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Intertwining Problems: Obesity, Alzheimer's Disease, and the Relationship of Obstructive Sleep Apnea Syndrome (OSAS) to Cognitive Decline

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Abstract

The relationship between obesity and the development of Alzheimer's disease is the subject of active research in the scientific field, and there is currently strong evidence that obesity and excess weight may be risk factors for the development of this disease. Obstructive sleep apnea syndrome (OSAS) is a disease characterized by snoring, upper airway collapse, and cessation of pulmonary ventilation, which leads to gross sleep fragmentation and a whole cascade of disorders, including cerebrovascular disease and the risk of sudden death. It is also known that the risk of OSAS is correlated with body mass index (BMI), and obesity remains one of the main modifiable risk factors for OSAS. However, the deep relationship between OSAS and the risk of Alzheimer's disease is poorly understood.

Objective: Using literature sources, to investigate the existing relationship between obesity and the development of Alzheimer's disease and to find a common ground between OSAS and cognitive decline.

Object: obesity and OSAS and their relationship with cognitive decline.

Research methods: review of literature sources.

Results: It is worth noting that the available data on the relationship between obesity and Alzheimer's disease are extremely contradictory, and sometimes radically opposite, therefore they remain one of the most debatable issues. In clinical studies, the degree of cerebral atrophy in individuals with moderate cognitive impairment is associated with an increase in BMI. According to population studies and meta-analyses, obesity has been significantly and independently associated with a high risk of developing Alzheimer's disease. Obesity in old age is inversely correlated with the risk of dementia, while being underweight (BMI < 20 kg/m2) is also associated with an increased risk of dementia. According to another meta-analysis, both being underweight and being overweight and obese in midlife were associated with a higher risk of developing dementia later in life. Obesity was also associated with a higher risk of developing vascular dementia. At the same time, weight loss was associated with a higher risk of dementia from all causes compared with maintaining weight. Weight gain was only slightly associated with a higher risk of vascular dementia. OSAS was associated with a significantly increased risk of dementia, especially for Alzheimer's and Parkinson's disease, but not for vascular dementia, in the meta-analyses. Studies have shown that some high-fiber foods, including whole grains, fruits, and vegetables, may help reduce inflammation and improve the composition of the microbiome, thus alleviating the course of Alzheimer's disease.

Conclusions: Thus, obesity is an independent risk factor for Alzheimer's disease, at least in middle-aged people.

The relationship between OSA and the specific etiology of dementia remains unclear and requires further research. According to the literature, patients with OSA are at increased risk of developing any type of neurocognitive disorder, such as Alzheimer's disease and Parkinson's disease. According to research, high-fiber foods can help reduce inflammation, promote improved microbiome composition, and, therefore, improve brain health through the microbiome-gut-brain axis.

Keywords: obesity; Alzheimer's disease; obstructive sleep apnea syndrome; dementia; cognitive function; microbiome

Introduction

The relationship between obesity and Alzheimer's disease is a subject of active research in the scientific community. There is strong evidence that obesity and increased body weight may be risk factors for the development of this disease.

There are certain key aspects of this relationship

Chronic systemic inflammation. Obesity is often accompanied by chronic inflammation, which can affect brain function and contribute to the development of Alzheimer's disease. Inflammation

can damage brain cells and changes in the microcirculation of the brain.

Insulin resistance: Obesity and high body weight are often associated with insulin resistance, a condition in which the sensitivity of tissues (muscle, fat and the liver itself) to insulin is reduced, as a result of which it acts ineffectively. This can affect glucose metabolism in the brain and contribute to the accumulation of beta-amyloid, one of the pathological proteins associated with Alzheimer's disease.

Cardiovascular pathology and dyslipidemia: Obesity can lead to cardiovascular disease, which can affect cerebral blood flow and contribute to the development of Alzheimer's disease. High cholesterol and triglyceride levels, which are often observed with obesity, can negatively affect brain function and contribute to the accumulation of beta-amyloid. Adiponectin and leptin. Adipocytes, the cells of fat tissue, secrete various hormones, such as adiponectin and leptin. Changes in the levels of these hormones can affect brain function and the clearance of beta-amyloid. The association between obesity and Alzheimer's disease may also be due to genetic factors [3,4,9,16,20,30,38,53,54,64].

