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Original Article

Resistance Training, Lipid Profile, and Homocysteine in Patients with Alzheimer's Disease☆

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SUMMARY

Background: The aims of this study were to verify the relation of the level of physical activity with the lipid profile and the homocysteine and to investigate the effects of resistance training on the concentrations of metabolic variables of patients with Alzheimer's disease.
Methods: Initially, the sample consisted of 37 community-dwelling patients with Alzheimer's disease. Eventually, only 30 patients participated in the intervention protocols offered, and they were divided into two groups: a training group with 14 patients and a social interaction group with 16 patients. All patients were evaluated using several instruments. We also analyzed the levels of serum homocysteine and lipid profiles.
Results: There were no significant relations between level of physical activity, lipid profile, and homocysteine. The training group exhibited reduced total cholesterol and low-density lipoprotein (LDL), as well as increased concentrations of high-density lipoprotein (HDL). However, the social interaction group exhibited decreased total, LDL, and HDL cholesterol. There were no significant differences in the homocysteine concentrations for the two groups.
Conclusion: No relationships were found between physical activity and metabolic variables. For both groups, changes were observed in the concentrations of total, LDL, and HDL cholesterol.

1. Introduction

Homocysteine is a sulfur-containing amino acid derived from methionine. Homocysteine is an intermediate metabolite of the biosynthetic pathway that converts methionine to cysteine[1].

Elevated concentrations of homocysteine are defined as constituting hyperhomocysteinemia. Changes in lipid profiles and hyperhomocysteinemia may be related to Alzheimer's disease (AD) and may also be associated with increased cognitive decline[2–7], especially in executive functions[8]. These concentrations may increase in cases of AD, depending on the evolution of the disease[9].

The literature includes controversial reports about the relationship between dyslipidemia and cognitive impairment, and the process of the formation of beta-amyloid and neurofibrillary tangles, which are classical markers of AD[6,9–15].

Given the possibility of these changes further worsening the clinical pictures of patients with AD, pharmacologic treatment has been combined with nonpharmacologic interventions such as physical activities to control the changes that arise from AD[16–20].

There is evidence that physical activity can modulate some of the peripheral risk factors that are related to dyslipidemia and indirectly improve brain function[21]. The data concerning physical activity and the modulation of homocysteine levels remain controversial[22].

☆ Conflicts of interest: All the authors assume that they have no financial interests related to the material described in this manuscript. There are no conflicts of interest.

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A review study conducted by Hurley et al[23] showed that resistance training can reduce the risk of metabolic syndrome, including dyslipidemia. Liu-Ambrose and Donaldson[24] found that resistance training reduces homocysteine concentrations in humans. Studies on elderly people who do not have cognitive impairments emphasize that resistance training is an important ally in improving lipid profiles and decreasing concentrations of serum homocysteine[25,26].

Few studies have investigated the effect of physical activities on the modulation of concentrations of homocysteine and lipid profiles in patients with AD. It is unknown which intensities, frequencies, and volumes of resistance training for controlling lipid and homocysteine concentrations are best. The aims of this study were to verify the relation of the level of physical activity with the lipid profile and homocysteine, and to investigate the effects of resistance training on the concentrations of homocysteine and the lipid profiles of patients with AD.

2. Materials and methods

2.1. Sample

Initially, the sample consisted of 37 community-dwelling patients. All of the patients were participants in the Programa de Cinesioterapia Funcional e Cognitiva para Idosos com Doença de Alzheimer[27].

The inclusion criteria were as follows: clinical diagnosis of AD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Test Revised (DSM-IV-TR)[28], and AD in mild or moderate stage, as assessed by the Clinical Dementia Rating Scale[29,30].

Overall, only 30 patients participated in the intervention protocols offered, and these patients were divided into two groups: the training group (TG; $n = 14$ patients) and the social interaction group (SIG; $n = 16$ patients). The groups were divided in order to comply with a similar distribution with respect to age, sex, education, and medical condition.

2.2. Methodological procedures

Clinical and sociodemographic data were obtained by asking the caregivers to undergo a structured interview. In order to characterize the cognitive profile, we used the Mini-Mental State Examination[31].

