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# Higher levels of thyroxine may predict a favorable response to donepezil treatment in patients with Alzheimer disease: a prospective, case–control study

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## Abstract

**Background:** Cholinergic hypothesis has been advanced as an etiology of Alzheimer disease (AD) on the basis of the presynaptic deficit found in the diseased brains, and cholinesterase inhibitors (ChEIs) are the treatment of choice for these patients. However, only about half of treatment efficacy was found. Because increasing evidence supports an extensive interrelationship between thyroid hormones (THs), cortisol level and the cholinergic system, the aim of the present study was to evaluate thyroid function and cortisol level in patients with mild to moderate AD before and after ChEIs treatment, and to identify possible variations in response. This was a prospective, case–control, follow-up study. Levels of cortisol and THs were evaluated in 21 outpatients with mild to moderate AD and 20 normal controls. All patients were treated with 5 mg/day of donepezil (DPZ) and were reevaluated after 24–26 weeks of treatment.

**Results:** The patients had worse cognitive function, higher cortisol level, and lower levels of triiodothyronine (T<sub>3</sub>) and its free fraction than the controls. There were no significant differences in global cognitive function or cortisol level after treatment, however, significant reductions in T<sub>3</sub> and thyroxin (T<sub>4</sub>) levels were observed. Responders had higher levels of T<sub>4</sub> than non-responders, followed by a significant reduction after treatment.

**Conclusions:** These results suggest that relatively higher levels of T<sub>4</sub> may predict a favorable response to DPZ treatment. Further studies are warranted to confirm the relationship between THs and ChEIs therapy in AD and to explore new therapeutic strategies. On the other hand, cortisol levels are more likely to respond to interventions for stress-related neuropsychiatric symptoms in patients with AD rather than ChEIs treatment. Further studies are warranted to investigate the association between cortisol level and the severity of stress-related neuropsychiatric symptoms in patients with AD.

**Keywords:** Alzheimer disease, Cortisol, Thyroid hormone, Donepezil, Cholinesterase inhibitors

## Background

Alzheimer disease (AD) is a degenerative disorder of the central nervous system (CNS), for which the cholinergic hypothesis has been proposed to be an etiology on the basis of presynaptic deficits found in diseased brains. Increasing evidence also supports an extensive interrelationship between thyroid hormones (THs), cortisol

level and the cholinergic system. Thyroxin (T<sub>4</sub>) has been shown to modulate choline acetyltransferase activity, and triiodothyronine (T<sub>3</sub>) has been shown to negatively regulate the expression of amyloid precursor protein in the brain [1, 2]. Regarding cortisol level, Degroot et al. [3] reported a parallel increase in levels of plasma cortisol and hippocampal acetylcholine (ACh) after acute stress. In addition, corticosterone administration, which mimics the increase in the plasma corticosterone concentration produced by stress, has also been shown to induce hippocampal ACh [4, 5].

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Currently, the most common drug treatments are based on the cholinergic hypothesis. This hypothesis states that a lower production of acetylcholine, a neurotransmitter, leads to AD, and thus cholinesterase inhibitors (ChEIs) are the recommended therapeutic option [6]. However, only about half of treatment efficacy was found [7], and the reasons for nonresponse remains largely unknown. The study aimed to evaluate thyroid function and cortisol level in patients with mild to moderate AD before and after ChEIs treatment, and to identify possible variations in response.

## Methods

### Participants

This was a prospective, case–control, 24- to 26-week follow-up study. Twenty one outpatients (7 men and 14 women; mean age:  $78.5 \pm 5.7$  years; mean years of education:  $5.0 \pm 5.1$  years) with mild to moderate AD according to the Clinical Dementia Rating scale [8] and a Mini–Mental State Examination (MMSE) [9] score of 10–24 [10] were enrolled. The diagnostic criteria were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) [11], the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association [12] for probable AD. All of the patients underwent a neurological examination, neuroimaging and laboratory workup to rule out other treatable causes of dementia. Twenty normal controls (9 males and 11 females; mean age:  $77.5 \pm 4.4$  years; mean years of education:  $6.6 \pm 4.4$  years) were also recruited from the hospital and general community.

None of the participants had a history of stroke, epilepsy, thyroid disease, pathological levels of urea or creatinine, other significant psychiatric diseases, either using or had used glucocorticoid supplements, or any CNS-active drug treatment. The study protocol had the approval of the Ethics Committee of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital. Written informed consent was obtained from all participants and authorized caregivers after the study had been fully explained and the potential risks and benefits had been discussed.

