



Endocrine Risk Factors for Cognitive Impairment

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Cognitive impairment, including Alzheimer's disease and other kinds of dementia, is a major health problem in older adults worldwide. Although numerous investigators have attempted to develop effective treatment modalities or drugs, there is no reasonably efficacious strategy for preventing or recovering from cognitive impairment. Therefore, modifiable risk factors for cognitive impairment have received attention, and the growing literature of metabolic risk factors for cognitive impairment has expanded from epidemiology to molecular pathogenesis and therapeutic management. This review focuses on the epidemiological evidence for the association between cognitive impairment and several endocrine risk factors, including insulin resistance, dyslipidemia, thyroid dysfunction, vitamin D deficiency, and subclinical atherosclerosis. Researches suggesting possible mechanisms for this association are reviewed. The research investigating modifiable endocrine risk factors for cognitive impairment provides clues for understanding the pathogenesis of cognitive impairment and developing novel treatment modalities. However, so far, interventional studies investigating the beneficial effect of the "modification" of these "modifiable risk factors" on cognitive impairment have reported variable results. Therefore, well-designed, randomized prospective interventional studies are needed.

Keywords: Cognition; Dementia; Risk factors

INTRODUCTION

The prevalence and incidence of cognitive impairment, such as dementia, increases rapidly with advancing age, which results in a huge socioeconomic burden [1]. Dementia is a diagnosis including all kinds of cognitive dysfunction resulting in interference with everyday activities. Alzheimer's disease, Lewy body dementia, and vascular dementia are types of dementia with various causes and pathogenesis. Dementia is a growing socioeconomic burden that is paralleled by the epidemic increase in its prevalence and incidence. The prevalence of dementia is estimated to be as high as 24 million worldwide and is expected to double every 20 years until 2040 [2]. Medical

expenses for people aged 65 years and older with dementia were more than \$200 billion in 2013 in the United States [3]. In addition, mild cognitive impairment (MCI), which is a risk for progression to dementia but not sufficient for a diagnosis of dementia, is a common condition in old age: 15% to 42% of people aged ≥ 65 years are estimated to have MCI, and from about 5% to 15% of them progress to dementia annually [4,5]. Although numerous investigators have attempted to develop effective treatment modalities or drugs, there is no reasonably efficacious strategy for preventing or recovering from cognitive impairment. Only two classes of drugs, cholinesterase inhibitors and memantine, have been approved for the treatment of dementia, and they have shown only modest effects. Therefore,

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modifiable risk factors for cognitive impairment have received attention, and the growing literature on metabolic endocrine risk factors for cognitive impairment has expanded from epidemiology and molecular pathogenesis to therapeutic management. This review focuses on the epidemiological evidences of the association between cognitive impairment and several endocrine risk factors, including insulin resistance, dyslipidemia, thyroid dysfunction, vitamin D deficiency, and subclinical atherosclerosis.

INSULIN RESISTANCE AND COGNITIVE IMPAIRMENT

The epidemiological association between insulin resistance or type 2 diabetes and cognitive impairment is well established. Several population-based prospective studies and meta-analyses have demonstrated an increased risk of dementia in diabetic patients [6,7]. A recent meta-analysis including 6,184 type 2 diabetes subjects and 38,350 subjects without diabetes pooled from 19 studies reported a combined overall relative risk (RR) of 1.51 (95% confidence interval [CI], 1.31 to 1.74) linking type 2 diabetes with dementia [7]. In particular, the risk of vascular dementia was increased in type 2 diabetes subjects with a RR of 1.46 (95% CI, 2.08 to 2.96) and the risk of Alzheimer's disease was also increased (RR, 1.46; 95% CI, 1.20 to 1.77) [7]. Diabetes increased not only the risk of MCI, an intermediate stage between normal cognitive function and dementia [8-10], but also the conversion rate to dementia in the subjects with MCI [11,12]. Despite this epidemiological evidence, the mechanisms underlying the association between insulin resistance and cognitive impairment have not been fully understood so far. In people without dementia, type 2 diabetes patients show slightly decreased cognitive function compared with subjects without diabetes in multiple cognitive domains [9,13]. This slight decline in cognitive function of diabetic patients starts from mid-life (about 40 years old) and slowly progresses throughout their lifetime, whereas the incidence of dementia increases sharply after the age of 65 to 70 years [9,14]. Therefore, cognitive decline in type 2 diabetes or insulin resistance and the pathologic process of dementia may be discrete processes, and insulin resistance seems to make the brain more vulnerable to the pathologic process of dementia. A recent review [9] suggested that type 2 diabetes or insulin resistance results in subtle brain atrophy [15], disrupted white matter integrity [16], and vascular abnormalities, including cortical and subcortical infarcts [17,18]. These subtle changes accumulate

