Thyroid Disorders and Development of Cognitive Impairment: A Review Study

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Keywords

Dementia · Cognitive impairments · Thyroid disorders · Hypothyroidism · Hyperthyroidism

Abstract

Dementia is a neurological disorder that is spreading with increasing human lifespan. In this neurological disorder, memory and cognition are declined and eventually impaired. Various factors can be considered as the background of this disorder, one of which is endocrine disorders. Thyroid hormones are involved in various physiological processes in the body; one of the most important of them is neuromodulation. Thyroid disorders, including hyperthyroidism or hypothyroidism, can affect the nervous system and play a role in the development of dementia. Despite decades of investigation, the nature of the association between thyroid disorders and cognition remains a mystery. Given the enhancing global burden of dementia, the principal purpose of this study was to elucidate the association between thyroid disturbances as a potentially modifiable risk factor of cognitive dysfunction. In this review study, we have tried to collect almost all of the reported mechanisms demonstrating the role of hypothyroidism and hyperthyroidism in the pathogenesis of dementia.

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Introduction

Background

Cognitive impairment is defined as low performance in one or more cognitive behavior that may not disrupt one's daily tasks completely; if it develops, in its more advanced state can be called dementia which includes severe or more severe forms of cognitive impairment/decline [1]. Dementia is a condition in which gradually amnesia and cognitive impairment occur. It also affects individuals, their families, and the economy, with global costs [2]. Worldwide, almost 50 million individuals suffer from dementia, and annual new cases are about 10 million people [2]. The prevalence of dementia in populations is expected to increase with increasing life expectancy [3]. On the basis of the WHO report, the onset of dementia symptoms in up to 9% of the cases is before the age of 65 years [4]. Dementia and cognitive decline prognosis include frontotemporal lobe dementia, neurodegenerative processes such as Alzheimer's disease (AD), and Lewy body dementia [5].

Patients with endocrine disorders may experience neurologic diseases [6]. Among endocrine disorders, thyroid disorders have been known as risk factors for progressive cognitive impairment development, either in the form of hyperthyroidism or hypothyroidism [7]. The present article tries to review the relationship between thyroid disorders with dementia and cognitive impairments.

Thyroid Hormones and Their Receptors

Hormones secreted by the thyroid gland, which include thyroxine (T4) and tri-iodothyronine (T3), are essential for various body activities, from prenatal development such as growth and differentiation of the nervous system to adulthood functions such as metabolic rate maintenance, feeding, thermogenesis, memory and concentration, reactive oxygen species balance, and cardiovascular function as well [8]. T4, T3, and a very limited amount of reverse T3 are separated from the thyroglobulin molecule by lysosomal proteases and then released into the bloodstream [9]. The main form of the thyroid hormones in the circulation is T4, characterized by a longer half-life than T3 [10]. T4 is chiefly bound to proteins in the bloodstream and is carried to the target tissues; the amount of free T4 in the circulatory system is about 0.03% of total T4 [11]. The metabolically active thyroid hormone is T3, and like T4, most of the T3 in the circulation is attached to the proteins [12]. T4 and T3 are formed in the thyroid gland as a result of coupling reaction: monoiodotyrosine and di-iodotyrosine (DIT) join to form T3, and two DIT molecules form T4 [13]. While a small amount of T4 is converted to T3 in the thyroid gland, the conversion of T4 to its biologically active form occurs predominantly in extrathyroidal tissues, including the liver, kidney, central nervous system (CNS), pituitary gland, and skeletal muscles [14]. The physiological functions of thyroid hormones are mostly conducted via T3 interaction with nuclear receptors of thyroid hormones, which are present in four isoforms, including $\alpha 1$, $\beta 1$, $\beta 2$, and $\beta 3$. The mentioned receptors are characterized by transcription factor activity, in which their activity is modulated by the presence of ligand T3 [8].

