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ORIGINAL RESEARCH

Assessment of the effects of glutamic acid decarboxylase antibodies and trace elements on cognitive performance in older adults

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Background: Homeostatic imbalance of trace elements such as iron (Fe), copper (Cu), and zinc (Zn) demonstrated adverse effects on brain function among older adults.

Objective: The present study aimed to investigate the effects of trace elements and the presence of anti-glutamic acid decarboxylase antibodies (GADAs) in human cognitive abilities among healthy older adults.

Methods: A total of 100 healthy subjects (65 males, 35 females; age range; 64–96 years) were recruited for this study. Based on Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) score, the participants were classified according to cognitive performance into normal (n=45), moderate (n=30), and severe (n=25). Cognitive functioning, leisure-time physical activity (LTPA), serum trace elements – Fe, Cu, Zn, Zn/Cu, and GADAs were assessed using LOTCA battery, pre-validated physical activity (PA) questionnaire, atomic absorption, and immunoassay techniques, respectively.

Results: Approximately 45% of the study population (n=45) had normal distribution of cognitive function and 55% of the study population (n=55) had abnormal cognitive function; they were classified into moderate (score 62–92) and severe (score 31–62). There was a significant reduction in the level of Zn and Zn/Cu ratio along with an increase in the level of Fe, Cu, and anti-GADAs in subjects of severe (P=0.01) and moderate (P=0.01) cognitive performance. LOTCA-cognitive scores correlated positively with sex, HbA_{1c}, Fe, Cu, Zn, and Zn/Cu ratio, and negatively with age, PA, body mass index, and anti-GADAs. Significant inter-correlation was reported between serum trace element concentrations and anti-GADAs which suggest producing a cognitive decline via oxidative and neural damage mechanism.

Conclusion: This study found significant associations among trace elements, anti-GADAs, and cognitive function in older adults. The homeostatic balance of trace elements should be recommended among older adults for better cognitive performance.

Keywords: LOTCA, trace elements, anti-GADAs, cognitive performance, older adults

Introduction

Certain cognitive domains and physical inactivity were significantly associated with human aging.[1,2] A number of cognitive processes, including attention, learning and memory, and executive control, were changed among older ages.[3,4] A decline in cognitive abilities was shown to produce more drastic problems for older adults to perform their daily life activities.[5]

The severity and prevalence rate of cognitive decline depend mainly on various biological, social, and physiological factors such as lifestyle,[6] social network,[7,8] and various biomarkers,[9] including oxidative stress and free radical damage.[10,11] Among these potential markers, trace elements such as iron (Fe), copper (Cu), and zinc (Zn)

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are biologically essential metals, normally present in the brain.[12,13] It was reported that less or excess accumulation of these metals in the brain may cause neurodegenerative disease and cognitive impairment.[14–16]

In older ages, the decline in brain function pathologically attributed with tissue damage, neural cell death,[17,18] and significant changes in neural and enzymatic biomarkers such as glutamic acid decarboxylase (GAD),[19] which modulates and synchronizes neural network activity in the central nervous system via impairment in the synthesis of γ-aminobutyric acid (GABA). Most research works suggested the association of glutamic acid decarboxylase antibodies (GADAs) in various neurological disorders including cognitive function by affecting the GABAergic system.[20,21]

Previously, it was reported that cognitive problems may be associated with dysfunction of the GABAergic system.[22–24] However, it is not known whether cognitive decline appears as a result of neurological changes in the central nervous system associated with anti-GAD antibodies and/or trace elements. So, to study the role of anti-GAD antibodies and trace elements Fe, Cu, and Zn as risk factors in human cognitive abilities, we assessed these parameters and its association with cognitive function in healthy older adults.

Materials and methods

Subjects

A total of 350 healthy subjects were subjected to randomized electoral roll selection. Out of them, only 100 healthy subjects (65 males, 35 females), aged 64–96 years with a mean age of 65.2±3.6 years, randomly participated in this study (Table 1).

