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ORIGINAL PAPER

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Difference in the Standard and Novel Lipid Profile Parameters Between Patients With Alzheimer's Disease and Vascular Dementia Stratified by the Degree of Cognitive Impairment

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ABSTRACT

Background: Lipids and lipoproteins are significantly involved in maintaining structural and functional components of the human brain and neurons, but their role in the development of Alzheimer's disease (AD) and vascular dementia (VD) remains unclear. **Objective:** The aim of the present study was to explore the differences in the standard and novel lipid profile parameters in patients with AD and VD, stratified by the degree of cognitive impairment (CI). **Methods:** Present study included 66 patients with AD, 50 patients with VD, and 60 control subjects. For an evaluation of the global cognitive function the Montreal Cognitive Assessment (MoCA) test was used. In order to distinguish patients with VD from those with AD the Hachinski ischemic score was used. 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 the Kruskal Wallis test followed by the Mann-Whitney test or with ANOVA followed by the Tuckey posthoc test. **Results:** Results of the conducted study have found that the patients in AD group with moderate CI and patients in AD group with severe CI exhibited significantly lower levels of serum TC, TG, LDL-C, VLDL-C, Non-HDL-C, atherogenic index, TG/HDL-C, TC/HDL-C

and LDL-C/HDL-C compared to cognitively normal control subjects. Moreover, patients in VD group with severe and moderate CI had significantly lower level of TG compared to control group of subjects. Our results have also shown that patients in AD group with moderate CI had significantly lower level of TC, TG, LDL-C, Non-HDL-C, atherogenic index, TG/HDL-C, TC/HDL-C compared to VD patients with moderate CI. In addition, patients in AD group with severe CI had significantly lower level of TC, LDL-C, Non-HDL-C and TC/HDL-C compared to VD patients with severe CI. **Conclusion:** The results of this study have shown dysregulation of lipid metabolism in AD and VD patients with different degree of CI. In both moderate and in severe CI, patients with AD had lower levels of majority of standard and novel lipid parameters compared to patients with VD. Further larger prospective studies are required to elucidate the accuracy of standard and novel lipid parameters in the assessment of different degree of CI in AD and VD.

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

1. BACKGROUND

Cognitive dysfunction is a pathological process that gradually and silently progresses into mild cognitive impairment and different forms of dementia. Increase of aging population has significantly contributed to the prevalence of cognitive impairment (CI) worldwide (1). Im-

paired cognitive functioning seriously affects the disease burden and the quality of life for patients and caregivers as well as. The risk of morbidity and mortality is increased in subjects with CI, which often remains unrecognized until it fully develops into Alzheimer's disease (AD) or other forms of dementia such as vascular dementia (VD). Unfortunately, there is still no etiological treatment for dementia, but early recognition of the CI is of pivotal importance (2).

A recent study reported that global dementia diagnosis had increased by more than fifty percent from 1990 to 2016 (3). The number of dementia cases is expected to rise by 2050 to 131 million. Causes of dementia can be diagnosed by medical history, physical and cognitive examination, brain imaging, and laboratory testing. Treatment of dementia should include both pharmacologic and non-pharmacologic approaches (4). Results of the systematic review and meta-analysis have shown that mild cognitive impairment might be seen as prodromal dementia and it can be classified into amnesic and no amnesic mild cognitive impairment. Moreover, fully developed dementia can be further stratified into mild, moderate, and severe dementia (5).

Numerous risk factors such as diabetes, hypertension, and smoking are involved in the pathogenesis of CI (6). Moreover, lipids are also considered to be important risk factors for cognitive dysfunction, although certain inconsistency in the literature exists regarding whether increased or decreased lipids are associated with better memory performance (7). Results of an earlier study showed significantly lower values of serum total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), and very low-density lipoprotein-cholesterol (VLDL-C) in patients with probable AD, whereas no significant difference in values of high-density lipoprotein-cholesterol (HDL-C) was observed in comparison with apparently healthy control subjects (8). Conversely, another study reported higher lipids levels in subjects with mild cognitive impairment than in individuals with normal cognitive function (7). Similarly, a study conducted in the United States showed that LDL-C levels are linked with small differences in memory (9).

Studies so far have shown that novel lipid indices such as TG/HDL-C ratio, TC/HDL-C ratio, and LDL-C/HDL-C are associated with cardiometabolic risk (10, 11). However, the scarce number of studies assessed these new lipid parameters in older individuals and patients with AD and VD, especially those stratified by the degree of CI.

