E-ISSN: 2833-3772 | Volume 3 (2024), Issue 4 | Jul-Aug 2024

The Scientific Journal of Medical Scholar

Publisher: Real-Publishers Limited (Realpub LLC)

30 N Gould St Ste R, Sheridan, WY 82801, USA

Associate-Publisher: SSESD, Egypt

Website: https://realpublishers.us/index.php/sjms/index

The Scientific Journal of Medical Scholar

Available online at Journal Website
https://realpublishers.us/index.php/sjms/index
Subject (Geriatric Rheumatology)

Original Article

Association between Trace Elements and Cognitive Function among Elderly Subjects with Osteoporosis: A retrospective Study

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Article information

Submitted: June 16th, 2024; Accepted: July 30th, 2024; DOI: 10.55675/sjms.v3i4.99

Citation: Elkerdasy YA, Nasrallah TM, Alzokm SM. Association between Trace Elements and Cognitive Function among Elderly Subjects with Osteoporosis: A retrospective Study. . SJMS 2024; 3 (4) Jul-Aug: 68-75. DOI: 10.55675/sjms.v3i4.99

ABSTRACT

Background: Cognitive dysfunction and osteoporosis (OP) are common among elderly subjects. Different mechanisms are reported. However the potential role of trace elements is not well studied. The current work aimed to estimate the toenail levels of trace elements in older patients with cognitive function with or without osteoporosis.

Patients and Methods: In a retrospective manner, we collected data of people older than 60 years of age. We collected data of 165 subjects, with 1:1:1 distribution for studied groups (i.e., 55 subjects in each group). The first group for normal cognition with no OP; the second for cognitive dysfunction with no OP and the third for cognitive dysfunction with OP. The cognitive function was determined by the mini-mental state examination (MMSE), while osteoporosis was diagnosed by the measurement of bone mineral density (BMD) with calculation of T-scores. Toenail samples were collected and prepared to estimate the levels of trace elements.

Results: Calcium and zinc were significantly reduced in groups (2 and 3) than the normal group (15.44±1.17 and 13.47±1.81 versus 18.93±1.90 µg/g, respectively; and 88.16±6.10 and 84.07±6.56 versus 104.27±4.79 µg/g, respectively). However, there were significant increase of toenail lead, aluminum and copper in the second and third groups than the first group. But, chromium and selenium were reduced in the second and third groups than the first group. The MMSE and T-scores were proportionately correlated with T-score, body mass index, calcium, zinc, chromium and selenium. But, inversely correlated with lead, aluminum and copper. Finally, calcium, zinc lead, age and BMI were the significant predictors of cognitive impairment and OP.

Conclusion: Trace elements are associated with cognitive impairment with or without osteoporosis. Some are protective and others had harmful effects with different mechanism. Thus, monitoring of these trace elements should be considered to avoid further cognitive decline with or without osteoporosis in future.

Keywords: Osteoporosis; Cognition; Trace Elements; T-Score.

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INTRODUCTION

Cognitive function describes the ability of the brain to process, store, and extract information. This includes memory, and language among others. Mild cognitive impairment describes a state of declined condition in a faster way than the expected for age and education levels. However, it does not affect the daily activities [(1)].

The prevalence of mild cognitive impairment (MCI) among people over 55 years was registered up to 12.2%. It is converted to dementia in 21.9% and to Alzheimer's disease and vascular dementia in 28.9% and 5.2% respectively. Globally, dementia affects more than 50 million, and the number is expected to r each 150 million by 2050. In addition, dementia lacks effective treatment. Thus, early diagnosis and recognition of potential treatable risk factors are of crucial importance [(2)].

Essential trace elements are of valuable importance for biological functions. Any deviation than normal values (either reduction of excess) can adversely affect human health and neurological function [(3)]. For example, experimental evidence showed that, oxidized form of chromium can lead to stimulate oxidative stress and lead to histological alterations of brain tissues [(4)].

In addition, high levels of copper can damage the synaptic function in hippocampus of mice [(5)]. Furthermore, the significant reduction of selenium can lead to cognitive defects, and alter the sensorimotor gating [(6)].

Previous evidence showed that, the reduction of trace elements (e.g., selenium) and increase of heavy metal exposure (e.g., lead) could potentially affect the cognitive function, as they are involvement in many biological functions (e.g., metabolic processes, oxidation-reduction reactions) in the central nervous system [(7)]. However, studies usually address the potential harmful effects of single trace elements of heavy metals. This is not the actual situation, where humans usually exposed to multi-metal effects at the same time.