### Procedures

Neuropsychological assessments, thyroid function tests and serum levels of cortisol were obtained at a screening appointment for all participants. Researches [6] showed patients with AD had most benefit from ChEIs treatment for cognition within the first 6 months followed by a gradual decline thereafter [6]. Therefore, we chose 24–26 weeks as the study period. All patients were treated with 5 mg/day of donepezil (DPZ) during the study period and underwent neuropsychological

assessments at 24–26 weeks. At that time, thyroid status and serum levels of cortisol were also measured. The neuropsychological assessment assessor was blinded to the results of THs and cortisol levels.

According to the Bureau of National Health Insurance in Taiwan, it is necessary to evaluate cognitive function at least every 1 year after the initial administration of DPZ to apply for continuing prescriptions, and patients with MMSE scores of 2 or more points lower than the pretreatment level will not be eligible for reimbursements for continuing prescriptions. Therefore, response was a priori defined as a stabilization or improvement in MMSE score in this study. The patients with MMSE scores of 2 or more points lower than the pretreatment level were defined as being non-responders.

### Laboratory assessments

Fasting blood samples (5 ml) were collected by venipuncture between 8:00 and 9:00 a.m. to determine levels of thyroid stimulating hormone (TSH),  $T_3$ ,  $T_4$ , free fractions ( $FT_3$  and  $FT_4$ ), and cortisol. Serum was separated immediately after blood collection, and the samples were stored at  $-20^\circ\text{C}$  until analysis. Quantitative determination of cortisol and thyroid status in the serum was measured using paramagnetic particles in a chemiluminescent immunometric assay using a Beckman Access system (Beckman Coulter Inc., Fullerton, CA, USA) for cortisol level and an Abbott I2000 system (Abbott Ireland Diagnostics Division, Longford, Ireland) for thyroid status. The lower limits of detection were 0.0025 mIU/l for TSH, 25.0 ng/dl for  $T_3$ ,  $<1.0$   $\mu\text{g/dl}$  for  $T_4$ ,  $<1.0$  pg/ml for  $FT_3$ , 0.4 ng/dl for  $FT_4$ , and 0.4  $\mu\text{g/dl}$  for cortisol. The intra-assay coefficient of variation averaged 5% for each item.

### Statistical analysis

Sex distribution between groups was compared using the  $\chi^2$  test. Group differences in age, years of education, neuropsychological, thyroid status and cortisol level assessments were evaluated using the Student's *t* test. Repeated measures ANOVA were used to compare the follow-up measurements with baseline data in terms of neuropsychological assessments, thyroid status and cortisol level, and age and years of education were used as covariates for neuropsychological assessments. To identify differences that may have resulted in variations in response, differences in baseline of those significant follow-up hormone measurements were compared between the responders and non-responders using the Student's *t* test. In responders, the significant hormone items were also compared the follow-up measurements with baseline data using repeat measures ANOVA. A *p* value less than 0.05 was considered to be statistically significant. The

partial eta-squared value was calculated for the follow-up measurements for each variable.

**Results**

There were no significant differences in sex, age, and years of education between the patients with AD and the controls. The baseline neuropsychological and hormone assessments for both groups are summarized in Table 1. Compared to the controls, the patients with AD had a higher cortisol level, lower levels of T<sub>3</sub> and FT<sub>3</sub>, and a lower MMSE scores. There were no significant differences in MMSE scores and cortisol level before and after 24–26 weeks of treatment with DPZ. However, significant reductions in T<sub>3</sub> and T<sub>4</sub> levels were observed (Table 2). There was no significant difference in baseline level of T<sub>3</sub> between the responders (61.9%) and non-responders (t(19) = -1.65, p = .115), and no significant reduction was found in T<sub>3</sub> level after 24–26 weeks of DPZ treatment in the responders (F(1, 12) = 3.01, p = .109). However, the responders had with

a higher baseline level of T<sub>4</sub> compared with the non-responders (t(19) = 2.29, p = .033) and a significant reduction in T<sub>4</sub> level after 24–26 weeks of DPZ treatment (F(1,12) = 13.13, p = .003) (Fig. 1). The reduction ratio was about 85.3 ± 16.0% of baseline T<sub>4</sub> levels.

