INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230 – 8407

Research Article

ALTERED SERUM MARKER OF THYROID PROFILE AND ANTIOXIDANT ENZYMES IN INDIVIDUALS ALZHEIMER'S DISEASE

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Article Received on: 17/11/18 Approved for publication: 22/01/19

DOI: 10.7897/2230-8407.100110

ABSTRACT

Thyroid dysfunction and oxidative stress are incriminated to play a central role in the pathological processes that lead to neuronal degeneration in patients with Alzheimer's disease (AD).This research study was mainly concerned with observing the changes in serum biochemical parameters including thyroid hormone (tri-iodothyronine (T_3) and thyroxine (T_4), thyroid-stimulating hormone(TSH), and antioxidants enzymes (glutathione peroxidase (GSH-Px), CAT(catalase), superoxide dismutase (SOD), total antioxidant status(TAS), and Glucose-6-phosphate dehydrogenase (G6PD)) in the serum samples of the in patients with AD (n=54) and compared with control subjects (n=54). Results: The statistical significance was evaluated by Student's t-test, Correlation-Coefficient test. All Values are given as mean ± SD. Serum T3, T4, TAS, GSH, SOD, G6PD, and catalase levels were decreased, whereas serum TSH, and MDA levels were increased in the study group compared to controls though statistically significant ($P < 0.05$). TSH showed a significant positive correlation with T_4, MDA, Cat, and TAS, whereas inverse correlation with T_3, G6PD, SOD, GSH, and GPx in AD patients. Conclusions: it could be suggested that increased TSH, whereas decreased T_3, and T_4 has a role in AD development and oxidative stress may exacerbate the condition. Oxidative stress as one of the risk factors, which can initiate and/or promote neurodegeneration in AD and was correlated to the severity of the disease. Therefore, further prospective studies with larger number of patients are required to strengthen the observations of the present study.

Keywords: Alzheimer disease, tri-iodothyronine, thyroxine, and TSH

INTRODUCTION

Alzheimer disease (AD) is the most common subtype of dementia in the elderly, but there are still no curative options. Neurofibrillary tangles and senile plaques are considered hallmarks of AD [1]. Thyroid hormones, tri-iodothyronine (T_3) and thyroxine (T_4) are secreted by the thyroid gland under the effect of thyroid stimulating hormone, It is known to play an important role in the development and maintenance of the central nervous system, and normal neural functions[2,3]. Normally TH exerts its biological function through thyroid hormone receptors which bind to nuclear receptors, and a decrease of thyroid hormone receptor mRNA levels in alzheimer hippocampal cells [2,3].

Oxidative stress, a pathophysiologic imbalance between the generation of reactive oxygen/nitrogen species and the capacity of cells to neutralize them by the antioxidant defence [4]. Oxidative stress may expedite the polymerization and phosphorylation of tau, and increase the production and compilation of A beta, Therefore forming a vicious cycle which initiated promotes the development of Alzheimer's disease [5,6].

Due to limited studies in Iraqi individuals, the present research work was undertaken to study the role of thyroid hormone and antioxidants enzymes in patients with AD.

MATERIALS AND METHODS

In this prospective study was carried out on 54 patients with AD (19 men, 35 women), with a mean age of 77.7 ±14.45 years and 54 healthy controls (24 men, 30 women), matched for sex and age 75.04±12.6 years were analyzed, randomly recruited from those attending the Kirkuk teaching hospital of the department of internal medical, in Kirkuk governorates, in a period of 8 months during 2016.

Exclusion criteria for the control group**:** Concurrent neurological issues, Severe anemia ,Severe malnutrition, Mental deficiency, Severe and unchecked arterial hypertension, Concurrent psychiatric issues or a history of psychological illness, cancer, HIV-AIDS, Stroke, and Alcoholism

Blood samples were collected from both groups following 10 – 12 hours of fasting. The blood samples were centrifuged at 3500rpm for 10 min and separated after collection and were stored at -80 °C until analysis.