2. OBJECTIVE

The aim of the present study was to explore the differences in the standard and novel lipid profile parameters in patients with AD and VD, stratified by the degree of CI.

3. PATIENTS AND METHODS

Participants

A cross-sectional study with 66 patients with AD, 50 patients with VD, and 60 control subjects who were community-dwelling, apparently healthy, asymptomatic individuals was conducted. All subjects were aged 65 and over. The patients were residents of a specialized unit at Sarajevo's Health-Care Hospice for people with disabilities.

The clinical diagnosis was made by a senior staff neurologist and psychiatrist using the NINCDS-ADRDA criteria for AD (12) and the NINDS-AIREN criteria for VD (13).

Procedure and ethical considerations

All procedures involving human subjects were carried out in accordance with the 2013 Helsinki Declaration. The study protocol was approved by the local Ethics Committee. Subjects and caregivers provided informed consent after a thorough explanation of the study procedure. The patients' confidentiality was ensured and is being maintained. All subjects provided a medical history (including socio-epidemiologic data such as smoking habits and alcohol consumption) prior to sample collection, and laboratory and clinical examinations were performed. Patients with cancer, hepatic or renal insufficiency, or a history of chronic inflammatory disease (asthma and rheumatoid arthritis) were excluded from the study.

Measures

The Montreal Cognitive Assessment (MoCA) test was used to assess overall cognitive function. The MoCA test is intended to be a quick screening tool for cognitive dysfunction. Attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation are all assessed by MoCA test. Anyone who understands and follows the instructions can use MoCA test, but only a health professional with expertise in the cognitive field can interpret the results. MoCA test has a 10-minute time limit. A total of 30 points is possible; a score of 26 or higher is considered normal (14). All subjects in the AD and VD groups had a MoCA score of ≤ 20 , whereas subjects in the control group (CG) had a MoCA score ranging from 27 to 30. The patients with AD and VD were further classified as those with severe cognitive impairment (MoCA score: < 10) and moderate cognitive impairment (MoCA score: 10-17) (15).

The Hachinski ischemic score (HIS) is a test that distinguishes between patients with VD and those with AD. The HIS assigns a total score of 18 based on the presence of thirteen clinical characteristics. A score of 7 or higher indicates VD, a score of 4 or lower indicates AD, and a score between 4 and 7 indicates mixed dementia (16). Our AD patients had a HIS score of ≤ 4 , while our VD patients had a HIS score of ≥ 7 .

Blood samples were drawn from the antecubital veins of fasting patients and subjects and placed in siliconized tubes for analysis (BD Vacutainer Systems, PL6 7BP, Plymouth, UK.). Plasma TC, HDL-C, and TG levels were measured at the Institute for Chemistry and Biochemistry University of Sarajevo Clinics Center using standard enzymatic colorimetric techniques on automated apparatus (Dimension RxL Max, Dade Behring, Germany). For calculating of LDL-C levels, the Friedewald formula was used (17). The formula for calculating very low density lipoprotein cholesterol (VLDL-C) levels was $VLDL-C = TG/2.2$ (8). 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 (18).

Statistical analysis

All statistical calculations were performed with the SPSS 19 software (version 19.0, SPSS Inc, Chicago, Illinois, USA).

Variables	AD group with moderate CI (N=18)	AD group with severe CI (N=48)	Control group (N=60)	p
Gender (F/M) (N (%))	17 (94.4%)/1 (5.6%)	42 (87.5%)/6 (12.5%)	48 (80.0%)/12 (20.0%)	0.265
Age (years)	80.5±5.3	83.2±5.5	78.9±5.8 [#]	0.016
MoCA score	12 (11.0-15.25)	5.0 (2.0-8.0)*	28.0 (28.0-29.0)* [#]	<0.001
Total cholesterol (mmol/L)	4.7±0.6	5.25±1.0	6.1±1.3* [#]	<0.001
Triglycerides (mmol/L)	1.0 (0.8-1.6)	1.3 (0.9-1.9)	2.0 (1.5-3.1)* [#]	<0.001
HDL-cholesterol (mmol/L)	1.2 (0.9-1.3)	1.2 (1.0-1.3)	1.16 (1.0-1.5)	0.780
LDL-cholesterol (mmol/L)	2.7 (2.5-3.4)	3.4 (2.6-3.9)	3.9 (3.2-4.6)* [#]	<0.001
VLDL-cholesterol (mmol/L)	0.5 (0.3-0.8)	0.6 (0.4-0.8)	0.85 (0.6-1.2)* [#]	<0.001
Non-HDL-cholesterol (mmol/L)	3.3 (3.0-3.9)	4.0 (3.1-4.7)	4.9 (3.9-5.4)* [#]	<0.001
Atherogenic index	2.3 (1.9-2.7)	2.7 (2.2-3.0)	3.2 (2.5-3.6)* [#]	<0.001
TG/HDL-C	1.9 (1.4-2.9)	2.3 (1.6-3.7)	3.7 (2.4-6.9)* [#]	<0.001
TC/HDL-C	4.0±0.8	4.3±1.2	5.2±1.5* [#]	<0.001
LDL-C/HDL-C	2.2 (2.0-2.9)	2.6 (2.0-3.3)	3.3 (2.5-3.8)* [#]	<0.001

