Metabolic, Inflammatory, and Microvascular Determinants of White Matter Disease and Cognitive Decline

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ABSTRACT

White Matter Disease is increasingly being recognized as an important cause of cognitive decline and dementia. Various investigations have linked chronic diet-related conditions to the development of white matter lesions, which appear as white matter hyperintensities on T2-weighted magnetic resonance imaging (MRI) scans of the brain. Thus, it can be postulated that the metabolic, inflammatory, and microvascular changes accompanying a western diet, hyperlipidemia, hypertension, and diabetes mellitus type II are potential mediators in the development and progression of white matter disease, which in turn contributes to the development and progression of cognitive decline. This review will examine evidence for potential metabolic, inflammatory, and microvascular determinants of white matter disease and cognitive decline. Specifically, we will focus on the effects of altered insulin signaling in diabetes, obesity-induced oxidative stress, neuroinflammation, arterial stiffness due to hypertension, ischemia secondary to cerebral small vessel disease, and blood brain barrier disturbances.

INTRODUCTION

- Alzheimer's disease is the most common cause of dementia and has be cited as the sixth-leading cause of death in the United States.
- Lower intake of nutrient-dense foods and higher intake of processed "fast foods" have been found to be independently associated with smaller left hippocampal volume, supporting the concept that consumption of the western diet contributes to the development and progression of cognitive dysfunction.
- Diffuse white matter disease has come to be recognized as an important cause of cognitive decline and dementia.
- On T2-weighted MRI scans, white matter disease is represented as white matter hyperintensities, which are increased signal intensities that are thought to reflect demyelination and axonal loss. These white matter hyperintensities have been shown to be predictive of an increased risk for dementia.
- Previous investigations have shown strong correlations between chronic diet-related conditions and brain imaging changes. For example, it has been shown that patients with Diabetes Mellitus Type II have increased white matter hyperintensity burden.
- The Mediterranean diet, which is believed to be protective against diabetes and cardiovascular disease, has been affiliated with lower white matter hyperintensity volume on MRI scans of the brain.
- The association between white matter hyperintensities and cognitive decline brings up the question on whether the white matter lesions themselves directly impact cognition or whether their presence is an indication of underlying metabolic, inflammatory, or microvascular pathologies.

METHODS

We systematically searched PubMed databases for both pre-clinical and clinical studies.

RESULTS

Metabolic Determinants

Diabetes

- Diabetic patients had greater white matter hyperintensity volume and brain tissue loss compared to non-diabetic patients. Cognitive function was also found to have an inverse relationship with hemoglobin A1C levels.
- Long-term weight loss interventions were associated with lower white matter hyperintensity volume, suggesting that treating diabetes itself may be the key to preventing neurodegeneration and thus, cognitive decline in diabetic patients.
- Current literature has proposed various theories that may explain why patients with diabetes are at higher risk of neurodegenerative diseases:

1) *Altered insulin signaling*: Reduced brain insulin signaling in mouse models of diabetes increased tau beta phosphorylation and amyloid beta peptide levels, both of which are hallmark characteristics of Alzheimer's disease.

2) *Insulin Resistance*: Some researchers suggest that insulin resistance at the blood brain barrier reduces the amount of glucose that can reach the brain, resulting in neuronal injury.

3) *Elevated brain glucose levels*: Others proposed that the diabetic state may lead to a hyperglycemic condition in the brain that would result in the formation of glycated end products, which in turn can induce neuroinflammation.

Obesity and Metabolic Syndrome

- Central obesity is an independent risk factor of dementia. Larger sagittal abdominal diameter was shown to be associated with an increased risk of developing dementia, and patients with higher body mass index (BMI) were more likely to develop Alzheimer's disease later in life.
- Obese individuals were more likely to have decreased total cerebral volume and reduced white matter integrity compared to non-obese individuals.
- Patients with metabolic syndrome have higher brain fatty acid uptake and greater accumulation of fatty acids in the brain in comparison to healthy subjects, with white matter having the highest mean percentage increment.
- In mouse model studies, it was shown that diet-induced obesity produced higher levels of reactive oxygen species in the brain. Hence, oxidative stress may be responsible for cognitive dysfunction following obesity.
- Although there is not sufficient evidence to support the use of bariatric surgery for the prevention and treatment of dementia in obese patients, there has been clinical research showing improved memory function two years following bariatric surgery.

