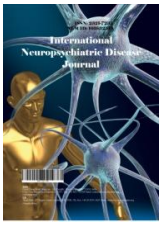

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Effect of Donepezil and Vitamin B_{12} Supplement on Serum Thyroid Profile in Alzheimer's Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this study was to investigate thyroid status in Alzheimer's Disease (AD) patients and its response to donepezil and vitamin B_{12} supplement therapy for 6 months.
Design: Case-Control Observational study.
Place and Duration: Department of Biochemistry, GGMC & Sir J. J. Group of Hospitals, Mumbai, India between March 2017 and July 2019.
Methodology: Case-Control study comprised of 71 AD patients and 70 healthy controls above 60 years of age. Blood serum samples were analyzed for thyroid hormones levels by the chemiluminescence method. AD patients were treated with donepezil (5 mg/day) and vitamin B_{12} supplement (1.5 mg/day) and thyroid profile was observed at intervals of 3 and 6 months. Statistical evaluation was done by using IMB SPSS statistics version 25.

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Results: Serum levels of thyroid hormones were low in euthyroid AD patients when compared with controls at the baseline level [T3 (120.64 ± 20.64 vs 127.8 ± 17.29), T4 (7.71 ± 2.34 vs 7.54 ± 1.85), FT3 (1.2 ± 0.13 vs 2.26 ± 0.63) and FT4 (0.79 ± 0.08 vs 1.29 ± 0.27)] except TSH which was increased in AD [TSH (2.71 ± 1.19 vs 2.34 ± 0.65)]. During follow-ups at 3 and 6 months, there was a slight decrease in TSH levels in response to the therapy.
Conclusion: The AD patients were euthyroid with low T3, FT3 and FT4 serum levels and high TSH serum levels. Thyroid hormones might play a role as markers for disease progression. Donepezil and vitamin B_{12} therapy could not benefit restore the normal thyroid functioning in a period of 6 months. Further longitudinal research with larger cohort might help in elucidating thyroid dysfunction in AD and develop novel therapeutic strategies.

Keywords: Thyroid stimulating hormone; Alzheimer's Disease; donepezil; vitamin B_{12}.

1. INTRODUCTION

Alzheimer's Disease (AD) is a degenerative disorder of the central nervous system (CNS) with pathological conditions involving the formation of neurofibrillary tangles and amyloid plaques within neuronal tissue. The cholinergic hypothesis has been proposed to be an etiology of AD, based on the presynaptic deficits found in diseased brains [1].

Alterations in the endocrine system have increasingly been linked to the pathogenesis of AD and other dementias [2]. The most widely recognized association between endocrine and cognitive functions involves the thyroid hormone supported by increasing pieces of evidence about an extensive inter-relationship between thyroid hormones and the cholinergic system. Thyroxin (T4) has been shown to modulate choline acetyltransferase activity, and triiodothyronine (T3) has been shown to negatively regulate the expression of amyloid precursor protein (APP) in the brain [3,4]. Although the progressive cognitive decline is a critical clinical feature of AD, mood disturbance and behavioral symptoms are very common in patients. Thyroid status has been profoundly associated with mood symptoms such as agitation, irritability, depression, fear, and fatigue [1]. Many studies have investigated the association between dementia, particularly AD and thyroid function, but the findings are inconsistent. In spite of the well-known effects of clinical thyroid disorders on cognitive function, the relationship between thyroid hormone levels and cognitive performance among older adults is unclear [5].

Considering the impact of thyroid hormones on nervous function, it could be stated that levels of thyroid hormones are tightly regulated and maintained within a narrow range even in the face of fluctuations in serum T4 levels. Such regulation suggests that even slight deviations from this range might result in cognitive dysfunction [2,6].

Currently, the most common drugs used for AD treatment are cholinesterase inhibitors (ChEI) including donepezil. Donepezil hydrochloride is an acetylcholinesterase inhibitor (AChEI) which inhibits the action acetylcholinesterase (AChE) in neuronal synapses, rendering increased acetylcholine action for better cognition [7,8]. AD patients are also found to be deficient for Vitamin B_{12}, which has a striking effect on cognitive dysfunction [9,10,11].

