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ORIGINAL ARTICLE

The relationship between thyroid deficiency and blood-based biomarkers of cognitive disorders

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Abstract

OBJECTIVE: Thyroid hormones play an essential role in metabolism regulation and circadian rhythm control. Recent studies approved their role in normal development and healthy function of central nervous system (CNS). The thyroid gland is a component of the hypothalamic-pituitary-thyroid axis disrupted during thyrotoxicosis and hypothyroidism, two main clinical conditions that induce more liability against dementia-related disease.

METHOD: In the first step, this study evaluated the circular level of neuropeptide Y (NPY), leptin, oxytocin, and vasopressin in hyperthyroidism and hypothyroidism patients. In the second step, we investigated neurological and cognitive abnormalities by assessment of the hallmark proteins and peptides such as amyloid β (Aβ) variants, glycogen synthase kinase 3β (GSK-3β), and tau protein in thyroid-deficient samples.

RESULTS: The results show increased content of leptin hormone in patients with hypothyroidism who also manifested high levels of vasopressin. Underactivation and overactivation of the thyroid gland are accompanied by reduced circular oxytocin. We may conclude that thyroid deficiency is associated with neurohormone dysregulation. Interestingly, both patient groups exhibited significant increases in $A\beta_{40}$ and $A\beta_{42}$ levels relative to the control group, which was also accompanied by the rise in GSK-3β; this might be interpreted as cholinergic system dysfunction and cognitive impairment. The results revealed tau content increased considerably in thyrotoxicosis but did not change significantly in hypothyroidism compared to the control group.

CONCLUSION: Therefore, our results have shown that thyroid gland dysfunction is a risk factor for cognitive impairment, mainly through neuroendocrine dysregulation. This study provides a relationship between hyperthyroidism/hypothyroidism and biomarkers of neurological abnormalities in blood serum.

INTRODUCTION

The thyroid gland is part of the body's endocrine system responsible for the synthesis and release of triiodothyronine (T3) and thyroxine (T4), which are iodine-containing tyrosine (Cheng *et al.* 2010). T3 and T4 exert their effects on various body activities from prenatal development to adulthood functions. Thyroid hormones influence neurogenesis during the prenatal period, which is associated with neuronal plasticity, cognition, mood control, brain development and maturation, myelination, cytoskeleton stabilization, and signaling between neurons and glia (Eslami-Amirabadi & Sajjadi, 2021; Bernal, 2022). Considering the hormones' widespread regulatory role, thyroid gland dysfunction could perturb whole-body homeostasis (McAninch & Bianco, 2014; Ahmed & Mohammed, 2020). Hyperthyroidism and hypothyroidism are medical conditions caused by the excessive and diminished secretion of hormones from the thyroid gland, so they have been related to neuropsychiatric symptoms such as poor memory, depression, anxiety, and dementia (Eslami-Amirabadi & Sajjadi, 2021).

Despite their distinct symptoms, hypothyroidism and hyperthyroidism share a susceptibility to dementia, but the underlying mechanism is not yet evident (Elbadawy *et al.* 2020; De Jong *et al.* 2009). Previous research indicates that every six months hyperthyroidism is associated with a 16 % increased risk of dementia, possibly due to cholinergic system impairment (Kim *et al.* 2022). Other studies demonstrated a significant correlation between hypothyroidism and a 2-fold increased risk of developing Alzheimer's disease compared to euthyroidism (Khaleghzadeh-Ahangar *et al.* 2022). The thyroid gland is one of the primary regulators of metabolism rate and energy production (McAninch & Bianco, 2014); thus, probable dementia and cognitive impairments were indirectly caused by high- or low-circulating thyroid hormones. The production and secretion of thyroid hormones are regulated by the thyroid-stimulating hormone (TSH) or thyrotropin, secreted by the pituitary gland. TSH secretion is increased by the thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus (Pirahanchi *et al.* 2022). Therefore, the thyroid gland is regulated predominantly by the hypothalamus and pituitary glands in a negative feedback loop (Hoermann *et al.* 2015). These three glands communicate with each other as the hypothalamic–pituitary–thyroid (HPT) axis to regulate metabolism, neurodevelopment and also stress response (Helmreich *et al.* 2005). The abnormal function of each counterpart causes HPT disruption that leads to metabolic and neural disorders (Costa-e-Sousa & Hollenberg, 2012; Shekhar *et al.* 2021). Hyperthyroidism and hypothyroidism could cause dementia-related changes, possibly by targeting the neurohormones, neuroproteins, and neuropeptides. Accordingly, this study aimed to investigate neuropeptide Y (NPY), oxytocin, and vasopressin hormones in patients suffering from hyperthyroidism and hypothyroidism. Leptin hormone was also evaluated between thyroid-deficient and control samples as the principal metabolic rate regulator and an upstream regulator of the HPT axis and thyroid gland (Nillni *et al.* 2000; Riccioni *et al.* 2004). We also tried to evaluate thyroid gland dysfunction effects on the circular contents of amyloid β (Aβ) variants, glycogen synthase kinase three β (GSK-3β), and tau protein, which play an important role in dementia initiation and development (Reddy, 2013; Sayas & Ávila, 2021).