Table 1. Baseline characteristics and lipid levels in patients with AD stratified according to the degree of cognitive impairment and in the control subjects. AD – Alzheimer’s disease; CI- cognitive impairment; *p<0.05 - in comparison to the AD group with moderate CI; #p<0.05 in comparison to the AD group with severe CI.

Variables	VD group with moderate CI (N=21)	VD group with severe CI (N=29)	Control group (N=60)	p value
Gender (F/M)	21 (100%) / 0 (0.0%)	27 (93.1%) / 2 (6.9%)	48 (80.0%)/12 (20.0%)	-
Age (years)	75.8±7.8	80.4± 4.7*	78.9±5.8	0.02
MoCA score	13.0 (12.0-15.0)	4.0 (1.0-7.0)*	28.0 (28.0-29.0)* [#]	<0.001
Total cholesterol (mmol/L)	5.5±1.1	5.7±0.9	6.1±1.3	0.14
Triglycerides (mmol/L)	1.6±0.6	1.6±0.6	2.4 1.5* [#]	0.003
HDL-cholesterol (mmol/L)	1.1±0.3	1.2±0.3	1.2±0.3	0.67
LDL-cholesterol (mmol/L)	3.5±1.1	3.7±0.8	4.0±1.0	0.19
VLDL-cholesterol (mmol/L)	0.6 (0.5-1.0)	0.8 (0.6-0.9)	0.85 (0.6-1.2)	0.07
Non-HDL-cholesterol (mmol/L)	4.3±1.0	4.5±0.8	4.8±1.1	0.12
Atherogenic index	3.0 (2.5-3.9)	2.7 (2.3-3.4)	3.2 (2.5-3.6)	0.55
TG/HDL-C	3.0 (1.9-4.2)	3.4 (1.6-4.7)	3.7 (2.4-6.9)	0.13
TC/HDL-C	4.6 (4.0-5.7)	4.6 (3.8-5.2)	4.9 (3.9-5.4)	0.50
LDL-C/HDL-C	2.9 (2.1-3.9)	2.6 (2.1-3.4)	3.3 (2.5-3.8)	0.51

Table 2. Baseline characteristics and lipid levels in patients with VD stratified according to the degree of cognitive impairment and in control subjects. VD – vascular dementia; CI - cognitive impairment; *p<0.05 - in comparison to the VD group with moderate CI; #p<0.05 in comparison to the VD group with severe CI

Each value was expressed as the mean, standard deviation, median, and interquartile range, or as an absolute number and corresponding percentage. The Shapiro-Wilk test was used to assess the distribution of variables. The differences between groups were assessed using ANOVA followed by the Tuckey posthoc test for variables with normal distributions or the Kruskal Wallis test followed by the Mann-Whitney test for variables with skewed distributions. The associations between the measured parameters in all groups were evaluated by Spearman’s rank correlation test. P values less than 0.05 were considered statistically significant.

4. RESULTS

A significant difference in gender was not observed between the AD study groups (p=0.265). Patients in AD

group with severe CI were significantly older compared to the CG (p=0.016), while mean age between AD stratified according to the degree of CI was not significantly different. Patients in AD group with moderate CI and with severe CI had a significantly lower level of TC, TG, LDL-C, VLDL-C, Non-HDL-C, atherogenic index, TG/HDL-C, TC/HDL-C and significantly lower LDL-C/HDL-C compared to control group of subjects (p<0.001). However, the values of HDL-C were higher in AD patients with moderate and severe CI compared to the control subjects but the difference was not statistically significant(p=0.780) (Table 1).

