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Characterization of the Lipid Profile in Dementia and Depression in the Elderly

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ABSTRACT

The purpose of the study was to examine the association of plasma lipid concentrations with changes in cognitive function and depressive states in elderly Greek individuals. The study population consisted of 3 groups: A) 37 subjects with dementia, B) 33 subjects with depression, and C) 33 controls. All individuals were screened with the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), and an evaluation of their psychiatric state. Lipid profile was assessed in all subjects, and the results were statistically evaluated at $P < .05$ level of significance. Groups A and B had significantly lower levels of total plasma cholesterol and HDL cholesterol than group C ($P < .01$). Triglyceride levels did not differ significantly between groups A and C, although they were significantly higher in group B. The results of this study suggest that an association does exist between the plasma concentration of cholesterol and HDL-C and depression and/or cognitive impairment. Further studies are required to explore the significance of these observations and establish if lipid levels could serve as markers for diagnostic and therapeutic purposes. (*J Geriatr Psychiatry Neurol* 2007;20:138-144)

Keywords: dementia; depression; elderly; lipids

Two of the most common mental disorders in the elderly are dementia and depression, both of which contribute substantially to the decline in the quality of life for senior citizens. The prevalence of dementia rises exponentially with age. Studies in developed countries have established a dementia prevalence of between 1% and 5% at 65 years of age, whereas by 75 years of age, it reaches approximately 6.5%.[1,2] Between 80 and 84 years of age, its prevalence is estimated as 10.5%,[3] and over 85 years, it exceeds 20%.[4] Estimates of late-life depression prevalence vary according to the diagnostic criteria used and the characteristics of the population. Community studies have shown that 25% of the elderly report depressive symptoms, and 1% to 9% meet the criteria of having major depression.[5]

In recent decades, efforts have been made to discover biological markers for dementia and depression. Such markers may play a key role in the early diagnosis and management of these disorders. Early diagnosis is of importance for depressive disorders because they are amenable to treatment and in many cases reversible. Moreover, nowadays medications that may delay the course of dementia are available.[6] Thus, there is an important clinical need for diagnostic biomarkers to identify incipient dementia and geriatric individuals prone to depression.

Plasma lipid concentrations are measured routinely in everyday practice with cheap, accurate, and slightly invasive methods. These measurements may, therefore, constitute a tempting potential marker for many diseases. However, with respect to dementia and depression,

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the results are inconsistent, although a number of studies have implicated lipids in the pathogenesis of these disorders. Cross-sectional studies have described an association between atherosclerosis, for which hypercholesterolemia is an important risk factor, and Alzheimer's disease (AD),[7] whereas longitudinal studies suggest a relationship between elevated midlife cholesterol levels and late-life cognitive impairment or AD.[8,9] However, the Framingham Study has shown that baseline and long-term average serum total cholesterol levels were not associated with the risk for incident AD.[10] Furthermore, some investigators have found no differences in plasma HDL-C levels between AD and controls.[11,12]

Morgan et al reported that depressive symptomatology was 3 times more common in elderly persons with lowered cholesterol levels,[13] a finding recently confirmed by Aijanseppa et al,[14] though other reports have claimed no connection between cholesterol levels and depression after adjusting for confounding factors.[15,16]

The discrepancy in the results of a significant number of recent studies indicates that further investigation of lipid parameters is required, particularly in view of their increased biological importance and the ease of evaluation in everyday practice.

The aim of this study was to investigate possible associations between lipid profile and dementia and/or depression in an elderly, community-dwelling population.

MATERIALS AND METHODS

Subjects

The study population consisted of older Greek community-dwelling adults. The participants were recruited over a period of 15 months beginning in October 2003. The main source of individuals was local municipal centers, where the elderly gather to meet and socialize. In addition, recruitment took place by door-to-door canvassing and in the respective health centers. The study was conducted in accordance with the Declaration of Helsinki, and all procedures were carried out with the adequate understanding and written consent of the subjects, or of close relatives when necessary.

Eligible subjects included individuals over 55 years of age with no history of any relevant psychiatric disease and no systematic use of psychotropic drugs or substance abuse. Initially, all subjects were screened with 2 scales, the Mini-Mental State Examination (MMSE) and the Geriatric Depression Scale (GDS). Elderly individuals who scored abnormally on either of these scales underwent further psychiatric evaluation with a nonstructured interview for dementia and depression. The diagnosis of dementia was made according to the criteria of *Diagnostic and Statistical Manual IV (DSM-IV)*. A similar procedure was followed for depression. Thus, 2 groups of individuals were formed, one with dementia and the other with depression.