MATERIAL AND METHODS

Experimental design and samples

This cross-sectional study was conducted on 50 hyperthyroidism samples (patients with low levels of TSH and high levels of T3 and/or T4), 50 hypothyroidism samples (patients with a high level of TSH and a low level of T4), and 50 euthyroid samples (control group) referred to the clinical laboratory of Medical City Hospital, Baghdad, Iraq. The reference range for TSH was 0.03–5.5 μIU/mL. According to this range and examination by a specialist internist, patients were divided into age and sex-matched groups of hypothyroid (TSH> 10 μIU/mL) and hyperthyroid (TSH <0.3μIU/mL) by internal medicine physician (Sheehan, 2016). Ethical approvals and patient consent statements were obtained from all patients. The inclusion criteria for patients (hypothyroidism and hyperthyroidism) are age>25 years old. Patients with liver and kidney disorders, acute coronary syndromes, different cancers, patients taking vitamin supplements, and people with a family history of dementia were excluded from the study. The control group was selected among age- and sex-matched euthyroid people without heart disease, diabetes, thyroid disorder, and diabetic nephropathy. General characteristics and circular lipoprotein levels related to the patients and control cases enrolled in this study are shown in Table 1.

Hormone measurement method

Hormones were assessed by using related kits according to the manual. Human Leptin ELISA Kit (Abcam, ab108879), Oxytocin ELISA Kit (ab133050), and Arg8-Vasopressin ELISA Kit (AVP, ab205928) were used for measurement of leptin, oxytocin, and vasopressin in blood serum of three experimental groups, respectively.

Aβ variants, tau, and GSK-3β evaluation

Venous blood was prepared in the morning after an overnight fast. Plasma samples were collected in ethylenediaminetetraacetic acid (EDTA) container tubes and were immediately centrifuged for 10 min at 3000 rpm. After centrifugation, each sample was labeled and stored at -20 °C until use. Quantification of $A\beta_{1-42}$ and $A\beta_{1-40}$ in plasma was performed using a specific ELISA kit (human Amyloid beta 42 elisa kit, MBS703888 from

Tab. 1. Demographic characteristics of the recruited patients and control. Low density apolipoprotein (LDL), high density apolipoprotein (HDL), Triglyceride (TG). Star symbols show different results compared to control ($p<0.05$).

Parameters	Control	Hypothyroidism	Hyperthyroidism
Age	39±14	41±13	41±9
Sex	Female: 25 Male: 25	Female: 23 Male: 27	Female:22 Male: 28
Cholesterol (mg/dL)	188.13±16.53	212.37±28.27 *	195.57±19.34 *
LDL (mg/dL)	85.17±13.06	100.97±15.10 *	86.23±12.88
HDL (mg/dL)	66.60±7.65	55.03±10.81 *	53.47±8.34 *
TG (mg/dL)	127.77±11.37	136.93±17.94	157.70±10.01 *

My Biosource company, and human Amyloid beta 40 elisa kit, MBS760432 from My Biosource company). Tau protein content in different samples was assessed using Human Tau ELISA Kit (ab273617), and the GSK-3β level also was measured by using the GSK-3β ELISA kit, MBS2506325 from My Biosource company. All assays were performed according to the manufacturer's protocol. All reagents were prepared at room temperature (20–25 °C) at least 30 min before use.

Measurement of elements in blood serum

We also evaluated the essential elements in blood serum as sodium (Na), potassium (K), calcium (Ca), and selenium (Se) by using the following kits according to the manual: human ELISA kits for the determination of sodium (Abcam, ab211096, UK), potassium (Abcam, ab252904, UK), calcium (Abcam, ab272527, UK) and selenium (Se, Mybiosource, USA).