The aim of the study was to investigate thyroid function in AD patients by the determination of serum levels of Triiodothyronine (T3), Thyroxine (T4), free triiodothyronine (FT3), free thyroxine (T4) and the thyroid-stimulating hormone (TSH). The effect of donepezil and vitamin B_{12} supplement therapy on thyroid hormones T3, T4 and TSH was also observed.

2. METHODOLOGY

The study comprised of 71 clinically diagnosed AD patients and 70 normal healthy controls. Recruited subjects were of both genders in the age group above 60 years. Patients admitted and those visiting Out Patient Department at Sir J. J. Group of Hospitals, Mumbai were included in the study. Subjects not willing to participate in the study and those suffering from a head injury, cerebral stroke, chronic diabetes, poisoning, schizophrenia, chronic alcoholism or any other mental illness were excluded. There was no history of thyroid disease or of any other major ailment in any of the patients. Venous blood samples of all the study participants were collected by venipuncture and serum was separated. Serum samples were analyzed for the thyroid profile (T3, T4, TSH, FT3, and FT4) as baseline investigation by using the

chemiluminescence method on Siemens Fully Automated Immulite 1000 Chemiluminescent Immunoassay. AD patients were treated with Donepezil (5 mg/day) and Vitamin B_{12} supplements (1.5 mg/day) for 6 months. Serum levels of T3, T4 and TSH were analyzed at intervals of 3 months and 6 months. Socioeconomic status of AD patients was categorised based on modified Kuppuswamy socioeconomic status scale [12]. Statistical evaluation was done by using IMB SPSS Statistics version 25.

3. RESULTS AND DISCUSSION

The age-sex wise distribution and Mini Mental State Examination (MMSE) score of the study participants is shown in Table 1 and the AD participants categorized according to socioeconomic status is shown in Table 8. M. E. B´egin et al. 2008 states that since the potentially increased risk of cognitive decline is linked with thyroid dysfunction and that progressive cognitive decline is the central clinical feature of Alzheimer's disease, it is possible that thyroid status contributes, at least in part, to the clinical manifestation of Alzheimer's disease [13,14]. Some studies have shown that there is no influence on the thyroid function in AD pathology [8,9], while some showed increased TSH serum levels associated with AD pathology [15,16,17]. A study by Karimi et al. 2011, suggested that a reduced level of T3, within the normal range, may be independently associated with cognitive decline in AD patients [18]. Similar to this study, our study shows reduced serum T3 levels within the normal range in AD which can be seen in Tables 2. Studies have shown that subclinical hypothyroidism may be a predisposing factor for cognitive impairment. Subclinical hypothyroidism is defined as an elevated TSH levels in the presence of normal circulating T4 and T3 concentrations plus the absence of features of clinical hypothyroidism [5,14]. We have found that there was slight increase in the serum levels of TSH in AD patients as compared to the healthy control. Simultaneously, there was decrease in serum T3, FT3 and FT4 with no significant change in T4 levels in AD in comparison to the controls. [Table 2] Summary independent samples T-test statistical analysis was performed to evaluate the significant differences between serum levels of thyroid hormones in control and AD patients which is summarised in Table 3. The changes in thyroid hormone levels and their correlations clearly represent the disturbed thyroid functioning in AD patients. Table 4 represents the correlation between the serum levels of thyroid hormones which shows that the serum FT4 levels in AD showed a significant negative correlation to healthy control ($p < 0.01$). Although not significant, but the serum TSH levels correlated negatively with T3, FT3 and FT4. There was no significant difference in the serum levels of T4 in both the study groups.