**Discussion**

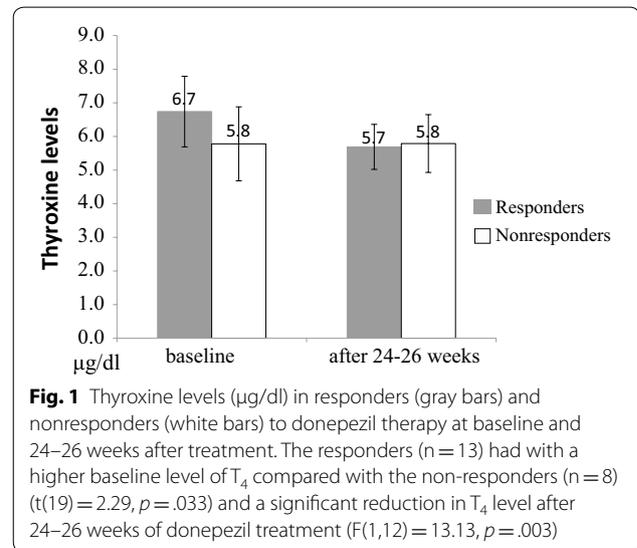
In this study, the patients with AD had a statistically significantly higher cortisol level, lower levels of T<sub>3</sub> and FT<sub>3</sub>, and a decline in global cognition compared with the controls. There were no significant differences in global cognitive function as measured by the MMSE and cortisol level after treatment, however significant reductions in T<sub>3</sub> and T<sub>4</sub> levels were observed. In addition, the responders had a higher level of T<sub>4</sub> than the non-responders, followed by a significant reduction after treatment.

Laboratory studies have implicated a relationship between THs and factors associated with the pathogenesis of AD, including β-amyloid (Aβ) deposition and

**Table 1 Demographic and clinical characteristics between in patients with Alzheimer disease (AD) and controls**

Variables (mean ± SD)	Controls	AD patients	t(39) or χ <sup>2</sup> (1) values	p value
n (M/F)	20 (9/11)	21 (7/14)	0.59	.530
Age (year)	77.5 ± 4.4	78.5 ± 5.7	-0.67	.504
Years of education	6.6 ± 4.4	5.0 ± 5.1	1.07	.293
MMSE scores	27.5 ± 1.9	16.1 ± 5.4	8.93	< .001
Cortisol (μg/dl)	7.8 ± 3.7	10.2 ± 2.9	-2.34	.025
Thyrotropin (mIU/l)	1.4 ± 0.7	1.4 ± 0.9	-0.01	.996
Total T <sub>3</sub> (ng/dl)	94.8 ± 10.2	85.5 ± 8.6	3.18	.003
Free T <sub>3</sub> (pg/ml)	2.5 ± 0.4	2.3 ± 0.3	2.56	.015
Total T <sub>4</sub> (μg/dl)	6.3 ± 1.1	6.4 ± 1.0	-0.33	.747
Free T <sub>4</sub> (ng/dl)	1.0 ± 0.1	1.0 ± 0.1	-0.23	.818

MMSE Mini-Mental State Examination



**Fig. 1** Thyroxine levels (μg/dl) in responders (gray bars) and nonresponders (white bars) to donepezil therapy at baseline and 24–26 weeks after treatment. The responders (n = 13) had with a higher baseline level of T<sub>4</sub> compared with the non-responders (n = 8) (t(19) = 2.29, p = .033) and a significant reduction in T<sub>4</sub> level after 24–26 weeks of donepezil treatment (F(1,12) = 13.13, p = .003)

**Table 2 Neuropsychological function and hormone levels in patients at baseline and after administered donepezil for 24–26 weeks (n = 21)**

Variables (mean ± SD)	Baseline	Follow up	F(1,18) <sup>a</sup> /F(1, 20)	p value	η <sub>p</sub> <sup>2</sup> (%)
MMSE scores <sup>a</sup>	16.1 ± 5.4	17.1 ± 5.2	0.25	.624	1.4
Cortisol (μg/dl)	10.2 ± 2.9	10.6 ± 1.8	0.45	.511	2.2
Thyrotropin (mIU/l)	1.4 ± 0.9	1.4 ± 1.0	0.42	.523	2.1
Total T <sub>3</sub> (ng/dl)	85.5 ± 8.6	81.4 ± 10.1	7.57	.012	27.4
Free T <sub>3</sub> (pg/ml)	2.3 ± 0.3	2.2 ± 0.3	1.52	.233	7
Total T <sub>4</sub> (μg/dl)	6.4 ± 1.0	5.7 ± 1.0	7.12	.015	26.3
Free T <sub>4</sub> (ng/dl)	1.0 ± 0.1	1.0 ± 0.1	0.07	.800	0.3

