 mg/dL), LDL-C (182.36 ± 57.8 vs. 130.9 ± 28.2 mg/dL), non-HDL-C (209.3 ± 46.8 vs. 152.4 ± 38.9 mg/dL), VLDL-C (41.9 ± 13.9 vs. 24.4 ± 8.4 mg/dL), cholesterol/HDL ratio (5.76 ± 1.7 vs. 4.2 ± 0.95), small dense LDL (sdLDL) (4809.2 ± 2147.2 vs. 2217.7 ± 1179.1), and Lp-PLA2 (123.35 ± 44 vs. 67.5 ± 21) were all significantly elevated in AD patients (all $p < 0.01$). Conversely, HDL-C was significantly lower among cases than controls (43.44 ± 8.2 vs. 48.86 ± 7.5 mg/dL; $p < 0.001$). Cognitive performance, assessed using the MMSE, was also significantly reduced in the AD group (12.2 ± 3.4 vs. 27.1 ± 2 ; $p < 0.03$).

Significant differences in lipid parameters were observed across ApoE genotypes. Individuals with the TT genotype exhibited the highest concentrations of total cholesterol (242.13 ± 51.7 mg/dL), triglycerides (198.75 ± 74.52 mg/dL), LDL-C (173.2 ± 60.9 mg/dL), non-HDL-C (197.75 ± 54.57 mg/dL), VLDL-C (39.75 ± 14.9 mg/dL), cholesterol/HDL ratio

(5.44 ± 1.8), and sdLDL particles (4410.45 ± 2328.76), all of which were significantly greater than those observed in CC and CT genotypes ($p \leq 0.005$). In contrast, HDL-C was significantly lower in TT carriers (44.38 ± 8.84 mg/dL) than in the CC (47.46 ± 7.55 mg/dL) and CT (49.71 ± 5.89 mg/dL) groups ($p = 0.040$). These findings suggest that the TT genotype is associated with a markedly more atherogenic lipid profile.

In this present study we observed that the ApoE TT genotype is strongly associated with Alzheimer's disease and is accompanied by a significantly more atherogenic lipid profile, characterized by elevated total cholesterol, triglycerides, LDL-C, non-HDL-C, VLDL-C, sdLDL, and reduced HDL-C. These alterations support the role of ApoE-mediated dyslipidemia in the pathogenesis of Alzheimer's disease.

Discussion:

The present study evaluated the association between ApoE (rs429358) polymorphism, lipid profile, small dense LDL (sdLDL), and Lp-PLA2 in patients with Alzheimer's disease (AD). Our findings demonstrate that the TT genotype and T allele were significantly associated with AD, accompanied by an unfavorable lipid profile characterized by elevated total cholesterol, triglycerides, LDL-C, non-HDL cholesterol, VLDL-C, sdLDL, and Lp-PLA2, together with reduced HDL-C. These observations support the growing evidence that disturbances in lipid metabolism play a critical role in AD pathogenesis.

The baseline demographic characteristics showed no significant differences in age or sex among the ApoE genotype groups, indicating that the observed biochemical alterations were unlikely to be confounded by these variables. However, diabetes mellitus and hypothyroidism were significantly more prevalent among individuals carrying the TT genotype. Metabolic disorders such as diabetes and thyroid dysfunction are recognized risk factors for cognitive decline because they promote chronic inflammation, oxidative stress, endothelial dysfunction, and dyslipidemia. Previous epidemiological studies have similarly demonstrated that metabolic diseases accelerate neurodegeneration through vascular and metabolic mechanisms (Biessels & Despa, 2018; Mullur et al., 2014).

A major finding of the present study was the strong association between the T allele and Alzheimer's disease. Individuals carrying the T allele had approximately 27-fold higher odds of AD, while the TT genotype increased disease risk nearly 26-fold compared with the CC genotype. Although the classical APOE $\epsilon 4$ allele remains the strongest genetic risk factor for late-onset Alzheimer's disease (Corder et al., 1993), variants involving the rs429358 locus have likewise been associated with altered ApoE protein structure, impaired cholesterol transport, and increased amyloid- β deposition. ApoE regulates neuronal cholesterol homeostasis, synaptic remodeling, and amyloid clearance. Structural alterations in ApoE reduce its ability to transport cholesterol efficiently and impair clearance of amyloid- β peptides, thereby accelerating plaque formation and neurodegeneration (Liu et al., 2013; Yamazaki et al., 2019). Our findings therefore reinforce the importance of ApoE-mediated lipid dysregulation in AD susceptibility.