In total, 683 individuals agreed to participate in the study, of whom 45 had abnormal MMSE scores and 39 had abnormal GDS scores. After the interview and the application of the DSM-IV criteria, 41 subjects were eligible for the dementia group and 36 for the depression group. Finally, because of dropouts, the dementia group contained 37 subjects who completed the study, and the depression group included 33 subjects. In parallel, a group of 33 controls was randomly selected from the same population. The participants of the latter group scored normally on both rating scales but failed to meet the diagnostic criteria for dementia or depression, though they fulfilled the rest of the inclusion criteria.

Mental Scales

The MMSE is a valid, reliable, widely used screening instrument for dementia and cognitive impairment in older adults. It has 11 items and tests 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language.[17] It can be scored immediately, with a maximum of 30 (no impairment). The GDS is a 30-item scale used to evaluate depression in the elderly.[18] It has been reported to be a useful screen for depression in elderly populations, because such cases are frequently missed by practitioners.[19,20]

Blood Sampling

Overnight fasting blood was collected from each participant by standard venipuncture. Blood samples were centrifuged at 1500 rpm, and plasma and serum were isolated and stored at –80°C until analysis.

Assays

Determination of cholesterol, HDL, and TG levels

Total cholesterol was measured by an enzymatic colorimetric method using cholesterol oxidase and peroxidase (Cholesterol LR, CHOD-PAP, Linear Chemicals, Barcelona, Spain). A direct method (HDL-Cholesterol, DIRECT, Linear Chemicals, Barcelona, Spain) was used to enzymatically assess HDL cholesterol. Triglycerides were measured using an enzymatic colorimetric method based on hydrolysis of plasma triglycerides to glycerol and free fatty acids by lipoprotein lipase (Triglycerides MR, Linear Chemicals, Barcelona, Spain). All measurements were performed on the ChemWell analyzer (Awareness Technology, Palm City, Fla).

Statistical Analysis

Demographic, clinical, and laboratory data were collected and statistically analyzed with the use of the

Table 1. Main Sociodemographic and Medical Characteristics of Demented and Nondemented Subjects (N = 70)

		Demented Subjects		*Nondemented Subjects (Controls)*		
	N		*%*		*%*	P *Value*[a]
Age (y) (mean ± SD)		69.72 ± 9.50		65.39 ± 9.06		>.05[b]
Weight (kg) (mean ± SD)		67.3 ± 9.4		66.5 ± 7.9		>.05[b]
Gender (n)						>.05
Male	28	15	53.5	13	46.5	
Female	42	22	52.3	20	47.7	
Marital status (n)						>.05
Married	44	20	45.4	24	54.6	
Widowed/divorced/single	26	17	65.3	9	34.7	
Education (n)						.003
Illiterate	10	8	80	2	20	
Literate: primary school	46	27	58.6	19	41.4	
Secondary: high school	14	2	14.2	12	85.8	
Chronic disease (n)						>.05
Diabetes	12	6	50	6	50	
Hypertension	26	13	50	13	50	
Hypercholesterolemia	7	3	42.8	4	57.2	
Stroke	8	5	62.5	3	37.5	

a. Pearson chi-square (except for age and weight).
b. Mann-Whitney.

SPSS program for Windows. A Pearson chi-square test was used to compare categorical variables. For quantitative values, the data were expressed as mean ± standard deviation (SD). Normality of all data was determined using the Kolmogorov-Smirnov test. Owing to the lack of normality of distribution of the values, nonparametric tests (Kruskal-Wallis and Mann-Whitney U test) were used. Additionally, Spearman correlations were used as measures of association for the continuous variables. Statistical significance was set at $P < .05$.

RESULTS

Of the 103 subjects, 60.19% (62) were women and 39.81% (41) were men. The mean (± SD) age of the participants was 66.57 ± 8.25 years. During statistical analysis, the dementia group as a whole was assessed without taking into consideration the different kinds of dementia. The depression group included individuals diagnosed with major depression, dysthymia, or depression not otherwise specified. The mean age in years (± SD) of the dementia, depression, and control groups was 69.72 ± 9.50, 65.81 ±6.36, and 65.39 ±9.06 respectively. There was no statistically significant difference in the ages of individuals in the 3 groups ($P > .05$). Female gender was dominant in all groups, with a percentage of 59.46%, 60.61%, and 60.61%, respectively. Most of the subjects were married and had a minimum educational level (literate and primary school).

