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Serum Lipid Levels in Patients with Alzheimer's Disease

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A B S T R A C T

The role of lipids in the aetiology and progress of Alzheimer's disease (AD) is still unclear. High lipid levels could be one of the risk factors for AD, but no association or even protective effects of high cholesterol levels in the development of the AD were also found. The aim of the study was to determine serum levels of total cholesterol, high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C) and triglycerides (TG) in female patients with AD and in healthy elderly controls. The 50 patients met the diagnostic criteria of probable AD according to the NINDS-ADRDA and DSM-IV criteria. Cognitive impairment was evaluated using the Mini Mental State Examination (MMSE). Patients were subdivided into two groups of 19 patients in the middle (MMSE 10-19) and 31 patients in the late (MMSE 0-9) phase of AD. Psychotic and non-psychotic features, evaluated by means of Neuropsychiatric Inventory, were presented in 13 and 37 patients with AD, respectively. Control group consisted of 58 subjects without cognitive impairment (MMSE >27) and with lipid levels within normal range. Serum lipid levels were determined by the enzymatic colour tests and by the enzymatic clearance assay. Significantly lower lipid levels were found in patients with AD, than in controls. Patients in the late phase of AD had significantly lower entire lipid profile than controls and significantly lower cholesterol and LDL-C levels than patients in the middle stage of AD. There was no difference in lipid levels between patients with and without psychotic features. The significant positive correlations were found between MMSE scores and cholesterol, LDL-C levels and age in all AD patients. The results support the presumption that lipid profile might be connected with the aetiology and progress of AD and showed the association between low serum cholesterol and LDL-C levels and cognitive decline in patients with AD. Further studies are needed to confirm the relationship between lipid levels and cognition, and to validate the lipid profile as a biological marker for the progress of AD.

Key words: *Alzheimer's disease, healthy controls, serum, total cholesterol, high-density-lipoprotein cholesterol, low-density-lipoprotein cholesterol, triglycerides, cognitive impairment, psychotic features*

Introduction

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder. Since the prevalence and incidence of AD increase with age, and population worldwide is getting older, AD is a serious global health problem. In spite of the intensive investigations, the cause and progression of AD are not well understood. Two biochemical hallmarks of AD are amyloid-beta peptides (Aβ) gathering in senile plaques, and intracellular accumulation of hyperphosphorylated protein tau in neurofibrillary tangles[1]. However, these morphological changes could only be detected by post-mortem neuropathological examination[2].

A variety of potential peripheral biomarkers for AD have been investigated in cerebrospinal fluid[3] and blood[4,5] including biomarkers for lipoproteins metabolism[6,7]. Lipids, and within particularly the cholesterol, are the important components of the myelin sheath and the membranes of neurons and astrocytes, that play a crucial role in the development and regulation of synaptic function

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and plasticity. Lipids regulate thickness of cell membrane, its permeability/fluidity and function of membrane-associated proteins (transporters, receptors)[8].

Several studies[9,10] reported the relationship between cholesterol levels, amyloid precursor protein (APP) metabolism and apolipoprotein E (ApoE) phenotype, suggesting that cholesterol metabolism might influence the expression of the APP and Aß in patients with AD[1,11,12]. Although clinical and epidemiological data suggest the aberration of cholesterol homeostasis in AD, it is not clear if cholesterol has a protective or neurotoxic role in the development of AD[13]. Some studies have found that high lipid levels could be the risk factor for the AD[14], whereas others have shown no association[15] or protective[16,17] effects of high lipids on the occurrence of AD. The longitudinal studies[18,19] indicated the decreased prevalence of AD, that could be associated with the use of cholesterol-lowering drugs statins, but their effect could be independent of the presence or absence of untreated hyperlipidaemia, and may be due to their well-known antioxidant and anti-inflammatory properties[19].

The data regarding blood lipid levels and incidence of AD are contradictory[13]. High serum total cholesterol levels may be associated with either increased[20], or decreased[17] risk for the development of the AD. Lower[6,16,22] or unaltered[14] total serum cholesterol levels were found in AD patients compared to healthy elderly subjects. In addition, lower high-density lipoprotein cholesterol (HDL-C) levels in AD patients compared to healthy elderly subjects were found in some[14,21] but not all[16] studies. Literature data suggest no alteration in serum triglycerides (TG) levels in AD[14,6,17,21].

The aim of the study was to determine serum total cholesterol, HDL-C, LDL-C and TG levels in female patients with AD subdivided according to the severity of disease or the presence of psychotic features and to compare their values with lipid levels in healthy elderly controls.