To verify the level of physical activity, we used the Baecke Questionnaire Modified for the Elderly[32].

The patients were referred to a clinical laboratory in the city of Rio Claro where they underwent laboratory tests for the purpose of verifying their metabolic profile (total cholesterol and fractions, triglycerides, and homocysteine). The procedures for blood collection followed the recommendations of the Brazilian Society of Clinical Pathology/Laboratory Medicine. Blood collection was performed at baseline and after 16 weeks of intervention.

The research project was approved by the Ethics Committee of the institution and was assigned protocol number 4827. The patients' caregivers signed a consent form, and this form was also approved by the Ethics Committee. This was performed in accordance with the rules established by resolution 196/96 of the National Health Council for research involving human beings.

2.3. Training protocol and social interaction group

The training protocol and the SIG were described by Garuffi et al[33].

The training program consisted of 16 weeks of activities that were carried out three times a week on nonconsecutive days. Each session lasted 60 minutes.

The patients performed five resistance exercises. The training sessions were held to 85% of the maximum load encountered during the test of maximum repetitions. During each exercise, the participants performed three sets of 20 repetitions with 2 minutes of recovery between sets and between exercises[33].

The SIG protocol lasted for 16 weeks; the participants met three times a week on nonconsecutive days, and had sessions that lasted 60 minutes.

The activities that this group engaged in included manual activities, drawing, writing, group dynamics, relaxation, musical activities, ecological tours, and other activities[33].

2.4. Statistical analysis

The statistical analysis involved applying the Student *t* test to determine whether there were differences between the two groups at baseline, and repeated two-way measurements analysis of variance (ANOVA) was performed to evaluate the effects of the experimental protocols. Analysis of covariance was used to verify if the level of physical activity (confounding variable) influenced the metabolic variables. Chi-square analysis was used to verify the differences between pre and post moments for the groups with hyperhomocysteinemia and without hyperhomocysteinemia. Data were expressed in terms of means and standard deviations. The Spearman correlation test was used to analyze the relation between level of physical activity, lipid profile, and homocysteine. The level of significance was a set at 5% for all of the analyses.

3. Results

The demographic details of the 37 community-dwelling patients with AD were as follows: mean age, 78.8 ± 7 years; educational level, 4.4 ± 3.6 years; level of physical activity, 3.2 ± 2.9 points. Of these 37 patients, 12 (32.43%) had hyperhomocysteinemia, which was determined by using a cutoff score of 15 μmol/L[34].

The Spearman correlation coefficients did not find any significant relationship between level of physical activity, lipid profile, and homocysteine.

The results were analyzed using appropriate statistical procedures. It was determined that there were no statistically significant differences between groups at baseline after taking into account covariates such as age, educational level, disease duration, overall cognitive profile, sex, and disease stages, except for the level of physical activity. The characterization data for the TG and the SIG sample are shown in Table 1.

Table 1
Sociodemographic, clinical, and cognitive characteristics of patients in the training group (TG) and social interaction group (SIG).

Characteristics of the sample	TG	SIG	*p*
Age (y)	78.5 ± 7.7	79.9 ± 5.7	0.5
Educational level (y)	5.8 ± 4	4.1 ± 2.8	0.2
Disease durations (mo)	34.6 ± 26.1	25.9 ± 38.2	0.08
MMSE (points)	18.4 ± 4.6	17.6 ± 4.8	0.6
Levels of physical activity (points)	6.4 ± 2.1	1.8 ± 2.4	0.0*
CDR 1, *n* (%)	10 (71.42%)	13 (81.25%)	—
CDR 2, *n* (%)	4 (28.58%)	3 (18.75%)	—
Males, *n* (%)	3 (21.43%)	4 (25%)	—
Females, *n* (%)	11 (78.57%)	12 (75%)	—

*$p < 0.05$.
CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination.

In the baseline, the level of physical activity was different between groups. Thus, we used the level of physical activity as a covariant, as this influenced the total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides, and homocysteine. The analysis of covariance showed that level of physical activity had no effect on metabolic variables (total cholesterol, HDL, LDL, VLDL, triglycerides, homocysteine).