All sociodemographic data for the individuals of the dementia and depression groups were compared with the data from the control group by the use of a Pearson chi-square test at the $P < .05$ level of statistical significance (Tables 1 and 2). No statistical significance was found for the sociodemographic data between the dementia, depression, and control groups, with the exception of educational level (lower in dementia). Prevalent diseases such as stroke, hypertension, and diabetes, which may be confounding factors, as they affect the values of the laboratory parameters of the study, did not differ significantly between demented individuals and controls or between depressed subjects and controls ($P > .05$).

The possible influence of such diseases on the values of the study parameters was tested in each group separately by the use of a Mann-Whitney U test. The test showed that in all 3 groups there were no significant associations between diabetes, stroke, hypertension, and the biochemical parameter values of the study ($P > .05$).

The mean (± SD) values of body weight were 67.3 ± 9.4 kg in the dementia group, 64.7±8.2 kg in the depression group, and 66.5±7.9 kg in healthy controls. There were no significant differences in mean body weight of the 3 groups of the study, as shown after statistical analyses with the Mann-Whitney and Kruskal-Wallis tests ($P > .05$). This finding might be attributed to the similar lifestyle and diet pattern of the elderly of the agricultural community that we studied.

Table 3 shows the scores of the scales from the participants of each group. Taking into consideration the lack of follow-up, the inclusion of only depressed subjects (and not demented with depressive symptomatology) in the second group was ensured by excluding all individuals with an MMSE score ≤ 25. Similarly, we avoided including persons with depressive pseudodementia in the group of demented subjects by eliciting a detailed history of the disorder and thorough clinical examination (psychiatric

Table 2. Main Sociodemographic and Medical Characteristics of Depressed and Nondepressed Subjects (N = 66)

		Depression		*Controls*		
	N		*%*		*%*	P *Value*[a]
Age (y) (mean ± SD)		65.81 ± 6.36		65.39 ± 9.06		>.05[b]
Weight (kg) (mean ± SD)		64.7 ± 8.2		66.5 ± 7.9		>.05[b]
Gender (n)						>.05
Male	26	13	50	13	50	
Female	40	20	50	20	50	
Marital status (n)						>.05
Married	46	22	47.8	24	52.2	
Widowed/divorced/single (n)	20	11	55	9	45	
Education (n)						>.05
Illiterate	3	1	33.3	2	66.7	
Literate: primary school	45	26	57.7	19	42.3	
Secondary: high school	18	6	33.3	12	66.7	
Chronic disease (n)						>.05
Diabetes	10	4	40	6	60	
Hypertension	27	14	51.8	13	48.2	
Hypercholesterolemia	8	4	50	4	50	
Stroke	5	2	40	3	60	

a. Pearson chi-square (except for age and weight).
b. Mann-Whitney.

Table 3. Scores for the Rating Scales of Each Group (± SD)

	Dementia (n = 37)	*Depression (n = 33)*	*Controls (n = 33)*
MMSE (mean ± SD)	15.00 ± 9.24	28.52 ± 1.43	29.03 ± 1.13
GDS (mean ± SD)	12.00 ± 5.08	13.82 ± 3.39	4.91 ± 1.82

Note: MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

evaluation), without excluding individuals with a GDS score of at least 10.

Total cholesterol was lower in the dementia and depression group than in the control group. The mean cholesterol value (Table 4) was 135.95 ± 5.16 mg/dL for demented individuals, 137.45 ± 5.29 mg/dL for depressed subjects, and 193.0 ± 25.47 mg/dL for normal controls ($P < .01$ for demented and depressed groups versus normal controls, respectively). However, the mean cholesterol level was below the cutoff point of 200 mg/dL in all 3 groups.

Similarly, HDL-C was significantly lower in demented and depressed individuals compared to normal subjects. The mean (± SD) value for HDL-C was 36.17 ± 4.43 mg/dL in the dementia group, 38.08 ± 3.66 mg/dL in the group with depression, and 50.05 ± 7.28 mg/dL in healthy controls. The difference was statistically significant for both dementia and depression groups versus the control group ($P < .01$). The mean value of HDL-C was significantly lower in the dementia group compared to the depression group ($P = .044$).

