Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://zumj.journals.ekb.eg/article_290702.html Volume 29, Issue 2, March 2023, Page (720-727)
Manuscript ID ZUMJ-2201-2457 (R1)
DOI 10.21608/zumj.2022.117551.2457

ORIGINAL ARTICLE

The Relation Between 25-dihydroxycholecalciferol, iron status and The Deteriorated Cognitive Function in Dementia patients

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Submit Date 2022-01-28
Revise Date 2022-04-12
Accept Date 2022-04-13

ABSTRACT

Background: Serum iron and Vitamin D3, have vital roles in regulating numerous cellular processes in nervous system. Additionally, vitamin D3 could affect iron metabolism, iron in turn is essential for vitamin D3 formation. Even with the different studies, it is still unclear whether serum iron and/or Vitamin D3 have a role in the decline of cognitive function and progression of dementia.

Aim: to investigate serum iron and Vitamin D3 levels and their association with cognitive function in dementia patients in Zagazig University Hospitals

Methods: Sixty male and female patients; 30 control and 30 newly diagnosed dementia patients were included in the study. Cognitive function tests were performed. Serum analysis of iron, ferritin, TIBC and vitamin D3 were analyzed.

Results: dementia patients showed significant decrease in cognitive function tests, iron status parameters and vitamin D3. additionally, significant association between vitamin D3 and cognitive tests, also between vitamin D3, ferritin and TIBC was found. Furthermore, an association between serum iron, ferritin with some cognitive tests was statistically significant.

Conclusion: Serum iron status and vitamin D3 is associated with cognitive function decline in newly diagnosed dementia patients.

Key words: Dementia, vitamin D3, iron, ferritin

INTRODUCTION

Dementia is a fatal neurodegenerative disease of unknown cause. Nearly forty-eight million persons around the world have been diagnosed as dementia, unfortunately, it is expected to rise to 2.73 times by 2050. 75% of all dementia cases was diagnosed as Alzheimer Disease, the most common type of dementia [1]. Dementia has varied risk factors; such as smoking, diabetes mellitus, hypercholesterolemia, cardiovascular diseases, and hypertension [2].

Vitamin D3 and iron have significant roles in the physiologic processes. However, there is a very high risk of deficiency in these two essential nutrients [3]. AS the role of vitamin D3 in neurotransmission, neuroplasticity, neuroprotection and neurotrophy has been suggested, vitamin D3 deficiency might play a significant role in the dementia progression and

its potential prognostic role has been proposed [4].

Iron is considered a key role in multiple pathophysiologic functions. It constitutes part of proteins needed for myelin production, neurotransmitters production and breakdown, oxygen transport, and oxidative phosphorylation. Inadequate iron might have potential cognitive impacts such as cerebral hypoxia, insufficient neurotransmitter synthesis and/or poor myelin integrity. [5].

Interestingly, it was noticed excess iron accumulation within brain tissue in numerous neurodegenerative diseases such as Alzheimer Disease that was accompanied by oxidative stress. Binding Fe^{3+} to the tau protein, then its conversion to the reduced form "Fe^{2+}", induce the production of neurofibrillary tangle [6].

Regarding serum iron conflicting data were reported Hosking et al. [7], higher serum iron levels were negatively associated with the decline in sensorimotor speed and word fluency [8], However, Cherbuin et al. [9] found that the risk of cognitive function decline was associated with greater iron intake. Meanwhile, Min and Min [10] found no association between iron level and dementia.

Moreover, contradictory data about the possible association between vitamin D deficiency and cognitive decline. it has shown that normal vitamin D was associated with decreased risk of dementia [11]. However, a study of Schneider et al. [12] reported no association between lower concentrations of vitamin D and cognitive decline during middle age.

Interestingly, an association between low vitamin D3 levels and poor iron status has been indicated. However, the mechanism/s for their association is still not known, but it is postulated that vitamin D3 might impact iron regulation via its effect on pro-inflammatory markers [4, 13].

Therefore, the present study aimed to examine serum iron indices and vitamin D3 level and the possible association between them and cognitive function tests in dementia patients.