There are various target genes for thyroid hormones; many are essential in brain functions, and more than 1,100 are important in brain development [15]. Among genes that are regulated by thyroid hormones, several genes possessing remarkable functions in the nervous system can be mentioned; for instance, *RELN* by producing Reelin, an extracellular matrix protein, is implicated in neuronal migration in the brain [16]; the next one is a protein kinase C substrate, *NRGN* (RC3/neurogranin) [17], which is involved in the neuronal plasticity processes such as long-term potentiation (LTP) in the hippocampus [18]. The amyloid precursor protein (APP) gene, which produces the precursor of β -amyloid (A β), is downregulated by T3 [19]. Laminin expression, the extracellular matrix protein binding to astrocytes surface, is regulated by thyroid hormones [20]. Brain-derived neurotrophic factor (BDNF) is a pivotal factor in the differentiation of several types of interneurons and synaptic plasticity, and its expression is regulated by thyroid hormones as well [21]. Neuroserpin,

which inhibits tissue plasminogen activator (tPA), is up-regulated by thyroid hormone [22]. Thyroid hormones also adjust neuromodulin/GAP-43 expression regulating synaptic plasticity and memory processes [23]. Thyroid hormones have nongenomic mechanisms of effects as well, such as activating Ca²⁺-ATPase, Na, K⁺-ATPase, mitogen-activated protein kinases, integrin $\alpha v \beta 3$, and G_q signaling, maintenance of actin cytoskeleton, human bone cell proliferation, airways smooth muscle cell proliferation, separation of cellular respiration, and metabolism [24].

Thyroid Disorders

Thyroid disorders have been determined to be among the most common diseases worldwide [25]. The incidence of thyroid disorders is approximately 0.2–8% in adults; with age, this rises and in women is higher than in men [25]. Most people with thyroid disturbances, ranging from hypothyroidism to hyperthyroidism, have autoimmune disease in iodine-rich areas [25]. Chronic autoimmune thyroiditis (Hashimoto's disease) is the most significant cause of hypothyroidism in iodine-sufficient regions [26]. Iodine deficiency is the most prevalent cause of goiter as thyroid dysfunctions, which leads to hypothyroidism in low-iodine areas [27]. Hypothyroidism and hyperthyroidism are usually triggered by pathological changes in the thyroid gland (the primary thyroid disorder) [28]. However, in rare cases, they can be caused by hypothalamus or pituitary gland disorders (secondary or central thyroid disorders) or by ectopic thyroid hormone secretion [29]. Based on the thyroid-stimulating hormone (TSH) and free T4 levels in the bloodstream, thyroid disorders are also categorized, which are mentioned in the following. Subclinical hypothyroidism is characterized when serum levels of TSH are higher than the normal range, but still, free T4 concentration is within the normal range of the population. Overt hypothyroidism is characterized somehow that serum concentration of TSH is higher than the normal range, and free T4 levels are lower than the normal range [30]. Similarly, the reverse hormone pattern is used to define overt hyperthyroidism (low serum TSH levels and high free T4 and T3 levels) and subclinical hyperthyroidism (low serum TSH level and normal free T4 and T3 levels) [31]. Subclinical thyroid diseases are more common than overt types; they are often asymptomatic and, hence, go undiagnosed and untreated, leading to significant adverse effects [32].

Thyroid Disorders and Cognitive Impairments

Psychological and cognitive changes have been documented for many years in adults with altered thyroid func-