During the treatment of AD patients with donepezil and vitamin B_{12} supplements, the thyroid profile was observed at 3 and 6 months intervals and the serum levels of thyroid hormones are presented in Table 5. The serum

Table 1. Age and sex wise distribution and MMSE score in control and AD groups

Sex	Age (years)				MMSE score			
	Mean ± S.D.	S.E. of Mean	Minimum	Maximum	Mean ± S.D.	S.E. of Mean	Minimum	Maximum
Control								
Male (n=40)	70.13 ± 5.59	0.88	60	80	24.98 ± 2.99	0.47	20	30
Female (n=30)	66.7 ± 6.02	1.09	60	86	25.07 ± 2.84	0.52	20	30
Total (n=70)	68.65 ± 5.98	0.72	60	86	25.01 ± 2.91	0.35	20	30
Alzheimer's Disease								
Male (n=46)	71.19 ± 7.52	1.11	60	89	14.63 ± 5.54	0.82	4	24
Female (n=25)	67.8 ± 5.47	1.11	60	80	15.6 ± 2.72	0.54	10	21
Total (n=71)	70 ± 7.02	0.83	60	89	14.97 ± 4.74	0.56	4	24

Table 2. Baseline levels of T3, T4, TSH, FT3 and FT4 in Control and AD

Parameters	Groups	Mean ± S.D.	S.E. of mean	Variance	Median	Mode	Minimum	Maximum
T3	Control	127.8 ± 17.29	2.067	299.26	124.5	122.0[a]	86	165
(81-178 ng/dl)	AD	120.64 ± 20.64	2.450	429.922	118	124	86	164.8
T4	Control	7.71 ± 2.34	0.279	5.47	7.8	7.8	4.7	12.1
(4.5-12.5 µg/dl)	AD	7.54 ± 1.85	0.219	3.43	7.47	4.86[a]	4.6	11.87
TSH	Control	2.34 ± 0.65	0.077	0.42	2.2	2.1	0.9	4.0
(0.4-4 µIU/ml)	AD	2.71 ± 1.19	0.141	1.47	0.96	2.28	0.64	6.92
FT3	Control	2.26 ± 0.63	0.075	0.39	2.05	1.70[a]	1.4	4.0
(1.5-4.1 pg/ml)	AD	1.2 ± 0.13	0.158	0.018	1.2	1.10	0.9	1.5
FT4	Control	1.29 ± 0.27	0.032	0.074	1.27	1.2	0.9	1.78
(0.89-1.76 ng/dl)	AD	0.79 ± 0.08	0.009	0.006	0.78	0.77	0.55	0.89

[a] *Multiple modes exist. The smallest value is shown.*

Table 3. Summary Independent Samples T-test between T3, T4, TSH, FT3 and FT4 in Control and AD groups at Baseline

Variables	Mean difference	Std. error difference	t - value	df	Sig. (2-tailed)
T3_C / T3_AD_B	7.16	3.209	2.231	139	0.027
T4_C / T4_AD_B	0.17	0.355	0.479	139	0.633
TSH_C / TSH_AD_B	- 0.37	0.162	- 2.287	139	0.024
FT3_C / FT3_AD_B	1.06	0.076	13.88	139	0.000
FT4_C / FT4_AD_B	0.5	0.033	14.953	139	0.000

levels of all thyroid hormones showed a slight decrease at 3 months and 6 months intervals which was statistically significant. Paired samples T-test was performed to analyse the significance of difference in the values at follow-up intervals and the Pearson's correlation showed that they had a positive correlation within similar variables. The serum T3 and TSH were significantly negatively correlated [Table 6 and 7]. Our study has shown results partially contrast to a study conducted by Kapaki et al. 2003 which stated that all the AD patients in their study were clinically and biochemically euthyroid, although at low-normal levels. They did not observe any significant difference in thyroid functions before and after ChEIs Rx. The beneficial effects of ChEIs in cognition may partially be mediated by up-regulation of thyroid function through increased ACh levels [18]. We observed that the therapy could not increase the reduced thyroid hormones levels in AD patients and the decline was progressive. Simultaneously, the TSH serum levels were found to be slightly decreased in response to the therapy which might be beneficial to stabilize the disturbed thyroid functions in AD [Tables 6].

