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Relationship between thyroid dysfunction and dementia

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Abstract

Background: Thyroid hormones are essential for normal development and function of the central nervous system. Thyroid dysfunction is associated with many neuropsychiatric disorders mainly cognitive impairment.

Results: We found a close correlation between thyroid status and cognitive dysfunction. Serum FT3 levels decreased, whereas the serum thyroid-stimulating hormone (TSH) level increased, with the decline in cognitive functions. Furthermore, the TSH level showed a negative correlation with the Mini-Mental State Examination (MMSE) scores. We suggested that thyroid function was associated with cognitive impairments induced by subcortical ischemic vascular dementia (SIVD).

Conclusion: We found that thyroid dysfunction especially subclinical hypothyroidism is associated with cognitive impairment. Dementia increases more with more increase in TSH, and the MMSE score decreases with the increase of age.

Keywords: TSH, Dementia, AD, VD, FTD, MMSE

Introduction

Dementia diminishes the individual's ability to live independently and the quality of life. Dementia, and its most frequent subtype which is Alzheimer's disease, has been associated with thyroid status.

Vascular dementia (VD), also known as vascular cognitive impairment (VCI), results from brain damage due to inadequate blood supply and is the second most common form of dementia only after Alzheimer's disease (AD) [1]. Dementia is defined as a collection of clinical syndromes including impairment of memory, judgment, reasoning, behaviors, and communication abilities and is one of the most disabling conditions affecting the aged population [2]. In the last two decades, thyroid status has emerged as maintenance of normal neural functions. One of the biological mechanisms underlying the relationship between thyroid dysfunction and dementia is suggested to be associated with cardiac vascular disease,

which can contribute to cognitive impairment in later life [3].

Methods

This study is a case-control, cross-sectional prospective study that was carried on 40 patients with dementia as well as 10 healthy volunteers as controls. The patients were recruited from the Neurology clinic at Benha University hospitals. All patients were informed about their participation in the study and signed a written consent that was reviewed by the local ethical committee of Benha University.

Inclusion criteria

Patients aged above 40 with dementia.

Exclusion criteria

Diagnosis with chronic or degenerative diseases, known thyroid disease, history of brain injury or alcohol abuse, treatment with medication which could influence thyroid or brain function within 4 weeks before the testing, inability to give informed consent.

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Study design

All subjects after giving informed consent were submitted to full medical history with a focus on age, sex, smoking, and body mass index. Sex; the presence of DM, HTN, and IHD; thorough medical examination; and laboratory tests were done as a serum level of TSH, FT3, and FT4 levels.

Statistical analysis

All collected data were tabulated and analyzed using Statistical Package for Social Science (SPSS) version 16 to obtain:

1. Descriptive data

Descriptive statistics were calculated for the data in the form of:

- (a) Mean and standard deviation for quantitative data
- (b) Frequency and distribution for qualitative data

2. Analytic analysis

- (a) Fisher’s exact test is used when you have two nominal variables
- (b) The Student “t” test compares between 2 means of 2 independent groups; *t* value is the ratio of the difference between the two means/calculated SD of this difference
- (c) Rho→Spearman’s correlation coefficient: It evaluates the linear association between 2 quantitative variables
- (d) The Kruskal-Wallis test (KW test) is used to compare quantitative variables among more than 2 independent groups

Results

Table 1 shows the demographic characters of the control and cases. Fifty-five percent of the patients were females

and 45% were males in the patient group, while 80% were females and 20% were males in the control group. The mean age of patients was 65.9 ± 13.6, while in the control group, it is 57.5 ± 12.6. There was no significant difference found in the studied groups in age and sex. *P* is 0.054 and 0.28 in order.

Table 2 shows the comparison of the studied groups as regards the presence of DM. None of the control subjects was diabetic, while 57.5% of patients were diabetic. There is a statistically significant difference between patients and controls in the presence of DM, and *P* is 0.001.

Table 3 shows a comparison between the studied groups as regards HTN. None of the control subjects was hypertensive, while 55.0% of patients were hypertensive. According to HPT, there was a significant difference between patients and controls, and *P* is 0.001 statistically significant.