PATIENTS AND METHODS

This is a case-controlled study that was approved by Institutional Research Board (IRB) at the Faculty of Medicine, Zagazig University, Egypt, in the period from January 2021-December 2021. The study was done according to The Code of Ethics of The World Medical Association (Declaration of Helsinki) for studies involving humans. We recruited 30 patients (dementia group) admitted to neurology department of Neurology Department Outpatient Clinic and 30 normal volunteers (control group). all participants or their relatives gave written informed consent. The procedures followed were in accordance with our protocol.

We recruited mild to moderate dementia patients of both sex over age of 60 years, while those with severe dementia, Psychiatric disorder or other medical conditions that may affect the neuropsychological performance, long term medications or dietary supplement that affect cognition were excluded from the study.

Methods of the study:

1. Neurocognitive assessment focused on assessment of attention, memory, and executive function. Neurocognitive tests were done at the first time of diagnosis of the condition and before receiving any medications. The test was held in a calm room. Five min were allowed as an interval between different tests.

I. **Wechsler intelligence scale for adult "Logical memory subtest":** This certified scale was used for adult memory assessment. A 25-items short story was presented to the contributors, then they were inquired to repeat it twice; directly and after half hour (30 min). The overall score was calculated by counting the number of the recalled items of the presented story by each participant. the maximum score is: 25 [14].

II. **Trail making test:** The test was employed to evaluate the executive function of the participants, depending on mental flexibility, the degree of attention, and performance as well as visuomotor organization. Contributors were requested to draw continuous lines amongst figures from 1: 25 (part A of the test) and letters

from A to L (B part of the test). The Score is calculated as the total time in seconds was taken by the participant to finish the test [15].

III. **Digit span test "Wechsler adult intelligence scale"**: it was subdivided into 2 parts: Forward test that was used to evaluate attention, and backward test that was used to assess central executive functions. Contributors were allowed to take back a list of 3, 4, and 5-digit span lengths numbers for seven trials each for a total of 21 trials, first the patient was asked to recall the numbers similar to the presentation order (forward), then in the opposite order (backward) [16].

IV. **Digit symbol test:** for evaluation of the attention, visual-motor coordination, and psychomotor speed processing. Contributors was given a code menu that display a correspondence between couples of numbers (1: 9) and images. Then, they were requested to draw the fitting image under each number presented in the menu. The test result is the numbers of the image copied correctly in a 90sec time limit [17].

2. Blood sampling: After 12h of Fasting, five ml of venous blood was withdrawn, allowed to clot for 1 hour, centrifuged at 3000 rpm, then serum was separated after 15 min of the centrifugation, and finally stored at - 80 °C until biochemical assessment of:

I. **Serum iron**: Using the colorimetric method described by Tietz et al. [18].

II. **Serum ferritin test:** It was determined photometrically depending on the interaction of sample ferritin with latex covalently bound anti-Ferritin antibodies. [18].

III. **Total iron binding capacity (TIBC):** The decrease in the absorbance of the colored dye-iron complex was directly proportional to the TIBC of the serum sample. It was measured at 660 nm spectrophotometrically [19].

IV. **Unsaturated iron binding capacity (UIBC):** UIBC = TIBC – serum iron [20].

V. **25-dihydroxycholecalciferol** was measured using liquid chromatography tandem mass spectrometry method [21].

Statistical analysis: It was performed using SPSS v. 18.0 for Windows "SPSS Inc., Chicago, IL, USA". Normality distribution was checked with Shapiro–Wilk test. Continuous variables were presented as mean ± SD. The association between 25-dihydroxycholecalciferol, serum iron, ferritin with the changes in cognitive parameters was assessed by Pearson correlation test that was done to evaluate correlation between vitamin D3 and iron indices in studied groups as well. linear regression was used with serum iron and ferritin as independent variables, and vitamin D as dependent variables. The statistical significance was set at $P \leq 0.05$.

RESULTS

There is statistically significant difference between the studied groups regarding results of all tests used to assess cognitive function. Trail making A and B tests, was significantly higher in patients within dementia group ($p<0.001$). However, those patients reported significantly lower scores for digit span forward ($p<0.001$), backward, digit symbol test ($p<0.001$), immediate and delayed memory ($p<0.001$) when compared with healthy control group (Table 1).