Significant difference in age was observed between the VD study groups (p=0.02). Patients in VD group with severe CI were significantly older compared to the VD group with moderate CI (p=0.02), while the mean age between

Variables	AD group with moderate CI (N=18)	VD group with moderate CI (N=21)	p	AD group with severe CI (N=48)	VD group with severe CI (N=29)	p
Total cholesterol (mmol/L)	4.7±0.6	5.5±1.1	0.012	5.25±1.0	5.7±0.9	0.028
Triglycerides (mmol/L)	1.2±0.5	1.6±0.6	0.042	1.3 (0.9-1.9)	1.8 (1.3-2.0)	0.07
HDL-cholesterol (mmol/L)	1.2±0.2	1.1±0.3	0.55	1.2±0.3	1.2±0.3	0.84
LDL-cholesterol (mmol/L)	2.9±0.5	3.5±1.1	0.03	3.3±0.8	3.7±0.8	0.042
VLDL-cholesterol (mmol/L)	0.5 (0.3-0.8)	0.6 (0.5-1.0)	0.14	0.6±0.2	0.7±0.2	0.06
Non-HDL-cholesterol (mmol/L)	3.5±0.5	4.3±1.0	0.003	3.9±0.9	4.5±0.8	0.012
Atherogenic index	2.3 (1.9-2.7)	3.0 (2.5-3.9)	0.02	2.6±0.8	2.9±0.7	0.49
TG/HDL-C	1.9 (1.4-2.9)	3.0 (1.9-4.2)	0.03	2.7±1.4	3.4±1.9	0.06
TC/HDL-C	3.7 (3.3-4.5)	4.6 (4.0-5.7)	0.002	4.3±1.2	4.9±1.2	0.042
LDL-C/HDL-C	2.2 (2.0-2.9)	2.9 (2.1-3.9)	0.07	2.7±1.0	3.1±1.0	0.08

Table 3. Lipid levels in patients with AD and VD with moderate and severe cognitive impairment. AD-Alzheimer's disease; VD -vascular dementia; CI- cognitive impairment.

Variables	MoCA score			
	AD group with moderate CI (N=18)	AD group with severe CI (N=48)	VD group with moderate CI (N=21)	VD group with severe CI (N=29)
Total cholesterol (mmol/L)	-0.256	-0.057	0.243	-0.119
Triglycerides (mmol/L)	0.148	-0.129	0.164	-0.256
HDL-cholesterol (mmol/L)	-0.259	-0.029	0.359	0.064
LDL-cholesterol (mmol/L)	-0.200	-0.047	0.104	-0.078
VLDL-cholesterol (mmol/L)	0.252	-0.058	0.209	-0.223
Non-HDL-cholesterol (mmol/L)	-0.105	-0.097	0.163	-0.157
Atherogenic index	0.100	0.157	-0.184	-0.002
TG/HDL-C	0.224	-0.087	-0.012	-0.173
TC/HDL-C	0.144	-0.025	-0.056	-0.112
LDL-C/HDL-C	0.062	-0.004	-0.138	0.076

Table 4. Correlation between lipid parameters and MoCA score in patients with AD and VD stratified according to the degree of cognitive impairment. Data are presented as Spearman's rank correlation coefficient. AD – Alzheimer's disease; VD - vascular dementia; CI- cognitive impairment.

VD stratified according to the degree of CI and CG was not significantly different. Patients in VD group with moderate CI and with severe CI had a significantly lower level of TG compared to the control group of subjects ($p=0.003$). However, there was no significant difference in other lipid parameters between the groups (Table 2).

Patients in AD group with moderate CI had significantly lower level of TC ($p=0.012$), TG ($p=0.042$), LDL-C ($p=0.03$), Non-HDL-C ($p=0.003$), atherogenic index ($p=0.02$), TG/HDL-C ($p=0.03$), TC/HDL-C ($p=0.002$) compared to patients with VD with moderate CI. Other lipids parameters did not differ significantly between the groups. Patients in AD group with severe CI had significantly lower level of TC ($p=0.028$), LDL-C ($p=0.042$), Non-HDL-C ($p=0.012$) and TC/HDL-C ($p=0.042$) compared to patients with VD with severe CI. Other lipids parameters did not differ significantly between the groups (Table 3).

There was no statistically significant correlation between lipid parameters and MoCA score in patients with AD and VD stratified according to the degree of CI (Table 4).

5. DISCUSSION

Undoubtedly, lipids and lipoproteins are significantly involved in maintaining structural and functional components of the human brain and neurons, but their role in the development of AD and VD remains unclear. So far, many studies have been performed to evaluate the role of different classes of lipids such as total cholesterol, triglyceride, HDL, VLDL and LDL-C in CI. As far as we know, data regarding novel lipid profile parameters in AD and VD patients with different degree of CI are missing. Therefore, to the best of our knowledge, the present study for the first time examined the standard and novel lipid profile parameters in older cognitively healthy individuals and patients with AD and VD stratified by the degree of CI.