Subjects and Methods

The study included 50 female patients with AD (age X±SD, 79.1±9.0 years, range 56–96 years). All patients met the diagnostic criteria of the probable AD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[22] and the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA)[23]. The exclusion criteria for all patients were the diagnoses of severe somatic diseases, major functional psychiatric disorders, smoking, alcoholism and use of cholesterol-lowering drugs. Cognitive impairment was evaluated using Mini Mental State Examination (MMSE)[24] that was translated and validated to Croatian population (www.parinc.com). Patients were subdivided according to the MMSE scores into two groups: 19 patients (74.8±9.9 years old, range 56–89 years) in the middle stage of AD with MMSE scores 15.1±3.5 (range 10–17) and 31 patients (81.7±4.5 years old, range 57–96 years) in the late stage of AD with

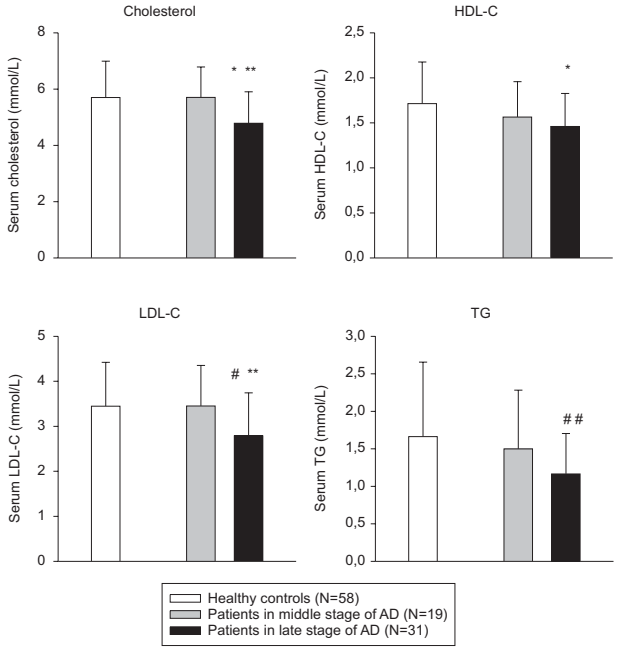

*Fig 1. Serum cholesterol, high density lipoprotein cholesterol (HDL-C) low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) values (X±SD) in healthy controls and in patients with Alzheimer's disease (AD) in the middle and late stage of disease. N is the number of subjects. *p<0.02 vs. healthy controls, **p<0.01 vs. patients in middle stage of AD; #p<0.049 vs. patients in middle stage of AD; ##p<0.02 vs. healthy controls (Tukey's test).*

MMSE scores 1.6±2.4 (range 0–9). Psychotic features were evaluated by means of the Neuropsychiatric Inventory[25]. Psychotic and non-psychotic features were presented in 13 (76.0±11.6 years old, range 56–96 years; MMSE scores 8±7.5, range 0–16) and 37 (80.1±7.8 years old, range 57–94 years; MMSE scores 6.1±7.1, range 0–17) patients, respectively. Control group consisted of 58 age-matched healthy older female (71.6±6.2 years old, range 63–90 years) with lipid levels within normal range and with MMSE scores from 27 to 30 (28.7±1.2), recruited from the local senior centres. They were evaluated with a clinical interview to rule out for Axis I disorders, current and past medical status and MMSE. Exclusion criteria were the use of cholesterol-lowering drugs, smoking and alcoholism. Participants or their guardians gave informed consent. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and was approved by the local Ethics Committee.

Serum cholesterol, HDL-C and TG levels were determined by the enzymatic colour test for clinical analyzers, with the linearity within concentrations range of 0.64–18 mmol/L for cholesterol, 0.05–4.65 mmol/L for HDL-C and 0.11–11.40 mmol/L for TG. Serum LDL-C levels were determined by the enzymatic clearance assay, with linearity up to 22.4 mmol/L.

All data are presented as X±SD. The differences between groups were assessed by one-way analysis of vari-

ance (ANOVA), followed by Tukey's test. The correlations between MMSE scores, age and lipid values were determined by a Pearson's coefficient of correlation. The significance level was $p<0.05$. The statistical package used was SigmaStat 3.1 (Jandell Scientific Corp., San Raphael, California, USA).