tion. In the late nineteenth century, the association of hypothyroidism and thyrotoxic diseases with mental disorders was reported for the first time [33, 34]. Although some studies have ruled out a correlation between thyroid hormones and cognition, it is confirmed that cognition is influenced by thyroid impairment [35]. Animal studies have demonstrated that adult hypothyroidism changes brain function and morphology in regions that affect cognitive functions [36]. In both hypothyroidism and hyperthyroidism, thyroid dysfunction plays a role in increasing the risk of AD development [37]. Other research studies showed that an increased risk of dementia was associated with both high and low TSH levels [38, 39]. In a study performed on mild AD patients, thyroid hormones have moderately changed. The authors suggested that decreased peripheral conversion of T4 to T3 caused increased serum levels of free T4 with decreased T3/T4 ratios. They also suggested that the serum level of T3 is related to brain structures involved in the development of AD [40]. It is also noteworthy that major cognitive and affective impairments, which affect various domains, are not characteristics of subclinical thyroid disorders. However, in subclinical thyroid disorder, subtle deficits in particular cognitive domains are likely to occur [41]. Cognitive and emotional indices can be significantly improved by using thyroid hormones in patients with thyroid disorders [42]. It was also reported that the T3 level is precisely regulated within a narrow range in the CNS [43]. It was suggested that slight deviations in normal brain T3 levels might lead to the cognitive deterioration [44]. Additionally, either reduced serum-free T3 or downregulating hippocampal thyroid hormone receptor signaling could develop cognitive and behavioral impairment in mice [45, 46]. Since the association between hyperthyroidism and/or hypothyroidism with dementia has already been studied and is still being investigated, it is necessary to consider the underlying pathology and mechanisms of this association and thus modify the management of dementia. In the three following sections, hyperthyroidism and hypothyroidism and their relationship with cognitive problems and dementia, along with possible mechanisms, are discussed separately; first, because of the importance of thyroid hormone in brain development, the impact of hypothyroidism on brain development, especially at the regions related to cognition, is briefly reviewed.

Hypothyroidism and Brain Development during the Embryonic Period

Throughout life, from fetus to senile, thyroid hormones have a multitude of effects on CNS development

and mediate huge influences on the brain [47]. During pregnancy, before 12–14 weeks of gestation, the fetus is dependent on the mother's thyroid hormones [48, 49]. It has been identified that 2.5% of women are affected by hypothyroidism during pregnancy, and the incidence of congenital hypothyroidism is approximately 1/3,500–4,000 births [25]. Experimentally induced thyroid hormone deficiency during sensitive stages of the fetus brain development decreases the number of neurons, dendritic arborization, and synaptogenesis and alters neuronal migration to the hippocampus and neocortex areas in rodents [50–53]. Thyroid hormone deficiency during early pregnancy by altering the neuronal migration leads to less well-defined cortical layering and also an alteration in the hippocampus and somatosensory cortex cytoarchitecture in rodents [51, 52]. Diminished intelligence quotient scores, subtle deficits in cognitive function, and memory were observed in children born from women with hypothyroxinemia during pregnancy [54]. During pregnancy, induction of hypothyroidism in mice causes alterations in DNA hypermethylation of several essential brain genes, such as BDNF, which is crucial for various activities in the brain, including neuronal plasticity processes related to hippocampal-dependent learning and memory [55]. In humans, even a moderate subclinical maternal hypothyroxinemia, particularly in early pregnancy, causes permanent neural damage [54] in addition to delayed motor and mental development [56]. Thyroid hormone deficiency in late pregnancy has also demonstrated irreversible alterations in neuronal plasticity and transmission in the hippocampus of adult animals [57, 58].

Postnatal Hypothyroidism and Brain Development

The examination of the structural and growth properties of the hippocampus in the rats that were exposed to early postnatal thyroid hormone deficiency showed a substantial reduction in the surface of this area, and the regions of CA1 and CA4 were more vulnerable to the devastating effects of early thyroid deficiency [59]. Early postnatal development studies in rats have also shown that the granule cell number in the dentate gyrus of the hippocampus decreases in hypothyroid animals, and irreversible neuronal cell death occurs in the hippocampal CA1 area after postnatal hypothyroidism induction. Additionally, CA3 pyramidal cell layer volume was reduced, but cell number in this layer did not decrease [60, 61]. The possible mechanisms involved in brain alterations due to developmental hypothyroidism are presented in Table 1.