Mechanisms of Alzheimer's Disease Development

Alzheimer's disease is a neurodegenerative disease characterized by the progressive destruction of neurons in the brain. The main symptoms are memory impairment, deterioration of mental functions and other cognitive disorders. The disease mainly develops in old age, but its origin and mechanisms remain the subject of research.

This disease is the most common form of dementia in old age, characterized by the gradual destruction of neurons and an increased content of pathological proteins in brain tissue. The mechanisms of development of this disease are multifactorial and include various mechanisms. An important mechanism in the development of Alzheimer's disease is the accumulation of protein aggregates, such as beta-amyloid and tau. Beta-amyloid forms beta-amyloid plates, which accumulate outside neurons in the form of amyloid plaques. Tau protein forms tau-weave around neurons inside them. These abnormal proteins damage neurons, disrupting their function. Another key mechanism in the development of this disease is inflammation, which can be caused by the accumulation of aggregated proteins and other factors. This leads to the activation of microglia and astrocytes, cells that normally regulate inflammation in the brain. Inflammation can exacerbate the loss of neurons and damage the connections between them. Disruptions in synaptic function led to a loss of the ability of neurons to communicate, and, consequently, to the transmission of information, which affects memory and cognitive function. Some cases of Alzheimer's disease have a genetic basis. For example, changes in genes such as ApoE (apolipoprotein E) can increase the risk of developing the disease. Genetic factors can affect the accumulation of proteins and other aspects of brain biology. Disruptions in the brain's microcirculation can lead to insufficient nutrition and oxygenation of neurons. This can damage the brain tissue and the development of Alzheimer's disease. Several other factors, such as age, gender, environment, and lifestyle, may also influence the risk of developing this disease. [10,21,23-26,43,57,62,67]

The relationship between obesity and Alzheimer's disease

It is known that approximately 70% of the risk of developing Alzheimer's disease is genetically determined. However, there is increasing evidence that factors such as cerebrovascular disease, diabetes, hypertension, obesity and dyslipidemia increase the risk of developing this disease [33]. The intertwining of obesity and Alzheimer's disease remains one of the most controversial issues today. Despite the discovery of a large number of pathogenetic mechanisms, the cause-and-effect relationship between these pathological conditions has not yet been fully established. It should also be noted that the available data on this issue are extremely contradictory, and sometimes radically opposite. The results of many experimental and clinical studies give reason to consider obesity as one of the risk factors for developing Alzheimer's disease. In particular, increased fat content in the diet of mice was accompanied by increased accumulation of β-amyloid (Aβ) in the hippocampus and cognitive dysfunction [6,27,31]. In clinical studies, the degree of cerebral atrophy according to neuroimaging data in individuals with moderate cognitive impairment is associated with an increase in body mass index (BMI) [22]. Many researchers indicate a higher prevalence of obesity and overweight in Alzheimer's disease. In particular, in a population-based study, overweight and obesity in midlife were associated with dementia with odds ratios of 1.71 and 3.88, respectively [66]. According to a meta-analysis by L.A. Profenno et al. [52], obesity is significantly and independently

associated with a high risk of developing Alzheimer's disease. In addition, the results of D. Gustafson et al. [19] showed that in women aged 70 years, each 1.0 increase in BMI was associated with a 36% increase in the risk of Alzheimer's disease. Another study showed an association between a high risk of Alzheimer's disease and a waist-to-hip ratio [37]. However, other studies have shown that the risk of dementia associated with obesity gradually decreases with age [65,41]. According to the Whitehall II Study [60], obesity (BMI ≥ 30 kg/m2) at age 50 years (hazard ratio (HR) = 1.93; 1.35–2.75), but not at age 60 or 70 years, was associated with the risk of dementia. A meta-analysis by Fitzpatrick et al. [15] reported that obesity in later life was inversely associated with the risk of dementia (HR: 0.63; 95% confidence interval (CI): 0.44–0.91). The same authors also reported that being underweight (BMI < 20 kg/m2) was also associated with an increased risk of dementia (HR: 1.62, 95% CI: 1.02–2.64). Another meta-analysis by Anstey et al. [2] reported that both being underweight and overweight, as well as being obese in midlife, were associated with a higher risk of dementia. Obesity was associated with a higher risk of vascular dementia. Weight loss was associated with a higher risk of dementia from all causes compared with maintaining weight. Weight gain was not associated with a higher risk of vascular dementia. The relationship between body size, weight change, and dementia is complex and shows nonlinear associations depending on the subtype of dementia.