Table 4 shows that serum TSH was significantly high in patients than in the control group. Serum FT3 was significantly low in patients in comparison to the control. There was no statistically significant difference regarding FT4 between patients and the control group. *P* is 0.03, 0.28, and 0.48 in order.

Table 5 shows a comparison between thyroid dysfunction in the studied groups. 62.5% of patients had subclinical hypothyroidism, 7.5% had subclinical hyperthyroid, and 30% of the patients were euthyroid, while 9% of the control group were euthyroid and 1% had subclinical hypothyroidism. There was a significant statistical difference in the patients than in the controls, and *P* is 0.003 (Table 6).

Table 7 compares the degree of dementia according to the history of DM. In patients with MCI, 12.5 % had DM; in patients with mild dementia, 65.2% had DM; and in patients with moderate dementia, 77.8% had a history of DM. There was a statistically significant difference between the degree of dementia and DM, when comparing between MCI and mild dementia, MCI, and moderate dementia. *P* is 0.015.

Table 8 compares the degree of dementia according to the history of HTN. In patients with MCI, 0% had hypertension, while in patients with mild dementia,

Table 1 Demographic characters of the studied sample descriptive data

Variable	Patients (n = 40)		Controls (N = 10)		Total (N = 50)		Test of significance	<i>P</i>	
	No.	%	No.	%	No.	%			
Sex	Male	18	45.0	2	20.0	20	40.0	FET	0.28 (NS)
	Female	22	55.0	8	80.0	30	60.0		
Age (years)	Mean ± SD	65.9 ± 13.6		57.5 ± 12.6				<i>Z</i> _{MWU} = 1.92	0.054 (NS)
	Range	40–88		40–74					
	Range	60–120		70–82					

FET was used. *P* = 0.001 (HS)

Table 2 Comparison of the studied groups regarding the history of DM

			Group		Total
			Patients	Controls	
DM	No	Count	17	10	27
		% within group	42.5%	100.0%	54.0%
	Yes	Count	23	0	23
		% within group	57.5%	0.0%	46.0%
Total	Count	40	10	50	
	% within group	100.0%	100.0%	100.0%	

FET was used. $P = 0.001$ (HS)

65.2% had hypertension and in patients with moderate dementia, 77.8% had a history of HTN. There was a statistically significant difference between HPT and the degree of dementia when comparing between MCI and mild dementia, MCI, and moderate dementia. P is 0.001.

Table 9 shows the relation between thyroid dysfunction and degree of dementia. There was a statistically significant difference in thyroid dysfunction with the degree of dementia especially when comparing subclinical hypothyroidism with MCI and mild dementia, MCI, and moderate dementia. P is 0.002.

Table 10 compares the degree of dementia according to sex. 12.5% of patients with MCI were males, 43.5% of patients with mild dementia were males, and 77.8% of moderate dementia were males, while 87.5% of patients with MCI were females, 56.5% of patients with mild dementia were females, and 22.2% of patients with moderate dementia were females. There was a statistically significant difference when comparing the degree of dementia with sex. P is 0.029.

Figure 1 compares the MMSE score according to TSH (there was a significant correlation). P is less than 0.001.

Figure 2 compares the MMSE score according to age (there is a highly significant correlation). P is less than 0.001.

Table 3 Comparing the studied groups regarding the history of hypertension

			Group		Total
			Patients	Controls	
HTN	No	Count	18	10	28
		% within group	45.0%	100.0%	56.0%
	Yes	Count	22	0	22
		% within group	55.0%	0.0%	44.0%
Total	Count	40	10	50	
	% within group	100.0%	100.0%	100.0%	

FET was used. $P = 0.001$ (HS)

Discussion

In our study, we investigate the relationship between thyroid status, cognitive status, and severity of dementia. Dementia is one of the most disabling conditions affecting the aged population and diminishes the individual's ability to live independently and the quality of life. Besides, it imposes a major burden on the health care system. Therefore, it would be of great advantage if modifiable risk factors for dementia could be identified [2].

Thyroid hormones have been demonstrated to play central roles in the development of the central neural system. The relation between thyroid functional state and the risk of AD and VD has been widely investigated, by assessing the serum levels of thyroid hormone including FT3, thyroxin (FT4), and TSH. Both subclinical hyper- and hypothyroidism have been established as risk factors for cognitive impairment [2]. The American Association of Clinical Endocrinologists (AACE) has proposed modifying target TSH levels from the widely accepted 0.5 to 5.0 mU/L to the narrower range 0.3 to 3.04 mU/L.