There is statistically significant difference between the studied groups regarding serum iron, ferritin, TIBC and vitamin D levels. Serum iron ($p<0.05$), ferritin ($p<0.01$), TIBC ($p<0.001$) and vitamin D ($p<0.001$) were significantly lower among patients within dementia group. While, UIBC was lower among dementia group yet with statistically non-significant difference ($P>0.05$) (Table 2).

There is statistically significant negative correlation between serum iron and both trail making A test ($r=-0.297$, $p<0.05$) and B test ($r=-0.308$, $p<0.05$). On the other hand, no significant correlation coefficient was found between serum iron and other cognitive tests (table3).

There is statistically significant negative correlation between serum ferritin and trail making A test ($r=-305$, $p<0.05$). There is statistically significant positive correlation between serum ferritin and both digit span forward ($r=+0.361$, $p<0.01$) and digit symbol

test (r=0.317, p<0.05). On the other hand, no significant correlation coefficient was found between serum ferritin and other cognitive tests (table3).

In addition, there is statistically significant negative correlation between serum vitamin D and both trail making A test (r=-0.822, p<0.001) and B test (r=-0.658, p< 0.001). There is statistically significant positive correlation between serum vitamin D and all of digit span forward (r=+0.789, p<0.001), backwards (r=0.723, p<0.001), digit symbol test (0.748, p<0.001) (table3).

There is statistically significant positive correlation between vitamin D and both serum ferritin (r=0.451, p<0.001) and TIBC (r=0.727, p<0.001). On the other hand, there is statistically non-significant correlation between vitamin D and either serum iron or UIBC **(Table 4).**

Serum ferritin (unstandardized β=0.071, p=0.016) and TIBC (unstandardized β=0.269, p=<0.001) were significantly independently associated with serum vitamin D **(Table 5).**

Table (1) Comparison between the studied groups regarding cognitive functions

Parameter	Groups		Test	
	Dementia group (n=30)	Control group (n=30)	t	p
	Mean ± SD	Mean ± SD		
Trail making A test	55.6 ± 6.58	22.27 ± 6.9	19.153	<0.001*
Trail making B test	103.63 ± 8.67	86.03 ± 9.05	7.691	<0.001*
Digit Span Forward	4.58 ± 0.81	7.58 ± 0.76	14.842	<0.001*
Digit Span backward	4.36 ± 0.67	5.96 ± 0.59	-9.782	<0.001*
Digit symbol test	46.09 ± 4.04	58.1 ± 3.53	12.249	<0.001*

t independent sample t test *p<0.05 is statistically significant

Table (2) Comparison between the studied groups regarding iron indices and vitamin D level:

Parameter	Groups		Test	
	Dementia group (n=30)	Control group (n=30)	t	P
	Mean ± SD	Mean ± SD		
Serum iron (ugdL)	104.63 ± 27.2	119.41 ± 27.92	-2.077	0.042*
Serum ferritin (mg/ml)	117.95 ± 32.04	142.47 ± 29.78	-3.071	0.003*
TIBC (ug/dL)	296.39 ± 13.51	334.62 ± 17.67	-9.409	<0.001*
UIBC (ug/dL)	221.97 ± 30.38	223.56 ± 22.18	-0.232	0.818
Vitamin D (ng/ml)	15.39 ± 3.76	33.67 ± 5.32	-15.373	<0.001*

T: independent sample t test, *p<0.05 is statistically significant

Table (3) Correlation between serum iron, ferritin, vita D and cognitive functions among the studied participants:

	Serum iron		Serum ferritin		Vitamin D	
	R	P	r	P	r	p
Trail making A test	-0.297	0.021*	-0.305	0.018*	-0.822	<0.001***
Trail making B test	-0.308	0.017*	-0.158	0.229	-0.658	<0.001***
Digit Span Forward	0.186	0.155	0.361	0.005**	0.789	<0.001***
Digit Span backward	0.105	0.426	0.203	0.121	0.723	<0.001***
Digit symbol	0.225	0.084	0.317	0.014*	0.748	<0.001***

