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Traditional and Non-traditional Lipid Profiles in Bosnian Patients with Probable Alzheimer's Disease and Vascular Dementia

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ABSTRACT

Background: Conflicting data exist on traditional lipid profiles in patients with Alzheimer's disease (AD) and vascular dementia (VD), whereas scarce number of studies evaluated non-traditional lipid profiles in patients with AD and VD. Studies have shown that ethnic background may affect lipid profile. **Objective**: The aim of the present study was to conduct comparative assessment of traditional and non-traditional lipid profiles in Bosnian patients with AD and VD. **Methods:** A controlled, cross-sectional study was performed with 66 patients with AD, 50 patients with VD, and 60 control subjects. The Montreal Cognitive Assessment (MoCA) test was used for an evaluation of the global cognitive function. The Hachinski ischemic score was used to distinguish patients with VD from those with AD. Plasma total cholesterol (TC), high-density lipoprotein -cholesterol (HDL-C), and triglycerides (TG) levels were determined using standard enzymatic colorimetric techniques, whereas the Friedewald formula was used to calculate low-density lipoprotein-cholesterol (LDL-C) levels. The non-traditional lipid indices such as TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C ratio were separately calculated. The differences between the groups were analyzed with ANOVA followed by the Tuckey posthoc test or with the Kruskal Wallis test followed by the Mann-Whitney test. **Results:** Results of the present study have shown that patients in AD group had significantly lower level of TC, TG, LDL-C, VLDL-C, Non-HDL-C and significantly lower atherogenic index compared to the control group (CG) and compared to the VD patients. Significant difference in values of TG and VLDL-C was observed between VD and the CG, whereas no significant difference in values of TC, LDL-C, atherogenic index and Non-HDL-C was observed between these two groups. Our results have also shown that TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C ratios were significantly lower in AD patients compared to the VD and CG. Moreover, TG/HDL-C ratio was significantly lower in VD compared to the CG. However, a significant difference in TC/HDL-C and LDL-C/HDL-C was not observed between VD and the CG. **Conclusion:** Based on the results of the present study it can be deduced that there is a difference in traditional and non-traditional lipid profiles between AD and VD patients of Bosnian descent. Obtained results suggest that lipids are decreased in AD and in VD to a certain extent. However, since there is an inconsistence in literature whether there is an association between cholesterol and cognition, large prospective studies are required to elucidate this controversy.

Keywords: Alzheimer's disease, vascular dementia, traditional lipid profiles, TG/HDL-C ratio, TC/HDL-C ratio, LDL-C/HDL-C ratio.

1. BACKGROUND

Aging is associated with systemic, multiple dysfunctions of the human body and is accompanied by disturbed lipid metabolism that, among other factors, contribute to dementia (1). Dementia represents thinking impairment and memory decline in at least two domains of cognition. Alzheimer's disease (AD) is the most common cause of dementia. Unfortunately, there is no treatment strategy currently available that could prevent or slow the rate of AD progression (2). Vascular dementia (VD) or according to some authors vascular cognitive impairment is the second most common form of dementia, accounting for around 15% of all dementia cases. Cognitive changes in VD are variable as well as other functions such as memory, praxis and language. In addition, noncognitive features are present in both AD and VD and can be very stressful for the patient and caregivers (3).

Dyslipidemia is a risk factor for dementia. Studies have shown that dyslipidemia may have neurotoxic and vascular effects, and is involved in the pathogenesis of AD and VD (4). Appropriate treatment of dyslipidemia can reduce the burden of neurodegenerative and vascular diseases. Results from the recent meta-meta-analysis have demonstrated a significant impact of low-density lipoprotein-cholesterol (LDL-C) on the AD development. The authors also reported no statistically significant difference between serum total cholesterol (TC), triglycerides (TG), and high-density lipoprotein -cholesterol (HDL-C) levels in patients with AD compared with healthy controls (5). Results of another meta-analysis have shown that high midlife TC may be associated with the onset of AD, and may increase risk of late-life AD. Results of the same meta-analysis have demonstrated that high late-life TC was not associated with any form of cognitive decline. Association between late-life TG and HDL-C with increased risk of VD was not established, and HDL-C did not correlate with any form of dementia (6). An earlier study has reported no difference in lipid profile between late-onset AD and VD patients, while low HDL-C values were associated with VD, but not with AD (7). Conversely, results from the large population-based study of elderly subjects have shown that higher TC and LDL-C concentrations were associated with an increased risk of AD, while HDL-C and TG levels were not associated with incident dementia or its subtypes (8).