Table 1 General characteristics of subjects

Parameters	Participants (n=100; mean ± SD)
Male/female	65/35
Age (years)	65.2±3.6
Education (some college) (%)	80
BMI (kg/m^2)	22.8±3.2
Waist (cm)	71.3±4.7
Hips (cm)	86.7±12.3
WHR	0.82±0.10
Systolic BP (mmHg)	115.5±7.3
Diastolic BP (mmHg)	72.9±2.3
Mean HbA_{1c} value, % (SD)	4.5±0.35
VO2 max (mL/kg min)	37.4±3.7
Mean LOTCA score (SD)	111.2±3.5
LTPA (MET-H/week)	125.2±4.3

Notes: Values are expressed as mean ± SD; Significance at $P<0.05$.
Abbreviations: BP, blood pressure; BMI, body mass index; LOTCA, Loewenstein Occupational Therapy Cognitive Assessment score; LTPA, leisure-time physical activity; WHR, waist to hip ratio; BMR, basal metabolic rate (kcal/day); VO2 max, maximal oxygen consumption; MET-H, metabolic equivalent in hours.

Subjects with endocrine, immune, psychiatric illness, eating disorders, and taking glucocorticoid medication that could interfere with cognitive ability measurements were excluded from this study. Based on the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) score, participants were classified according to their cognitive performance into normal (93–123; n=45), moderate (62–92; n=30), and severe (31–62; n=25). Standardized measures of weight and height were taken in light clothing and body mass index (BMI; in kg/m^2) was calculated. All study participants gave informed consent prior to inclusion. This study was approved by ethical committee of Rehabilitation Research Chair of King Saud University, under file number (RRC-2014-016).

Assessment of cognitive abilities

Instrument

Trained research assistants assessed the cognitive abilities of older adult's pre- and post-supervised aerobic exercise using the LOTCA battery. Assessments required between 45 and 90 minutes. The LOTCA consists of seven major domains divided into 26 subtests, with each subtest scored on a 4- or 5-point Likert scale. The assessment of LOTCA test was performed according to instruction manuals as reported in the literature.[25]

Results are presented as a profile along all subtests. A composite score for each domain was calculated by summing the scores of the relevant subtests. The LOTCA score was calculated by summing the score of all subtests. The maximum score on the test is 123 and the minimum score is 27. A higher score indicates a better cognitive performance. Based on the LOTCA score, the cognitive performance of participants was classified into nrmal (93–123; n=45), moderate (62–92; n=30), and severe (31–62; n=25).

LOTCA test validity

The test has excellent intra-rater reliability (100%), and good inter-rater reliability (86%) as well as criterion validity (78%).[26] This LOTCA test was chosen because of its psychometric properties and primarily non-verbal nature, making it potentially more suitable for evaluating the cognitive abilities of individuals from non-Western and non-English-speaking cultures. Several studies have been conducted using this instrument in both Western[26] and Arab populations.[2]

Assessment of physical activity

Physical activity of the participants was assessed in relation to the time spent in performing moderate and intense exercise programs. The activity denoted as leisure-time physical

activity (LTPA) was measured by metabolic equivalents as previously reported.[27,28]

Assessment of anti-GADAs

Serum anti-GAD antibody titers were measured using a commercially available ELISA kit (RSR cat GDE96, RSR Limited, Cardiff, UK), which provides a specific and sensitive method for evaluating GAD antibodies.

Assessment of serum trace elements

Levels of Fe, Cu, and Zn in the sera were determined using an atomic absorption spectrophotometer device (Varian AA240FS Model, Varian Inc., Belrose, Australia). The measurements were conducted twice for each sample, using light at 2,139 wavelength according to a flame atomization method. Levels of serum Fe, Cu, and Zn were determined as µg/dL.

Statistical analysis

Descriptive statistics were expressed as mean and standard deviation. Student's *t*-test was used to compare groups. Spearman's correlations were used to assess correlations between cognitive performance score and related biochemical and demographic factors. *P*-values <0.05 were considered to be significant. Statistical analysis was performed using SPSS version 17.

Results

A total of 100 healthy subjects aged 64–96 years were subjected for cognitive ability measurements and estimation of biochemical related factors. Most of subjects (80%) participated in these study had attended some college or more. Statistical significant analysis of other demographic and cognitive function parameters is shown in Table 1. According to cognitive ability measurements, approximately 45% of the study population (n=45) had normal distribution of cognitive function with 111.2 mean LOTCA-7 score, and 55% of the study population (n=55) had abnormal cognitive function; they were classified into moderate (score 62–92), and severe (score 31–62) (Table 2).