from mid-life onwards, reducing the reserve capacity of the brain. Some experimental studies have demonstrated direct mechanisms explaining the association between insulin resistance and Alzheimer's disease. Insulin-degrading enzyme (IDE) breaks down excessive insulin in extracellular milieu and also degrades amyloid β —a key peptide of Alzheimer's disease pathogenesis, which is derived from the proteolytic cleavage of the amyloid precursor protein and forms the core of senile plaques. Excessive insulin resulting from insulin resistance can compete with amyloid β for the binding site on IDE, resulting in accumulating amyloid β in the central nervous system (CNS) [19]. Interventional studies investigating the effect of diabetes treatment on cognitive function have shown heterogeneous results. The Memory in Diabetes study as part of Action to Control Cardiovascular Risk in Diabetes study (ACCORD-MIND) [20], the largest published randomized controlled study, reported no difference in cognitive decline between type 2 diabetes patients who received intensive glycemic control and those who received conventional glycemic control. A small randomized double-blind trial including 145 subjects demonstrated significant cognitive improvement by add-on therapy of rosiglitazone or glyburide in type 2 diabetes patients receiving metformin monotherapy [21].

DYSLIPIDEMIA AND COGNITIVE IMPAIRMENT

The association between hypercholesterolemia and cognitive impairment is still controversial. Several prospective studies demonstrated that hypercholesterolemia in mid-life increased the risk of Alzheimer's disease and vascular dementia [22-24]. However, a study that followed 1,462 women over 32 years failed to demonstrate any association between midlife hypercholesterolemia and the risk of Alzheimer's disease, and some studies reported the protective effect of hypercholesterolemia in late life against Alzheimer's disease [25-27]. Although vigorous treatment of hypercholesterolemia has been thought to decrease the risk of vascular dementia considering the benefits of statins in the primary and secondary prevention of stroke, the beneficial effect of statin therapy on cognitive impairment has not been firmly established. Based on isolated case reports without established causality, there has been concern that statins may actually worsen cognitive function and memory [28,29]. A prospective study evaluating 1,674 participants without dementia showed that statin therapy decreased the risk of dementia during the 5-year follow-up period after adjust-

ment for conventional risk factors for dementia [30]. Other cross-sectional and prospective studies also reported the beneficial effect of statin therapy on cognitive impairment [31-33]. Experimental studies have suggested that the cholesterol distribution in neuronal cell membrane was associated with amyloid β synthesis and metabolism [27]. Proteins required for cholesterol recycling and trafficking, such as apolipoprotein E, low density lipoprotein (LDL) receptor, and low density lipoprotein receptor-related protein 1 (LRP1), also play a role in amyloid β homeostasis in the brain [34-36]. In addition, LDL receptor and LRP1 have been reported to be regulated by statin drugs [37]. Altogether, lipid metabolism might be associated with the pathogenesis of Alzheimer's disease and vascular dementia, and some experimental and clinical studies have provided some evidence for this association. However, further studies, including well-designed interventional studies, are needed to confirm the association between dyslipidemia and cognitive impairment.