The National Association of Clinical Biochemistry argues that the upper limit of serum TSH euthyroid range should be reduced to 2.5 mU/L, citing data that over 95% of rigorously screened normal. Both clinical and subclinical hypothyroidism have been shown by several although not all studies to affect cardiovascular risk.

Hyperthyroidism is associated with an increase in vascular basement membrane thickness and capillary destruction. In parallel, vascular risk factors have been correlated with an increase in the risk for AD. Thus, through an increase in vascular risk factors, thyroid function may indirectly affect AD risk (Tan et al., 2006).

In our study, we found that there is a strong link between high thyroid dysfunction and risk (Tables 5 and 6) and the degree of dementia (Table 9). One of the biological mechanisms underlying the relationship between thyroid dysfunction and dementia is suggested to be associated with cardiac vascular disease, which can contribute to cognitive impairment in later life. Our results were in agreement with Davis et al. who proposed thyroid hormones as risk predictors of dementia. Subclinical hypothyroidism with T4 and elevated TSH has been identified as a common predisposing factor of depression, cognitive impairment, and dementia [4].

Also, this was concordant with Carole Rieben et al. who found that the risk of dementia increases with more increase in TSH level. Among older adults, subclinical hyperthyroidism with a TSH < 0.10 mIU/L was associated with a higher risk of dementia and a larger cognitive decline, while subclinical hyperthyroidism with mildly decreased TSH or subclinical hypothyroidism were not (Rieben et al, 2017).

Table 4 Comparing the studied groups regarding thyroid function tests

Variable	Patients (n = 40)			Controls (N = 10)			Z _{MWU} test	P
	Mean	±SD	Range	Mean	±SD	Range		
TSH	3.99	2.28	0.81–8.32	2.31	0.99	1.04–4.31	2.16	0.03 (S)
FT3	2.14	1.65	0.25–7.92	3.02	0.49	2.32–3.76	2.19	0.028 (S)
FT4	1.52	0.91	0.01–3.77	1.47	0.36	1.1, 2.3	0.70	0.48 (NS)

1 Also, this was concordant with Scherr et al. who found
2 that cognitive function was closely related with serum
3 T3, which has been widely characterized to be a notable
4 preventive and therapeutic target in thyroid disorders,
5 and even in neuropsychological diseases [5, 6].

6 Also, this was in agreement with Shindo et al. who at-
7 tributed the relation of dementia and FT3 to the critical
8 roles of T3 in the maintenance of inner mitochondrial
9 membrane fluidity and permeability through regulating
10 the fatty acid and phospholipid composition of the
11 membrane. It is likely that T3 deficiency may lead to the
12 onset of mitochondrial dysfunctions, thus affecting brain
13 metabolic activity and intracellular signal transduction
14 and contributing to the cerebral ischemia [7].

15 Also, this was concordant with Chen et al. who found
16 higher serum TSH and lower T3 levels may be associated
17 with cognitive impairment induced by SIVD and recog-
18 nized the neuropsychological features of VD stages [8].

19 Also, this was concordant with Annerbo and Lökk
20 who found the association between TSH and cognitive
21 impairment in community-dwelling and hospitalized
22 elderly [9].

23 This was in agreement with Hogervorst et al. who re-
24 ported that cognition was investigated at baseline and
25 after a 2-year follow-up in 1047 participants over 64
26 years of age, without physical frailty or severe cognitive

impairment at baseline, and found an association be-
tween high FT4 levels and an accelerated cognitive de-
cline as well as dementia progression [10].

Also, this was not concordant with Hofman and his
colleagues who, in the [Rotterdam Study](#), after adjust-
ment for variables including age, sex, and cardiovascular
disease risk factors, showed that those with higher
thyroid-stimulating hormone (TSH) levels—typically a
sign of an underactive thyroid—had a lower risk of de-
mentia [11].

This was not concordant with Jorde et al. who found
lack of association between subclinical hypothyroidism
and cognitive impairment is also in line with the results
of other placebo-controlled randomized clinical trials
[12, 13].