Statistical analysis

Analysis of variance with Bron-Forsite correction was used to determine statistical differences between results related to hyperthyroidism, hypothyroidism, and control. Differences between experimental groups have been shown in each plot by indicating the star symbol according to the p value. Tukey's test was also used to make pairwise comparisons. All statistical analyses were performed using GraphPad Prism software (version 9.5, GraphPad Software, Inc. San Diego, CA, USA).

RESULTS

Considering the important role of thyroid gland deficiency in mood and cognition, particularly in memory and dementia, the purpose of this study was to investigate the responsible mechanism by evaluating certain neuroactive hormones and proteins in the blood serum of patients with hyperthyroidism and hypothyroidism and comparing them with the control group. About 100 patients with hypothyroidism and hyperthyroidism and 50 controls (euthyroid) participated in this experiment. The average age of patients in each of the three categories is 40±14, and there is no statistically significant difference between them ($p>0.05$). The number of male and female patients in the three groups does not differ significantly.

Impact of thyroid disorders on leptin hormone concentration

As shown in Figure 1, patients with hypothyroidism have higher levels of leptin in circulation than patients with hyperthyroidism or in the control group. Higher leptin level in underactive thyroid patients is significant (****, $p=0.0001$), but there is no significant change between the control and thyrotoxicosis groups. The significant difference between hypothyroidism and hyperthyroidism groups was also perceived (****, $p=0.0001$).

Thyroid gland deficiency affects the circular content of hypothalamic and pituitary neuropeptides

Oxytocin and vasopressin are pituitary neuropeptides that have been shown to affect CNS and thyroid gland function. According to the analysis of variance with Bron-Forsite correction, our results revealed a significant difference in circular oxytocin content between

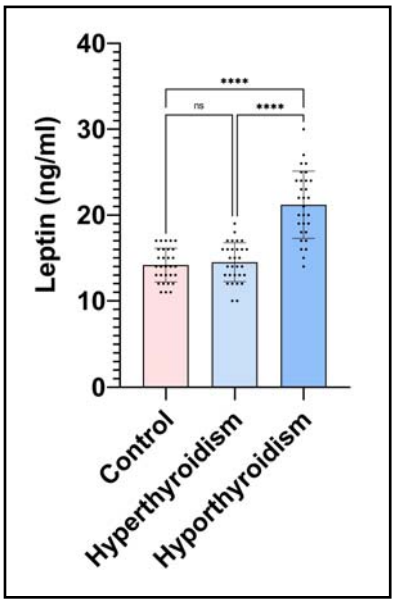

Fig. 1. The level of leptin hormone in hypothyroidism and hyperthyroidism in comparison with control. All data were expressed as mean ± SD. Significant differences indicated by star symbol (****, $p=0.0001$) on columns.

control and hypothyroidism/hyperthyroidism (****, p=0.0001) groups, and the oxytocin is significantly lower in both patient groups (Figure 2A). However, there is no significant difference between hypothyroidism and hyperthyroidism groups (p=0.5).

Figure 2B shows that the level of vasopressin in the control group is 1.6±0.75 pg/ml, and in hypothyroid patients is 4.37±1.39 pg/ml. Based on the results, vasopressin is significantly higher in patients with underactive thyroid (****, p=0.0001). However, there is no significant difference between vasopressin levels in control and hyperthyroidism groups.

Neuropeptide Y (NPY) originated from hypothalamic neurons and modulated the effects of leptin on the CNS. Our results also revealed a significant reduction of NPY due to thyroid disorders (Figure 2C). NPY concentration ranged from 10.70 pg/mL to 35.60 pg/mL, and analysis of variance could detect significant changes between the three experimental groups (p<0.05). The NPY count in control was evaluated as 28.16±4.8 pg/mL, more than both patient groups. Figure 2C reveals that the levels of NPY in the hyperthyroidism and hypothyroidism groups are significantly lower than in the control group, at 22.384.08 and 17.224.39 pg/mL, respectively.