Osteoporosis (OP) is a chronic systemic disease of the skeletal system. It is characterized by a progressive and insidious reduction of bone mineral density (BMD) leading to more fragile bones. It is a widespread condition and representing a worldwide medical challenge [(8)]. For examples, it affects more than 40 million of middle-age and old peoples in the United States, with significant impact on the patient's quality of life [(9)].

OP increased significantly in peoples in their sixth decade of life, and the prevalence rates increased in coming decades. This adds to the significant burden of the problem on the health care system and society [(10)].

Recognizing the potential risk factors for development of OP is an important measure to prevent the OP development [(11)].

Heavy metals are prevalent in different environments and it can reach the human by different ways (e.g., food chain, drinking water, and occupational exposure) [(12)]. The exposure to heavy metals is a known risk factor for the development of different chronic bone diseases (e.g., OP and fractures) [(13, 14)].

The effect of heavy metals on the bone can be exerted through genetic, nutritional and metabolic mechanism [(15)]. For example, the environmental lead (Pb) after absorption is accumulated in the bone trabeculae and cortex being the main, with significant reduction of BMD leading to development of different bone-related chronic diseases [(16)]. However, exposure to single heavy metal is not known and usually the human inevitably exposed to multiple metals and exposure to single metal cannot fully explain the onset and progression of different bone diseases. The synergistic or antagonistic interactions between meals may play a role. Thus, it is of utmost importance to study a mixed exposure of trace elements to explore its role in the development of different conditions [(17, 18)].

The current work aimed to estimate the toenail levels of multiple trace elements and minerals in older patients with cognitive function with or without osteoporosis.

PATIENTS AND METHODS

We collected data of subjects older than 60 years of age at the time of inclusion, with no known terminal or mental illness. All subjects were able to communicate and provided their informed consents. We were able to collect data of 165 subjects with 1:1:1 distribution for studied groups (i.e., 55 subjects in each group). The first group included subjects with normal cognition who had no osteoporosis (OP); the second group included subjects with cognitive dysfunction with no OP and finally the third group for subjects who had cognitive dysfunction with OP. The data collected by a structured questionnaire that covers socio-demographics, medical history and special habits (e.g., smoking).

The mini-mental state examination (MMSE) was used to assess the state of cognition. It is formed of six different domains with a total score of 30. The domain are the orientation to time and place, attention, memory, language and visual structure. The lower the score, the worse the cognition. Cognitive impairment was confirmed at values lower than 23, as all subjects received education more than 6 years [(19)].

In addition, the cognitive dysfunction was further assessed by a geriatrist using a translated and validated (Cronbach's alpha was 0.76) version of Montreal

Cognitive Assessment (MoCA screening tool. Different domains were evaluated by the tool. These included orientation, memory (short term recall), attention, concentration, working memory, mental arithmetic ability, language comprehension, cognition, visuospatial domain, abstract thoughts, and naming of objects [20].

Analysis of trace elements

Toenails were used to assess the concentrations of trace elements/each gram of tissues. The samples were clipped from all toes using a stainless-steel instrument. Then, samples were stored in plastic bags (labeled by the code number of the subject). Then 10 mg of samples were weighed and washed and washed as described by **Rodushkin and Axelsson [21].** The digested sample in a final dilution of 10 ml deionized water kept at 4^{o}C till the time of analysis. Blanks were prepared in the same manner as the sample tubes. Then, trace elements (calcium, iron, zinc, lead, aluminum, chromium, selenium and copper) were determined plasma mass spectrometry (inductively-couple) on Elan 9000, PerkinElmer, USA (All trace elements assessment were performed at the analytical chemistry department, faculty of science, Damietta University, Egypt).

Statistical analysis:

The collected data was anonymized, coded and fed to personal computer for statistical analysis. All tests were performed by the statistical package for social sciences, for windows, version 18 (IBM®SPSS® Inc., Chicago, USA). The arithmetic means and standard deviations (SD) were the statistical measures for the quantitative, normally distributed data, while relative frequency and percentages were the statistical measures of qualitative data. Quantitative variables were compared by the one way analysis of variance (ANOVA) test with Post-Hoc Least significant differences (LSD) for comparison between two means. On the other side, Chi square test was used to test associations between qualitative variables. Correlation between MMSE and T-scores (indicator of OP) with other variables were performed by the calculation of Pearson's correlation coefficient. P values < 0.05 was considered significant.