R: Pearson correlation coefficient, *: p<0.05 is statistically significant, **: p<0.01 is statistically significant , ***:p<0.001is statistically highly significant

Table (4) Correlation between vitamin D and iron indices among the studied participants

	r	p
Serum iron	0.186	0.155
Ferritin	0.451	<0.001**
TIBC	0.727	<0.001**
UIBC	-0.036	0.787

R: Pearson correlation coefficient, **p≤0.001 is statistically highly significant

Table (5) Linear regression analysis of factors significantly associated with serum vitamin D:

	Unstandardized Coefficients		Standardized Coefficients	t	P	95.0% Confidence Interval for B	
	B	Std. Error	Beta			**Lower Bound**	**Upper Bound**
Ferritin	0.071	0.029	0.229	2.490	0.016*	0.014	0.128
TIBC	0.269	0.038	0.649	7.062	<0.001**	0.193	0.345

**: p≤0.001 is statistically highly significant, *: p<0.05 is statistically significant

DISCUSSION

Dementia is a result of various neuropathological processes, including neuro-inflammation, neuro-degenerative, and vascular diseases, additionally, hypoxia, and oxidative stress could contribute to the pathogenesis of dementia [22]. Moreover, anemia leads to a rise in the risk of dementia and Alzheimer Disease by 34% and 41%; respectively [23]. However, the pathogenesis process that links anemia to dementia are not well understood yet.

Interestingly, the findings of this study showed a significant decrease in serum iron, ferritin and TIBC in dementia group when compared to control group. Which was in line with those of Alexander et al. [1], Kweona, et al. [6] and Hare et al. [24] Who found similar findings in Alzheimer's patients. They explained their findings by the significant reduction in transferrin-associated iron in those patients and assumed that transferrin desaturation might be the reason of the observed decrease in serum iron. Consequently, decreased iron may also influence the TIBC and may inhibit rate-limiting enzymes in brain cells metabolism, disturbing its functions [25].

That supported the significant negative association between serum iron, serum ferritin and Trail making A and B, and the significant positive association between serum ferritin and Digit Span Forward and Digit symbol in dementia group of the present work.

Additionally, the decreased iron, ferritin, and TIBC may be an evidence of iron deficiency anemia [26]. Decreased iron indices could predispose to dementia as one theory stated that low iron level results to decrease hemoglobin concentrations that might cause chronic brain cells hypoxia, precipitating beta-amyloid, and subsequently lead to neuro-inflammation that can cause deteriorated brain functions [23]. Another hypothesis is linked to brain's erythropoietin receptors, which act as neuro-protective factor against both hypoxia and stroke. Therefore, low erythropoietin may be a risk factor of neuronal damage and cognitive decline [27].

The second interesting observation of the current work was the considerable decline in serum vitamin D in dementia group, that was significantly associated with cognitive function tests in the same group.

Vitamin D3 is an endogenously synthesized steroid hormone, it exerts several biological activities [28]. It has a role in adult brain development and function. The brain displays the capability to produce and receive Vitamin D active form, which can support

neurotransmission, synaptic plasticity, and neuroprotection. As, it has been shown that 1,25(OH)2D can help the amyloid plaques phagocytosis and clearance by the innate immune cells [29]. It also has a critical role in lowering cerebral inflammation and oxidative stress, that are considered as possible mechanisms of neurodegeneration and Alzheimer Disease progression [28, 30]. However, contradictory outcomes were found by **Messinis et al.** [31] **and Karakis et al**. [32] who reported no association between vitamin D3 levels and Alzheimer Disease development.

Notably, a significant positive correlation between serum vitamin D3, ferritin and TIBC was detected in dementia group, and both were significantly independently associated with serum vitamin D3. One of the mechanisms that could clarify the impairment of iron indices existing with vitamin D3 deficiency is the increase in IL-6 or IL-1B [33].

From another point of view, iron is a constituent of vitamin D 25-hydroxylase, cytochrome P450 mono-oxygenase member, which contributes to cholecalciferol conversion to 25 cholecalciferol, and it is also a constituent of 25-hydroxyvitamin D 1-α-hydroxylase which is responsible for final activation of vitamin D3 [34]. Therefore, iron lack may lower the activity of these enzymes, and thus, lower vitamin D_3 concentration.