Thyroid deficiency disrupted the circular level of neuroactive proteins and peptides

Amyloid-beta (Aβ)

The cleavage of amyloid precursor proteins produces Aβ into a monomeric form with different lengths, such as $A\beta_{1\text{-}40}$ or $A\beta_{1\text{–}42}$, which is then transformed into the blood and considered a core biomarker of cognitive deficiency. This study evaluated the Dynamics of Aβ peptides, and the results revealed that thyroid deficit triggers an abnormal increase in serum $A\beta_{1\text{-}40}$ and $A\beta_{1\text{–}42}$ content. According to the results, $A\beta_{1\text{–}42}$ content was evaluated to be 51.04±20.93 pg/ml in the circulation of control samples, while hypothyroid samples showed 50.67±21.14 pg/ml and hyperthyroid patients showed 84.39±47.72 pg/ml (Figure 3A). Therefore, thyrotoxicosis significantly increases the blood concentration of $A\beta_{1\text{–}42}$ (**, p=0.0005), whereas hypothyroidism does not affect the circular $A\beta_{1\text{–}42}$. According to Figure 3B, the amount of $A\beta_{1\text{-}40}$ also increased in thyroid abnormalities. Results revealed near the 3-fold increase of circular $A\beta_{1\text{-}40}$ in patients with thyroid deficiency. According to Figure 3B, the changes of $A\beta_{1\text{-}40}$ are efficient in both groups of patients. As stated in previous reports, $A\beta_{1\text{-}42}/A\beta_{1\text{–}40}$ ratio is more informative than each type of Aβ individually. According to the evaluated results, the $A_{1\text{-}42}/A_{1\text{–}40}$ ratio is 0.48 for control cases, 0.28 for patients with thyrotoxicosis, and 0.16 for patients with hypothyroidism. Therefore, this ratio decreased in both groups compared to the control group, but it was more effective in patients with hyperthyroidism.

Tau protein

Considering the role of the tau protein in brain function and cognitive abnormalities, the study focused on the tau concentration in plasma samples from patients with hyperthyroidism or hypothyroidism. Results revealed that tau protein content is at the same level in control and hypothyroid patients. Thus, analysis of variance with Bron-Forsite correction could not detect significant changes in the tau level of blood serum due to underactive thyroid (ns, p=0.81) (Figure 3C). Since thyrotoxicosis caused a substantial increase in the circulation of tau protein (*, p=0.01), the two patient groups differ in terms of their tau content (*, p=0.01).

Glycogen synthase kinase-3 beta (GSK-3β)

This study sought to evaluate GSK-3 β by considering changes in the circular tau and Aβ levels in thyroid deficiency. Without considering its enzymatic activity, both patient groups showed elevated levels of GSK-3β