Results

MMSE scores were significantly ($F_{1,106}=406.20$; $p<0.001$, ANOVA) different between patients with AD (6.8±7.2) and control women (28.7±1.2). A significant ($F_{1,48}=259.658$, $p<0.001$) difference in the severity of dementia was found within the group of patients with AD, with higher MMSE scores in patients in the middle (15.1±3.5) than in patients in the late (1.6±2.4) phase of AD. Patients with AD were significantly ($F_{1,106}=25.636$; $p<0.001$) older than healthy controls. There was a significant difference ($F_{1,48}=7.686$; $p=0.008$) in age between patients with AD subdivided according to the different phases of the disease. Tukey's test showed that patients in the late phase of AD were significantly ($p< 0.008$) older than patients in the middle phase of disease.

Serum cholesterol ($F_{1,106}=5.54$, $p<0.020$), TG ($F_{1,106}=4.945$, $p<0.028$), LDL-C ($F_{1,106}=4.7814$, $p<0.031$) and HDL-C ($F_{1,106}=6.861$, $p<0.010$) levels were significantly lower in all patients with AD than in healthy subjects (Table 1). Serum cholesterol ($F_{2,105}=6.342$, $p=0.003$), HDL-C ($F_{2,105}=3.779$, $p=0.026$), LDL-C ($F_{2,105}=5.272$, $p=0.007$) and TG ($F_{2,105}=3.473$, $p=0.035$) levels were significantly different between patients in various stages of AD and healthy controls. Patients in the late stage of disease had significantly lower cholesterol, HDL-C, LDL-C and TG levels than healthy controls (Figure 1), and significantly lower cholesterol and LDL-C levels than patients in the middle stage of disease (Figure 1).

When patients were subdivided according to the presence of psychotic features, serum cholesterol ($F_{2,105}=3.210$, $p<0.044$), LDL-C ($F_{2,105}=3.40$, $p<0.037$) and HDL-C ($F_{2,105}=3.407$, $p=0.037$) levels differed among psychotic and non-psychotic patients and healthy controls. AD patients with non-psychotic features had significantly lower serum cholesterol, HDL-C and LDL-C values than healthy controls, while serum TG levels were similar ($F_{2,105}=2.725$, $p=0.070$) among groups (Table 1). There were no significant ($p>0.05$) differences in serum lipid levels between AD patients with psychotic and non-psychotic features.

The significant correlation was found between MMSE scores and serum cholesterol ($r=0.348$, $p=0.013$) and LDL-C ($r=0.302$, $p<0.033$) levels, but not between MMSE scores and serum HDL-C ($r=0.165$, $p=0.251$) and TG ($r=0.174$, $p=0.236$) levels in patients with AD. There was a significant negative correlation ($r= –0.345$, $p=0.0142$) between MMSE scores and age of patients with AD. No significant correlation was observed between age and cholesterol ($r=0.024$, $p=0.860$; $r=–0.210$, $p=0.143$), age and HDL-C ($r=–0.163$, $p=0.221$; $r=–0.051$, $p=0.725$), age and LDL-C ($r=0.124$, $p=0.926$; $r=–0.223$, $p=0.120$) and age and TG ($r=0.058$, $p=0.662$; $r=–0.232$, $p=0.105$) levels in healthy controls and patients with AD, respectively.

Discussion

The main findings of the present study are that a) serum lipid levels are reduced in female patients with AD compared to lipid values in elderly female healthy controls, b) serum lipid levels are the lowest in patients in the late stage of AD and c) serum lipid levels are not related to the presence of psychotic features. To the best of our knowledge, this is the first report of the significantly lower serum cholesterol and LDL-C levels in patients in the late phase of AD compared to levels in patients in the middle phase of AD.

The results of reduced serum cholesterol, LDL-C and HDL-C levels in patients with AD compared to healthy controls is in agreement with some previously published data[6,16,21], but are in contrast with elevated LDL-C levels[14,26,27] and increased[26,27] or unaltered cholesterol[14] levels found in patients with AD. The finding that TG levels are similar between controls and AD patients as a group is in agreement with other studies[14,17]. However, the result of a significantly lower TG levels in patients in the late phase of AD suggests that TG could be involved in the progress of AD. Although psychotic features, that

TABLE 1
SERUM LIPID LEVELS (X±SD) IN PATIENTS WITH ALZHEIMER'S DISEASE SUBDIVIDED ACCORDING TO THE PRESENCE OF PSYCHOTIC FEATURES AND IN HEALTHY CONTROLS