These facts may also explain the lower concentration of iron indices and vitamin D3 in dementia group of this research; however, no significant correlation between serum iron and vitamin D3 in the present work was found, the cause for this may be the degree of iron defect. Up till now it is not well-established how serious iron shortage has to be to affect vitamin D3 production. The odd ratios analyzed for various levels of ferritin (30 to 12 µg/L) revealed that the probability of vitamin D3 insufficiency began to be meaningful at ferritin levels <30 µg/L, suggesting that disturbed vitamin D3 synthesis can develop along with deteriorating iron status **[4].**

In contrary, there are previous studies that found no effect of iron supplementation on 25(OH) vitamin D3 level [3, 35].

Any discrepancy between our results and those of other studies could be related to genetic, environmental, species, age, health status, sample size differences, serum levels defined for Vitamin D3 deficiency, insufficiency, and sufficiency between their studies and the findings of the present study. One limitation of this study is the small sample size of the examined groups.

Conclusion: Serum iron, ferritin, TIBC and vitamin D3 levels in dementia patients were significantly lower than in normal participants, and they were significantly associated with cognitive function tests. Serum iron profile measurements and serum vitamin D3 in newly diagnosed cases with early symptoms of cognitive impairment may be valuable for the identification of dementia. It will be important for future research to examine how iron and/or vitamin D3 supplementation could improve cognitive functional changes in those patients.

Declaration of interest: The authors report no conflicts of interest.

Funding information .Authors did not receive any financial support or fund from any organization.

Authors contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by Nanees F El-Malkey and Tamer S. Elserafy and Emad L. Agban . The final draft of the manuscript was revised by Nanees F. El-Malkey and Wesam MR Ashour and Walid M Reda Ashour. All authors read and approved the final manuscript and were involved in revising and rewriting the manuscript and shared in final data representation

REFERENCES

1. Alexander RA, Deniz GS, James H, Subhojit C, Kieren A, Robert FP et al. Hepcidin Increases Cytokines in Alzheimer's Disease and Down's Syndrome Dementia: Implication of Impaired Iron Homeostasis in Neuroinflammation. Frontiers in Aging Neuroscience 2021;13: 188. DOI=10.3389/fnagi.2021.653591