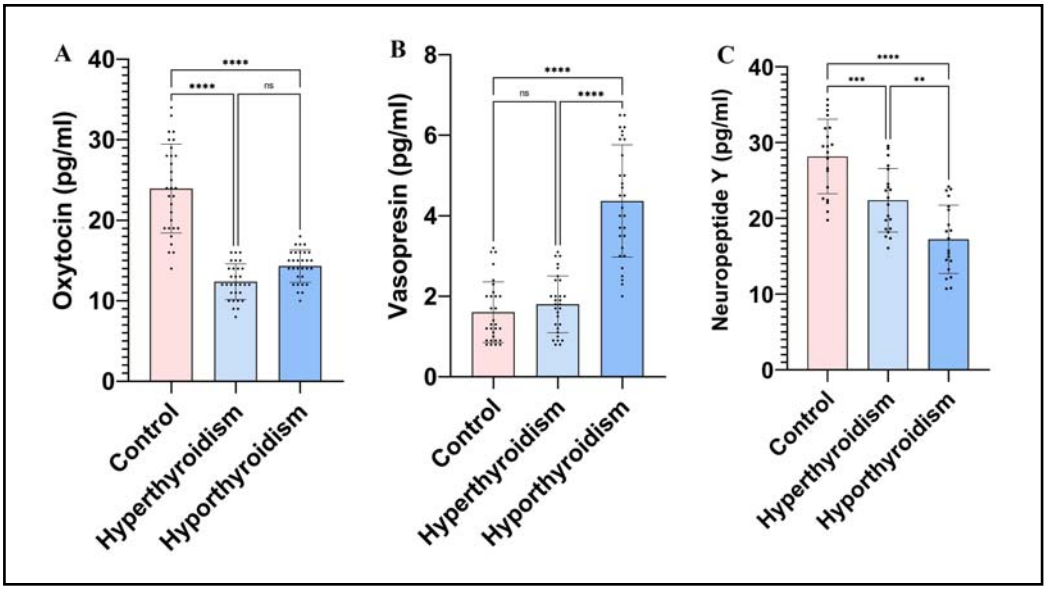

Fig. 2. Effects of thyroid deficiency in circular level of the hypothalamic and pituitary neuropeptides. (A) Compared to control, Oxytocin and (B) vasopressin levels in hyperactive thyroid and hypothyroidism patients. (C) Reduction of NPY level in thyroid deficiency rather than control. All data were expressed as mean ± SD. Significant differences indicated by star symbol (**, p=0.002; ***, p=0.0005; ****, p=0.0001)

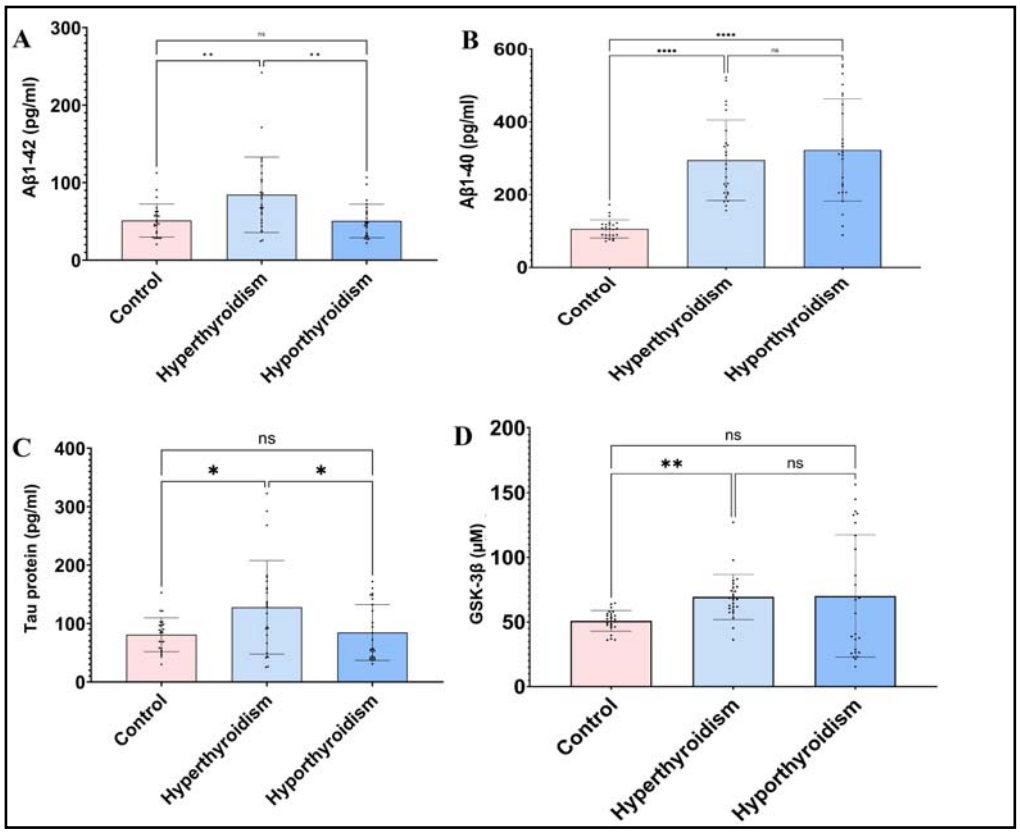

Fig. 3. Changes of the Aβ variants and important neuroproteins in thyroid deficiency. (A) Aβ1-42 and (B) Aβ1-40 are two variants of amyloid beta peptide which significantly increased due to thyroid under and overactivation. (C) Showed the evaluation of tau protein and (D) Manifested GSK-3β content in circulation of patients suffering from thyroid deficiency compared to control. All data were expressed as mean ± SD. Significant differences indicated by star symbol (*, p=0.01; **, p=0.001; ****, p<0.0001)

compared to the control group. (Figure 3D). Its content was evaluated as 50.96±7.77 μM in control samples, while GSK-3β content was 69.76±19.11 μM in hyperthyroid samples, which is remarkably higher than control (p=0.001**). This parameter was determined to be 70.2346.44 μM in the hypothyroidism group, which did not differ significantly from the control (ns, p=0.38) and hyperthyroidism (ns, p=0.16) groups due to the large range of data and high standard deviation (Figure 3D).