Inflammatory Determinants

RAGE Signaling, COX-2 expression, and Platelet Activation

- Various studies have linked high serum levels of inflammatory markers, such as C-reactive protein, tumor necrosis factor alpha (TNF-alpha), and interleukin 6 (IL-6), with cognitive dysfunction.
- RAGE activation turns on nuclear factor kappa B (NF-kB), which is a transcription factor that controls several pro-inflammatory genes. Activation of RAGE signaling may be involved in the injury of the brain in Alzheimer's disease.
- Diabetic patients with mild cognitive impairment had significantly higher serum levels of advanced glycated end-products (AGEs), RAGE, and C-reactive protein compared to diabetic patients without mild cognitive impairment.
- Amyloid-beta peptides activate cyclooxygenase-2 (COX-2) expression in a dose-dependent manner and treatment with COX-2 inhibitors or ibuprofen was shown to reverse this effect, suggesting that non-steroidal anti-inflammatory drugs (NSAIDs) may be used to reduce the risk of Alzheimer's disease; however, other studies suggest that COX-2 inhibitors may hasten dementia. Hence, it remains controversial whether NSAIDs can be used to treat Alzheimer's disease.
- Activation of platelet function also has been associated with white matter lesions accompanied by cognitive decline.

Microvascular Determinants

Hypertension: Arterial stiffness and Ischemia

- Although the exact mechanism behind how hypertension exacerbates cognitive dysfunction is still unclear, various studies have suggested that arterial stiffness is responsible for cognitive decline in patients with hypertension.
- Current literature also has shown strong direct correlations between arterial stiffness and white matter hyperintensities, reinforcing the link between hypertension and cognitive decline.
- An additional explanation of how hypertension contributes to cognitive decline is ischemia caused by cerebral small vessel disease. Studies have shown that elevated blood pressure is a risk factor of cerebral small vessel disease and that severity of cerebral small vessel disease is strongly correlated with severity of cognitive impairment.
- Blunting or reversing the decrease in cerebral blood flow through the use of antihypertensive treatments has been associated with improved cognitive function.

Blood Brain Barrier Dysfunction

- Blood brain barrier injury has been recognized as another contributory factor to the development and progression of cognitive impairment
- It has been observed in multiple studies that rats fed with high energy diets, specifically diets rich in saturated fats and cholesterol, have increased blood brain barrier permeability along with cognitive dysfunction .
- Anti-inflammatory and lipid-lowering agents were shown to reverse the high fat-induced blood brain barrier damage in rats.
- However, the current level of evidence from several randomized controlled trials have been inconclusive in showing whether lipid-lowering medications, such as statins, can be used for the prevention or treatment of dementia.

Proposed Relationship between Western Diet, White Matter Disease, and Cognitive Decline

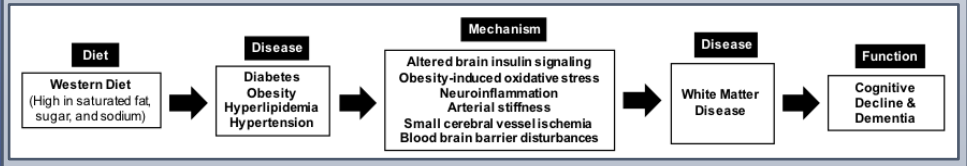

Figure 1. Proposed relationship between western diet, white matter disease, and cognitive decline. Consumption of the western diet contributes to the development of major chronic conditions, such as diabetes, obesity, hypertension, and hyperlipidemia, which in turn results in metabolic, inflammatory, and microvascular changes that induces injury to the white matter of the brain. Subsequently, white matter disease promotes the development and progression of cognitive decline and dementia.

CONCLUSIONS AND CLINICAL IMPLICATIONS

- Consumption of the western diet contributes to the development of major chronic diseases, such as diabetes, obesity, hyperlipidemia, and hypertension. In turn, these chronic conditions lead to metabolic, inflammatory, and microvascular changes that affect many parts of our body, including the brain. The western diet is also suspected to directly contribute to cognitive impairment as a result of increases in blood lipids, sugars, and sodium.
- Our review shows that metabolic, inflammatory, and microvascular changes accompanying chronic diet-related diseases play a significant role in promoting cognitive decline. Abundance evidence shows that there is a strong correlation between these factors and white matter lesions in the brain, allowing us to reasonably speculate that these factors do so by inducing damage to the white matter.
- Consequently, treating these chronic conditions, such as obesity, diabetes, and hypertension, may be the key to preventing the development and progression of white matter disease and cognitive decline. However, sufficient evidence to recommend anti-inflammatory or lipid-lowering drugs for the prevention and treatment of dementia is not currently available.
- Further investigation is needed to elucidate the exact mechanistic interactions between these metabolic, inflammatory, and microvascular determinates and white matter disease. A mechanistic understanding of white matter disease is essential to improving our current approach to preventing and treating neurodegenerative diseases, as well as identifying potential targets for further drug development.

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REFERENCES

See reference sheet.

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