Thus, obesity is an independent risk factor for Alzheimer's disease, at least in middle-aged people. Most scientists believe that the cause of dementia is not so much obesity itself, but its metabolic complications - diabetes mellitus, hypertension, dyslipidemia, and other components of the metabolic syndrome (MS) [7,17,34,59]. The pathogenesis of dementia in MS is multifactorial, including both vascular damage and non-ischemic neuronal death due to neurodegeneration. Neurodegenerative and ischemic lesions do not simply coexist in the brain, but rather reinforce each other, leading to more serious consequences for cognition than any other pathology. In addition to the universal mechanisms of cognitive dysfunction common to all components of MS, other pathogenetic pathways also lead to cognitive deficits and dementia that are specific to each component. Epidemiological studies, imaging, and autopsy findings have suggested the presence of both cerebrovascular and neurodegenerative mechanisms of brain damage [29,44,50,55,61].

The impact of sleep apnea on the development of Alzheimer's disease

OSAS and Alzheimer's disease are two problems that "hide from us at night." The global community is becoming increasingly aware of the issue of sleep apnea and its impact on health. However, little is known about the deep relationship between sleep apnea and the risk of developing Alzheimer's disease. Obstructive sleep apnea syndrome (OSAS) is a disease characterized by the presence of snoring, periodic collapse of the upper airway at the level of the pharynx and cessation of pulmonary ventilation, decreased blood oxygen levels, gross fragmentation of sleep and excessive daytime sleepiness. This condition poses a serious threat to health, as it leads to reduced oxygenation, sleep disruption and a whole cascade of symptoms. Many studies have shown a strong association between OSA and hypertension, heart failure, coronary artery disease, cardiac arrhythmias, cerebrovascular disease, erectile dysfunction, and cardiovascular mortality. The etiology of OSAS is multifactorial, involving a complex interaction between anatomical, neuromuscular, and genetic factors. Established risk factors include male gender, older age, and obesity. Race/ethnicity, family history, craniofacial dysmorphisms, endocrine disorders, including hypothyroidism, menopause in women, Down syndrome, and some neurological disorders are associated with additional risk. Morphological abnormalities are the most common factors that cause upper airway obstruction, such as retrognathia, enlarged tonsils, and soft tissue in the neck, etc. Craniofacial anatomical anomalies can narrow the upper airway and are important risk factors for the development of OSAS, as quantified by the modified Mallampati classification. Additional risk factors for OSAS include smoking, a family history of OSAS, and nocturnal nasal congestion. In addition, some substances/drugs worsen pre-existing OSAS, such as alcohol, benzodiazepines, and opiates. The risk of OSAS is correlated with body mass index (BMI), and obesity remains a major modifiable risk factor for OSAS. In a population-based cohort study, a 10% increase in body weight was associated with an almost 32% increase in the apnea/hypopnea index, and even moderate weight control was effective in reducing new cases of sleep-disordered breathing.

There is an even stronger correlation between OSAS and increased waist circumference and neck size.

Neck circumferences associated with OSAS are >43 cm in men and 40 cm in women. Neck circumference has been found to be an independent predictor of OSA even after adjusting for BMI and in patients with OSAS has a stronger correlation with individual measures of disease severity, such as saturation and apnea/hypnea index, than BMI. [42]. Sleep apnea is a potentially modifiable risk factor for dementia. However, its association with specific dementia etiologies remains uncertain. In 2022, Canadian researchers conducted a systematic review and meta-analysis of cohort studies examining the association between sleep apnea and specific etiologies of dementia, including Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia. Data were collected on the use of biomarkers to confirm clinical diagnoses in relevant studies. Eleven studies were included, involving 1,333,424 patients. Patients with sleep apnea had an increased risk of developing any type of neurocognitive disorder (HR: 1.43 [95% CI 1.26–1.62]), Alzheimer's disease (HR: 1.28 [95% CI 1.16–1.41]), and Parkinson's disease (HR: 1.54 [95% CI 1.30–1.84]). No statistically significant association was found with vascular dementia. One study reported a twofold increased risk of dementia with Lewy bodies (HR: 2.06 [95% CI 1.45–2.91]). No studies examined the risk of frontotemporal dementia, and none of the studies reported results related to biomarkers. The researchers concluded that OSAS is associated with a significantly increased risk of dementia, particularly Alzheimer's and Parkinson's disease, but not vascular dementia. Therefore, future studies should examine the effects of sleep apnea on specific biomarkers of dementia, the researchers said. [18]. It should be noted that sleep apnea is often the result of a combination of factors, and each person may have unique reasons for developing the condition. Treatment for sleep apnea can range from lifestyle changes to the use of special devices and medications, and even surgery [11-13,32,39,49,54].