Table 1. Possible mechanisms through which hypothyroidism affects brain development

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Decreasing the number of neurons, dendritic arborization, and synaptogenesis
Alteration in neuronal transmission
Alteration in neuronal migration to the hippocampus and neocortex
Alterations in DNA hypermethylation of several essential brain genes, such as BDNF
Irreversible alterations in neuronal plasticity
Reduction in the surface of the hippocampus, particularly in CA1 and CA4 regions
Neuronal cell death in the dentate gyrus and CA1
Reduction in the volume of CA3 pyramidal cell layer

Search Strategy

All 3 authors have used ScienceDirect, PubMed, Scopus, and Google Scholar search engines to obtain all published papers related to the subject. The search covered all articles (from past to present) that have been published online and are available through these websites. For all articles, we tried to access the full text and extract their methods and findings. Attempts were made to use all relevant articles that added new content. Keywords used were thyroid disorders, hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism, thyroxine, tri-iodothyronine, thyroid-stimulating hormone, thyroid autoimmunity, Hashimoto's disease, Hashimoto's thyroiditis, cognitive impairments, dementia, learning and memory impairments, brain development, Alzheimer's disease, β -amyloid, tau hyperphosphorylation, and related words and abbreviations. Furthermore, a combination of thyroid and cognitive-related words were used, such as thyroid disorders and cognitive impairment, hyper/hypothyroidism and cognitive impairment, and thyroid autoimmunity and cognitive impairment. Totally, 681 articles were found. Duplicated articles, articles with no concomitant relationships of dementia and thyroid hormones, articles with duplicated results, articles without available full text, and articles with newer versions were excluded. Ultimately, 83 articles were used. The authors tried to present and analyze the articles with no bias.

Adult-Onset Hypothyroidism and Cognitive Impairments

It has been shown that a variety of cognitive domains can be impaired by overt hypothyroidism. Several studies demonstrate reductions in attention/concentration, general intelligence, memory, language, perceptual function, executive function, and psychomotor activity. It is indicated that the most consistently influenced do-

main is memory [62], with specific deficits in verbal memory [63, 64]. According to studies, the prevalence of cognitive dysfunction is high among patients with hypothyroidism. Increased age, increased disease duration, and high levels of TSH are statistically related to cognitive deficits [65]. A previous study has shown various neuropathological signs of AD in adult rats with hypothyroidism, namely, hippocampal tau hyperphosphorylation and impaired signaling molecules expression related to synaptic plasticity and memory, as well as elevated levels of pro-inflammatory cytokines. Spatial memory is also impaired in hypothyroidism [66]. It has been documented that people with hypothyroidism have a 2-fold higher chance of AD [67]. Also, older individuals seem to be more susceptible to the cognitive consequences of subclinical hypothyroidism than the young population; treating hypothyroidism may protect the aging brain against cognitive dysfunctions. However, with L-thyroxine treatment, all the cognitive dysfunctions caused by thyroid disorder cannot be treated completely; it improves attention, memory, verbal fluency, reaction time, visual memory, and executive functions, but still, significant memory deficit can persist in middle-aged and older people [68]. It seems that the brain becomes more susceptible to thyroid disorders during aging; therefore, thyroxine treatment may not restore all aspects of cognitive dysfunctions [69]. Adult-onset hypothyroidism in rats decreases hippocampal synaptic plasticity and diminishes learning as well [36]. Furthermore, in thyroidectomized adult rats, intense dysfunction in learning and both short-term and long-term memory was identified [70]. Thyroid hormone deficiency disrupts LTP in both early and late phases [71], so the memory encoding and consolidation may become disrupted. Belandia et al. [19] have reported that in a cell line of rat neuroblastoma, T3 negatively regulates APP gene expression. It seems that low levels of thyroid hormones in the CNS by elevating the expression of APP and, subsequently, A β protein levels may predispose the patients to AD [72]. Additionally, an in-

Table 2. Possible mechanisms through which hypothyroidism is involved in cognitive impairment

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Hippocampal tau hyperphosphorylation
Impaired signaling molecules expression leading to reduced hippocampal synaptic plasticity and memory
Elevated levels of pro-inflammatory cytokines
Decreasing the numbers of dentate gyrus granule cells and CA1 pyramidal neurons in the hippocampus
Decrease in the apical dendritic spine density of pyramidal cell in the CA1 area
LTP disruption
Elevation in APP gene expression and, subsequently, β -amyloid
Decreasing the cerebral blood flow
Impairment in the hippocampal cholinergic neurons and also the synthesis of this neurotransmitter
Decrease in choline acetyltransferase activity
Alteration in the catecholamine, GABA, serotonin, tryptophan, neuromodulators, and growth factors in the hippocampus
Reduction in hippocampal Na^+ , K^+ -ATPase activity, and glutamate levels
Hippocampal tau protein hyperphosphorylation
Reduction in the expression of several genes such as laminin and BDNF
Glucose metabolism impairment
IL-1-dependent autophagy and apoptosis in hippocampal neurons