There was no relationship between plasma triglyceride levels and dementia ($P > .05$), however, the mean triglyceride values were significantly higher in depressed individuals compared to controls ($P = .002$) and demented individuals ($P < .01$).

Total cholesterol (TC) and HDL-C concentrations presented a positive linear correlation with the score on the MMSE rating scale (Spearman's rho = 0.375 and 0.452, respectively, $P < .05$), which means that total cholesterol and HDL-C levels were negatively correlated with the severity of cognitive impairment. Moreover, total cholesterol and HDL-C were negatively correlated with depressive symptomatology, as expressed by the negative linear correlation between TC and HDL serum levels and the performance in GDS (Spearman's rho = –0.348 and –0.372, respectively, $P < .05$). The Spearman test failed to show any correlations between plasma triglyceride concentrations and the scores in the rating scales.

DISCUSSION

It is not uncommon for depression and cognitive disorders to be underdiagnosed or misdiagnosed, which may lead to inadequate or inappropriate treatment and subsequently, to either rapid deterioration or prolonged duration of the disease.[21] Unfortunately, at the present time, there are no recognized laboratory parameters that may facilitate diagnostic purposes in everyday practice in the community, although a large amount of work is currently in progress with promising results.

Numerous factors have been studied reflecting the need and value of biological markers for these disorders. In this present study, possible implications and associations of the plasma lipid profile with depression and/or dementia in a geriatric population were investigated. Of all sociodemographic data, only the level of education differed between demented individuals and controls. Educational level has been proposed to correlate

Table 4. Laboratory Findings of the Subjects of All Groups (N = 103)

	Dementia (mean ± SD)	*Depression (mean ± SD)*	*Control (mean ± SD)*	P *Value*[a] *(Dementia vs Control)*	P *Value*[a] *(Depression vs Control)*	P *Value*[a] *(Dementia vs Depression)*
Triglycerides (mg/dL)	72.78 ± 31.05	107.76 ± 39.90	76.79 ± 34.51	.986	<.01	<.01
Cholesterol (mg/dL)	135.95 ± 5.16	137.45 ± 5.29	193.00 ± 25.47	<.01	<.01	.212
HDL-C (mg/dL)	36.17 ± 4.43	38.08 ± 3.66	50.0545 ± 7.28	<.01	<.01	<.05

a. Kruskal-Wallis.

inversely with the risk of dementia,[22] although for some this finding may be attributed to compensatory strategies of educated individuals that delay the detection of the disease.[23] However, in this study a significant positive relationship between a low level of education and dementia was detected. It should be mentioned, though, that the small size of the sample may not have allowed further differences of sociodemographic characteristics of the study groups to reach statistical significance.

Total plasma cholesterol concentration differed significantly between the dementia and control groups. Taking into consideration the number of studies that have suggested hypercholesterolemia as a risk factor for dementia, the finding of an association between lower blood cholesterol and cognitive impairment is interesting.[7,8,24,25] However, other reports have failed to agree with this hypothesis and have suggested that there is no relationship between plasma cholesterol and cognitive decline,[10] at least regarding AD. Furthermore, some studies support a positive association between total cholesterol and cognitive impairment.[26,27] In this present study, it should be noted that although there was a significant difference in the total cholesterol levels of the 2 groups, the mean value of both groups was in the normal range (below 200 mg/dL).

Inconsistency in the findings of this study may be explained by the differences in plasma levels of HDL-C between the 2 groups. Because total cholesterol levels were normal in both groups, HDL-C may play an important role in cognitive impairment in the elderly. The HDL-C level was significantly lower in demented individuals compared to controls. The mean value of HDL in the dementia group was < 40 mg/dL, which defines a high-risk group. The finding of low levels of HDL-C in demented individuals agrees with several recent studies of vascular dementia,[28,29,30] although contradictory results exist for AD.[11,12] High-density lipoprotein-C may play a role in the removal of excess cholesterol in the brain and preserve cerebral microvessels. However, cholesterol is mainly synthesized in situ in the brain and is not transferred from the plasma.[31] Thus, it is not clear whether there is a direct effect of plasma lipids on vascular events in the brain or whether lipids in the peripheral blood reflect further biochemical brain processes.