MMSE Mini-Mental State Examination

<sup>a</sup> Age and years of education as covariates

neuronal apoptosis. Circulation  $T_4$  are the major form of the THs which be transported into the brain by transthyretin [13].  $T_4$  is then converted to the active form  $T_3$  and inactive  $rT_3$  by deiodinase.  $T_3$  has been shown to negatively regulate the expression of the amyloid precursor protein gene [2],  $T_4$  has been shown to modulate choline acetyltransferase activity [1], and transthyretin has been shown to create soluble  $A\beta$  complexes [14]. Compared with age-matched controls [15], the level of transthyretin has been reported to be lower in the cerebrospinal fluid (CSF) of patients with AD, suggesting a possible reduction in  $T_4$  transport into the brain in patients with AD. However, most  $T_3$  within the brain is produced locally by the intracerebral conversion of  $T_4$  to  $T_3$  [16]. In addition, increased  $rT_3$  levels and an increased  $rT_3$  to  $T_4$  ratio were also found in the CSF of AD patients [16]. Taken together, these findings suggest abnormal intracerebral THs metabolism and possibly brain hypothyroidism in AD [17]. Even though circulating THs do not properly reflect the bioactive portion of CNS activity, the lower levels of  $T_3$  and  $rT_3$  in our results also suggest a link between abnormalities in the hypothalamic–pituitary–thyroid axis and dementia.

High levels of glucocorticoid receptors have been reported in the hippocampus where is supposed to engage in the negative-feedback of glucocorticoid secretion [18]. However degeneration of the hippocampus is a prominent characteristic of AD [19], the loss of hippocampal cells can lead to hypercortisolemia, and this can increase degeneration of the hippocampus as the disease progresses. We also found higher levels of cortisol in the patients with AD than in the controls.

In the current, significant reductions in  $T_3$  and  $T_4$  levels were observed 24–26 weeks after DPZ treatment, indicating a relationship between THs and treatment. Thyroid glands are known to secrete about 80–90% of  $T_4$  and about 10–20% of  $T_3$ , and that this process is regulated by TSH which is released by the anterior pituitary gland. Deiodinase enzymes in peripheral tissues convert  $T_4$  to  $T_3$  and  $rT_3$ , and this is a major source of both  $rT_3$  (95%) and  $T_3$  (87%) in peripheral tissues [20]. However, thyroid activity is influenced by both neuroendocrine control of TSH release and also various neurotransmitters including Ach. Maayan et al. [21] reported that Ach possible involved of muscarinic receptors in the thyroid to inhibit TSH- induced  $T_4$  release. In addition, numerous acetylcholinesterase-positive nerve fibers, probably cholinergic, were found in the thyroid [22]. Therefore, our results of decreased  $T_3$  and  $T_4$  levels after treatment implicated the effect of Ach on the thyroid gland. However, there were no significant changes in TSH level after treatment in our study.

ChEIs treatment in AD has been reported to be most beneficial with regards to cognition after 3–4 months of administration [23], followed by a gradual decline after 24–36 weeks of treatment [6, 24]. DPZ is a ChEIs that has also been shown to exhibit a significantly greater improvement in cognitive function within 3 months of 5 mg/day administration, and to maintain a response defined by stabilization of cognitive function for 1 year [25]. Accordingly, the global cognitive function was improved after treatment in this study but did not have statistically significant. This may be because of the small sample size, or because we did not perform evaluations during the period of maximum benefit.

Many studies have reported interactions between glucocorticoids and Ach in the brain [26–28]. Stress-induced responses not only activate the hypothalamic–pituitary–adrenal (HPA) axis but also the septo-hippocampal cholinergic pathway. Activation of the HPA axis leads to the release of corticosterone, and activation of the septo-hippocampal cholinergic pathway results in an increase in Ach in the hippocampus. Ach also mediates neuroendocrine, emotional, and physiological responses by stimulating the HPA axis. Thus, the hippocampus in tandem with basal forebrain cholinergic pathways is involved in regulating HPA axis stress responses. Hence, neurodegeneration of cholinergic neurons in patients with AD makes them vulnerable to stress, resulting in cognitive impairment.