THYROID HORMONE AND COGNITIVE IMPAIRMENT

Thyroid hormone is an important neuroregulator in fetal development of the CNS and plays an important role in neurocognitive function after development. Overt hypothyroidism is a well-known reversible factor causing cognitive impairment including dementia [38]. Overt hyperthyroidism or thyrotoxicosis has also been known to be associated with altered concentration and perception [39]. Epidemiologically, thyroid dysfunction, depression, and cognitive impairment commonly increase in older adults and recent studies have reported that thyroid dysfunction is one of the risk factors for irreversible cognitive impairment, such as Alzheimer's disease [40]. On the basis of this association between thyroid dysfunction and psychiatric disorders, a number of investigators have sought to determine whether subclinical thyroid dysfunction is a risk factor for cognitive impairment, especially in older adults. Although the effect of subclinical hypothyroidism on cognitive impairment is still questionable [40,41], the association between subclinical hyperthyroidism and cognitive impairment has been validated in several studies [39,42-44]. In the Rotterdam study [42] that followed up 1,843 non-demented participants for 2 years, subjects with thyroid stimulating hormone (TSH) levels below 0.4 mIU/L at baseline had a greater than 3-fold increased risk of dementia (RR, 3.5; 95% CI, 1.2 to 10.0) and Alzheimer's disease (RR, 3.5; 95% CI, 1.1 to 11.5) after adjusting for age and

sex compared with those at the euthyroid level. In the Thyroid Epidemiology, Audit, and Research Study [44], a large observational study including 12,115 euthyroid and subclinical hyperthyroid subjects with a median follow-up period of 5.6 years, participants with serum TSH levels below 0.4 mIU/L at baseline had a 2-fold increased risk of dementia. Moreover, a few cross-sectional studies suggested that even a normal serum TSH level, when ranging in the lower reference level, might be associated with the risk of dementia [45,46]. A recent community-based prospective cohort study demonstrated that lower serum TSH concentration within the reference range was associated with the development or progression of cognitive impairment including MCI and dementia in older adults [47]. MCI or dementia developed in 12.5% of 200 subjects with baseline TSH of more than 1.82 mIU/L, whereas MCI or dementia developed in 25.7% of 113 subjects with baseline TSH of less than 1.82 mIU/L [47]. However, there was no difference in the cognitive function between elderly patients with differentiated thyroid carcinoma who received long-term TSH suppressive therapy (iatrogenic subclinical thyrotoxicosis) and euthyroid control subjects; moreover, there were positive correlations between serum free thyroxine (T4) levels and some cognitive domains [48].

The mechanism underlying the association between low TSH and the risk of cognitive decline is still unclear. Of the two widely accepted explanations, the first and most conventional explanation is the toxic effect of excessive thyroid hormone on the CNS [39]. Brain oxidative stress caused by an excess of thyroid hormone or thromboembolism from the cardiac effects of mild hyperthyroidism have been suggested as underlying mechanisms [39,49]. Second, neurodegenerative changes in the brain, which may cause a cognitive decline, can also result in a reduced secretion of thyrotropin releasing hormone (TRH) in the brain and, in turn, reduce the secretion of TSH [39]. TRH is secreted not only from the hypothalamus but also from other areas of the brain, and is known to play a role as a CNS neurotransmitter, suggesting that TRH secretion may decrease in the brain of subjects with cognitive impairment [39,50]. As mentioned above, long-term iatrogenic subclinical thyrotoxicosis or a mild excess of thyroid hormone did not result in a cognitive decline in elderly subjects [48]. This finding suggests that reduced TRH in the degenerated brain is the most reliable explanation. Furthermore, the positive correlations between serum free T4 levels and some cognitive domains suggest the potential beneficial effect of exogenous levothyroxine on cognitive function.