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verse association between serum TSH levels, but not free T3 or T4, with blood flow in the inferior and middle areas of the right temporal lobe of patients with AD has been observed [73, 74]. Objective evidence provided by imaging studies shows that brain function and structure are altered in the hypothyroid state by reducing the volume of the hippocampus and cerebral blood flow, particularly in regions mediating visuospatial processing, attention, motor speed, and working memory [75–77]. Hypothyroidism may also impair the hippocampal cholinergic neurons, which are abundant in this area; additionally, choline acetyltransferase activity and the level of this enzyme involved in the synthesis of acetylcholine are reduced in hypothyroidism in rats [78]. By altering the expression of growth factors, neuromodulators, and neurotransmitters in the brains of the adult rats, thyroid dysfunction indirectly influences CNS activity, including regions implicated in cognitive and emotional functions [41, 79]. Decreased thyroid hormones, for instance, change the expression of enzymes in the hippocampus, which are involved in the regulation of catecholamine, GABA, and serotonin systems in rodents [79–81]. Hypothyroidism causes brain serotonin reduction and its precursor, tryptophan (5-HTP), as well [82]; since the brain serotonin system is a pivotal part of the memory improvement and cognitive behavior enhancer [83, 84], it can be a probable mechanism of hypothyroid-induced cognitive impairment. Hippocampal Na^+ , K^+ -ATPase activity, and glutamate levels are also reduced in hypothyroidism conditions which could be involved in memory deficit in mice [85]. Additionally, hippocampal-related memory deficits dis-

played by hypothyroid rats were reduced by T3 supplementation, and key markers of thyroid function in the hippocampal tissue, including A β production, neuroinflammation, and several signaling pathways identified to be implicated in memory function and neuronal plasticity, were normalized [86]. There is also evidence that thyroid hormones are implicated in the regulation of tau protein phosphorylation, another hallmark of AD, and it was reported that hypothyroidism leads to hippocampal tau hyperphosphorylation [66, 86]. Besides, there are various genes whose expression decreases with a decline in thyroid hormones, such as laminin, a guidance molecule implicated in the migration of neuronal cells [87], and BDNF, involved in the synaptic structural changes [21, 88, 89]; therefore, hypothyroidism may influence the cognition by altering neuronal migration and synaptic structure. In addition, hypothyroidism worsens cognition at any age by preventing energy (glucose)-consuming functions required for critical CNS activities, namely, neurotransmission, memory, and other higher brain function [68]. Hypothyroidism-induced disorders of glucose metabolism in several brain areas, including the hippocampus, may precede the clinical onset of dementia [90]. Furthermore, long-term developmental hypothyroidism from the embryonic period till adulthood triggers an interleukin1-dependent autophagy mechanism as an essential mediator which promotes apoptosis in hippocampal neurons and cognitive impairment in rats [91]. The possible mechanisms involved in cognitive impairments due to adult-onset hypothyroidism are also presented in Table 2. Treatment of overt hypothyroidism improves symp-

toms of mood or cognitive deficits (although that may not be fully resolved); however, therapy for subclinical hypothyroidism is more challenging. In subclinical hypothyroidism, thyroid-related emotional or cognitive impairment is subtle (executive function and working memory); overt hypothyroidism, however, is related to a clinically considerable reduction in affective and cognitive function (particularly memory) [62].

Thyroid Autoimmunity and Cognitive Impairment

Thyroid autoimmunity is a multifactorial disease with genetic backgrounds and is influenced by several environmental factors; chronic lymphocytic thyroiditis, also called Hashimoto's thyroiditis (HT) or Hashimoto's disease, is the most common thyroid autoimmunity in humans in which most of them are euthyroid, and others show hypothyroidism [92]. HT occurs more frequently in adults and predominantly in women and girls. The HT is characterized by increased thyroid peroxidase antibody levels in the serum [93].