Mechanisms of Interaction

A key part of understanding the relationship between sleep apnea and Alzheimer's disease is understanding the mechanisms of interaction. It is hypothesized that sleep disruption and hypoxia during sleep apnea may contribute to the accumulation of protein aggregates that disrupt neuronal function and promote brain inflammation. This may trigger chain reactions that lead to damage to brain structures and cognitive decline. The interaction between OSAS and Alzheimer's disease is complex and is being studied continuously to elucidate its exact mechanisms. There are several theories and hypotheses regarding this interaction. During sleep apnea, a person stops breathing, which can lead to a decrease in oxygen levels in the blood and brain. Prolonged and insufficient oxygenation can contribute to the deterioration of brain function and the development of cognitive disorders, including Alzheimer's disease. At the same time, sleep apnea can lead to the activation of neuroimmune responses and the release of inflammatory mediators. The inflammatory process can have a negative impact on brain function and can contribute to the development of neurodegenerative diseases such as Alzheimer's disease. OSAS also leads to disruption of circadian rhythms, which in itself can be a risk factor for the development of cognitive disorders, including Alzheimer's disease. Patients with OSAS are patients at high cardiovascular risk, as they often have arterial hypertension and atherosclerotic diseases, which also negatively affect brain function and increase the risk of Alzheimer's disease. In addition, during apnea, the brain is in a state of hypoxia, which can lead to neuronal damage and be a risk factor for the development of Alzheimer's disease.

Prevention and Treatment

Since sleep apnea may be a risk factor for developing Alzheimer's disease, it is important to consider preventive measures and possible treatments. Preventive measures include a healthy lifestyle, including a balanced diet and regular physical activity; these measures can reduce the risk of developing diseases associated with obesity, including Alzheimer's disease. Regarding the treatment of sleep apnea, there are various methods, including continuous positive airway pressure (CPAP) and surgical interventions. Prevention and treatment of Alzheimer's disease are important tasks in modern medicine, but it should be borne in mind that Alzheimer's disease, unfortunately, is incurable, so these efforts are aimed at delaying the progression of the disease and alleviating symptoms.

Prevention of Alzheimer's disease

Lifestyle changes, including a balanced diet, regular physical activity, avoiding smoking, and reducing alcohol consumption, can reduce the risk of developing Alzheimer's disease. Various cognitive exercises, puzzles, memorizing poems, reading and learning new skills, etc. have a positive effect on brain activity. Controlling blood pressure, blood sugar and

lipids and achieving target values for these indicators can help reduce the risk of developing Alzheimer's. Maintaining social activity, communicating with friends and family, and participating in social activities can maintain brain activity. Healthy sleep and its importance. Data from a study that included 172,321 people showed that men who get enough sleep live 5 years longer than those who do not get enough sleep. For women, this figure reaches 2 years. Another study conducted at the Mayo Clinic - one of the largest research centers - showed that lack of sleep leads to increased blood pressure, both during the day and at night. People who sleep less than 7 hours a day experience accelerated ageing of the heart and blood vessels. Studies have shown that consistently short sleep duration in the 50s, 60s, and 70s is associated with a 30% increased risk of dementia, regardless of socioeconomic status, lifestyle, and general and mental health status. Short sleep duration in midlife is associated with an increased risk of dementia in later life [1,8,14,28,35,36,56].

