ALTERED SERUM MARKER OF THYROID PROFILE AND ANTIOXIDANT ENZYMES IN INDIVIDUALS ALZHEIMER’S DISEASE
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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. Thyroid hormones, tri-iodothyronine (T₃) and thyroxine (T₄), 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 T₃, MDA, Cat, and TAS, whereas inverse correlation with T₄, G6PD, SOD, GSH, and G-Px in AD patients. Conclusions: it could be suggested that increased TSH, whereas decreased T₄, and T₃ 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

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

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 T₃ (1.39 ± 0.168 vs. 1.61 ±0.179 ng/mL), T₄ (80.4 ±5.271 vs. 89.3 ±5.55 ng/mL), TSH (0.51 ±0.386 vs. 1.788 ±0.256 mmol/L trolox equiv), 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. 2.07±0.51).

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.
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_{4}(-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)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (Control)</th>
<th>Group B (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>24/30</td>
<td>19/35</td>
</tr>
<tr>
<td>Age (years)</td>
<td>75.04±12.6</td>
<td>77.7±14.45</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (Control)</th>
<th>Group B (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 (ng/mL)</td>
<td>1.6109±0.17991</td>
<td>1.390±0.16843</td>
</tr>
<tr>
<td>T4(ng/mL)</td>
<td>89.3±5.55133</td>
<td>80.4±5.2711</td>
</tr>
<tr>
<td>TSH (IU/L)</td>
<td>5.54±0.84455</td>
<td>6.210±0.87795</td>
</tr>
<tr>
<td>TAS (mmol/L Trolox equiv.)</td>
<td>1.788±0.25613</td>
<td>0.510±0.38642</td>
</tr>
<tr>
<td>GSH-Px (U/g Hb)</td>
<td>61.39±1.66485</td>
<td>41.1±4.79464</td>
</tr>
<tr>
<td>GSH (µmol/g Hb)</td>
<td>78.0±6.9401</td>
<td>4.050±0.86620</td>
</tr>
<tr>
<td>SOD (U/L)</td>
<td>3.520±0.88139</td>
<td>2.07±0.51169</td>
</tr>
<tr>
<td>G6PD (U/g Hb)</td>
<td>17.7±0.32391</td>
<td>9±0.15938</td>
</tr>
<tr>
<td>Catalase (K/ml)</td>
<td>26.5±1.43846</td>
<td>23.2±1.6977</td>
</tr>
<tr>
<td>MDA (mmol/L)</td>
<td>2.120±0.40110</td>
<td>4.542±0.77923</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01

Figure 1: Correlation between TSH and T4 in 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.
DISCUSSION

Thyroid hormone can reform intracellular \( H^+ \) accumulation by motivation of the \( Na^+/H^+ \) exchanger and can shore suitably low [Ca\(^{2+}\)]\(_{\text{e}}\) 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 / T4 compared to circulation or nervous tissues. In the brain T3 is produced from T4 by type II deiodinase (DIO\(_2\)), which is an enzyme important in preserving the intracellular T3 levels in the CNS. During hypothyroidism the expressions of DIO\(_2\) increase in the brain to maintain T3 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.
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 O2 to H2O2 in cells resulting from direct interaction of Aβ peptides with Fe2+.

AD patients in our study showed lower levels of GSH-Px, CAT, SOD, and G6PD as compared to controls, might be interpreted 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.

The brain has increased oxygen and glucose deprivation, 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. Our findings are also in agreement with some researchers like, 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 surfet 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 crocinol is an that is increased in AD brains.

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. In a similar study like ours, In AD decreased catalase and SOD in neurons decreases the capacity to eliminate increased H2O2, which is converted to highly reactive hydroxyl radical through Fenton reaction in the existence of enriched Fe2+/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.

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.

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REFERENCES


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