A study demonstrated that in AD patients, T4 levels were about 10 times higher than normal, suggesting that there is a reduction in expression of an isoform of the enzyme D2 (deiodinase) or oxidative cholinergic neurodegeneration contributes to the enzymatic activity of D2. In their study, patients with AD had increased T4 levels and reduced T3 levels [19]. Partial substitution of T4 with T3 has been shown to improve mood and neuropsychological function [20]. On the contrary to these studies, our results showed no significant difference in the T4 levels in AD patients as compared to controls. Also, during the follow-up period, negligible change was observed in T4 serum levels in response to the therapy. A study conducted by Yu San Chang et al. 2018 has shown that the responders had a higher level of T4 than the non-responders, followed by a significant reduction after donepezil treatment. These results indicate that relatively higher levels of T4 may predict a favorable response to donepezil treatment [3]. In our study, no beneficial effects of the donepezil and Vit B_{12} therapy were observed on the thyroid profile in a duration of 6 months. Since the thyroid functions are strictly regulated to normal range, the change in serum levels of thyroid hormones due to AD require a larger observation time period.

Our study has been conducted in Mumbai, which is a cosmopolitan city with busy lifestyle consisting of population with different castes, socioeconomic and nutritional status. It is recommended that people should not ignore the preliminary symptoms of cognitive decline in their relatives and should seek early diagnosis of

Table 4. Pearson's correlations between T3, T4, TSH, FT3 and FT4 in control and AD groups at baseline

Groups		AD (Baseline)									
		T3		T4		TSH		FT3		FT4	
		r-value	*P-value*	r-value	*P-value*	r-value	*P-value*	r-value	*P-value*	r-value	*P-value*
Control (Baseline)	T3	-0.056	.65	-0.186	.12	-0.185	.13	-0.068	.57	0.149	.22
	T4	0.017	.89	-0.058	.63	0.226	.06	0.030	.81	0.027	.83
	TSH	0.087	.48	0.159	.19	0.089	.46	-0.197	.10	-0.105	.39
	FT3	0.170	.16	0.065	.59	-0.072	.55	0.049	.69	-0.117	.34
	FT4	0.043	.73	-0.099	.42	-0.072	.55	0.171	.16	-0.373**	.001

** Correlation is significant at the 0.05 level (2-tailed)*
*** Correlation is significant at the 0.01 level (2-tailed)*

Table 5. Serum levels of T3, T4, and TSH in AD groups at intervals of 3 and 6 months

Parameters	Group	Mean ± SD	S.E. of Mean	Variance	Median	Mode	Minimum	Maximum
T3 (81-178 ng/dl)	3 M	119.98 ± 20.67	2.45	427.47	117.4	98.1[a]	85.2	164.1
	6 M	119.33 ± 20.7	2.46	428.672	117	84.77[a]	84.77	163.66
T4 (4.5-12.5 µg/dl)	3 M	7.5 ± 1.85	0.22	3.41	7.33	7.45	4.55	11.88
	6 M	7.46 ± 1.86	0.22	3.47	7.42	4.8a	4.1	11.79
TSH (0.4-4 µIU/ml)	3 M	2.59 ± 1.11	0.13	1.23	2.41	1.8	0.62	5.81
	6 M	2.38 ± 0.93	0.11	0.931	2.21	1.89	0.76	5.56

a Multiple modes exist. The smallest value is shown

the disease. Since these limitations exist in the present study, our findings need to be validated with other regional populations of India. Therefore, further longitudinal epidemiological studies in a larger population cohort are needed to determine the nature of the association of serum thyroid hormones with AD and to confirm the relationship between thyroid functions and ChEIs therapies in AD which may explore new therapeutic strategies.