Triglycerides (TG) did not significantly differ between the 2 groups. At present, there are insufficient data for TG alone, although some studies have shown no relationship between memory and TG levels.[26] The findings in this study support this observation.

Total plasma cholesterol differed significantly between the depression group and the control group. The finding of a positive association between low levels of cholesterol and depressive symptomatology is in agreement with a number of studies.[13,14,32-34] However, others have failed to replicate these findings and strongly disagree with the hypothesis of a key role of low cholesterol in late-life depression.[15,16,35] In this study, lipids differed significantly between the depression and control groups. This finding was independent of chronic diseases such as diabetes, stroke, and hypertension.

It is of interest that total cholesterol and HDL levels differed significantly in the dementia and depression groups as compared with controls. The pattern is rather similar for the 2 disorders, and it is tempting to speculate on a common substrate or underlying pathophysiological mechanism.

Lipids are implicated in vascular function and pathology. This statement is in agreement with the interesting concept of "vascular depression" in the elderly[36,37] and with the hypothesis of a link between vascular pathology and neurodegenerative disorders such as dementia of Alzheimer's type.[38] Different forms of dementia share common neuropathologies, and the nosological boundaries are now reconsidered.[39] In elderly individuals with vascular risk factors, it has been suggested that AD may arise as a secondary event related to atherosclerosis. This hypothesis is supported by postmortem findings of atherosclerotic burden in various vascular territories of brains from individuals with AD.[38]

There have been studies supporting that elevated plasma cholesterol levels correlate with AD presence and that treatment with lipid-lowering drugs reduces the incidence of dementia of the Alzheimer's type.[40,41] Moreover, animals fed a cholesterol-rich diet have a tendency to accumulate amyloid β (Aß) in the brain, and in cell cultures increased levels of cholesterol promote the formation of Aβ from amyloid precursor protein

(APP).[38,42] However, other studies have disputed these findings, arguing that lowering brain cholesterol can lead to AD. In vivo studies have shown that statins may increase amyloid production and senile plaque deposition in rodents.[43] Genetic disorders characterized by cholesterol lowering have been found to cause significant neurodegeneration and early death.[44] Greeve et al, and lately Ledesma et al, suggested that the gene seladin-1 is homologous to the one responsible for the conversion of 7-dehydrocholesterol into cholesterol, and it is down-regulated in patients with AD, especially at areas with higher amyloid deposition.[45,46] Loss of neuronal membrane cholesterol may contribute to excessive amyloidogenesis in AD, which is prominent in the hippocampus of patients with AD.[47,48] The latter findings are in agreement with the present study data and may explain the association of the lower total cholesterol levels with cognitive impairment in this population sample.

The results presented here may imply the presence of a more integral pathophysiological mechanism for both dementia and depression in late life, which can lead to a more convenient and simple approach to the disorders of the geriatric population, further defining an area of attention and prevention for the elderly. Future investigation in this field is important, as it is a cornerstone of human pathology. Genetic studies, neuroimaging techniques, and research for biological markers in general will help clarify the pathophysiology of dementia and depression in late life and promote more effective therapeutic strategies.

LIMITATIONS

The present study is a cross-sectional analysis involving only one clinical and laboratory evaluation of the lipid profile of the individuals without any further follow-up. The changes in cholesterol levels over time could not be taken into consideration, and therefore, it is not possible to discriminate whether the differences in lipid levels preceded the onset of the diseases or whether they developed during the course of the diseases.

Another limitation of the study is the lack of data for the APOE 4 genotype of the population sample, which is a rather confirmed risk factor for AD.[49]

Finally, it should be mentioned that our results were not adjusted for the lower educational status in persons with dementia.

However, the findings of this study support a potential usefulness of lipid profile measurement in dementia and depression in the elderly, and they are mostly indicative of the necessity of future studies without establishing lipids as definite markers of these disorders.

CONCLUSION

Low plasma levels of total cholesterol and HDL-C are associated with cognitive impairment and depressive symptomatology in elderly individuals. This study does not establish the above biochemical factors as markers; however, it does enhance their value for preventive, diagnostic, and therapeutic purposes and enforce the necessity for further investigation, possibly within the framework of a common underlying pathophysiology for dementia and depression in the elderly.

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