The role of the cardiovascular risks factors in the pathogenesis of dementias is largely acknowledged. Non-traditional lipid indices such as TG/HDL-C ratio, TC/HDL-C ratio, and LDL-C/HDL-C ratio are regarded as risk factors for cardiovascular disease (CVD) (9). Scarce data exist on the levels of these lipid ratios in older individuals, especially in patients with AD and VD. Although incidence and prevalence of AD and related dementias are different across various ethnicities, there are still significant gaps in the scientific literature concerning the impact of ethnic and racial factors on the development of different forms of cognitive decline (10).

2. OBJECTIVE

The aim of the present study was to conduct comparative assessment of traditional and non-traditional lipid profiles in Bosnian patients with AD and VD.

3. PATIENTS AND METHODS

Participants

A controlled, cross-sectional study was performed with 66 patients with AD, 50 patients with VD, and 60 control subjects that were community-dwelling, apparently healthy, asymptomatic individuals. All participants of the study were aged 65 and over. The patients were recruited from a specialized unit at the Health-Care Hospice for people with disabilities in Sarajevo, Bosnia and Herzegovina. A senior staff neurologist and psychiatrist made the clinical diagnosis based on the NINCDS-ADRDA criteria for AD (11) and the NINDS-AIREN criteria for VD (12). All procedures on human subjects were performed in accordance with the Helsinki Declaration of 2013. The local Ethics Committee approved the study protocol. After a thorough explanation of the study procedure, subjects and caregivers provided informed consent. The confidentiality of the patients was ensured and is being maintained. Prior to sample collection, all subjects provided a medical history (including socio-epidemiologic data such as smoking habits and alcohol consumption), and laboratory and clinical examinations were performed.

Research methods

Each subject's body mass index (BMI: kg/m^2) was calculated using direct weight and height measurements. A mercury sphygmomanometer was used to measure blood pressure by trained professionals. The study excluded patients with a history of chronic inflammatory disease (asthma and rheumatoid arthritis), hepatic or renal insufficiency, or cancer.

The Montreal Cognitive Assessment (MoCA) test was used for an evaluation of the global cognitive function. MoCA test is designed as a quick screening instrument for cognitive dysfunction. This test evaluates different cognitive domains such as: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. The application of MoCA test can be done by anyone who understands and follows the instructions, but only a health professional with expertise in the cognitive field can interpret the results. The time for the MoCA test is 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal (13). All subjects in the AD and VD groups had a score ≤20, while the control group (CG) subjects had a score between 27 and 30.

The Hachinski ischemic score (HIS) is a test that distinguishes patients with VD from those with AD. The HIS evaluates the presence of thirteen clinical characteristics and assigns a total score of 18. A score of 7 or higher indicates VD, while a score of 4 or lower indicates AD, and a score between 4 and 7 implies a mixed form of dementia (14).

Blood samples for the analysis were drawn from the antecubital vein of patients and control subjects who were fasting, and placed in siliconized tubes (BD Vacutainer Systems, PL6 7BP, Plymouth, UK). Plasma TC, HDL-C, and TG levels were determined at the initial assessment using standard enzymatic colorimetric techniques, on automated apparatus (Dimension RxL Max, Dade Behring, Germany) at the Institute for Chemistry and Biochemistry University of Sarajevo Clinics Center. The Friedewald formula was used to calculate LDL-C levels (15). The formula for calculating very-low-density lipoprotein cholesterol (VLDL-C) levels was VLDL-C = TG/2.2 (16). The atherogenic index was calculated as a logarithmically transformed ratio of molar concentrations of TG to HDL-cholesterol. Non-HDL-C was calculated by subtracting HDL-C from TC, and the TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C ratio were separately calculated (17).