Treatment

Unfortunately, there is currently no effective treatment to stop the progression of Alzheimer's disease and dementia. Currently, spontaneous treatment is used to improve the well-being of patients. Medications may be prescribed to improve memory and cognitive impairment. Some drugs are aimed at increasing the level of acetylcholine in the brain, which alleviates symptoms. Psychological support and psychotherapy can help patients and their families cope with stress and symptoms of the disease. It is important to provide the patient with a comfortable and safe space, as well as to create a care plan. In the case of a patient with OSAS, an effective method of treating apnea is CPAP (positive airway pressure system). This system helps patients breathe normally during sleep, reducing or eliminating pauses in breathing. It is used as a therapeutic tool to ensure normal airflow into the lungs during sleep and has many benefits. CPAP works by applying gentle pressure to the patient's upper airway. This helps prevent the airway from collapsing and obstructing airflow. The CPAP creates a constant flow of air, which helps the patient overcome the obstruction and breathe normally during sleep. Treatment with CPAP can significantly reduce the symptoms of OSAS, such as loud snoring, waking up at night with shortness of breath, and daytime sleepiness. Patients who use CPAP typically report improved sleep quality and less fatigue during the day [5, 46]. Research into the treatment and prevention of Alzheimer's disease is ongoing, and scientists are currently investigating new methods and drugs to delay the progression of the disease.

Alzheimer's disease and the Microbiome

The effects of diet on brain function.

Trillions of microbes live in your digestive tract. These different types of bacteria, viruses, fungi, and other microorganisms—collectively known as the gut microbiome—play a vital role in maintaining overall health by helping you digest food and produce nutrients. They also support your body's immune system and produce chemicals that affect brain function. Imbalances in your gut microbiome can contribute to a variety of diseases. The idea that the community of microbes living in your gut could affect brain function may seem strange at first. However, research shows that the brain and gut microbiome are connected through the gut-brain axis—a complex network of neurons, proteins, and chemicals that relay messages between your digestive system and your brain. Researchers around the world are interested in whether diseases, including Alzheimer's disease, can be prevented or slowed by altering the composition of the microbiome. Studies have shown that chronic inflammation in the brain may contribute to the development of Alzheimer's disease. In response to infection or injury, immune cells release inflammatory cytokines, resulting in chronic inflammation that, over time, can lead to neuronal damage and death [44,45]. In this context, an interesting question is: can reducing inflammation be beneficial for brain health, and can inflammation be reduced through diet? Studies have shown that certain high-fiber foods, including whole grains, fruits, and vegetables, can help reduce inflammation. Certain gut bacteria convert the fiber from these foods into compounds called short-chain fatty acids (SCFAs), which have anti-inflammatory properties and have been shown to improve memory in animals [40].

Rodney V. Johnson, PhD, a professor and animal nutrition researcher at the University of Illinois, has been studying the effects of dietary fiber on microglial activity and inflammation in the brain. His team found that ageing mice have low levels of SCFAs, as well as dysregulated, hyperactive microglia. To test the effects of a high-fiber diet on age-related microglial dysregulation, Johnson's team fed adult and elderly mice diets high or low in inulin, a type of fiber found in some plant foods that are easily metabolized by gut

bacteria into SCFAs. In both adult and elderly mice, the high-fiber diet changed the types of bacteria in the gut microbiome, increased the production of SCFAs, and reduced the expression of certain genes that control inflammation in the brain. Moreover, in a subsequent study, a high-fiber diet switched the majority of microglia in aged mice from a dysregulated state to the normal, healthy state observed in young adult mice [61]. Further research on this pressing topic may provide important insights into the impact of diet on altering microbiome composition and maintaining brain health.

Conclusions

Thus, obesity is an independent risk factor for Alzheimer's disease, at least in middle-aged people. According to most scientists, the cause of dementia is not so much obesity itself, but its metabolic complications - diabetes, hypertension, dyslipidemia and other components of the metabolic syndrome (MS). The relationship of OSAS with the specific etiology of dementia remains unclear and requires further research. According to the literature, patients with OSAS have an increased risk of developing any type of neurocognitive disorder, such as Alzheimer's disease and Parkinson's disease. No statistically significant relationship with vascular dementia was found. It should be noted that most often sleep apnea is the result of a combination of several factors, and each person may have their own unique reasons for developing this condition. Treatment of sleep apnea can vary from lifestyle changes to the use of special devices and medications, and even surgery. Thus, obstructive sleep apnea syndrome, like obesity, is now a potentially modifiable risk factor for dementia. Studies have shown that high-fiber foods may help reduce inflammation and promote improved microbiome composition, which may, in turn, improve brain health through the microbiome-gut-brain axis. Further research on this important topic could provide important insights into the impact of diet on altering microbiome composition and supporting brain health. Sleep apnea and Alzheimer's disease are two serious conditions that may be linked. Research continues to explore this connection, and it is important to consider it when discussing prevention and treatment strategies for both conditions.

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