Lipophilic Antioxidants and Cognitive Function in the Elderly

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ABSTRACT

OBJECTIVE: To determine the relationship between blood serum lipophilic antioxidant levels and cognitive function (CF) in older adults aged 60 and above guided by the oxidative stress theory of aging.

METHODS: Cross-sectional data from the National Health and Nutrition Examination Survey ($n = 291$) for older adults aged 60 and above were examined using Pearson correlation coefficient and multiple linear regression to determine whether blood serum antioxidant status predicted CF while controlling for age, sex, race, hypertension, smoking status, and body mass index.

RESULTS: Alpha-tocopherol, retinyl palmitate, trans-lycopene, and retinyl stearate were all significantly correlated with CF. After controlling for covariates, α-tocopherol and retinyl palmitate were associated with CF. Age, sex, and current smoking status were significant predictors of CF.

CONCLUSIONS: The benefits of antioxidants in CF may be a part of nutritional recommendations which include α-tocopherol and retinyl palmitate for delay of CI, and subsequently a better quality of life.

KEYWORDS: Antioxidants, cognitive function, older adults, oxidative stress

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Introduction

Aging has become a major focus in populations all over the world because the numbers of elderly individuals are expected to increase. The growing numbers are presumed to have a great impact on social, economic, and health systems.[1] A major contribution is poor cognitive function (CF) commonly seen in the elderly. Albert et al defined poor functioning or cognitive impairment (CI) as the display of a decreased performance in at least one of the cognitive domains including memory, executive function, attention, language, or visuospatial ability.[2] This is translated to an inability for self-care or to conduct normal daily activities including management of medication or comorbidities.[3]

Worldwide it is estimated that 47 million people have some form of dementia, with projected growth to 75 million by the year 2030.[4] In the United States, approximately 1 in 8 individuals aged 60 years and above have some degree of CI from memory loss.[5] Trowbridge et al[5] added that less than 20% speak of it to their healthcare provider. In addition, CI and dementia are not identified and/or not documented by healthcare providers in more than 50% of patients seen.[6] This points to an inaccurate diagnosis and underestimation of the problem.

Structurally in CI both brain atrophy and ventricle spaces expand at faster and greater rates than what is considered normal.[7] As CI progresses, parietal and temporal lobes experience cortical atrophy, followed by the frontal lobes where executive function is affected.[7] Morrison and Baxter[8] reported the signs as impaired working memory. Progressive memory difficulties and language impairment were also reported.[9] To address the growing problem, an understanding of the risk factors and possible prevention strategies need to be discovered and evaluated. According to McGill,[10] this is the current focus in the field.

Diet, as a modifiable risk factor, has been an area of interest as a health-protective behavior. Antioxidants are molecules found in fruits and vegetables and are considered protective for many disorders. Fruits, vegetables, and other plant material contain phytochemicals (PCs) that have antioxidant attributes.[11] Phytochemicals are numerous, with more than 5000 identified and grouped.[11] Antioxidant attributes of PCs include their ability to defend against reactive oxygen species (ROS) created through oxidation reactions within the tissues.[12,13] Studies have indicated an association between consumption of antioxidants and improved cognition[14] and have been called neuroprotective.[15,16]

The oxidative theory of aging states that damage to body cells and tissues occurs through oxidative stress (OS).[17] Production of ROS is a normal occurrence and can be kept in check by antioxidant actions that mitigate OS caused by an imbalance between ROS and antioxidants.[18] Reactive oxygen species damage is suspected as a major contributor to neurogenerative disorders, including age-related cognitive decline and Alzheimer disease (AD).[19-21]

The purpose of this study was to evaluate a possible association between blood serum antioxidant status and CF in individuals aged 60 years and above in the United States.[22]

Methods

Research design

Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2001-2002 database ($n = 11\,039$).[22] NHANES is a series of studies performed to assess health and nutritional status in adults and children in the United States where approximately 5000 people make up the yearly sample and are from various counties across the country.[23] NHANES uses a complex multistage probability cluster design consisting of primary sampling units, segments within counties, and then dwelling units or households.[24] Data collection was carried out by staff chosen based on previous experience, academic training, knowledge, skills, and abilities including the ability to speak English and Spanish.[25] Questionnaires were completed using a computer-assisted personal interview system, and laboratory and physical examinations took place in Mobile Exam Centers.[25]