As shown, a significant increase in BMI ($P=0.05$), waist to hip ratio (WHR) ($P=0.05$), and glycemic control parameter; HbA_{1c} ($P=0.01$) was reported in participants with abnormally distributed cognitive function as was the lack of physical fitness measured by leisure-time physical activity (LTPA) ($P=0.01$) as shown in Table 3.

The results showed a statistically significant difference in the level of serum concentrations of trace elements, anti-GADAs, and HbA_{1c}%. There was a significant reduction in the level of Zn and Zn/Cu ratio along with an increase in the level of Fe, Cu, anti-GADAs, and HbA_{1c}% in subjects of severe ($P=0.01$) and moderate ($P=0.01$) cognitive performance compared to normal control group (Table 3).

Based on the presence of anti-GADAs, the data obtained showed a significant reduction ($P=0.01$) in serum concentrations of Zn and Zn/Cu ratio along with a significant increase in the level of serum Cu, Fe, and HbA_{1c}% in subjects with positive anti-GADAs compared to control negative cases as shown in Table 4.

Correlation coefficients of the studied independent factors were estimated using a stepwise regression analysis. There was significant correlation among serum concentrations of trace elements, BMI, PA status, HbA_{1c}, anti-GADAs, and LOTCA-cognitive score analyses in older adults. LOTCA-cognitive scores correlated positively with sex, HbA_{1c}, trace elements; Fe, Cu, Zn, Zn/Cu ratio and negatively with age, PA, BMI, and anti-GADAs as shown in Tables 5 and 6.

Discussion

More than 20% of cognitive decline was reported in older adults.[29,30] Many research studies supported that age-related cognitive impairment may be associated with many demographic, physiological, and modifiable risk factors.[8,9,31,32]

Table 2 Cognitive performance in the studies population based on LOTCA-7 scores (n=100)

Parameters	Normal (93–123), n=45	Moderate (62–92), n=30	Severe (31–62), n=25
Orientation	14.5±2.3	11.2±1.2**	7.5±1.5**
Visual perception	18.2±3.2	13.5±3.1**	8.6±1.7**
Spatial perception	11.8±0.8	6.4±0.6**	6.9±0.9**
Motor praxis	9.7±0.75	6.8±0.56**	5.3±0.81**
Vasomotor organization	26.7±3.4	18.1±4.3**	12.3±2.4**
Thinking operations	25.5±4.1	16.2±2.7**	11.4±3.9**
Attention and concentration	4.8±0.72	2.9±4.3**	1.8±0.76**
Total LOTCA score	111.2±3.5	75.1±4.1**	53.8±6.1**

Notes: Values are expressed as mean ± SD; **$P<0.01$. Significance at $P<0.05$.
Abbreviation: LOTCA, Loewenstein Occupational Therapy Cognitive Assessment score.

Table 3 Associations of serum trace elements, HbA_{1c}, BMI, WHR, and anti-GADAs titers with cognitive performance of older adults (n=100)

Variables	Cognitive performance (LOTCA score)		
	Normal (93–123), n=45	Moderate (62–92), n=30	Severe (31–62), n=25
BMI (kg/m^2)	22.8±3.2	23.8±5.3*	24.9±6.1*
WHR	0.82±0.10	0.92±0.18*	0.98±0.21*
HbA_{1c}%	4.2±0.51	5.7±0.38**	6.3±0.65**
LTPA (MET-H/week)	125.2±4.3	98.5±7.1**	48±2.3**
GADAs (U/mL)	3.5±0.85	5.7±2.6**	9.6±4.2**
Fe (µg/dL)	68.5±6.3	98.2±3.5*	114.2±1.9**
Cu (µg/dL)	102.3±6.3	123.4±4.7*	142.3±6.9**
Zn (µg/dL)	78.3±2.5	65.4±1.6*	48.9±3.4**
Zn/Cu ratio	0.78±0.95	0.53±0.62*	0.34±0.78**

Notes: Values are expressed as mean ± SD; *$P<0.05$, **$P<0.01$. Significance at $P<0.05$.
Abbreviations: BMI, body mass index; GADAs, glutamic acid decarboxylase antibody; LOTCA, Loewenstein Occupational Therapy Cognitive Assessment score; LTPA, leisure-time physical activity; WHR, waist to hip ratio; MET-H, metabolic equivalent in hours.