RESULTS

The current work included 55 subjects in each one of three groups. In groups 1 and 2 (with no OP) showed comparable sex distribution (the majority were of male gender), while the group with OP had significant increase of female gender (69.1%). However, the three groups were comparable regarding age distribution (the mean age was 67.05±4.67, 67.09±4.81 and 68.05±4.54 in the first, second and third groups respectively). The T-score was significantly lower among group with OP than those groups without OP regardless of the cognitive function. In addition, body mass index was significantly lower among the group of cognitive dysfunction with OP than those without OP regardless of cognitive function. Hypertension and DM were significantly higher among groups 2 and 3 than group 1. However, smoking did not differ significantly between study groups. The physical activity was significantly lower in the OP with cognitive dysfunction than those without OP either normal or with cognitive dysfunction and calcium supplementation was significantly higher among group 3 than groups 1 and 2 (Table 1).

In the current work, the toenail values of calcium were significantly lower among the groups of cognitive dysfunction (2 and 3) than the group of normal cognition with no OP (15.44±1.17 and 13.47±1.81 versus 18.93±1.90 µg/g, respectively). In addition, values were significantly lower in the third than the second group. However, the toenail levels of iron d id not differ significantly between study groups. The toenail zinc levels were significantly lower in groups 2 and 3 than the first group (88.16±6.10 and 84.07±6.56 versus 104.27±4.79 µg/g, respectively). In addition, the values of zinc were significantly lower in the third group (cognitive impairment with OP) than the second group (cognitive without OP). On the other side, there was significant increase of toenail lead, aluminum and copper in the second and third groups than the first group. But, toenail chromium and selenium were significantly reduced in the second and third groups than the first group and in the third than the second group (Table 2).

The cognitive function (MMSE) was proportionately and significantly correlated with each of T-score, body mass index, calcium concentrations, zinc, chromium and selenium. But, there was inverse significant correlation between MMSE score and each of lead, aluminum and copper. However, the correlation with iron was statistically non-significant. Similarly, osteoporosis (T-score) was proportionally and significantly correlated with body mass index, calcium, zinc, chromium and selenium; but the correlation with lead, aluminum and copper was inverse and statistically significant. However, the correlation with iron is statistically no-significant (Table 3).

When linear regression analysis was performed to recognize determinants of cognitive dysfunction with OP, calcium, zinc lead, age and BMI were the significant determinants. Cognitive dysfunction was associated with reduced calcium or zinc and increased lead or body mass index (Table 4).

Table (1): Patient characteristics and associated comorbid conditions among study groups

		Normal cognition with no OP (n=55)	Cognitive dysfunction with no OP (n=55)	Cognitive dysfunction with OP (n=55)	Test	P
Sex (n,%)	Male	33 (60.0)	30 (54.5)	17 (30.9)	***10.53***	***0.005****
	Female	22 (40.0)	25 (45.5)	38 (69.1)		
Age (year)		67.05±4.67	67.09±4.81	68.05±4.54	0.809	0.447
T-Score		0.116±0.41	0.109±0.37	-4.84 ± 0.87	***1280.1***	***<0.001****
BMI (kg/m^2)		23.62±0.54	23.56±0.38	22.93±1.18	***13.31***	***<0.001****
Marital state	Married	35(63.6)	38(69.1)	42(76.4)	2.99	0.55
	Divorced	8(14.5)	5(9.1)	6(10.9)		
	Widow	12(21.8)	12(21.8)	7(12.7)		
Smoking (n,%)		9(16.4)	18(32.7)	12(21.8)	4.23	0.12
Hypertension		22(40.0)	35(63.6)	38(69.1)	***10.76***	***0.005****
DM		12(21.8)	22(40.0)	28(50.9)	***10.12***	***0.006****
Physical Activity	Light	12(21.8)	10(18.2)	28(50.9)	***21.80***	***<0.001****
	Middle	35(63.6)	43(78.2)	24(43.6)		
	Heavy	8(14.5)	2(3.6)	3 (5.5)		
Ca Supplementation		11 (20)	9(16.4)	26(47.3)	***15.61***	***<0.001****

Table (2): Toenail trace elements among study groups

	Normal cognition with no OP (n=55)	Cognitive dysfunction with no OP (n=55)	Cognitive dysfunction with OP (n=55)	Test	P
Calcium (µg/g)	18.93±1.90	15.44±1.17	13.47±1.81	***152.154***	***<0.001****
Iron (µg/g)	3.07±0.24	3.05±0.25	3.14±0.53	1.115	0.330
Zinc (µg/g)	104.27±4.79	88.16±6.10	84.07±6.56	***182.429***	***<0.001****
Lead	0.34±0.05	0.55±0.13	0.60±0.07	***133.660***	***<0.001****
Aluminum	43.89±3.47	48.91±7.86	56.84±9.25	***44.120***	***<0.001****
Chromium	4.46±0.43	3.68±0.55	3.35±0.46	***77.247***	***<0.001****
Selenium	0.47±0.06	0.39±0.09	0.33±0.04	***68.906***	***<0.001****
Copper	6.08±0.32	7.35±0.67	8.69±0.52	***341.149***	***<0.001****

Table (3): Correlation between MMSE and T-score from one side and other variables from the other side, among study groups.