Statistical analysis

Variables	AD group (N=66)	VD group (N=50)	Control group (N=60)	p value
Gender (F/M)	59 (89.4%)/ 7 (10.6%)	48 (96.0%)/ 2 (4.0%)	48 (80.0%)/ 12 (20.0%)	0.033
Age	81.3±5.5	78.5±6.6	78.9±5.8	0.07
MoCA score	9.7±5.0	11.7±5.2	28.6±1.0	<0.001**,¶
Total cholesterol (mmol/L)	5.1±1.0	5.7±1.1*	6.1±1.3**	<0.001
Triglycerides (mmol/L)	1.3 (0.9-1.8)	1.6 (1.2-2.0)*	2.0 (1.5-3.1) **,¶	<0.001
HDL-cholesterol (mmol/L)	1.24 (1.1-1.4)	1.2 (0.9-1.5)	1.16 (1.0-1.5)	0.68
LDL-cholesterol (mmol/L)	3.0 (2.6-3.9)	3.7 (3.2-4.2)*	3.9 (3.2-4.6)**	<0.001
VLDL-cholesterol (mmol/L)	0.6 (0.4-0.8)	0.7 (0.6-0.9) *	0.85 (0.6-1.2) **,¶	<0.001
Non-HDL-cholesterol	3.9±0.9	4.5±0.9*	4.9±1.1**	<0.001
Atherogenic index	2.6±0.8	3.2±1.1*	3.2±0.8**	0.02

Table 1. Baseline characteristics and lipid levels in Alzheimer- and vascular-dementia patients and in the control group of subjects. *-Significant difference between AD and VD group (p<0.05); ** -Significant difference between Control and AD group (p<0.05); ¶-Significant difference between Control and VD group (p<0.05); AD group – patients with Alzheimer disease; VD group – patients with vascular dementia

All statistical calculations were performed with the SPSS 19 software (version 19.0, SPSS Inc, Chicago, Illinois, USA). Each value was expressed as the mean ±SD, median and interquartile range or absolute number and corresponding percentages. The distribution of variables was tested by the Kolmogorov-Smirnov test. The differences between the groups were analysed with ANOVA followed by the Tuckey posthoc test for the variables with normal distribution or with the Kruskal Wallis test followed by the Mann-Whitney test for the variables with the skewed distribution. *P* values less than 0.05 were considered statistically significant.

4. RESULTS

A significant difference in gender was observed between the study groups (p<0.033). The mean age between AD, VD, and control group was not different (p=0.07). A significant difference in the MoCA score between control and AD and VD group was observed (p<0.001). However, the MoCA score was similar between AD and VD groups (p=0.14). Patients in AD group had significantly lower levels of TC, TG, LDL-C, VLDL-C, Non-HDL-C (p<0.001) and significantly lower atherogenic index (p=0.04) compared to the control group of subjects (Table 1). There were also significant differences in lipid levels between AD and VD group, except for HDL-C level, which was not significantly different between AD and VD groups. Patients in AD group had lower levels of TC (p=0.016), TG (p=0.012), LDL-C (p=0.012), VLDL-C (p=0.026), Non-HDL-C (p=0.003), and lower atherogenic index (p=0.04) compared to VD group of patients (Table 1). However, there was no significant difference in TC (p=0.13), LDL-C (p=0.23), atherogenic index (p=0.99) and Non-HDL-C (p=0.09) between VD and control group.

Median TG/HDL-C ratio was significantly lower in AD patients [2.2 (1.5-3.5)] compared to VD group of patients [3.1 (1.8-4.6); p=0.024] and compared to the control group [3.7 (2.4-6.9); p<0.001]. Also, the median TG/HDL-C ratio was significantly lower in VD patients compared to the control subjects (Figure 1).