Table 6. Paired samples T-test between T3, T4 and TSH in AD groups at baseline, 3 months and 6 months

Variables	Mean difference	Std. deviation	Std. Error difference	t - value	df	Sig. (2-tailed)
T3_AD_B / T3_AD_3M	0.669	0.283	0.034	19.91	70	0.000
T3_AD_B / T3_AD_6M	1.317	0.355	0.042	31.29	70	0.000
T3_AD_3M / T3_AD_6M	0.648	0.239	0.028	22.76	70	0.000
T4_AD_B / T4_AD_3M	0.039	0.085	0.010	3.94	70	0.000
T4_AD_B / T4_AD_6M	0.077	0.094	0.011	6.93	70	0.000
T4_AD_3M / T4_AD_3M	0.038	0.099	0.012	3.21	70	0.002
TSH_AD_B / TSH_AD_3M	0.120	0.335	0.039	3.03	70	0.003
TSH_AD_B / TSH_AD_6M	0.326	0.611	0.073	4.50	70	0.000
TSH_AD_3M / TSH_AD_6M	0.206	0.410	0.049	4.24	70	0.000

Table 7. Pearson's correlations between T3, T4, and TSH in control (Baseline) and AD (3 and 6 Months) groups

Groups		AD (3 Months)					
		T3		T4		TSH	
		r-value	*P* value	r-value	*P* value	r-value	*P* value
Control (Baseline)	**T3**	-0.054	.65	-0.179	.14	-0.165	.17
	T4	0.016	.90	-0.062	.61	0.169	.16
	TSH	0.09	.46	0.161	.18	0.127	.29
		AD (6 Months)					
	T3	-0.054	.66	-0.172	.15	-0.177	.14
	T4	0.014	.91	-0.070	.56	0.125	.30
	TSH	0.088	.47	0.165	.17	0.055	.65
		AD (3 Months)					
AD (Baseline)	**T3**	1.000**	.000	0.277*	.019	-0.019	.45
	T4	0.276*	.02	0.999**	.000	0.154	.2
	TSH	0.125	.29	0.116	.134	0.960**	.000
		AD (6 Months)					
	T3	1.000**	.000	0.270*	.023	-0.136	.26
	T4	0.275*	.02	0.999**	.000	0.134	.26
	TSH	-0.127*	.29	0.105*	.383	0.858**	.000
		AD (6 Months)					
AD (3 Months)	**T3**	1.000**	.000	0.257*	.02	-0.127	.29
	T4	0.270*	.02	0.999**	.000	0.105	.38
	TSH	-0.136	.26	0.134	.264	0.858**	.000

** Correlation is significant at the 0.05 level (2-tailed)*
*** Correlation is significant at the 0.01 level (2-tailed).*

Table 8. Categorization of AD patients by socioeconomic status

Category	I	II	III	IV	V
Socioeconomic status	Upper class	Upper Middle class	Middle class	Lower Middle Class	Lower class
No. of AD patients	2	5	32	28	4

5. CONCLUSION

The present study suggest that, even in a clinical euthyroid state, high serum TSH levels and low T3, FT3 and FT4 levels are associated with AD. Upon follow-up for 6 months, along with the treatment of AD patients with donepezil and vitamin B_{12}, the serum levels of thyroid hormones were slightly decreased with no cognitive benefits. The drugs could not benefit restore the normal functioning of thyroid metabolism in the 6 months therapy period. Thyroid function might contribute to early diagnosis and prevention of subsequent progression to AD. It might also play a role as marker for studying the disease progression. Novel therapeutic strategies could be developed to prevent deleterious metabolic effects due to disturbed thyroid status. Further longitudinal and interventional studies along with molecular studies are needed to clarify whether targeting serum thyroid hormone levels and its stricter correction will be helpful for attenuating and treating AD.

CONSENT

Informed consent was obtained from the participant's representatives of diagnostically confirmed AD patients recruited in the study.

ETHICAL APPROVAL

Ethical Clearance approval was taken from the Institutional Ethics Committee of Grant Government Medical College and Sir J. J. Group of Hospitals, Mumbai (IEC approval letter no.: IEC/pharma/328/15).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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