Thyroid gland deficiency dysregulated blood serum elements

The serum elements such as Se, Na, K, and Ca^{2+} are important ions that could regulate enzymatic function and also oxidative stress in circulation. According to the results, thyroid deficiency did not affect Se, Na, and K serum levels, whereas Ca^{2+} was significantly decreased. Ca^{2+} concentration in control blood serum was 88.13±7.34 mg/L and was diminished to 77.7±5.66 mg/L due to hyperthyroidism. This change is significant according to the statistical analysis (****, p=0.0001). Hypothyroidism also affects Ca^{2+} levels in blood serum and causes about 18 % reduction (72.63±7.64 mg/L).

DISCUSSION

The thyroid gland is part of the endocrine system responsible for regulating metabolism and stress response (Ahmed & Mohammed, 2020; Costa-e-Sousa & Hollenberg, 2012). The normal function of this organ is essential for the HPT axis and body homeostasis, whereas abnormal function is associated with an increased risk of dementia or cognitive disease (Costa-e-Sousa & Hollenberg, 2012; Shekhar *et al.* 2021). Thyroid gland dysfunction, including hyperthyroidism and hypothyroidism, may impair neural functions via neurohormones and certain upstream factors, such as insulin and leptin (Yang *et al.* 2009). This study aimed to investigate the hyperthyroidism and hypothyroidism impact on the level of NPY produced by hypothalamic neurons (Yang *et al.* 2009), oxytocin and vasopressin released by the pituitary gland (Baribeau & Anagnostou, 2015) in blood samples. We also tried to clarify how thyroid dysfunction could cause dementia. Previous studies confirmed that the risk of dementia in people suffering from long-term thyroid deficiency is more than usual (Kim *et al.* 2022, Khaleghzadeh-Ahangar *et al.* 2022). For this purpose, some of the important dementia hallmarks, including neuroproteins and neuropeptides such as Aβ, tau, GSK-3β and Ca^{2+} ion (Sayas & Ávila, 2021; Ullah *et al.* 2021; Lauretti *et al.* 2020; Wang *et al.* 2020) were assessed in blood serum of experimental groups.

According to the results, hypothyroidism patients manifested more leptin hormone levels than control and hyperthyroidism groups. Leptin is an upstream regulator that impacts the HPT axis and thyroid gland to maintain body homeostasis (Nillni *et al.* 2000; Riccioni *et al.* 2004) (Figure 4). Despite the different