One of the HT consequences is encephalopathy [94]. In HT, mild cognitive impairment and subtle dementia may occur [93]. It influences visual attention, speech fluency, and conceptual tracking in humans [95]. During HT, cerebral metabolism changes, and thereupon, neural activity reduces [96]. It also can affect the human brain's bioelectrical activity [97, 98]; via altering neuronal activity, it can affect cognition. Furthermore, in compensated euthyroid HT patients also the cognitive dysfunction may occur [97].

Adult-Onset Hyperthyroidism and Cognitive Impairments

Some studies have reported that increased levels of free T4 or decreased levels of TSH are linked to cognitive dysfunction or dementia [99, 100]. Kalmijn et al. [39] stated that subclinical hyperthyroidism raises AD and dementia risks among the elderly population. A 3-fold increase in the risk of dementia of the Alzheimer type among all hyperthyroid participants was also presented [39]. Increased risk of dementia was found in hyperthyroid patients using large-scale registry-based data. Compared to people with a normal level of TSH, every 6 months of reduced TSH was associated with a 16% increased risk of dementia [101, 102]. Prolonged exposure to thyroid hormone can cause cardiovascular

and cerebrovascular diseases such as systolic hypertension and fibrillation, associated with an increased risk of dementia [103, 104]. Imaging studies through magnetic resonance spectroscopy have demonstrated that Graves' patients have abnormal brain metabolism in the mid-frontal, mid-occipital, and parieto-occipital areas, which maps to the domains of working memory and executive function [105, 106]. Furthermore, Schreckenberger et al. [107], by using positive emission tomography scanning, reported an irregular glucose metabolism in the limbic system of the right hemisphere, a major site involved in long-term memory, in patients with Graves' disease. On the other hand, in a study performed by Zhu et al. [108], no difference was found in a specific and sensitive test of working memory or functional magnetic resonance imaging results in thyrotoxic patients compared with euthyroid controls. Other studies reported that higher levels of free T4 are associated with elevated rates of atrophy in the amygdala and hippocampus on MRI and increased neocortical neurofibrillary tangles and neuritic plaques at autopsy [109, 110]. Additionally, hyperthyroidism by altering some genes' expression, such as neurogenesis ones, may cause dementia [104]. Another possible mechanism by which excess thyroid hormone may affect brain function is its effect on cholinergic neurons. Depleting acetylcholine and presynaptic cholinergic metabolites in the hippocampal tissue and cerebral cortex has been established in both hyperthyroid individuals with cognitive impairment and AD [110]. Arguing against these potential mechanisms, however, T4 administration in a mouse model of AD enhanced spatial learning and memory, antioxidant enzyme levels, cholinergic activity, ATP content, and survival of the neuronal cells [111]. It should be noted that in this study, the hormone was injected into mice for only 4 days, and the observed result could be related to the short-term effects of hyperthyroidism.

Increased neuronal death by thyroid hormone exposure and hyperthyroidism, resulting in reduced metabolites of antioxidants and induced oxidative stress, has also been indicated to cause cognitive impairment [35, 112, 113]. Li et al. [114] demonstrated that participants with hyperthyroidism had remarkably higher circulating total tau protein levels than their euthyroid counterparts, which may be implicated in the pathogenesis of AD. Döbert et al. [115] reported an enhanced risk of dementia, particularly vascular dementia, in participants with reduced or borderline TSH levels. Neuroserpin, whose expression is enhanced by thyroid hor-

Table 3. Possible mechanisms through which hyperthyroidism is involved in cognitive impairment

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Cardiovascular and cerebrovascular diseases such as systolic hypertension and fibrillation
Abnormal brain metabolism
Atrophy in the amygdala and hippocampus
Increased neocortical neurofibrillary tangles and neuritic plaques
Alteration in gene expression
Depletion of acetylcholine and presynaptic cholinergic metabolites in the hippocampal tissue and cerebral cortex
Increased neuronal death and reduction in antioxidant level
Higher levels of circulating total tau protein
Upregulation of neuroserpin

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mones, has been indicated to be upregulated in AD [22]. This protein, by inhibition of tPA activity, results in decreased brain plasmin levels, one of the essential enzymes involved in the breakdown and clearance of A β and its plaques from the brain [22]. The possible mechanisms involved in cognitive impairments due to adult-onset hyperthyroidism are also presented in Table 3.