The present study aimed to investigate the effects of trace elements and the presence of anti-GADAs in human recognition among healthy older adults.

In the present study, approximately 45% of participants had a normal distribution of cognitive function with 111.2 mean LOTCA-7 score and 55% of participants had abnormal scores of cognitive performance; they were classified into moderate (score 62–92; 30%), and severe (score 31–62; 25%).

There was statistical significant variability in the studied cognitive parameters such as motor praxis, vasomotor organization, thinking operations, attention, and concentration in older adults with moderate or severe cognitive impairment. Also, there was significant correlation among age, sex, HbA_{1c}, BMI, PA status, and LOTCA-7 score in all stages of cognitive performance. LOTCA-7 cognitive score variables correlated positively with sex, HbA_{1c} and negatively with age, BMI, WHR, and PA in participants with moderate and severe cognitive disorders compared with the control group. Previous research reports suggested the influence of life style and demographic parameters on cognitive function in older adults, whereas more than 20% of adult populations were suffering from cognitive disorder.[30,33,34] Also, several research studies reported positive effects of physical activity on cognitive performance scores among older adults.[2,35] In a study, Dunton et al[36] reported improvement of cognitive function in older adults following physical activity. In the same manner, our results were inconsistent with other studies showing that the beneficial effects of PA in reducing the risks of cognitive impairment,[37,38] as well as better processing speed, memory, and executive function.[38] In agreement with other studies, our results showed that obesity-related variables and higher level of HbA_{1c} were associated with a significant degree of cognitive decline among older adults.[39–41]

In addition, other studies revealed correlation among age, sex, lack of physical activity, higher BMI, and the coexistence of depression and cognitive disorders.[42–46]

In the present study, there was a significant increase in the level of anti-GADAs in participants with a moderate and severe decline of cognitive function compared to healthy group. The results showed that LOTCA-cognitive scores correlated negatively with anti-GADAs in the participants with abnormal cognitive function.

The results of our study matched with other studies that reported the association of GADAs with various neurological disorders including cognitive function by affecting the GABAergic system.[20,21] Similarly, Saidha et al[23] and Black et al[24] reported that cognitive problems may be associated with dysfunction of the GABAergic system.

Recently, it was reported that higher anti-GAD antibody levels are significantly related to more neurological disorders via stimulating anti-GAD autoimmunity which considers the potential cause of the cerebral involvement and cognitive decline.[20,47]

There was a significant association between trace elements and cognitive function in older adults of the present study.

Table 4 Serum trace elements concentrations in studied population based on anti-GADAs titers (n=100)

Variables	GADAs negative (<5 U/mL); (n=50)	GADAs positive (≥5 U/mL); (n=50)
Fe (µg/dL)	86.5±12.4	110.5±6.3**
Cu (µg/dL)	118.2±15.2	138.6±15.1**
Zn (µg/dL)	89.7±4.8	56.4±6.3**
Zn/Cu ratio	0.76±0.85	0.41±0.56**
HbA_{1c}%	3.92±0.58	5.82±0.35**

Notes: Values are expressed as mean ± SD; **$P<0.01$. Significance at $P<0.05$.
Abbreviation: GADAs, glutamic acid decarboxylase antibody.

Table 5 Results of stepwise multiple regression analysis of cognitive ability predicted by serum trace elements, and anti-GADAs, and demographic related variables

Variables	Cognitive performance (LOTCA score)					
	Normal (93–123), n=45		Moderate (62–92), n=30		Severe (31–62), n=25	
	β	R^2	β	R^2	β	R^2
Age (years)	–0.045*	0.542	–0.035*	0.325	–0.029*	0.385
Sex	0.082*		0.55*		0.035*	
BMI (kg/m^2)	–0.023*		–0.045**		–0.065**	
WHR	–0.035*		–0.065**		–0.045**	
HbA_{1c}%	0.075*		0.035**		0.028**	
Physical activity	–0.425*		–0.358**		–0.298**	
Anti-GADAs titer (U/mL)	–0.541*		–0.387**		–0.595**	
Fe (μg/dL)	0.042*		0.075**		0.086**	
Cu (μg/dL)	0.031*		0.049**		0.048**	
Zn (μg/dL)	0.058*		0.061**		0.059**	
Zn/Cu ratio	0.036*		0.037**		0.045**	

Notes: Estimated standardized regression coefficients (β) and variance explained (R^2) are presented. Significance at *$P<0.05$, **$P<0.01$.
Abbreviations: GADAs, glutamic acid decarboxylase antibody; BMI, body mass index; LOTCA, Loewenstein Occupational Therapy Cognitive Assessment score; WHR, waist to hip ratio.