This was not concordant with Roberts et al. who
showed a lack of association between subclinical
hypothyroidism and cognitive impairment that largely
drew upon the results from large population-based stud-
ies [14].

In our study, we found that the increase in TSH level
is associated with more decrease in MMSES and AD and
VD patients with the worse cognitive performance pre-
sented distinctly lower MMSE scores than the healthy
control, and there was a significant link between TSH
concentrations and patients converting from mild

Table 5 Comparison of the studied groups regarding thyroid dysfunction

		Group		Total
		Patients	Controls	
Euthyroid	Count	12	9	21
	% within group	30.0%	90.0%	42.0%
Overt hypothyroidism	Count	0	0	0
	% within group	0	0%	0%
Subclinical hypothyroidism	Count	25	1	26
	% within group	62.5%	10.0%	52.0%
Overt hyperthyroidism	Count	0	0	0
	% within group	0	0%	0%
Subclinical hyperthyroidism	Count	3	0	3
	% within group	7.5%	0%	6.0%
Total	Count	40	10	50
	% within group	100.0%	100.0%	100.0%

FET = 10.9. P = 0.003 (S)

Table 6 Distribution of the degree of dementia according to age

Variable	Mild cog impairment (N = 8)		Mild dementia (N = 23)		Moderate dementia (N = 9)		KWT	P	Sig pairs
	Mean	± SD	Mean	± SD	Mean	± SD			
Age (years)	45.7	6.84	71.9	10.01	72.7	5.86	17.4	< 0.001 (HS)	Mild cog≠mild dementia Mild cog≠mod dementia

cognitive impairment to Alzheimer's disease. This was concordant with Zongsheng Chen who found that a close correlation between thyroid status and cognitive dysfunction in SIVD was observed. Serum TT3 and FT3 levels decreased, whereas serum TSH level increased, with the decline in cognitive functions. Furthermore, TT3 levels showed a positive correlation, whereas TSH level showed a negative correlation, with the Mini-Mental State Examination (MMSE) scores, suggesting that thyroid function was associated with cognitive impairments induced by SIVD. Also, thyroid function and thyroid hormone level could be a risk factor in the development of SIVD. Serum TT3 and TSH levels might also be used as biomarkers for cognitive dysfunction [8].

Also, this was concordant with Johe who found a linear relationship between thyroid hormone and MMSE scores was conducted. Higher TSH and lower T3 significantly lowered the MMSE scores, which indicated worse cognitive performance. A central role of T3 in neuronal differentiation has been uncovered, which directed stem cells to generate clones of neuro-oligodendrocytes from the central nervous system [15].

Also, this was concordant with [16], who found that VD patients with worse cognitive performance presented distinctly lower MMSE scores than the healthy control. The cognitive performance of VD patients was significantly declined, as indicated by the significantly altered scores of several neuropsychological tests, for example MMSE as measurements of global cognitive function.

Also, this was in agreement with Roman et al. who indicated a consistent positive correlation between TSH levels and cognitive decline in VD. However, most of the associations found in subclinical hypothyroidism concerned participants in particular with a TSH level of 5 mIU/L or above [17].

But this was not concordant with Jorde et al. who found that there was a lack of association between subclinical hypothyroidism, high TSH, and cognitive impairment and MMSE which was also concordant with the results of two placebo-controlled randomized clinical trials which stated the same results [12].

In our study, we found that dementia increases in the presence of DM (Table 2). There was a relationship between impaired glucose tolerance and stroke-related dementia as DM is one of many other risk factors of vascular disease.

This was in agreement with the Rotterdam study which included 9446 participants with a mean age of 65 years. During follow-up (mean 8.0 years), 601 participants had developed dementia and it was found that diabetes is an attributable risk for dementia of which 8.8% suggests that diabetes may have contributed to the clinical syndrome in a substantial proportion of all dementia patients [18].

This was not concordant with J.D. Curb et al. who found that there is no association between AD and diabetes, present either 25 or 15 years previously; it was found after adjustment for age and education in a multiple regression model [19].

In our study, we found that dementia increases in the presence of hypertension which is one of the many risk factors of vascular disease.