	Patients with Alzheimer's disease			Healthy controls (58)
	All (50)	Psychotic features		
		With (13)	Without (37)	
Cholesterol (mmol/L)	5.14±1.18*	5.42±1.21	5.04±1.17*	5.70±1.29
HDL-C (mmol/L)	1.50±0.38*	1.50±0.35	1.51±0.45*	1.71±0.46
LDL-C (mmol/L)	3.03±0.99*	3.36±1.09	2.92±0.94*	3.45±0.97
TG (mmol/L)	1.30±0.65*	1.46±0.73	1.25±0.63	1.66±0.99

* $p<0.05$ *vs.* corresponding values in healthy controls (Tukey's test), HDL-C – high-density-lipoprotein cholesterol, LDL-C – low-density-lipoprotein cholesterol, TG – triglycerides

distress patients and could be associated with the faster progress of AD[28], were presented in one third of patients, the results showed no association between lipid levels and psychotic features and no difference in lipid profile between patients with and without psychotic features.

The reason for the dissimilar results among studies might be due to the variety of confounding factors like age, gender, diet, alcohol, exercise, smoking and different methods for the determination of lipid levels. To avoid the complex gender-related differences observed in the clinical presentation[29] and cognitive deficits[30] in AD, and gender related difference in cholesterol, lipoproteins and apolipoproteins levels observed in healthy subjects[31], with higher serum cholesterol[31,32] and HDL-C[31,32] and lower LDL-C[32] or TG[31] levels in women than in men, present study included only female subjects. In this respect it is difficult to compare the results of lipid levels among studies since several articles did not specified the gender[14] of patients with AD or reported lipid levels in the groups of patients and controls that consisted of both male and female subjects[16,21]. Additionally, the severity of AD or the phases of AD were not specified[14,16,21] and different methods i.e. enzymatic[21] (present study) or high performance gel filtration chromatography[14], were used for the determination of serum lipid levels.

Age is also one of the factors that could influence cholesterol values. Aging was associated with the decline in cholesterol synthesis in hippocampus of healthy subjects[33] but not in AD[34]. Although the patients in the late stage of AD were the oldest, there was no significant correlation between age and lipid levels in the present study, suggesting no influence of aging on serum lipid levels.

The most important findings of the present study are significant differences in total lipid levels among patients with diverse degrees of the cognitive impairment. The subdivision of patients with AD according to the cognitive decline has shown that the difference in lipid levels among healthy controls and patients with AD is due to the low serum lipid profile in AD patients in the late stage of the disease. It is noteworthy that all components of lipid profile were significantly lower in patients in the late stage of AD compared to values in healthy controls, while a pronounced decrease in cholesterol and LDL-C was found in the late stage of AD compared to lipid values in the middle phases of disease. The results have shown a positive correlation between MMSE scores and cholesterol and LDL-C levels in patients with AD indicating that more severe AD symptoms are associated with reduced cholesterol and LDL-C values. In the present study the reduced serum HDL-C levels were also found in patients with late stage of AD. HDL-C is the cholesterol fraction, and the key extracellular acceptors for cholesterol and low HDL-C levels could be associated with poor memory and progressive decline in memory in the middle aged adults[35], while elevated HDL-C could be related to decreased incidence of dementia independent of ApoE status[26].

It seems that the data on blood lipid levels and incidence of AD depend on the time when lipid levels were determined, i.e. over the life course, or in relation to the underlying course of AD[13]. Although we have determined serum lipid levels in patients with AD that were in middle or late stage of disease, the positive correlation between MMSE scores and serum cholesterol and LDL-C levels suggests that increased lipid levels could be the protective factor in the occurrence of AD. This result is in agreement with the findings that increased plasma cholesterol levels are associated with a reduced risk of dementia in older subjects[17], but is in contrast with the data from the longitudinal studies showing a positive[20,36] or non-significant[15,37] association between high cholesterol and HDL-C levels in midlife and the development of AD in the late life.

Although peripheral cholesterol content does not contribute to the brain cholesterol levels, because plasma lipoproteins are unable to cross lipophilic blood-brain barrier[11], and there are many differences between cholesterol metabolism in the brain and periphery[13], several data[38,39] suggest that decrease in cerebral cholesterol metabolism could be present in AD. The results of the present study on the reduced extra-cerebral, i.e. serum lipid levels, are in agreement with the decrease in cerebrospinal fluid cholesterol and HDL-C[40] levels, low hippocampal membrane cholesterol levels[38], decreased activity of enzyme seladin-1[38], and reduced concentration of plasma 24S-hydroxycholesterol levels, which is a marker for the brain cholesterol metabolism[41] in patients with AD.