Variable measurements

Blood serum concentrations of 11 antioxidants were used.[22] The antioxidants were α-carotene, trans-β-carotene, cis-β-carotene, β-cryptoxanthin, g-tocopherol, combined lutein/zeaxanthin, trans-lycopene, retinyl palmitate, retinyl stearate, retinol, and α-tocopherol. Cognitive function was measured using the Wechsler Adult Intelligence Scale, Third Edition (WAIS III) Digit Symbol (DSS) Test during household interviews.[26] The test is considered an initial indicator of neurological dysfunction and is able to recognize problems in several cognitive abilities, including cognition/writing speed, perceptual speed, visual-scanning ability, learning and memory, and executive functions.[27] Individuals must exhibit proper functioning such as pairing, free recall, perception, and graphomotor speed, which are necessary to complete the test.[26] The DSS Test is a good choice as a sensitive measure of dementia.[26] The test requires participants to copy symbols that are paired with the appropriate number.[28] The test is scored on the number of correct symbols drawn within 120 seconds, with 133 being a maximum score.[26] A higher score equates to more blocks being completed and better cognition.

Additional variables included age in years grouped as 60-64, 65-69, 70-74, 75-79, 80-84, and ⩾85. Sex was male or female. Race was grouped as non-Hispanic white, non-Hispanic black, and Mexican American/Hispanic. Smoking status was grouped as current smoker or former smoker. Hypertension was determined if the participant was taking a prescription medication for the condition. Body mass index (BMI) was measured in 4 categories defined as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), or obese (>30).[22]

In total, 1558 completed the cognition DSS Test.[29] The participants were men and women aged 0 to 150 years of several races. After selecting for elderly individuals aged 60 and above, the sample size was reduced to 1787. The number of participants differed by specific antioxidant measured. Alpha-carotene was measured in 8359 individuals, trans-β-carotene in 8358, cis-β-carotene in 8359, β-cryptoxanthin in 8317, g-tocopherol in 8308, combined lutein/zeaxanthin in 8353, trans-lycopene in 8348, retinyl palmitate in 8053, retinyl stearate in 8106, and retinol in 8365.[29] Once cases with missing data were excluded, 291 comprised the sample.[22]

Data analysis

Statistical Package for the Social Sciences (SPSS) version 21.0 was used to conduct the analyses. Correlation analyses were performed to assess the relationship between blood serum antioxidants and CF. *T*-tests and analysis of variance (ANOVA) tests were used to evaluate covariates and DSS Test scores. Multiple linear regressions were performed where regression coefficients and R^2 values were calculated to assess the overall predictive ability of blood serum antioxidant status with CF.[22] Statistical significance was set at .05.

Results

Descriptive sample participant characteristics were summarized. In this sample, 67.5% of the participants were aged 60 to 74 years, and 62.7% of them were men.[22] Mexican-Americans/Hispanics comprised 84.9% of the sample, followed by non-Hispanic whites at 13.7%. Most participants in the sample were taking a prescription medication for hypertension (89.7%), and 81.8% were current nonsmokers at the time of the survey. Body mass indices showed 39.9% of the sample were overweight, 35.7% were classified as obese, and 24.4% were considered normal weight or underweight. Most participants in this sample (75.6%) were overweight or obese.[22]

In DSS Tests scores, the mean number correct was 42.4 with a range of 88. The most correct was 88 out of a possible 133, and the least correct was 0. The score earned most was 33 by 14 participants, making up 4.80% of the total.[22]

Characteristics of the participants and CF were evaluated using 1-way ANOVAs.[22] Results are shown in Table 1. The ANOVA for age was significant, $F_{5,285} = 6.66$, $P < .01$, with an eta squared of 0.16. Follow-up tests were conducted to evaluate pairwise differences among the mean DSS Test scores. There was a significant difference in the mean scores between the 60 to 64 age group and the 70 to 74, 80 to 84, and 85 and older age groups. Those aged 60 to 64 had the highest average score (48.0), and those aged 85 and above had the lowest average score (30.3). Body mass index was statistically significant, $F_{3,287} = 4.08$, $P < .05$, with an eta squared of 0.04. Follow-up tests were again conducted to evaluate pairwise differences, and there was a significant difference in the mean DSS Test scores between the normal BMI group and the obese BMI group.