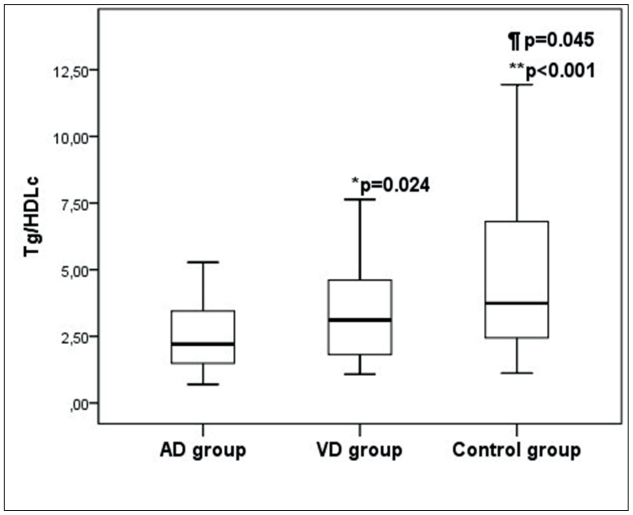

Figure 1. TG/HDL-C ratio in Alzheimer- and vascular-dementia patients and in the control subjects *-difference between AD and VD group; ** -difference between Control and AD group; ¶-difference between Control and VD group; AD group – patients with Alzheimer disease; VD group – patients with vascular dementia

Median TC/HDL-C ratio was significantly lower in AD patients [3.9 (3.4-4.8)] compared to the VD group of patients [4.7 (4.0-5.6); p<0.001] and compared to the control group [5.0 (4.0-5.9); p<0.001]. However, no significant difference in the median TC/HDL-C ratio was observed between VD and the control group (Figure 2).

Median LDL-C/HDL-C ratio was significantly lower in AD patients [2.5 (2.1-3.2)] compared to VD group of patients [3.1 (2.3-3.8); p=0.01] and compared to the control group [3.3 (2.5-3.8); p<0.001]. However, no significant difference in the median LDL-C/HDL-C ratio was observed between VD and the control group (Figure 3).

5. DISCUSSION

Conflicting data exist on traditional lipid profiles in patients with AD and VD. An earlier study reported significantly lower values of serum TC, TG, LDL-C, and VLDL-C in patients with probable AD, whereas no significant difference in values of HDL-C was observed

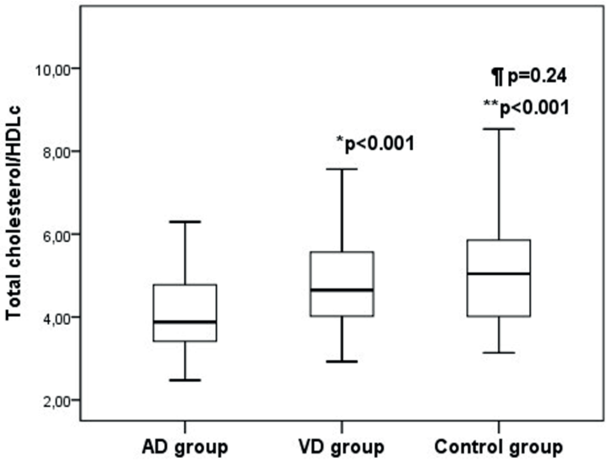

Figure 2. Total cholesterol/HDL-C ratio in Alzheimer- and vascular-dementia patients and in the control subjects. *-difference between AD and VD group; ** -difference between Control and AD group; ¶-difference between Control and VD group; AD group – patients with Alzheimer disease; VD group – patients with vascular dementia