	MMSE		T-score	
	r	*p*	*r*	*p*
T-score	0.506	***<0.001****		
BMI	0.226	***0.004****	0.382	***<0.001****
Ca	0.755	***<0.001****	0.620	***<0.001****
Fe	-0.036	0.647	-0.093	0.237
Zn	0.814	***<0.001****	0.536	***<0.001****
Pb	-0.779	***<0.001****	-0.505	***<0.001****
Al	-0.465	***<0.001****	-0.523	***<0.001****
Cr	0.667	***<0.001****	0.466	***<0.001****
Se	0.627	***<0.001****	0.539	***<0.001****
Cu	-0.770	***<0.001****	-0.746	***<0.001****

Table (4): Linear regression analysis for determinants of cognitive dysfunction with OP

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Ca	-.048	0.010	-.282	***-4.983***	***<0.001****
Fe	-.072	0.049	-.056	-1.483	0.140
Zn	-.017	0.003	-.385	***-6.225***	***<0.001****
Pb	.938	0.209	.280	***4.496***	***<0.001****
Al	-.002	0.002	-.044	-.971	0.333
Cr	-.065	0.036	-.092	-1.789	0.076
Se	.220	0.298	.042	.740	0.461
Cu	.039	0.028	.099	1.397	0.165
age	-.008	0.004	-.082	***-2.228***	***0.027****
BMI	.045	0.021	.080	***2.111***	***0.036****
Sex	-.012	0.042	-.013	-.288	0.774
Marital state	-.015	0.022	-.025	-.673	0.502
Smoking	-.006	0.050	-.006	-.125	0.901
Hypertension	-.069	0.042	-.072	-1.640	0.103
DM	.024	0.042	.024	.563	0.574
Physical activity	.015	0.031	.019	.506	0.614
Calcium supplementations	-.005	0.040	-.005	-.122	0.903

DISCUSSION

The current work provided an evidence for the association between trace elements and cognitive function with or without osteoporosis. Calcium, zinc, chromium, and selenium were significantly reduced, while lead and aluminum were significantly increased in diseased groups (with cognitive dysfunction with and without OP) than subjects with normal cognition with no OP. The cognitive function was significantly, moderately and proportionately correlated with bone mineral density (T-scores). Both were inversely correlated with lead, aluminum and copper. But, positively correlated with BMI, calcium, zinc, chromium and selenium. Reduced calcium or zinc and at the same time increased age, lead concentration and BMI were the significant determinants of cognitive function with OP.

We used MMSE tool, as it is the commonest cognitive function assessment tool used in clinical, and research settings with higher reliability (0.91) [(22)]. To explain the positive correlation between chromium and cognition, it was reported that, chromium improves glucose disposal and preserves glucose homeostasis. This distribution of glucose homeostasis lead to impairment of insulin signaling, neuronal integrity and vascular function. This could affect the cognitive function due to effects on the vascular system of the brain [(23)]. This was confirmed in an experimental study examined the effect of chromium supplementation and reported that, chromium could improve memory, upregulates insulin signaling and ameliorate neuroinflammation and oxidative stress through different mechanisms [(24)]. However, **Janka** [(25)] stated that, the excess chromium also may lead to the development of cognitive function by alteration of the expression of neuro-related genes leading to neurotoxicity. A previous clinical trial suggested that the supplementation of chromium enhanced the cognitive function among old populations with a high risk for the development of neurodegenerative disease [(26)]. As in the current work, a previous study found a negative association between copper levels and cognitive dysfunction in old people (the decade before death) [(27)]. This was attributed to the high redox activity of copper. In addition, copper is a vital component and cofactor of many enzymes dealing with electron transfer reactions. The disturbed copper levels is a characteristic feature of Alzheimer Disease (AD) (the most severe form of cognitive dysfunction [(28)].