T_3, T_4 and TSH were analysed by enzyme linked fluorescent assay (ELFA) technique using Minividas auto analyser from Biomeriuex, France. Serum SOD, GSH, MDA, G-Px, and catalase levels were measured by spectrophotometric kit,

All values were expressed as mean ± standard deviation for normally distributed data. Variances between the two groups were analyzed using U test. Significance was set as $P < 0.05$.Statistical analysis was performed using standard statistical software (SPSS version 16.0).

RESULTS

The serum from 54 patients with AD and 54 controls was analysed. Table 1 shows the distribution of ages in both cases and controls. The mean age (years) in controls was (75.04±12.6) and cases (77.7 ±14.45) in AD.

It is evident from the table 1 that there is decrease in levels of T_3(1.39 ± 0.168 vs. 1.61 ±0.179 ng/mL), T_4 (80.4 ±5.271 vs. 89.3 ±5.55 ng/mL), TAS (0.51 ±0.386 vs. 1.788 ±0.256 mmol/L trolox equvi), GSH-Px (41.1±4.794 vs. 61.39±5.06 U/g Hb) , GSH (4.05±0.866 vs. 7±0.69 µmol/g Hb), SOD (2.07±0.51 vs.

3.52±0.88 U/L), G6PD (9±1.149 vs. 17.74±2.335 U/g Hb), Catalase(23±2.169 vs. 26.5±1.438 K/ml), in subjects with AD when compared to healthy controls. The p-value is highly significant for T3, T4, TAS, GSH-Px, CAT, SOD, and GSH.

Also it is evident from table 1 that the estimated levels of TSH in AD are increased when compared to healthy controls and p value is significant for TSH. In patients with AD, a direct correlation was recorded between the TSH and T_4 (0.298), MDA (0.097), Cat (0.104) TAS(0.315) (Fig.1-4). In contrast, in Fig.(5-9), an inverse correlation between TSH and G6PD (-0.035), SOD(-0.145), GSH(-0.022), GPx (-0.023), T_3(-0.147) was observed in patients with AD, ($p<0.005$).

Table 1: Basic characteristics of study groups: Group A (n=54), Group B (n=54)

Parameters	Group A (Control)	Group B (AD)
No. of subjects	**54**	**54**
Sex (M/F)	24/30	19/35
Age (years)	75.04±12.6	77.7 ±14.45

* P < 0.05, ** P < 0.01

Table 2: Biochemical parameters of patients and the controls. Group A (n=54), Group B (n=54)

Parameters	Serum	
	Group A (Control)	**Group B (AD)**
T3 (ng/mL)	1.6109±0.17991	1.39±0.16843
T4(ng/mL)	89.3±5.55313	80.4±5.2711
TSH (IU/L)	5.54±0.84455	6.2101±0.87795
TAS (mmol/L trolox equvi.)	1.7888±0.25613	0.5106±0.38642
GSH-Px (U/g Hb)	61.3901±5.06448	41.1±4.79464
GSH (µmol/g Hb)	**7**±0.69401	4.0510±0.86620
SOD (U/L)	3.5201±0.88139	2.07±0.51169
G6PD (U/g Hb)	17.74±0.32391	9±0.15938
Catalase(K/ml)	26.5±1.43846	23±2.16977
MDA(mmol/L)	2.1205±0.40110	4.5428±0.77923

* P < 0.05, ** P < 0.01

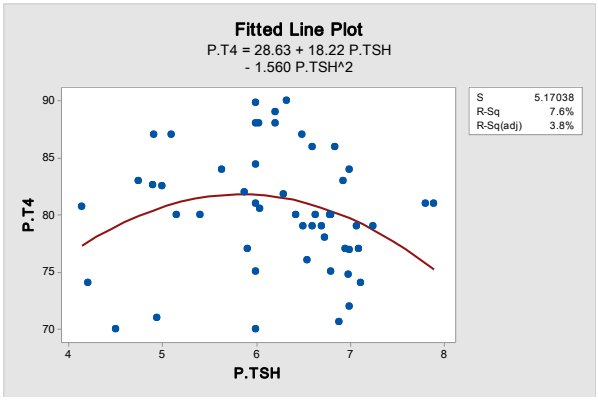

Figure 1: Correlation between TSH and T4in patients with AD.