Patients with Alzheimer's disease exhibited significantly higher concentrations of total cholesterol, triglycerides, LDL-C, non-HDL cholesterol, VLDL-C, cholesterol/HDL ratio, sdLDL, and Lp-PLA2 compared with cognitively healthy controls, while HDL-C was significantly reduced. These findings agree with previous reports showing that dyslipidemia contributes to AD through increased oxidative stress, endothelial dysfunction, and neuroinflammation (Anstey et al., 2017; van der Kant et al., 2020). Elevated circulating cholesterol promotes amyloidogenic processing of amyloid precursor protein (APP), resulting in increased production and deposition of amyloid- β within the brain. Furthermore, excess cholesterol disrupts neuronal membrane fluidity and synaptic transmission, leading to progressive cognitive impairment.

Among all lipid parameters, small dense LDL (sdLDL) demonstrated one of the most striking elevations in AD patients. Small dense LDL particles are highly susceptible to oxidation, possess prolonged plasma residence time, and readily penetrate the vascular endothelium. Oxidized sdLDL induces endothelial dysfunction and stimulates inflammatory pathways that compromise cerebral microvascular integrity. Increasing evidence indicates that vascular dysfunction precedes neuronal degeneration in Alzheimer's disease, making sdLDL a potentially important biomarker of disease progression (Ivanova et al., 2017; Hirano, 2010). Our findings therefore support the hypothesis that sdLDL contributes to cerebrovascular injury and neurodegeneration.

Similarly, circulating Lp-PLA2 levels were significantly elevated in AD patients. Lp-PLA2 is an inflammatory enzyme primarily bound to LDL particles, particularly sdLDL, and hydrolyzes oxidized phospholipids to produce lysophosphatidylcholine and oxidized fatty acids. These bioactive molecules amplify vascular inflammation, oxidative stress, and endothelial injury. Elevated Lp-PLA2 has been associated with cerebral small vessel disease, cognitive

decline, and increased risk of dementia (Davidson et al., 2012; Ballard et al., 2019). The simultaneous elevation of sdLDL and Lp-PLA2 observed in our study suggests enhanced oxidative modification of LDL particles, which may accelerate vascular-mediated neurodegeneration.

Another important observation was that lipid abnormalities progressively worsened among individuals carrying the TT genotype. TT carriers exhibited significantly higher total cholesterol, triglycerides, LDL-C, non-HDL cholesterol, VLDL-C, cholesterol/HDL ratio, and sdLDL concentrations; whereas HDL-C was significantly lower than in CC and CT carriers. These findings suggest that ApoE polymorphism influences systemic lipid metabolism in addition to its direct effects on amyloid processing. ApoE regulates cholesterol transport between astrocytes and neurons, and impaired ApoE function disrupts neuronal membrane repair, synaptic plasticity, and cholesterol recycling (Mahley & Huang, 2012). Consequently, genetically determined dyslipidemia may increase neuronal vulnerability to amyloid toxicity and tau pathology.

The significantly lower MMSE scores among AD patients correspond well with the observed metabolic abnormalities. Accumulating evidence indicates that dyslipidemia, oxidative stress, and vascular inflammation contribute to cognitive deterioration through reduced cerebral perfusion, blood-brain barrier dysfunction, and enhanced neuroinflammatory responses (Livingston et al., 2024). Therefore, the combined assessment of ApoE genotype, lipid profile, sdLDL, and Lp-PLA2 may improve early identification of individuals at high risk for Alzheimer's disease.

Conclusion:

The findings of the present study support the concept that Alzheimer's disease is not solely a neurodegenerative disorder but also a disease linked to lipid dysregulation and vascular inflammation. The strong association between ApoE polymorphism and an atherogenic lipid profile suggests that genetic susceptibility interacts with metabolic abnormalities to accelerate the development of disease. Future longitudinal studies with larger sample sizes are required to determine whether sdLDL and Lp-PLA2 can serve as reliable predictive biomarkers and therapeutic targets for preventing cognitive decline.

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