2. Fishman MP, Lombardo SJ, Kharrazi FD. Vitamin D deficiency among professional basketball players. Orthop J Sports Med 2016; 4 .2325967116655742 :(7) doi2325967116655742/10.1177 :
3. Azizi-Soleiman F, Vafa M, Abiri B, Safavi M. Effects of iron on Vitamin D metabolism: A systematic review. Int J Prev Med 2016; 7: 126. DOI.7802.195212-2008/10.4103 :
4. Malczewska-Lenczowska J, Sitkowski D, Surała O, Orysiak J, Szczepa´nska B, Witek K. The Association between Iron and Vitamin D Status in Female Elite Athletes. Nutrients 2018; 10(2):167. doi:10.3390/nu10020167
5. Ndayisaba A, Kaindlstorfer C, Wenning GK. Iron in Neurodegeneration - Cause or Consequence .?Front Neurosci 2019; 13:180. doi:10.3389/fnins.2019.00180
6. Kweona OJ, Younb YC, Lima YK, Leea M-K, Kima HR. Clinical utility of serum hepcidin and iron profile measurements in Alzheimer's disease. J Neurol Sci 2019; 403: 85–91 .doi: 10.1016/j.jns.2019.06.008 .
7. Hosking DE, Ayton S, Beckett N, Booth A, Peters R. More evidence is needed. Iron, incident cognitive decline and dementia: a systematic review .Ther Adv Chronic Dis 2018; 9(12): 241-256. doi:10.1177/2040622318788485.
8. Schiepers OJ, van Boxtel MP, de Groot RH, Jolles J, de Kort WL, Swinkels DW, et al .Serum iron parameters, HFE C282Y genotype, and cognitive performance in older adults: results from the FACIT study .J Gerontol A Biol Sci Med Sci 2010; 65(12):1312-21 .doi: 10.1093/gerona/glq149. Epub 2010 Sep 2.
9. Cherbuin N, Kumar R, Sachdev PS, Anstey KJ . Dietary Mineral Intake and Risk of Mild Cognitive Impairment: The PATH through Life Project .Front Aging Neurosci 2014; 6:4 . doi/10.3389 :fnagi.2014.00004.
10. Min JY, Min KB .The Folate-Vitamin B12 Interaction, Low Hemoglobin, and the Mortality Risk from Alzheimer's Disease .J Alzheimers Dis 2016; 52(2):705-12 . https://doi.org/10.3233/JAD-151095.
11. Jayedi A, Rashidy-Pour A, Shab-Bidar S. Vitamin D status and risk of dementia and Alzheimer's disease: A meta-analysis of dose-response. Nutr Neurosci 2018; 22(11):750-759 .doi: 10.1080/1028415X.2018.1436639.
12. Schneider ALC, Zhao D, Lutsey PL, Gottesman RF, Sharrett AR, Rawlings AM, et al. Serum Vitamin D Concentrations and Cognitive Change Over 20 Years: The Atherosclerosis Risk in Communities Neurocognitive Study. Neuroepidemiol 2018; 51(3-4):131-137. doi: 10.1159/000490912 .
13. Lee JA, Hwang JS, Hwang IT, Kim DH, Seo J-H, Lim JS. Low vitamin D levels are associated with both iron deficiency and anemia in children and adolescents. Pediatr Hematol Oncol 2015; 32, 99–108 .DOI08880018.2014.983623/10.3109 :
14. Drozdick LW, Raiford SE, Wahlstrom D, Weiss LG. The Wechsler Adult Intelligence Scale—Fourth Edition and the Wechsler Memory Scale—Fourth Edition. In D. P. Flanagan & E. M. McDonough (Eds.), Contemporary intellectual assessment: Theories, tests, and issues. The Guilford Press; 2018: 486–511 .
15. Llinàs-Reglà J, Vilalta-Franch J, López-Pousa S., Calvó-Perxas, L., Torrents Rodas, D & ,.Garre-Olmo, J .(2016) .The trail making test Assessment, 24(2), 183–196. doi:10.1177/1073191115602552.
16. Elkana O, Tal N, Oren N, Soffer S, Ash EL. Is the Cutoff of the MoCA too High? Longitudinal Data From Highly Educated Older Adults. J Geriatr Psychiatry Neurol 2020; 33(3):155-160. doi: 10.1177/0891988719874121 .
17. Messinis L, Bakirtzis C, Kosmidis MH, Economou A, Nasios G, Anyfantis E, et al. Symbol Digit Modalities Test: Greek Normative Data for the Oral and Written Version and Discriminative Validity in Patients with Multiple Sclerosis. Arch Clin Neuropsychol 2021; 36(1):117-125. doi: 10.1093/arclin/acaa028 .
18. Tietz NW, Rinker AD, Morrison SR. When is a serum iron really a serum iron? The status of serum iron measurements. Clin Chem 1994; 40: 546–551.
19. Gambino R, Desvarieux E, Orth M, Matan H, Ackattupathil T, Lijoi E, Wimmer C, Bower J, Gunter E. The relation between chemically measured total iron-binding capacity concentrations and immunologically measured transferrin concentrations in human serum. Clin Chem 1997; 43(12): 2408-12. PMID: 9439462 .
20. Yamanishi H, Iyama S, Yamaguchi Y ,Kanakura Y, Iwatani Y .Total iron-binding capacity calculated from serum transferrin concentration or serum iron concentration and unsaturated iron-