According to our results, although females were more predominant than males, a significant difference in gender was not observed between patients with AD stratified according to the degree of CI and the control subjects. Moreover, all groups were correctly matched and comparable. The current findings fit well with the results from a previous study which showed that women's rate for AD alone is higher than men's after age 80 and that rates were relatively

similar for both genders before age 80. Hence, the authors concluded that women's survival to longer age might be one of the possible explanations for women's higher incidence of dementia and AD (19).

In our study, only patients in the AD group with severe CI were significantly older than controls, while the mean age between AD patients stratified according to the degree of CI was not significantly different. Obtained results are in accordance with the findings from an earlier study, which included 50 female patients with AD and 58 healthy controls, and showed that patients with AD were significantly older than healthy controls. Authors also reported that there was a significant difference in age between patients with AD subdivided according to the different phases of the disease. Patients in the late phase of AD were significantly older than patients in the middle phase of the disease (20).

In our cohort, VD patients with severe CI were significantly older than patients with moderate CI, while the mean age between VD patients stratified according to the degree of CI and CG was not significantly different. As the previous study has reported, the prevalence of VD increases with age from 0.3% (65 - 69 years) to 5.2% (90+ years) (21). Considering that the age is the main risk factor for dementia, and that the pathological processes leading to dementia start many years before clinical diagnosis, it is easy to conclude that older age is associated with more severe degree of the disease.

Group comparison of our data has revealed that the patients in AD group with moderate CI and patients in AD group with severe CI exhibited significantly lower levels of serum TC, TG, LDL-C, VLDL-C, Non-HDL-C, atherogenic index, TG/HDL-C, TC/HDL-C and LDL-C/HDL-C compared to cognitively normal control subjects. Even though the serum HDL-C values were higher in both groups of patients with AD compared with matched controls, the difference was not statistically significant. Our results are in the good agreement with the findings from an earlier study who compared the serum lipid levels in 50 female AD patients subdivided according to the severity of disease or the presence of psychotic features and 58 healthy subjects. According to these authors, all female patients with AD had significantly lower serum cholesterol, TG, LDL-C and HDL-C levels than healthy subjects. These authors also reported that patients in the late phase of AD disease had significantly lower serum cholesterol, HDL-C, LDL-C and TG levels than healthy controls and significantly lower cholesterol and LDL-C levels than patients in the middle phase of disease (20).

Some previous studies have emphasized that HDL-C plays a major role in cognitive function. A decrease in levels of HDL-C increases the risk of mild cognitive impairment (MCI) and dementia (22, 23). According to a previous study, higher levels of HDL-C were associated with a decreased risk of both probable and possible AD (24). In contrast, results of a recent meta-analysis (25) have shown that HDL-C levels were not found to be strongly correlated with the risk of MCI, AD, and other forms of dementia. Our results of increased serum HDL-C levels in patients with AD compared to healthy controls are in contrast with previously published data where significantly lower levels

of HDL-C in all patients with AD than in healthy subjects were reported. Moreover, significantly lower HDL-C levels in patients in the late stage of disease than healthy controls were found (20). These dissimilar results may be due to the characteristics of the study population, differences in the normal expected range of HDL assessment, different methods for the determination of lipid parameters or the different guidelines. It is also important to note that HDL-C can be increased relatively easily through some lifestyle interventions including diet containing monounsaturated and polyunsaturated fats, regular exercise, eliminating smoking, and using some medications, for example niacin and statins (26). Hence, all those preventive and therapeutic strategies have to be taken into consideration when interpreting the role of HDL-C in AD and VD.

In this study, it was also found that patients in the VD group with severe and moderate CI had significantly lower level of TG compared to the control group of subjects. These results indicate that TG levels in VD patients were dependent on the degree of CI. However, the evidence regarding relationship between serum TG level and CI is still scarce and debatable. Studies have shown that high TGs can increase the blood-brain barrier transport of insulin, and in that way improve cognition function (27). In addition, an earlier study reported lower TG plasma levels in patients with dementia compared to the control group, but the difference was not significant (28). Results of the previous cross-sectional study based on 1762 subjects showed that increased TG was negatively associated with cognitive impairment in male aged 40 - 55 years (29). In contrast, a prospective study performed on the oldest-old Chinese participants (majority females) aged > 80 years found that high normal plasma TG was associated with preservation of cognitive function while lower concentrations were not (30). Having in mind that pathogenesis of different subtypes of cognitive impairment in VD is different and still unclear, we assume that TG might be differently involved in the underlying vascular pathologies of the different degrees of cognitive impairment. It also might be that lower TG levels in VD patients than in control subjects are a consequence of the cross-sectional design of the present study.