This was in agreement with Nelson et al. who found that previously increased blood pressure may increase the risk for dementia by inducing small-vessel disease and white-matter lesions. To what extent the decline in blood pressure before dementia onset is a consequence or a cause of the brain disease remains to be elucidated [20].

This was not concordant with Luchsinger et al. who found that hypertension after age 65 years is not

Table 7 Distribution of the degree of dementia according to the history of DM

			Dementia degree			Total
			Mild cog impairment	Mild dementia	Moderate dementia	
DM	No	Count	7	8	2	17
		%	87.5%	34.8%	22.2%	42.5%
	Yes	Count	1	15	7	23
		%	12.5%	65.2%	77.8%	57.5%
Total	Count	8	23	9	40	
	%	100.0%	100.0%	100.0%	100.0%	

FET = 8.3. P = 0.015 (S)

Table 8 Distribution of the degree of dementia according to the history of hypertension

		Dementia degree			Total	
		Mild cog impairment	Mild dementia	Moderate dementia		
HTN	No	Count	8	8	2	18
		%	100.0%	34.8%	22.2%	45.0%
	Yes	Count	0	15	7	22
		%	0.0%	65.2%	77.8%	55.0%
Total		Count	8	23	9	40
		%	100.0%	100.0%	100.0%	100.0%

FET = 12.9. $P = 0.001$ (HS)

associated with AD and does not adversely affect memory, language, or general cognitive function. A history of hypertension may be an antecedent to VD, particularly in the presence of heart disease or diabetes [21].

In our study, we found that the degree of dementia increases with FT3 decrease and TSH increase (hypothyroidism) but with no relation with the FT4 level.

This was concordant with Francesco et al. who found that lower TSH levels were found to be predictive factors of AD progression in subjects with mild cognitive impairment (Francesco et al, 2017).

But this was not in agreement with Hogervorst et al. who reported that cognition was investigated at baseline and after a 2-year follow-up in 1047 participants over 64 years of age, without physical frailty or severe cognitive impairment at baseline, and found an association between high FT4 levels and an accelerated cognitive decline as well as dementia progression. It is unclear why high normal FT4 levels were independently associated with accelerated cognitive decline in those without overt thyroid disease [10].

In our study, we found an increase severity of dementia with age. Patients with mild dementia and those with moderate dementia are older than those with MCI. People are living longer, and dementia is becoming more common in the population as a whole.

This was in agreement with Constantine et al. who found that the severity of dementia increases with age (American Journal of Psychiatry as the mean of age was 74 and severity increased with age) [22].

Also, this was in agreement with [23] who found the same results.

This was not in agreement with Holland et al. who found that dementia and AD severity decrease with age as they found that the phenotypic expression of AD is relatively mild in individuals older than approximately 85 years, and this may affect the ability to distinguish AD from normal aging in the very old ([24]).

In our study, we found that the dementia degree increases more in females. The relationship between sex and AD has been inconsistent across studies although in many studies women are reported to have higher rates

Table 9 Relation between the degree of dementia and thyroid dysfunction

		Dementia degree			Total
		Mild cog impairment	Mild dementia	Moderate dementia	
Euthyroid	Count	4	5	3	12
	%	50.0%	21.7%	33.3%	30.0%
Overt hypothyroidism	Count	0	0	0	0
	%	0%	0%	0%	0%
Subclinical hypothyroidism	Count	1	18	6	25
	%	12.5%	78.3%	66.7%	62.5%
Overt hyperthyroidism	Count	0	0	0	0
	%	0%	0%	0%	0%
Subclinical hyperthyroidism	Count	3	0	0	3
	%	37.5%	0.0%	0.0%	7.5%
Total	Count	8	23	9	40
	%	100.0%	100.0%	100.0%	100.0%

FET = 13.8. $P = 0.002$ (S)

Table 10 Distribution of the degree of dementia according to sex

			Dementia degree			Total
			Mild cog impairment	Mild dementia	Moderate dementia	
Sex	Male	Count	1	10	7	18
		%	12.5%	43.5%	77.8%	45.0%
	Female	Count	7	13	2	22
		%	87.5%	56.5%	22.2%	55.0%
Total		Count	8	23	9	40
		%	100.0%	100.0%	100.0%	100.0%

FET = 7.07. P = 0.029 (S)

of AD than men even after adjusting for differential survival. Significant differences between sex usually occur.