Table 1. Participant characteristics and cognitive function.[a]

VARIABLE	M	SD	TOTAL
Age			
60–64	48.0	17.0	78
65–69	42.4	16.2	59
70–74	39.5	15.2	60
75–79	47.3	15.1	42
80–84	34.2	14.1	41
⩾85	30.3	15.5	11
Sex			
Male	41.1	16.0	183
Female	44.5	17.2	108
Race			
Non-Hispanic white	40.2	19.3	40
Non-Hispanic black	42.3	16.6	3
Mexican-American/Hispanic	42.8	16.1	247
Hypertension			
Yes	42.7	16.6	261
No	39.8	16.3	30
Current smoker			
Yes	39.3	16.4	53
No	43.1	16.5	238
Body mass index			
<18.5	32.5	14.1	8
18.5–24.9	37.3	16.2	63
25.0–29.9	43.5	15.9	116
>30	45.0	16.9	104

[a]Data from Niemchick et al.[22]

There was no statistically significant difference in DSS Test mean scores between men and women, race, hypertension, or smoking.[22]

Bivariate correlation studies were conducted to evaluate the associations between each antioxidant, covariates, and CF. Cognitive function was measured by the number of correct responses on the DSS Test. The results of the correlational analysis showed that 4 of the 11 antioxidants were moderately correlated with CF, and 2 were weakly correlated with CF.[22]

For covariates of age, sex, race, hypertension, smoking status, BMI, and CF, the results showed the variables with relationships that were statistically significant were age, $r = -0.239$, and BMI, $r = 0.189$, with $P = .001$ for both.[22] These are shown in Table 2.

Table 2. Correlations between antioxidants, covariates, and cognitive function.[a]

VARIABLE	CORRELATION COEFFICIENT	*P* VALUE
Antioxidant, μg/dL		
α-carotene	−0.054	.359
Trans-β-carotene	−0.031	.593
Cis-β-carotene	−0.068	.248
β-cryptoxanthin	−0.004	.943
Combined lutein/zeaxanthin	0.042	.474
Trans-lycopene	0.196	.001*
Retinyl palmitate	0.248	.000*
Retinyl stearate	0.136	.020*
Retinol	0.088	.136
α-tocopherol	0.257	.000*
g-tocopherol	−0.098	.095
Covariate		
Age group	−0.239	.000[b]
Sex	0.099	.093
Race	0.054	.361
Hypertension	−0.054	.359
Smoking status	0.087	.138
BMI	0.189	.001[b]

Abbreviation: BMI, body mass index.
[a]Data from Niemchick et al.[22]
[b]*Correlation is significant at the .05 level (2-tailed).

To assess how well antioxidants and covariates predicted CF, multiple linear regressions were performed. The 4 antioxidants found to be statistically significant from correlation tests (α-tocopherol, retinyl palmitate, trans-lycopene, retinyl stearate) were included as well as the 6 covariates.[22]

Table 3 provides the regression results with 95% confidence intervals (CIs).[22] The first model predicted CF from age, sex, race, hypertension, smoking status, and BMI. A significant regression equation was found, $F_{6,283} = 6.43$, $P < .001$, with an R^2 of 0.120, showing these variables accounted for a significant amount of CF.[22] The predicted CF is equal to $24.24 - 2.98$ (age) $+ 5.17$ (sex) $+ 2.59$ (race) $- 2.53$ (hypertension) $+ 5.14$ (smoking status) $+ 1.93$ (BMI). Niemchick et al[22] found that age, sex, and smoking status were significant predictors of CF as measured in correct answers on the DSS Test with less than .01 *P* values. Part correlations indicated the relationship between age and CF was −0.249. As age increased, the number of correct scores decreased. The relationship between sex and CF was 0.148, with women scoring a higher average. The relationship between being a current smoker and CF was 0.113.

Table 3. Linear hierarchical regression model of predictors of cognitive function (n = 291).[a]

ANTIOXIDANT	*B*	SE *B*	β
Step 1[b]			
Constant	24.24 (7.46 to 41.02)	8.53	
Age	−2.98 (−4.30 to −1.67)	0.669	−0.047
Sex	5.17 (1.34 to 9.00)	1.95	0.151
Race	2.59 (−0.119 to 5.30)	1.38	0.109
Hypertension	−2.53 (−8.58 to 3.52)	3.07	−0.047
Smoking status	5.14 (0.166 to 10.11)	2.53	0.120
Body mass index	1.93 (−0.456 to 4.309)	1.21	0.096
Step 2[b]			
Constant	22.56 (6.42 to 38.69)	8.20	
α-tocopherol	0.005 (0.002 to 0.008)	0.001	0.209
Retinyl palmitate	2.07 (0.322 to 3.82)	0.888	0.314
Retinyl stearate	−3.79 (−8.56 to 0.980)	2.42	−0.191
Trans-lycopene	0.002 (−0.206 to 0.209)	0.106	0.001

[a]Data from Niemchick et al.[22]
[b]$R^2 = 0.120$ for step 1 and 0.214 for step 2. ($Ps < .01$); step 2 R^2 change = 0.094.