Fukui et al. [116] reported that in a patient with overt hyperthyroid dementia, specific abnormalities related to AD were steadily normalized after correcting the hyperthyroid state. Also, it was strongly advised to assess thyroid function in patients with radiologically and clinically recognized AD because treatable and manageable hyperthyroid dementia might be overlooked [116]. In the two previously published studies, the authors claim that cognitive dysfunction has only been observed in subclinical hyperthyroidism and not in overtly hyperthyroid patients, which seems somewhat illogical. The authors believe that this disparity could be attributable to the fact that overt hyperthyroidism is almost always detected and handled immediately, whereas subclinical hyperthyroidism may not be treated for an extended period; as a result, the patient is exposed to an abnormal hormonal environment, albeit less deranged, for a more extended period [117, 118]. Additionally, some studies connected dementia to a specific type of hyperthyroidism [101, 104], some studies connected subclinical hyperthyroidism to dementia [39, 118, 119], and other ones indicate that overt hyperthyroidism with elevated free T4 is associated with dementia [109, 120, 121]. Some believe that hyperthyroidism dementia is because of TSH decline [101, 118], whereas another study does not confirm the association of thyroid disorders nor TSH with cognitive function [122]. Medication can readily treat subclinical hyperthyroidism despite diverse known risk factors that promote cognitive impairment [123]. Therefore, assessing thyroid function is an essential need, especially in the elderly population.

Conclusion

It should be fully emphasized that despite decades of widespread investigations, the elucidation of the relationship between thyroid function and cognition is not entirely conclusive. Many studies have shown that thyroid disorders cause cognitive impairment. Various mechanisms have also been suggested to show this association, including tau hyperphosphorylation, decreased neuron's number, alteration in DNA hypermethylation, shrinking different parts of the hippocampus, hippocampal neuron's death, LTP disruption, altered brain bioelectrical activity, decrease in Na, K-ATPase activity, abnormal brain metabolism and glucose consumption, upregulation of neuroserpin, altered neural activity, increased A β levels, inflammation, oxidative stress, cell death, altered gene expression, changes in synaptic plasticity, decreased cerebral blood flow, cardiovascular and cerebrovascular diseases, abnormal brain metabolism, and changes in different neurotransmitters' levels. It seems that the brains of older people are more susceptible to thyroid alteration, and compensated euthyroid state may not restore all aspects of cognitive impairment caused by thyroid dysfunction. Therefore, assessing thyroid function is an essential need to avoid cognitive consequences. However, some other studies have denied this association, and some investigations have demonstrated that an increased risk of dementia is only associated with specific kinds of thyroid dysfunction such as subclinical hyperthyroidism and not all types of thyroid disorders. Therefore, further studies are needed to reveal the correct associations and identify the mechanism that causes this relationship.

Conflict of Interest Statement

There are no conflicts of interest.

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Author Contributions

Hossein Khaleghzadeh-Ahangar has written the search strategy, thyroid hormones and their receptors, thyroid disorders, thyroid disorders and cognitive impairments, and conclusion sections

and edited all of the manuscript. Anis Talebi has written the abstract and a part of the introduction section. Parvaneh Mohseni-Moghaddam has prepared the tables. She has also written the following sections including the other part of the introduction, hypothyroidism and brain development during embryonic period, postnatal hypothyroidism and brain development, adult-onset hypothyroidism and cognitive impairments, thyroid autoimmunity and cognitive impairment, and adult-onset hyperthyroidism and cognitive impairment. The original idea of the review was also designed by Parvaneh Mohseni-Moghaddam.

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