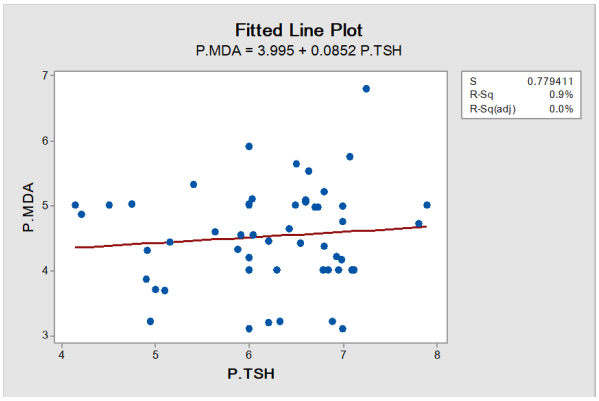

Figure 2: Correlation between TSH and MDA in patients with AD

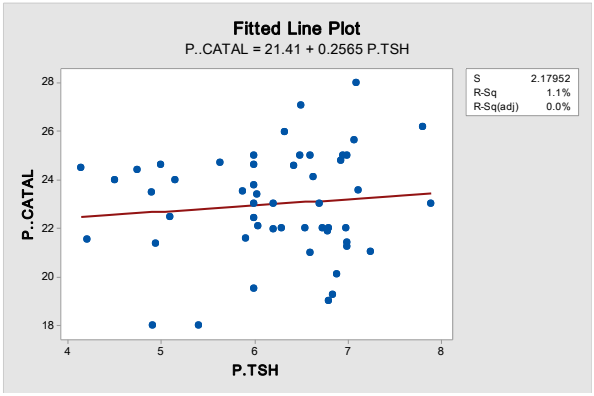

Figure 3: Correlation between TSH and catalase in patients with AD

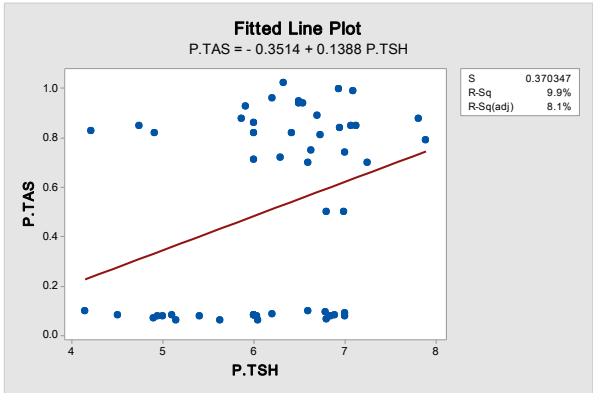

Figure 4: Correlation between TSH and TAS in patients with AD

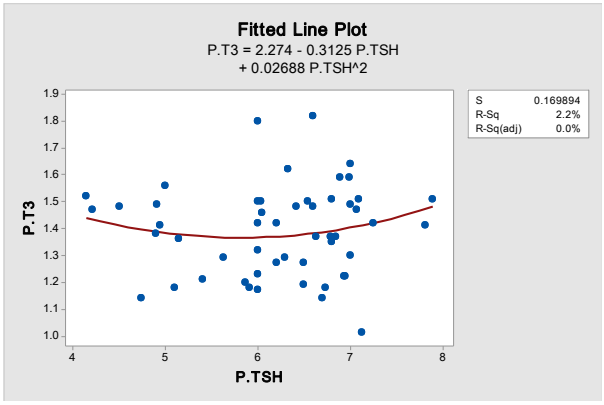

Figure 5: Correlation between TSH and T3 in patients with AD

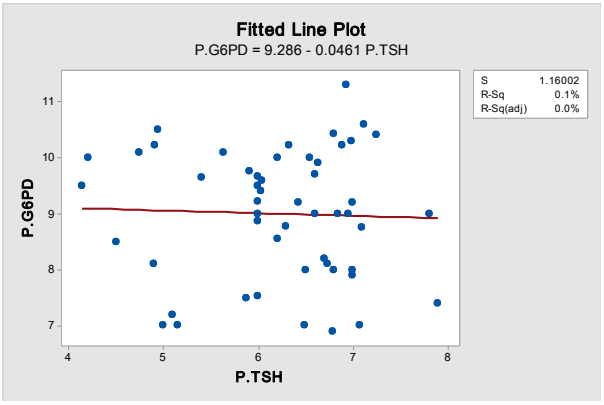

Figure 6: Correlation between TSH and G6PD in patients with AD

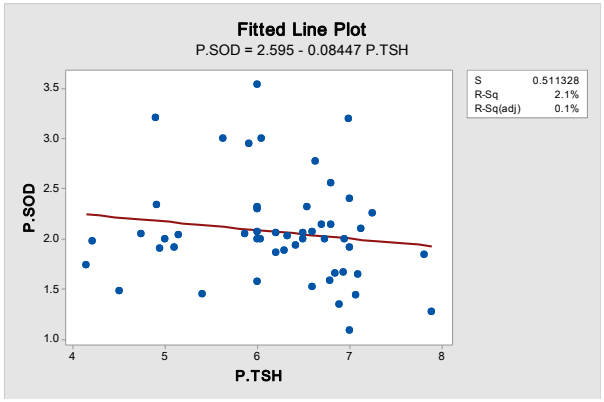

Figure 7: Correlation between TSH and SOD in patients with AD

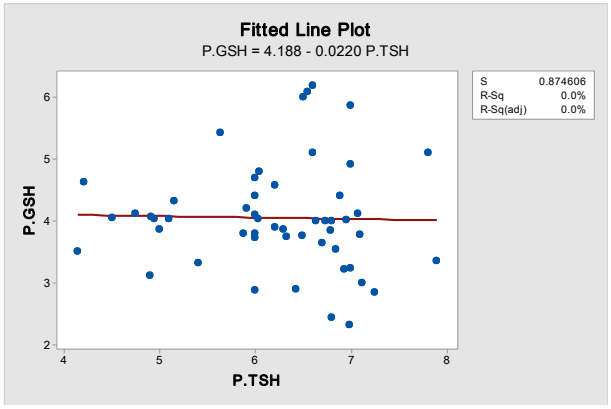

Figure 8: Correlation between TSH and GSH in patients with AD

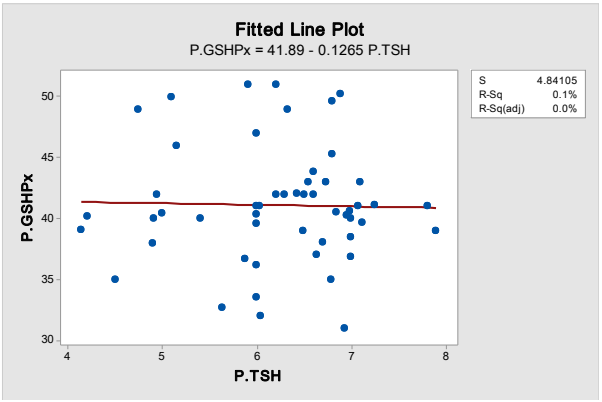

Figure 9: Correlation between TSH and GPx in patients with AD

DISCUSSION

Thyroid hormone can reform intracellular H^+ accumulation by motivation of the Na^+/H^+ exchanger and can shore suitably low $[Ca^{2+}]_{i.c.}$ by stimulation of plasma membrane Ca^{2+}–ATPase. Thyroid hormone encourages astrocyte glutamate uptake. The hormone supports the integrity of the filaments cytoskeleton by its impact on actin [7].

Our study showed that serum T3, and T4 levels were significantly lower, whereas TSH was significantly higher in AD patients compared to controls.

Possible mechanisms assumed that in AD the accumulation of amyloid plaques and neurofibrillary tangles lead to a reduction in secretion of hypothalamic thyrotrophic Releasing Hormone (TRH) which associated with enhanced phosphorylation of tau protein or reduced pituitary response to TRH, demonstrating as reduced TSH and thyroxin levels [8].