It is possible that dementia itself modifies lipid levels, due to the changes in diet or metabolism, leading to low cholesterol, LDL-C and HDL-c levels in patients with AD. The role of dyslipidemia in the development and progress of AD remains unclear. A net flux of peripheral cholesterol in the form of 27-hydroxycholesterol, a side chain oxidized cholesterol, through blood-brain-barrier was reported recently in healthy volunteers[42], that could contribute to the cholesterol homeostasis in the brain through its effect on several cholesterol-sensitive genes. A synthesis of cholesterol could be also decreased due to the lower activity of seladin-1, an enzyme involved in cholesterol synthesis[38].

The limitations of the present study were that the results are restricted to changes of serum lipid levels, and that dietary habits of patients were not controlled. Namely, serum lipid levels are partially under influence of diet[11]. In contrast to the uncontrolled dietary habits of the patients in middle stage of AD, patients in the late stage of AD, who had the lowest lipid levels, were hospitalized and fed with the balanced hospital diet, and therefore the influence of the diet might be excluded. The advantages of the study were in ethnically uniform Caucasian sample, matched patients with AD, and elderly control group in terms of race, age, gender and in determination of all components of the lipid profile in both patients and healthy controls.

In conclusion the results of this study showed the alterations in serum lipid levels in patients with AD and the association between serum cholesterol and LDL-C and severity of the AD. The mild but significant positive

correlations between MMSE scores and serum cholesterol or LDL-C levels point out to the relationship between lipid levels and cognition in patients with AD. Further studies are needed to clarify the role of cholesterol and lipoproteins in the pathogenesis and progress of the AD.

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KONCENTRACIJA SERUMSKIH LIPIDA U BOLESNIKA S ALZHEIMEROVOM BOLESTI

SAŽETAK

Uloga lipida u etiologiji i razvoju Alzheimerove bolesti (AB) još uvijek je nejasna. Rezultati dosadašnjih istraživanja su pokazali da ne postoji povezanost između serumskih lipida i kognitivnih promjena u oboljelih od AB, ali i protektivni pa čak i pozitivni učinak povišenih vrijednosti serumskih lipida u razvoju AB. Cilj istraživanja bio je odrediti vrijednosti ukupnog serumskog kolesterola, lipoproteina velike gustoće (HDL-C), lipoproteina male gustoće (LDL-C) i triglicerida (TG) u 50 žena oboljelih od AB i u 58 zdravih žena starije životne dobi. Dijagnoza vjerojatne AB postavljena je na temelju NINDS-ADRDA i DSM-IV kriterija. Težina kognitivnog oštećenja je procijenjena pomoću Mini Mental State Examination (MMSE). Bolesnice su podijeljene u skupinu od 19 bolesnica u srednjoj (MMSE 10-19) i u skupinu od 31 bolesnice u kasnoj (MMSE 0-9) fazi AB. U procjeni psihotičnih simptoma korištena je Neuropsychiatric Inventory.

Psihotički simptomi su bili prisutni u 13 bolesnica, a bez psihotičkih simptoma bilo je 37 bolesnica. Kontrolna skupina bila je sastavljena od žena starije životne dobi bez kognitivnog oštećenja (MMSE>27) i s normalnim rasponom koncentracije serumskih lipida. Vrijednosti serumskih lipida određene su enzimatskim testovima. U bolesnica s AB opažene su značajno niže vrijednosti serumskih lipida od onih u serumu kontrolne skupine. Bolesnice u kasnoj fazi AB imale su značajno niže vrijednosti svih serumskih lipida od kontrolne skupine, te značajno niže vrijednosti ukupnog kolesterola i LDL-C od oboljelih u srednjoj fazi bolesti. Vrijednosti serumskih lipida nisu bile povezane s psihotičnim simptomima. Opažena je mala, ali značajna pozitivna korelacija između bodova MMSE i vrijednosti kolesterola ili LDL-C, te između MMSE i životne dobi bolesnica. Rezultati istraživanja upućuju da bi vrijednosti serumskih lipida mogle biti povezane s etiologijom i razvojem AB. Pokazana je povezanost između niskih vrijednosti serumskog kolesterola i LDL-C i kognitivnog propadanja u oboljelih od AB. Neophodna su daljnja istraživanja kako bi se ustanovilo da li bi vrijednosti serumskih lipida mogle biti biološki pokazatelj progresije AB.