Finally, two-way ANOVA revealed the main effects of time on both groups with respect to the following variables: total cholesterol and LDL ($F_{1,29} = 8.6$, $p = 0.007$ and $F_{1,29} = 10.32$, $p = 0.003$, respectively). Thus, there was a significant reduction in total cholesterol and LDL in both groups.

As regards the variable HDL, two-way ANOVA demonstrated an interaction for group × time ($F_{1,29} = 7.73$, $p = 0.01$). In the TG, there was an increase in HDL, which is considered “good” cholesterol. Meanwhile, the SIG exhibited a decrease in HDL.

Table 2 presents the results of comparing the metabolic variables for TG and SIG.

Table 3 shows the number of patients with or without hyperhomocysteinemia prior to and after the intervention period. Hyperhomocysteinemia was determined by using a cutoff score of 15 μmol/L[34]. Chi-square analysis showed no frequency of differences between pre and post moments for both groups.

As regards the use of medications, two patients in the TG consumed vitamin complex B12 once a day, and continued using this vitamin for 16 weeks after the intervention. In the SIG, one patient took folic acid and B complex vitamins prior to and after 16 weeks of intervention. We also observed that TG members used the following medications: statins, 43%; memantine, 35%; anticholinesterases, 57%; antihypertensive agents, 29%; anxiolytic, 21%. For the SIG, the following was noted: statins, 12%; memantine, 25%; anticholinesterases, 87%; antihypertensive agents, 44%; anxiolytic, 25%.

Table 3
Number of patients with or without hyperhomocysteinemia in the training group (TG) and the social interaction group (SIG) in pre and post moments.

Hyperhomocisteinemia	TG		SIG	
	Pre	Post	Pre	Post
With	12	11	9	8
Without	2	3	7	8

The hyperhomocysteinemia was determined using a score cutoff (15 μmol/L).

4. Discussion

We observed that the group that engaged in resistance training exhibited significant reductions in total cholesterol and LDL, and a significant increase in HDL. We also observed that SIG members exhibited reductions in their concentrations of HDL, total cholesterol, and LDL.

A literature review conducted by Cotman et al[21] showed that regular and systematic physical exercise can reduce central and peripheral risk factors in the human body. Some growth factors such as neurotrophins are directly linked to benefits derived from exercise, such as brain-derived neurotrophic factor, vascular endothelial growth factor, and the insulin-like growth factor 1[21].

Therefore, we note that it is important for AD patients to engage in physical exercise, given that the majority of these patients exhibited hyperhomocysteinemia, hyperglycemia, and dyslipidemia, among other factors.

Regular and systematic physical activity promotes an improved lipid profile in the elderly[35]. Fahlman et al[25] found that elderly women without cognitive impairment exhibited a reduction in triglycerides and LDL and increased HDL after 11 weeks of resistance training. However, other studies of elderly people who underwent a period of resistance training did not find significant improvements in lipid profile after training[26,35,36,37].

A review study by Hurley et al[23] found that resistance training reduces triglyceride levels in the elderly. The findings of the present study do not corroborate these results, because there were no significant reductions in triglyceride concentrations in both groups.

One important result of our study was the increase in HDL in the TG and the reduction of the same variable in the SIG. However, it is important to note that SIG members also showed reduction in LDL and total cholesterol. The lack of control for other variables such as diet may have influenced this result. Moreover, the fact that these patients participated in a program of social interaction may have been enough to stimulate the patients and their caregivers to adopt healthier lifestyles.

Another factor that may help explain the reduction in total cholesterol and LDL in both groups was the difference found in their levels of physical activity. The SIG presented a lower level of physical activity in comparison with the TG at baseline.

An interesting result found in this study is that for both groups, the concentrations of total cholesterol and LDL passed a threshold considered high for normal values.

The concentrations of homocysteine were not significantly reduced in both groups after the intervention periods. Homocysteine can be influenced by factors such as medications, comorbidities, alimentation, alcoholic drinks, caffeine, and vitamin B_{12}/folate[4,38].

When we look at the mean values of homocysteine at baseline, we note that the TG had values below 15 μmol/L[34], which are considered normal, and patients in the SIG had hyperhomocysteinemia. Given this fact, homocysteine concentrations may not have changed significantly in the TG because people in this

Table 2
Comparison between the training group (TG) and the social interaction group (SIG) with respect to metabolic variables: total cholesterol, HDL, LDL, VLDL, triglycerides, and homocysteine.