Our results have also shown that patients in the AD group with moderate CI had significantly lower level of TC, TG, LDL-C, Non-HDL-C, atherogenic index, TG/HDL-C, TC/HDL-C compared to VD patients with moderate CI. On the other hand, patients in the AD group with severe CI had a significantly lower level of TC, LDL-C, Non-HDL-C and TC/HDL-C compared to VD patients with severe CI. Other lipids parameters did not differ significantly between the groups. Obtained results indicate that lipid metabolism not only depends on type of dementia, but also on the degree of CI. These results may be related with the differences in serum lipid metabolism, but also with the differences in pathogenesis of the VD and AD. We hypothesize that lipids increase the risk of cognitive impairment in VD and AD differently and that this impact depends on the underlying pathologies. Because there is relatively insufficient research about the relationship between serum lipids and cognitive function stratified by the degree of CI, the present study may be of special importance in filling this gap.

In our study of AD and VD patients stratified according to the degree of CI, we show that none of the standard or novel lipid parameters tested showed a significant association with MoCA scores. A possible reason for no association can be the age of the study population. It is important to note that lipid levels decrease in the older age and may not have the same significance that they have in the middle age. This implies the possibility that cross-sectional studies or higher baseline age lack the ability to evaluate association between lipid parameters and degree of CI. Results of a novel study showed a strong and statistically significant relationship between lower HDL level or higher TG level and the MoCA-INA score in geriatric patients. Total cholesterol level and LDL level did not show a statistically significant association with MoCA-INA score in geriatric patients (31 Putra et al., 2021). The possible explanation for the discrepancy between ours and the results of the mentioned study may be the differences in the study population and sample size, study design, and the differences in the methodology.

The strength of our research is that we, for the first time, compared standard and novel lipid profile parameters between Bosnian AD and VD patients stratified by the degree of CI, which is of importance since studies have shown that the levels of lipid profile components vary depending on the race and ethnicity (32 Rodriguez et al., 2002). The results of this study have shown dysregulation of lipid metabolism in AD and VD patients with different degree of CI. In both moderate and in severe CI, patients with AD had lower levels of majority of standard and novel lipid parameters compared to patients with VD. Further larger prospective studies are required to elucidate the accuracy of standard and novel lipid parameters in the assessment of different degree of CI in AD and VD.

Current study also has some limitations. First of all, our study is a cross-sectional study consisting of small, uniform Bosnian sample of AD and VD patients from a single unit at the Health-Care Hospice for people with disabilities, which limits the generalization of our results over the whole population. The second limitation is that cognitive function was assessed using the MoCA test as a screening tool for the cognitive function. However, use of other assessment tests for measuring cognition could have provide a more detailed and deeper assessment of cognitive function. Finally, in a group of patients with AD, we did not obtain screening for identification of the participant's apolipoprotein E (ApoE) genotype, which is known to be a genetic risk factor for cognitive and cardiovascular diseases (33). Further, we did not have information on the positive family history of any type of dementia and on lifestyle factors including educational level, eating habits, medications, and exercise which can modified blood lipid levels and contribute to the worsening of CI in AD and VD. Since no previous study investigated the relationship between the standard and novel lipid profile parameters in patients with AD and VD stratified by the degree of CI, our results need confirmation in the larger samples.

6. CONCLUSION

As far as we know, the present study, for the first time, examined the standard and novel lipid profile parameters

in older cognitively healthy individuals and patients with AD and VD stratified by the degree of CI. To the best of our knowledge, we are the first to report that AD patients with moderate AD had lower levels of almost all tested standard and novel lipid parameters compared to VD patients with moderate VD. Moreover, AD patients with severe CI had lower levels TC, LDL-C, non-HDL-C and TC/HDL-C compared to VD patients with severe CI. These results suggest that low circulating lipids levels are closely related to the pathogenesis of different degrees of CI in patients with AD and VD. Since no previous study investigated the relationship between the standard and novel lipid profile parameters in patients with AD and VD stratified by the degree of CI, future longitudinal studies with ApoE data available and larger sample size are warranted to validate our findings.

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