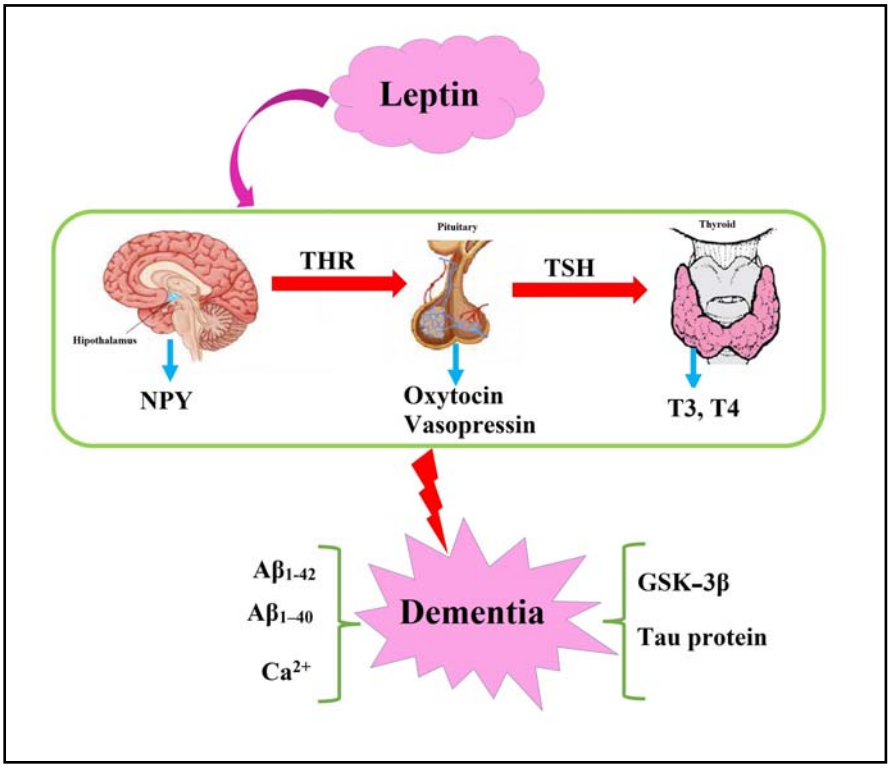

Fig. 4. Schematic illustration of studied pathway. Leptin are upstream regulators that affects hypothalamus, pituitary and thyroid glands and finally causes dysregulation of dementia hallmarks. TSH: thyroid-stimulating hormone, TRH: the thyrotropin-releasing hormone, NPY: neuropeptide Y, GSK-3β: glycogen synthase kinase three β, T3: triiodothyronine, T4: thyroxine, Aβ: amyloid β.

symptoms of hypothyroidism and hyperthyroidism, patients with both disorders experience a twofold decrease in oxytocin levels. Vasopressin levels increased more than two-fold in the hypothyroidism group, which also showed increased leptin levels. Oxytocin reduction is observed in some cases of memory impairment, and according to reports, this hormone could potentially alleviate Alzheimer's disease-related cognitive impairments (El-Ganainy *et al.* 2022). These results may be interpreted as neuroendocrine and HPT axis dysfunctions as a cause or effect of thyroid deficiency.

According to the results, thyroid gland impairment causes the abnormally highest level of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in the peripheral circulation. Transport of Aβ peptide from the brain into the peripheral blood has been demonstrated in Alzheimer's disease patients and related animal models; therefore, an elevated plasma level of Aβ is a strong biomarker of dementia. (Cheng *et al.* 2020). According to previous reports, the increased plasma Aβ level represents a higher Aβ content in the brain, leading to amyloid plaque formation (Yang *et al.* 2020). Although, dynamics of Aβ content in circulation were reported in different metabolic disorders like diabetes (Rahat *et al.* 2021). GSK-3β was also increased as a result of thyroid deficiency which possibly causes cholinergic system dysfunction (Wang *et al.* 2017). It is a multifunctional serine/threonine kinase directly linked to a higher level of Aβ peptide and causes Aβ to be more labile to fibrillation, tau hyperphosphorylation, and synaptic damage in dementia patients and animal models (Sayas *et al.* 2021; Lauretti *et al.* 2020). In patients with thyrotoxicosis, previous studies (Li *et al.* 2020) and our results (Figure 3C) have shown an increase in the tau content of the blood serum. In contrast, hypothyroidism is not affected by thyroid gland abnormalities. It is possible that the amount of phosphorylated tau (P-tau) in the circulation and brain tissue of underactive thyroid samples rises due to an increase in GSK-3β, but this hypothesis requires further investigation. According to a previous study, this controversial result may be attributable to the fact that the disease duration of the studied patients varied (Kim *et al.* 2022). Subsequently, increased GSK-3β, as a consequence of thyroid dysfunction, could cause hyperphosphorylation of tau, senile formation, β-secretase hyperactivation, Aβ plaque formation, and also neuroinflammation (Lauretti *et al.* 2020). The dysregulation of this multifunctional enzyme was reported to be important in developing cancer, diabetes, Alzheimer's disease, schizophrenia, and bipolar disorder, too.

Our results indicate a positive feedback loop between thyroid gland deficiency, neurohormone dysregulation, and dementia. This loop seems an effective risk factor in developing Alzheimer's disease and dementia-related disorders in hyperthyroidism and hypothyroidism. Because hypothyroidism is associated with an increase in leptin hormone, it is possible to conclude that thyroid hormones regulate metabolism rate primarily through their effect on the HPT axis. Our results also revealed a significant correlation between the increase of circular GSK-3β, Aβ, and tau proteins, which may be interpreted as GSK-3β 's dominant role. Given its significance in the neuropathology of hypothyroidism and hyperthyroidism, GSK-3β could be considered

a promising therapeutic target. Previous research and our findings confirmed that thyroid hormones affect virtually the entire body's metabolism and organs, including the heart, central nervous system, autonomic nervous system, and bone, and that thyroid dysfunction is a risk factor for cognitive impairment through the dysregulation of neurohormones.

DECLARATION OF COMPETING INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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