binding capacity. Clin Chem 2003; 49:175–178 .https://doi.org/10.1373/49.1.175.
21. Singh RJ, Taylor RL, Reddy GS ,Grebe SKG .C-3 epimers can account for a significant proportion of total circulating 25-hydroxyvitamin D in infants, complicating accurate measurement and interpretation of vitamin D status. J Clin Endocrinol Metab 2006; 91:3055–3061. doi:10.1210/jc.2006-0710.
22. Gattas BS, Ibetoh CN, Stratulat E, Liu F, Wuni GY, Bahuva R, et al. The Impact of Low Hemoglobin Levels on Cognitive Brain Functions. Cureus 2020; 12(11):e11378. doi:10.7759/cureus.11378
23. Wolters FJ, Zonneveld HI, Licher S, Cremers LGM; Heart Brain Connection Collaborative Research Group, Ikram MK, et al. Hemoglobin and anemia in relation to dementia risk and accompanying changes on brain MRI. Neurology 2019; 93:e917–e926. doi: 10.1212/WNL.0000000000008003 .
24. Hare DJ, Doecke JD, Faux NG, Rembach A, Volitakis I, Fowler CJ et al. Decreased plasma iron in Alzheimer's disease is due to transferrin desaturation. Chem. Neurosci 2015; 6(3): 398–402 .https://doi.org/10.1021/cn5003557
25. Jeong S-M, Shin DW, Lee JE, Hyeon JH, Lee J, Kim S. Anemia is associated with incidence of dementia: a national health screening study in Korea involving 37,900 persons. Alzheimers Res Ther 2017; 9:94. https://doi.org/10.1186/s13195-017-0322-2
26. Madu AJ, Ughasoro MD. Anaemia of Chronic Disease: An In-Depth Review. Med Princ Pract 2017; 26(1):1-9. doi:10.1159/000452104
27. Shah R, Buchman A, Wilson R, Leurgans S, Bennett D. Hemoglobin level in older persons and incident Alzheimer disease: prospective cohort analysis. Neurology 2011; 77: 219–226 . DOI/10.1212 :WNL.0b013e318225aaa9.
28. Bivona G, Gambino CM, Iacolino G, Ciaccio M. Vitamin D and the nervous system. Neurol Res 2019; 41: 827–835 .doi: 10.1080/01616412.2019.1622872.
29. Bivona G, Agnello L, Bellia C, Iacolino G, Scazzone C, Lo Sasso B et al. Non-Skeletal Activities of Vitamin D: From Physiology to Brain Pathology. Medicina 2019; 55: 341 . doi/10.3390 :medicina55070341
30. Bivona G, Lo Sasso B, Gambino CM, Giglio RV, Scazzone C, Agnello L, et al. The Role of Vitamin D as a Biomarker in Alzheimer's Disease. Brain Sci 2021; 11: 334. https://doi.org/ 10.3390/brainsci11030334.
31. Ulstein I, Bøhmer T. Normal Vitamin Levels and Nutritional Indices in Alzheimer's Disease Patients with Mild Cognitive Impairment or Dementia with Normal Body Mass Indexes. J Alzheimers Dis 2017; 55: 717–725 .doi: 10.3233/JAD-160393.
32. Karakis I, Pase MP, Beiser A, Booth SL, Jacques PF, Rogers G et al. Association of serum vitamin D with the risk of incident dementia and subclinical indices of brain aging: The Framingham Heart Study. J Alzheimers Dis 2016; 51: 451–461 .doi: 10.3233/JAD-150991 .
33. Zughaier SM, Alvarez JA, Sloan JH, Konrad RJ, Tangpricha V. The role of vitamin D in regulating the iron-hepcidin-ferroportin axis in monocytes. J Clin Transl Endocrinol 2014; 1: e19–e25 . doi/10.1016 :j.jcte.2014.01.003.
34. Toxqui L, Vaquero MP. Chronic iron deficiency as an emerging risk factor for osteoporosis: A hypothesis. Nutrients 2015; 7: 2324–2344 .doi/10.3390 :nu7042324.
35. Katsumata S, Katsumata R, Matsumoto N, Inoue H, Takahashi N, Uehara M. Iron deficiency decreases renal 25-hydroxyvitamin D 3-1-hydroxylase activity and bone formation in rats. BMC Nutr 2016; 2, 33. Doi : https://doi.org/10.1186/s40795-016-0072-8.

How to Cite:
Ashour, W., El-Malkey, N., Agban, E., Ashour, W., El-Serafy, T. The Relation Between 25-dihydroxycholecalciferol, iron status and The Deteriorated Cognitive Function in Dementia patients. *Zagazig University Medical Journal*, 2023; (720-727): -. doi: 10.21608/zumj.2022.117551.2457