Participants with moderate and severe cognitive disorders showed significantly different concentrations of Fe, Cu, and Zn and different patterns of associations between these minerals and cognitive function scores. Analyses using trace minerals as continuous variables showed that higher concentrations of Fe, Cu, and lower concentrations of Zn and Zn/Cu ratio were greatly associated with poorer cognitive performance on tests of long-term memory, motor praxis, and vasomotor organization, thinking operations, attention and concentration compared to intermediate concentrations.

In previous study, positive relationship between cognitive function and dietary intake of Zn and Fe was reported among healthy elderly adults.[48] In addition, copper intake was found to be a risk factor for cognitive decline in persons with high-saturated and trans-fat levels.[49]

Previous finding supported the association of plasma copper and cognitive score among elderly people of our study.[50] The severity of copper on cognition depends on oxidative stress and neurotoxicity mechanism,[51] especially in individuals with high-saturated or trans-fat levels.[48,52]

The homeostatic balance of Fe, Cu, and Zn is essential for optimized brain function.[53,54] Whereas, the lower change in the levels of these mineral effects on cognitive abilities via poor neurotransmission,[55,56] and impair neuropsychological function,[57] and that higher levels produce impairment of brain function via oxidative stress and neuro-degeneration processes.[53,58]

In addition, Faber et al[59] reported that the change in Zn and Cu is inversely related and the normal Zn-to-Cu ratio in children and adults is close to 1:1. In our study, a significant decrease in the Zn-to-Cu ratio was reported in participants with poorer cognitive performance. The lower Zn/Cu ratios may reflect total body Zn deficiency or accumulation of Zn-antagonistic toxic metals which effects on the metallothionein system.[60]

Table 6 Correlation of LOTCA cognitive function scores with serum trace elements, and anti-GADAs of older adults (n=100)

Parameters	Trace elements[a]				GADAs[a]
	Fe (μg/dL)	Cu (μg/dL)	Zn (μg/dL)	Zn/Cu ratio	
Orientation	–0.45*	–0.012*	0.48*	0.71*	–0.25*
Visual perception	–0.65*	–0.25*	0.65*	0.55*	–0.65*
Spatial perception	–0.85*	–0.17*	0.81*	0.74*	–0.49*
Motor praxis	–0.89*	–0.42*	0.45*	0.63*	–0.39*
Vasomotor organization	–0.561*	–0.51*	0.54*	0.38*	–0.58*
Thinking operations	–0.047*	–0.32*	0.42*	0.45*	–0.64*
Attention and concentration	–0.054*	–0.31*	0.39*	0.31*	–0.31*
Total LOTCA score	–0.125*	–0.28*	0.58*	0.88*	–0.78*

Notes: [a]Estimated standardized regression coefficients (β) and variance explained (R^2) are presented. Significance at *$P<0.05$.
Abbreviations: GADAs, glutamic acid decarboxylase antibody; LOTCA, Loewenstein Occupational Therapy Cognitive Assessment score.

In the present study, there was a significant correlation between Fe, Cu, Zn concentrations and the level of anti-GADAs in participants with poorer cognitive performance. The increase in Cu and Fe levels is attributed with a significant increase in anti-GADAs which reflects the inhibition rate of GAD enzyme via oxidative stress mechanism including hydroxyl radicals.[61] Also, it was reported that copper plays a significant role in oxidative attack on GAD enzyme through Fenton-like reactions.[62,63]

Conclusion

This study found significant associations among trace elements, anti-GADAs, and cognitive function in older adults. The homeostatic balance of trace elements should be recommended among older adults for better cognitive performance.

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Disclosure

The authors report no conflicts of interest in this work.

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