Characteristics of the sample	TG		SIG	
	Pre	Post	Pre	Post
Total cholesterol (mg/dL)	221.6 ± 60.5	199.9 ± 37.1[a]	212.7 ± 43.3	193.3 ± 32.3[a]
HDL (mg/dL)	47.2 ± 10.3	50.5 ± 9.5[b]	48.4 ± 9.7	43.6 ± 6.4
LDL (mg/dL)	149.2 ± 57.1	126.6 ± 32.9[a]	138.2 ± 39	119.5 ± 30.4[a]
VLDL (mg/dL)	25.2 ± 6.1	22.9 ± 7.6	26.2 ± 10.1	17.6 ± 11.4
Triglycerides (mg/dL)	125.8 ± 30.5	114.5 ± 38	130.9 ± 50.7	150.6 ± 66.8
Homocysteine (μmol/L)	12.5 ± 4.6	13 ± 4.7	16.5 ± 10.1	17.6 ± 11.4

HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.
[a] Main effect of time.
[b] Interaction group × time.

group already have normal values. When we analyzed the delta of this variable, we note that both groups showed a slight increase in homocysteine concentrations; however, the groups remained in their previous ratings, i.e., high and normal.

Vincent et al[26] conducted a study of 43 individuals without cognitive impairments. The participants were divided into three groups: one group performed resistance training at low intensity (50% 1 Repetition Maximum – RM), the second group performed resistance training at high intensity (80% 1 Repetition Maximum – RM), and the third group (the control group) performed no physical activity. Both groups engaged in the protocols for 24 weeks (three times a week). The authors found that the groups that carried out the protocols for resistance training experienced significantly reduced concentrations of homocysteine after the training period, whereas the control group experienced significantly increased concentrations of homocysteine.

However, the present study did not find reductions in homocysteine concentrations after the resistance training protocols. It may be that the intensities, frequencies, and volumes were insufficient to reduce homocysteine concentrations, and more intense training may be required. Herrmann et al[3] noted that the duration and intensity of exercise can be important factors in the modulation of homocysteine concentrations.

It is important to emphasize that both groups experienced changes in concentrations of homocysteine at their baselines, but the SIG was less active and had higher concentrations of this component. However, there was no reduction in the concentrations of homocysteine in either of the groups, which shows that resistance training does not appear to have reached the appropriate intensity necessary to reduce the levels of this variable.

Joubert and Manore[22] stated that the decrease in concentrations of homocysteine after physical exercise might be related to protein turnover, resulting in a catabolism of methionine, which consequently reduces the concentrations of homocysteine.

It is important to note that high concentrations of homocysteine are related to an unhealthy lifestyle and are incompatible with physical exercise[39]. Regarding lifestyle, a recent study by Johari et al[40] has shown that older adults with mild cognitive impairment, who underwent a nutritional and educational intervention for 12 months, had a reduction in homocysteine concentrations (34.6%). However, the control group also showed reduced homocysteine concentrations, but in a smaller proportion (21.1%).

The literature offers insufficient evidence to confirm the effects of systematic and regular physical activity on concentrations of homocysteine and lipid profiles in patients with AD. We thus suggest additional studies in order to develop a consensus regarding which types of physical activities, frequencies, intensities, and durations produce positive modulations of concentrations of homocysteine and improvements in the lipid profiles of patients with AD.

Furthermore, there were no significant relationships between level of physical activity and lipid profile and between level of physical activity and metabolic variables. This result can be attributed to the small sample size, and also the difficulty of measuring the level of physical activity in this population or even the lack of control of some variables, such as food, which may have altered the concentrations of homocysteine and lipid profiles. Another factor that can be considered a limitation of this study was the fact that we did not measure vitamin B_{12}/folate, since their concentrations can directly influence the concentrations of homocysteine.

The TG exhibited a reduction in concentrations of total cholesterol and LDL and increased concentrations of HDL. However, the SIG exhibited decreased concentrations of total cholesterol, LDL, and HDL. There were no significant differences in the concentrations of homocysteine for either of the groups.

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