VITAMIN D DEFICIENCY AND COGNITIVE IMPAIRMENT

Vitamin D status is determined by the serum level of 25-hydroxyvitamin D, or 25(OH)D, and a low vitamin D status is common and considered a major health problem in elderly populations [51-53]. Several studies have reported that low vitamin D status is associated with poor bone health and other conditions including cardiovascular disease (CVD), insulin resistance, autoimmune diseases and certain malignancies [54-56]. Low vitamin D status has also received attention as a potential metabolic risk factor for dementia. A number of studies have shown that a low serum 25(OH)D concentration is associated with an increased risk of dementia and Alzheimer's disease in older adults [57,58]. A recent community-based prospective study of the elderly demonstrated that low vitamin D status increased the risk of MCI as well as dementia [59]. They reported that the RR of MCI development during a 5-year follow-up was 7.13 (95% CI, 1.54 to 32.92; $P=0.012$) in the elderly subjects whose serum 25(OH)D concentration was <25.0 nmol/L compared with those with a serum 25(OH)D concentration ≥ 50.0 nmol/L [59]. Several studies have suggested that long-term hypovitaminosis D status results in CNS inflammation and A β accumulation via oxidative stress, alteration in CNS cytokine levels, neurotransmitter dysregulation, and macrophage dysfunction [60]. However, it is still unclear whether vitamin D replacement therapy can prevent or aid recovery from cognitive impairment, and well-designed interventional studies are needed.

SUBCLINICAL ATHEROSCLEROSIS AND COGNITIVE IMPAIRMENT

Recent large-scale prospective cohort studies have demonstrated that CVD risk factors, including 10-year CVD risk scores and individual CVD risk factors, are associated with cognitive decline [61-68]. A longitudinal British cohort study (Whitehall-II) including 5,810 participants showed that elevated stroke risk as measured by the Framingham stroke risk (FSR) score in mid-life is associated with accelerated cognitive decline over 10 years [67]. The English Longitudinal Study of Aging including 8,780 subjects also reported the association between high FSR score and cognitive decline over 4 years [66]. FSR score was also associated with the 4-year cognitive decline in 1,907 stroke-free subjects [65]. The sex-specific 10-year CVD risk score was reported to be associated with the 10-year cogni-

tive decline in 1,116 aged Mexican Americans [68]. Other individual CVD risk factors including hypertension, dyslipidemia, obesity, and diabetes in mid-life have been suggested as risk factors for cognitive decline and dementia in later life [61-64]. Surrogate markers for CVD risk, including carotid intimal-media thickness (CIMT) and pulse wave velocity (PWV) have been reported to be associated with cognitive impairment in a number of studies [69-76]. A recent prospective cohort study investigated the association between CVD risk factors, including CIMT, PWV, ankle-brachial index and other biochemical and anthropometric markers, and the future risk of clinically diagnosed MCI or dementia [77]. They demonstrated that CIMT was the best predictor of the development of MCI and dementia over 5 years and the hazard ratio for the development of MCI and dementia per 0.1 mm increase in CIMT was about 1.25 [77].

At present, it remains unclear whether a vascular pathology such as increased CIMT can cause cognitive decline in elderly subjects or whether it simply develops as an early vascular response associated with neuronal degeneration. Recent studies have shown that vascular dysfunction is involved in the pathogenesis of not only vascular dementia but also Alzheimer's disease [78]. Vascular dysfunction results in the restriction of oxygen and glucose supply to the brain, and A β accumulation in the brain affects vascular pathology and exacerbates blood flow restriction to the brain [78-80]. In addition, vascular dysfunction can cause reduced A β clearance across the blood-brain barrier, and oxidative stress is also a common pathogenic mechanism between vascular dysfunction and Alzheimer's disease [78]. Therefore, vascular dysfunction and A β deposition might have synergistic effects on neuronal degeneration [78].

CONCLUSIONS

The effort to discover modifiable risk factors for cognitive impairment has identified important endocrine risk factors for cognitive impairment. Epidemiological studies have reported associations between metabolic risk factors and cognitive impairment, and experimental studies have suggested mechanisms that can explain these associations. This effort is important for providing a theoretical basis of novel treatment modalities for cognitive impairment. However, so far, interventional studies to investigate the beneficial effect of the "modification" of these "modifiable risk factors" on cognitive impairment have reported variable results. Therefore, future well-designed randomized controlled trials are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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