Participants who were not current smokers scored higher on the DSS Test. Current smokers had an average DSS Test score of 39.3 versus 43.1 for nonsmokers.[22]

A second model evaluated whether blood serum antioxidant status predicted CF while controlling for age, sex, race, hypertension, smoking status, and BMI.[22] These can be seen in Table 3 with 95% CIs. Again, a significant regression equation was found, R^2 change = 0.094, $F_{4,279} = 8.37$, $P < .001$, indicating the 4 antioxidants that were significantly associated with CF accounted for a significant proportion of CF after controlling for the effects of the covariates. The CIs for retinyl stearate and trans-lycopene indicate uncertainty regarding their relationship to CF.[22]

The predicted CF is equal to 22.55 + 0.005 (α-tocopherol) + 2.07 (retinyl palmitate) + 0.002 (trans-lycopene) − 3.79 (retinyl stearate). Cognitive function increased 0.005 correct answers for each microgram per deciliter of α-tocopherol, 2.07 correct answers for each microgram per deciliter of retinyl palmitate, and 0.002 correct answers for each microgram per deciliter of trans-lycopene and decreased 3.79 correct answers for each microgram per deciliter of retinyl stearate.[22] Alpha-tocopherol and retinyl palmitate were significant predictors of CF as measured in correct answers on the DSS Test. Partial correlations for each antioxidant were statistically significant, with the relationship between α-tocopherol and CF at 0.271, retinyl palmitate at 0.226, retinyl stearate at 0.128, and trans-lycopene at 0.157. Coefficients of determination (R^2) ranged 12% for covariates and 21% with antioxidants added to the model. The adjusted R^2 of 0.101 for step 1 and 0.186 for step 2 demonstrated an estimate of the strength of the relationships in the population.[22]

Discussion

Previous research has provided inconsistent results due to the use of different methods for antioxidant measurement in the body and their association with CF, including food frequency questionnaires and food recall diaries. Regression analysis showed that α-tocopherol, retinyl palmitate, retinyl stearate, and trans-lycopene were significant predictors for CF while controlling for age, sex, race, hypertension, current smoking status, and BMI.[22] In addition, regression analysis showed age, sex, and current smoking status were significant predictors of CF. Correlational analysis demonstrated age was significantly correlated with CF, and there was a significant difference between BMI groups and CF.[22]

The analysis supported the association between antioxidants and CF. Cognitive function was measured in NHANES 2001-2002 using the DSS Test, which is believed to measure several cognitive domains. The test is a valuable tool in research involving aging individuals.[30] Test results from previous studies are considered valid for comparison purposes due to administration and scoring of the test.[30] In a meta-analysis, Hoyer et al[30] found that in 141 studies for older populations (mean age of 69.8 years), the average DSS score was 48.2 (range of 38.8-66.8). In this study, the older population (mean age of 70.7 years) had an average DSS Test score of 43.4 (range of 0-88).[22] Age was a

significant predictor in regression analysis with a value of −2.07 (95% CI = −2.12 to −2.03) found by Hoyer et al[30] compared with −2.99 (95% CI = −4.30 to −1.67) found in this study. As age increased, the DSS Test score decreased by approximately 3 points.[22]

Antioxidants are vital for life due to their ability to protect against ROS in OS.[31] Previous evidence has supported numerous health benefits of antioxidants affecting the brain, kidneys, digestive system, and cardiovascular system.[32] The significant antioxidants in this study, α-tocopherol, and retinyl palmitate, are well-studied carotenoids.[22] Vitamin E is found in 4 forms. Alpha-tocopherol is the form found in highest amounts in the bloodstream.[33] This was seen in this sample where the blood serum mean concentration of α-tocopherol was the highest at 1.552 μg/dL. The master overseer of OS in the body is Nrf2, which has been found to effectuate the protective mechanisms of α-tocopherol in OS and mitochondrial dysfunction.[34] Alpha-tocopherol is also the most active form, giving it higher antioxidant ability through donation of hydrogen atoms from a hydroxyl group to neutralize radical molecules.[35] Alpha-tocopherol was found to be the most strongly correlated to CF with a correlation coefficient of 0.257, $P < .001$, in this study.[22] Gugliandolo et al[36] stated that vitamin E may be beneficial as treatment for patients with AD by counteracting OS caused by Aβ. Reactive oxygen species production and neurotoxicity were prevented in animal models.