Squitti *et al.* [(29)] also reported that the increased circulating free copper contributes to the copper dysregulations with the development of neurodegenerative diseases among elderly. **Zhang *et al.*** [(18)] reported a significant positive correlation between copper and cognitive impairment, as in the current work. **Behzadfar *et al.*** [(30)] demonstrated that the overload of copper in the rat hippocampus is associated with a mitochondrial dysfunction and oxidative stress, with subsequent cognitive impairment. They added, copper enhances the harmful effects of amyloid-beta on the memory and brain functions. **Lin *et al.*** [(31)] confirmed the association between chromium and selenium with the cognitive function. They said that, chromium was especially linked to the registry, recall and language domains of cognition, and selenium was positively correlated with total MMSE score and all domains. Interestingly, they reported a dose-response association between selenium and cognition, but within limits. At increased levels of chromium of selenium, the cognition impairment was reported due to narrow safe range.

Besides the narrow safety range of selenium the neuroprotective and neurotoxic effects can be explained by the action of selenium on different substances. For example, selenium is an important element for the synthesis of selenoproteins (neuroprotection) and it was in organic form. However, selenium is also a neurotoxic when it is worked in the selenomethionine in an inorganic form [32].

In addition, selenium is found to be inversely association with the systemic inflammation. It is a critical process in the pathogenesis of age-related cognitive impairment and dementia [33, 34]. Furthermore, the selenium levels reduction is associated with the destruction of neurons, with increased risk of cognitive impairment [35].

Previous studies reported that the lower levels of selenium in patients with cognitive impairment and when compared to normal healthy adults in different fluids of the body (e.g., plasma, blood, CSF) and nails (as in the current work) [36-38]. The affected central nervous system (CNS) areas include temporal lobe, hippocampus and cortex. Finally, reports from China demonstrated a significant association between reduced levels of selenium in nails and poor cognitive performance [39, 40].

Of major interest, it is crucial to note that, in cases of selenium deficiency, the brains stores are the last to be depleted and are the first to be replenished when levels returned to normal values [41]. This reflects the utmost importance of selenium for the brain function.

Results of this work are also in line with previous works, indicating that, an evidence is present linking the trace elements and cognitive function. For example, cognition and motor functions were impaired after arsenic and lead exposure in children and in adults [42-44], and the same results were observed in elderly [45].

Consisting with the current results, **Gu L *et al*.** [21] reported that, higher levels of aluminum are associated with cognitive impairment. In addition, **Shen X-L** [46] among others reported comparable results, where higher levels of aluminum and other heavy metals were considered as a risk factor for cognitive impairment [43, 47]. However, others reported no association between higher levels of aluminum and cognitive dysfunction [48, 49]. This contradictory results were explained by small sample size, different samples used for measurement of aluminum (e.g., urine, blood, toenails, etc…) and different detection methods.

Interestingly, the current results are in line with the study of **Meramat *et al.*** [50] who reported that, elderly with cognitive dysfunction had higher levels of trace elements (e.g., lead and copper) than subjects with normal cognitive function. In addition, they linked an oxidative stress to increased trace elements and cognitive impairment. Specifically, lead and copper are the predictors of cognitive impairment, with significant damage of DNA

The results of the current work are in line with previous literature, as it is reported that, aluminum as an environmental pollutant lead to serious health problems including reduction of bone mineral density and increased risk of osteoporosis. In addition, a prospective study demonstrated that aluminum exposed neonates have reduced bone mass, especially of lumbar spine during adulthood, which may increase the risk of osteoporosis later in life. This can be produced by the action of aluminum. It can inhibit the mineralization process of osteoblast, increased apoptosis and reduce osteoblast differentiation. In addition, aluminum can induce damage of the bone and lead to development of osteoporosis [51, 52].

Thus, aluminum can lead to osteoporosis by different mechanisms. However, the exact molecular mechanisms of aluminum-induced osteoporosis is still largely unknown and more studies are required to explore the situation. Previous studies showed that OP caused by cadmium and aluminum exposure is usually associated with oxidative stress. Both cadmium and aluminum increased the risk of bone metabolism disorders, and osteoporosis [53].

The current work had some limitations, mainly the retrospective nature, with possibility of bias and small sample size. However, this work is one of the earliest studies linking cognitive dysfunction to osteoporosis and both to the poly-metal exposure. However, the results must be treated cautiously due to small sample size and future studies are recommended.

Conclusion: Trace elements are associated with cognitive impairment with or without osteoporosis. Some are protective and others had harmful effects with different mechanism. Thus, monitoring of these trace elements should be considered to avoid further cognitive decline with or without osteoporosis in future.

Disclosure:

Non to be disclosed, no conflict of interest or financial disclosure

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E-ISSN: 2833-3772 | Volume 3 (2024), Issue 4 | Jul-Aug 2024

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