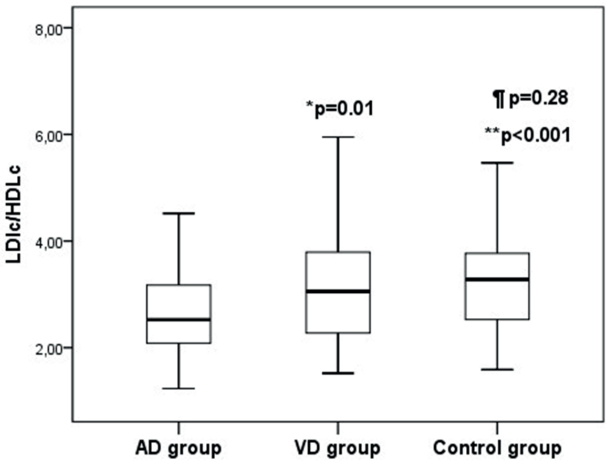

Figure 3. LDL-C/HDL-C ratio in Alzheimer- and vascular-dementia patients and in control subjects *-difference between AD and VD group; ** -difference between Control and AD group; ¶-difference between Control and VD group; AD group – patients with Alzheimer disease; VD group – patients with vascular dementia

compared with apparently healthy control subjects (16). Accordingly, another study demonstrated significantly lower entire lipid profile in the late phase AD compared to controls, and significantly lower TC and LDL-C levels than in patients with the middle stage AD (18). Conversely, it has been shown that in AD group, 18 patients had TC levels within the normal range, whereas 25 patients had elevated levels of TC. In the VD group, 11 patients had TC levels within the normal range, whereas 12 patients had elevated levels of TC. Results of the same study have demonstrated that TC, LDL-C, and HDL-C levels were higher in the group of patients with VD; however, the difference was not statistically significant (19). Results of the present study have shown that patients in AD group had significantly lower level of TC, TG, LDL-C, VLDL-C, Non-HDL-C and significantly lower atherogenic index compared to the control group of subjects and compared to the VD patients. Obtained results are not in accordance with some previous studies in which higher TG, TC, LDL-C, and lower HDL-C were associated with the progression of AD (20). On the other hand, no association between cognitive impairment and dyslipidemia has been reported (21). Furthermore, although earlier studies have shown that hypertriglyceridemia and hypercholesterolemia lead to cognitive impairment *via* t hyperphosphorylation, b-amyloid generation, and inflammation in the brain, studies have shown that higher LDL-C and TC values are related to better memory function in the elderly population (22). Based on guidelines from a previous study, TC values of 4.96 mmol/L and LDL-C values of 2.66 mmol/L are appropriate for preserved cognitive function, whereas lower values of TC and LDL-C lead to cognitive impairment in the old individuals (23).

Non-traditional lipid profile is not extensively investigated in patients with AD and VD. To the best of our knowledge, the present study is the first to report values of non-traditional lipid indices in Bosnian patients with AD and VD. Our results have shown that TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C ratios were significantly lower in AD patients compared to the VD group of patients and compared to the control group. Moreover, TG/HDLc ratio was significantly lower in VD patients compared to the control subjects. However, a significant difference in TC/HDL-C and LDL-C/HDL-C was not observed between VD and the control group. Obtained results are partially in accordance with the study conducted among those aged 80 and older-free of dementia which found that lower TG/HDL-C ratios and higher LDL-C values were associated with better memory performance after controlling for confounders (9). Our results are not in line with the results from an earlier study, in which elevated levels of LDL-C, TG, and TC were found together with normal levels of HDL and TC/HDL-C ratio in patients with AD. According to these authors, cholesterol is not associated with cognition in AD (24). Based on the findings of the present study, we argue that lower levels of both traditional and non-traditional lipid indices may be regarded as specific for AD and to a certain extent for VD in our study sample.

Although there is a controversy concerning the overall importance of dyslipidemia in the pathogenesis of AD and VD, studies have shown that the calculation of LDL-C/HDL-C ratio can be used in the estimation of the coronary heart disease risk (25). Moreover, the use of TG/HDL-C ratio in prediction of cardiovascular events in the general population, and in certain group of patients at high risk has been reported (26). In this line of evidence is also the study conducted among middle-aged Chinese adults, which demonstrated that the TG/HDL-C ratio can be used in the identification of individuals with cardio-metabolic risk, whereas LDL-C/HDL-C ratio, TC/HDL-C ratio, and TG/HDL-C may be considered comparable in their association with atherosclerosis, renal dysfunction and liver steatosis (27). Sim-

ilar results were found in Japanese (28), Canadian (29), and Italian (30) populations.