Retinyl palmitate was also significantly correlated with CF with a correlation coefficient of 0.248, $P < .001$, for significance.[22] Retinyl palmitate is a vitamin A ester and is stored in the liver after absorption in the small intestine.[37] During certain stressful internal pathophysiological conditions including alcohol-induced liver disease, viral hepatic disease, and low levels of dietary vitamin A, retinyl palmitate and other retinol esters are mobilized for use.[38] Retinyl palmitate is the most common retinoid form stored in the liver.[39] In this study, retinyl palmitate had the highest average concentration of other retinol esters in the blood plasma at 2.44 μg/dL.[22] Retinyl palmitate is readily hydrolyzed to retinol or vitamin A.[39] Retinol is the form with the greatest antioxidant capability.[35] Vitamin A can also cross the blood-brain barrier; this has been shown in rat brain mitochondria where peroxidation was prevented.[35]

Covariates

Niemchick et al[22] found significant associations between CF and age, sex, and current smoking status. There were more men (62.7%) in the sample than women, with no significant difference in DSS Test score. There was no significant difference in DSS Test score based on race. Unequal numbers of the race categories made up the sample. Most of the population consisted of Mexican-American/Hispanic individuals (248), followed by 40 non-Hispanic whites and 3 non-Hispanic blacks. There was no significant difference in DSS Test score between participants with hypertension and those without. There were more in the sample with hypertension (261). Most in the sample were current nonsmokers (238), and there was no significant difference between smokers and nonsmokers. Body mass index overall was not significantly correlated with CF, although there was a significant difference descriptively between groups based on BMI, $F_{3,290} = 4.08$, $P < .01$.[22]

The results of this study were somewhat consistent with similar studies. A meta-analysis showed 3 of 7 cross-sectional studies did not find an association with smoking status and 3 of 6 did find an association between vitamin E and better CF.[40] Nooyens et al[41] found no association between vitamin E and CF, although the mean age was younger at 55 compared with this study at 70.7. Pastor-Valero et al[42] found a significant association between age and CF but none with smoking status or hypertension. Inconsistencies in BMI and CF in several studies on elderly individuals were reported by Miller and Spencer.[43] One of these studies showed higher BMI associated with lower CF, and another showed a deficit in the memory cognitive domain only.[43] In elderly individuals in Spain, overweight and obese participants did not score as well on cognition tests as normal-weight individuals.[44] Each of these studies used different cognition tests in their assessment, preventing direct comparisons.[43]

Strengths and limitations

The strengths of this study included the use of a representative sample of older adults in the United States and the inclusion of several covariates. Antioxidants were found to be significantly associated with CF. Limitations included using secondary data from a cross-sectional study of elderly individuals in the United States. The data used several methods of collection including self-report.[22] Social desirability bias is always a possibility for certain behaviors.

The question regarding the use of medication prescribed for hypertension may show inaccuracies. Self-reporting by the elderly on prescription medications and chronic conditions has not been shown to align with medical claims data.[45] Unmeasured confounders may have been a factor in this study. The sample was not weighted to be representative of the US general population, and this study is limited due to the disproportionate subsamples by sex and race.[22]

Conclusions

Modifiable risk factors, such as diet, provide an important option in the prevention and delay of disease. Two antioxidants, α-tocopherol and retinyl palmitate, exhibit benefits to elderly individuals related to CF as well as a significant association between CF and age, sex, and current smoking status.[22] Because the study sample consisted of mostly Mexican-American/Hispanic individuals, this population could be targeted for interventions involving dietary recommendations and behavior change interventions. Healthcare providers who regularly see this population may translate the results targeting lifestyle

factors.[22] On a larger scope, the results speak to the prevention and delay of CI through simple strategies such as incorporating foods that contain vitamins A and E.

The results also encourage further research to confirm these results in other populations. Differences in previous research in the covariates and antioxidants evaluated underscore the need for further assessment. Using plasma or tissue antioxidant levels can be calculated easily for carotenoids, but not for other antioxidants such as flavonoids.[46] Finally, studies following individuals over longer life spans may help address comorbidities and other variables that play a role in cognition.

Understanding OS in neurodegeneration is still expanding, and antioxidants as therapy continue to be considered as a way to counter the growing numbers of elderly with CI. For example, current research showed a melatonin-based hybrid drug containing antioxidants were neuroprotective against AD and toxic assaults from hydrogen peroxide.[47] Further confirmation of the benefits of antioxidants in CF may be a part of nutritional recommendations for delay of CI, and subsequently a better quality of life. Alpha-tocopherol and retinyl palmitate may play a role in those recommendations. As the prevalence of CI and dementias continue to increase, simple, safe, and cost-effective methods to delay potential onset should be evaluated and promoted.[22]

Author Contributions

KLN and GAL contributed to the concept and design of this study. CR and GAL provided input into overall project. All authors provided critical feedback and helped shape the research. KLN analyzed the data and wrote the manuscript with all revisions.

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