Circulation or non-nervous system tissues contain a relatively lower ratio of T3 / T_4 compared to circulation or nervous tissues [9].In the brain T_3 is produced from T_4 by type II deiodinase (DIO_2), which is an enzyme important in preserving the intracellular T_3 levels in the CNS. During hypothyroidism the expressions of DIO_2 increase in the brain to maintain T_3 level [10].

The thyroid dysfunction appears to be associated with increased oxidative stress and decreased antioxidant enzymes, and enhance neuronal death [11].The occurrence of thyroid dysfunction has been revealed following the process of dementia progress may result to a decline in exudation of thyroid hormones which leads neurodegeneration [12].

β-amyloid (Aβ) has been concerned as a potential cause of oxidative stress in AD. Possible mechanisms for Oxidative damage caused by Aβ.

1. Accumulation of ROS resulting from direct interaction of Aβ peptides with anti-oxidant enzymes [13].
2. Uncontrolled calcium influx resulting from direct interaction Aβ peptides with cellular membranes. As a result of the formation of ion channel like pore; mitochondrial dysfunction due to disturbance of calcium homeostasis , followed by generation of high levels of ROS and increased production of H2O2.
3. Catalytic reduction of O_2 to H_2O_2 in cells resulting from direct interaction of Aβ peptides with Fe^{2+} [14,15].

AD patients in our study showed lower levels of GSH-Px, CAT, SOD, and G6PD as compared to controls, might be interpret by elevation free radical production occurring in this condition due to low activity of antioxidant enzymes might pave way for numerous complications and can participate to the neurodegeneration in AD [16].

The brain has increased oxygen and glucose depreciation, which makes them more vulnerable to oxidative damage. Free radicals can aggression the phospholipid membrane of cells, which then converted by peroxidation to MDA, which can be evaluated by reactivity to thiobarbituric acid [17]. Our findings are also in agreement with some researchers like [18]. Demonstrate an increased level increased MDA and decreased SOD and GPX.

β-amyloid acts via the production of free radicals through interacts with vascular endothelial cells, producing a surfeit of free superoxide radicals which can scavenge the endothelium-derived relaxing factor and produce oxidizing agents causing lipid peroxidation that create highly reactive electrophilic aldehydes such as acrolein is an that is increased in AD brains [19].

The increase in the oxidative stress due to low activity of antioxidant enzymes might pave way for numerous complications and can participate to the neurodegeneration in AD. The activity antioxidants reduced in the existence of a low level of TAS resulting in compensatory rise of SOD Activity. A possible mechanism for the decreased level of TAC could be that due to malnutrition and the scavenger antioxidants were consumed by the increased free radical activity [20]. In a similar study like ours [21,22]. In AD decreased catalase and SOD in neurons decreases the capacity to eliminate increased H_2O_2, which is converted to highly reactive hydroxyl radical through Fenton reaction in the existence of enriched Fe^{2+}/$Cu1^{+}$, that pose a great threat to the brain.

Cytosolic GST, GSH reductase, and G6PD, are secondary enzymes, which act to detoxification of (ROS) by reducing peroxide levels or preserving a stable supply of GSH and NADPH required for the performance of Proverbs of the primary antioxidant enzymes [23].

CONCLUSION

Our results indicate a link between the damage caused by oxidative stress and TSH marker may be used to distinguishing subjects with and without AD. These results need to be confirmed by further prospective longitudinal studies with adequate sample size. Oxidative stress as one of the risk factors, which can initiate and/or promote neurodegeneration in AD and was correlated to the severity of the disease.

STUDY LIMITATION: Sample size in the present study was small. Large prospective studies in Iraqi population are necessary to support the results of current study.

ACKNOWLEDGMENTS: The research was supported by college of dentistry, Tikrit University.

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Cite this article as:

Entedhar R. Sarhat. Altered serum marker of thyroid profile and antioxidant enzymes in individuals Alzheimer's disease. Int. Res. J. Pharm. 2019;10(1):56-60
http://dx.doi.org/10.7897/2230-8407.100110

Source of support: Nil, Conflict of interest: None Declared