In this study, we found no statistical difference in cortisol levels after DPZ treatment. A previous large prospective study did not find a relationship between cortisol levels and the risk of developing AD, and concluded that dysregulation of the HPA axis in patients with AD seemed to be a consequence rather than a cause of AD [29, 30]. In addition, other studies have reported that chronic exposure to high levels of endocrine glucocorticoids probably contributes to the intensification of neuropsychiatric symptoms, particularly in stress-related symptoms such as depression and anxiety [31–33]. It is therefore possible that cortisol levels in patients with AD would be more likely to respond to interventions for stress-related neuropsychiatric symptoms rather than ChEIs treatment. This may be why we did not find a relationship between cortisol levels and the effect of DPZ treatment in patients with AD.

In our results, the responders had a higher level of  $T_4$  than the non-responders, followed by a significant reduction after treatment. Although THs in the CNS depend almost entirely on the uptake of  $T_4$  and its intracellular deiodination to the active compound  $T_3$  [16], deiodinase enzymes have also been shown to convert  $T_4$  to  $T_3$  in peripheral tissues [20]. Thus, the reduction of serum

T<sub>4</sub> levels, as seen during DPZ treatment, may not only be due to enhanced conversion of T<sub>4</sub> to T<sub>3</sub> in the CNS. However, many neurotropic medications such as antidepressants, anticonvulsants, neuroleptics and benzodiazepines may affect deiodinase activity and THs concentration in the CNS [34]. Therefore, the effect of DPZ beyond that of ChEIs may involve the upregulation of deiodinase activity in the brain. Alternatively, the responders to DPZ presented with higher baseline T<sub>4</sub> levels before treatment and showed a significant reduction after treatment, which may indicate that a higher level of T<sub>4</sub> characterizes a subgroup of AD patients who would be expected to benefit from ChEIs treatment.

There are several limitations to the present study. First, the small sample size limits the interpretation of the findings. Second, circulating hormone assessments do not properly reflect the bioactive portion involved in the CNS. Third, we did not record body mass index or concomitant diseases such as diabetes mellitus and hypertension, all of which could have affected the levels of THs and cortisol. Fourth, the study lacks supporting epidemiological data to make an association between THs and the expected favorable therapeutic response to DPZ treatment. However, the clinical relevance of the preliminary findings provide information to identify possible variations in response. Finally, the study was restricted to DPZ, and thus the findings cannot be extrapolated to other ChEIs.

## Conclusions

In summary, we found that the patients with AD had no significant differences in cortisol levels after 24–26 weeks of treatment with DPZ, but significant reductions in T<sub>3</sub> and T<sub>4</sub> levels. The responders had a higher level of T<sub>4</sub> than the non-responders, followed by a significant reduction after DPZ treatment. These results indicate that relatively higher levels of T<sub>4</sub> may predict a favorable response to DPZ treatment. Further studies are warranted to confirm the relationship between THs and ChEIs therapy in AD and to explore new therapeutic strategies. On the other hand, cortisol levels are more likely to respond to interventions for stress-related neuropsychiatric symptoms in patients with AD rather than ChEIs treatment. Further studies are warranted to investigate the association between cortisol level and the severity of stress-related neuropsychiatric symptoms in patients with AD.

## Abbreviations

Ach: acetylcholine; AD: Alzheimer disease; Aβ: β-amyloid; ChEIs: cholinesterase inhibitors; CNS: central nervous system; CSF: cerebrospinal fluid; DPZ: donepezil; FT<sub>3</sub>: free fractions of triiodothyronine; FT<sub>4</sub>: free fractions of thyroxine; T<sub>3</sub>: triiodothyronine; T<sub>4</sub>: thyroxine; THs: thyroid hormones; TSH: thyroid stimulating hormone; HPA: hypothalamic–pituitary–adrenal; MMSE: Mini–Mental State Examination.

## Authors' contributions

YSC provided overall supervision and designed the study and wrote the manuscript and gave final approval of the version to be submitted. YHW and CJW contributed to the interpretation and analyzed of data as well as wrote the manuscript methods and results sections. SHT contributed to cognition evaluation and acquisition of data. HLC contributed to laboratory exam and acquisition of data. All authors read and approved the final manuscript.

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None.

## Competing interests

The authors declare that they have no competing interests.

## Availability of data and materials

Not applicable.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

The study protocol had the approval of the Ethics Committee of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital. Written informed consent was obtained from all participants and authorized caregivers after the study had been fully explained and the potential risks and benefits had been discussed.

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