This was concordant with Pike et al. who found that an association between sex and AD assumes a greater significance as there is increasing evidence that estrogen replacement therapy in postmenopausal women improves cognitive function and reduces the risk for both cognitive impairment and AD [25].

This was concordant with Hotze Health who worked on around 2000 patients who were evaluated for dementia over the course of 13 years. In that time, 209 patients developed Alzheimer’s. The study concluded that women with the lowest serum concentrations of TSH and those with the highest concentrations were more than twice as likely to develop Alzheimer’s disease than the women with normal/mid-range levels. The study

was unable to determine the same sort of link among men [26].

In Framingham study, participants were followed up for a period of 12.7 years, close to 2000 participants who were tested periodically for thyroid function using thyroid-stimulating hormone (TSH) levels and tested for dementia using the Mini-Mental Status Examination (MMSE). A relationship one way or the other was thought to maybe be found, but it was interesting to find that both low and high levels of TSH were associated with Alzheimer’s disease. It is also unclear why thyroid hormone levels affect Alzheimer’s disease risk in women but not in men. It may be that the brain of women or the hormonal milieu of women makes them more prone to this effect [27].

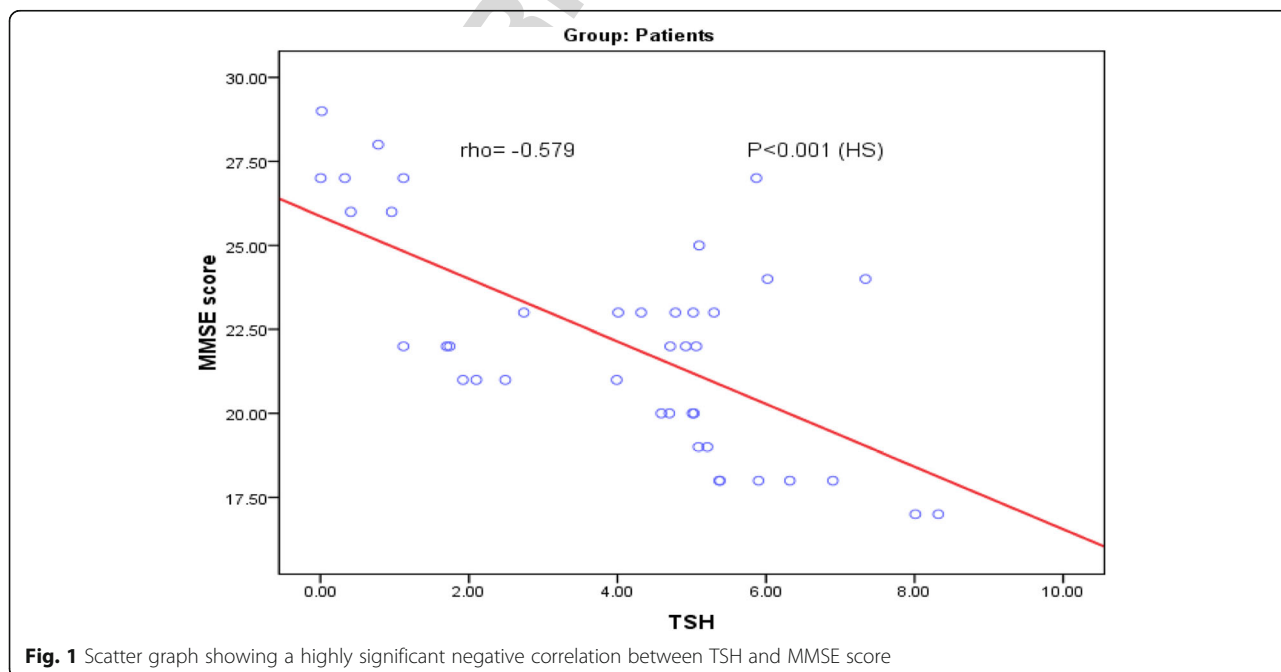


Fig. 1 Scatter graph showing a highly significant negative correlation between TSH and MMSE score