The non-traditional lipid indices are not only related with the assessment of cardio-metabolic risk and CVD but also with diabetes mellitus in hypertensive patients. Accordingly, results of the recent study have shown that LDL-C/HDL-C ratio was independently correlated with diabetes mellitus in patients with hypertension. In the same study, multiple regression analysis revealed that TC/HDL-C was strongly associated with diabetes in hypertensive population (17). Studies have shown that TC/HDL-C can be used as an independent risk factor for acute myocardial infarction (31) as well as ischemic heart disease in women (32), whereas results of the another study have demonstrated that TC/HDL-C may be used as a significant predictor for nonalcoholic fatty liver disease (33). A large retrospective cohort study conducted among Chinese adults has reported an association between LDL-C/HDL-C and incident diabetes (34). Moreover, prospective cohort study has demonstrated that LDL-C/HDL-C ratio can serve as the potent predictor of all-cause mortality in elderly hypertensive patients (35). The LDL-C/HDL-C ratio has also been reported as an independent risk factor for ischemic stroke in non-valvular atrial fibrillation (36). As for the TG/HDL-C ratio, novel findings suggest that it can be used as a marker of insulin resistance (37). Furthermore, results of the recent study have shown that both TG/HDL–C and LDL-C/HDL-C ratios can be used as significant predictors of CVD risk in men, while only TG/HDL-C ratio can be utilized as a significant predictor for CVD in women (38).

The strength of the present study is that it represents the first study that compared traditional and non-traditional lipid profiles between AD and VD in Bosnian patients, which is of importance since studies have shown that ethnic background may affect lipid profile (39). Contrary to certain reports, we have found lower levels of both traditional and non-traditional lipid indices in AD and to certain extent in VD. It remains to be elucidated in larger prospective studies whether decreased lipid indices have specific and sensitive power in diagnosing AD and VD. Furthermore, it would also be important to assess lipid profiles in elderly subjects with preserved memory to evaluate the possible predictive value of traditional and non-traditional lipid indices in deterioration of cognitive function.

In interpreting the findings of the current study, several limitations should be acknowledged. Firstly, the sample size was relatively small, consisting of AD and VD patients from a single unit at the Health-Care Hospice for people with disabilities, and, therefore, the results cannot be generalized over the whole population. Secondly, the cross-sectional design of the study prevents us from deducing any causal relations between our findings. Thirdly, we only used one test in assessing cognition in order to minimize test-taking stress and interview time. Hence, the use of other tests for measuring cognition could have yield results different from the ones obtained in our study. Finally, in a group of patients with AD, we did not determine the apolipoprotein E (APOE) genotype, which has been known to be a risk factor for this disease. Since possible difference in the association of memory function with lipid profile has been reported between APOE- ε4 allele carriers and non-carriers (22), the results might have interacted with APOE genotype or may be confounded.

6. CONCLUSION

Based on the results of the present study it can be deduced that there is a difference in traditional and non-traditional lipid profiles between AD and VD patients of Bosnian descent. We were limited in comparison of our findings with the findings of other authors since extensive search of literature has yield only scarce number of studies that comparatively evaluated traditional, and especially non-traditional lipid profiles between AD and VD patients. Obtained results suggest that lipids are decreased in AD and in VD to a certain extent. However, since there is an inconsistence in literature whether there is an association between cholesterol and cognition, larger prospective studies are required to elucidate this controversy.

- **Patient Consent Form**: All participants were informed about subject of the study.
- **Author's Contribution**: A.Z., O.L., A.V., and A.D. gave substantial contributions to the conception and design of the work. A.Z., A.D., O.L., and S.S. gave substantial contribution to acquisition of data. A.V. gave substantial contribution to analysis and data interpretation. A.Z., A.V., O.L., and A.F. had a part for drafting the article. A.V., I.H., and R.J. gave substantial contribution in critically revising and approval final version to be published.
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