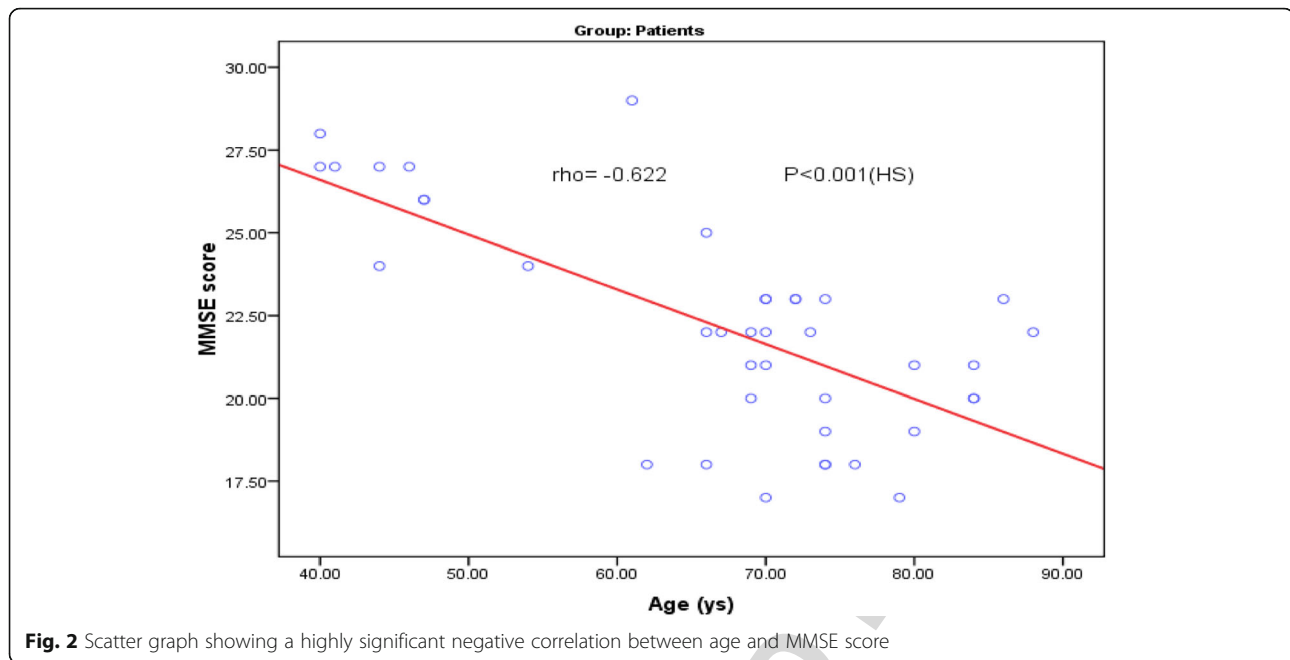


Fig. 2 Scatter graph showing a highly significant negative correlation between age and MMSE score

Conclusion

We found that thyroid dysfunction especially subclinical hypothyroidism is associated with cognitive impairment. Dementia increases more with more the increase in TSH, and the MMSE score decreases with the increase of age. So we suggest screening for subclinical hypothyroidism in all patients with cognitive dysfunction

Abbreviations

TSH: Thyroid-stimulating hormone; FT3: Tri-iodothyronine; FT4: Thyroxin; DM: Diabetes mellitus; HTN: Hypertension; VD: Vascular dementia; AD: Alzheimer disease; MCI: Mild cognitive impairment; MMSES: Mini-Mental Status Examination Score; SIVD: Subcortical ischemic vascular dementia; FTD: Frontotemporal dementia

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Authors' contributions

A.E contributed to the data collection, design of the study, and writing of the discussion. E.A. contributed to the study design, interpretation of data, writing of the discussion, and results; drafted the work and revised it; and created the new software used in the work. I.A contributed to the data collection and writing of the discussion and revised the data. R.O contributed to the data collection and interpretation, the creation of new software used in the work, and the writing of the discussion and results. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of Benha Faculty of Medicine, Benha University with approval number "I can not provide it now but I will bring it soon."

A written consent was obtained from all participants in the study.

Consent for publication

Not applicable

Competing interests

No financial and non-financial competing interests

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