Blood sugar disorders can lead to Alzheimer's disease.

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Abstract

The number of Americans that will be diagnosed with Alzheimer's disease (AD), and the cost associated with treating AD, will rise exponentially in the next 40 years. Research has shown that blood sugar disorders may be linked to AD, with some even calling AD "type 3 diabetes". Of the 103 published studies evaluated, 15 were chosen. The studies covered a variety of evidence, explaining detailed causes as well as preventive methods. The evidence reinforced the idea that blood sugar disorders are linked to AD, while the exact reasons have not all been confirmed. The evidence emphasized several preventive tools that can be implemented to mitigate the development of blood sugar related AD: exercise, melatonin, circadian rhythm, diabetes medications, iron metabolism, vitamin and mineral optimization, and diet. Public health professionals need to take note. The evidence also exhibited several limitations. Blood sugar disorders and their link to AD is still relatively new, so the length of most studies may not be sufficient to make a strong conclusion about the connection. In addition, because the genetic component linking blood sugar disorders to AD is so important, yet in its infancy still, caution needs to be taken before making conclusions.

Keywords: blood sugar disorders, Alzheimer's disease, dementia, diabetes, melatonin, circadian rhythm, insulin, Insulin-like Growth Factor, sulfonylureas, metformin, glucagon-like peptide 1, inflammation, oxidative stress, iron, mitochondrial dysfunction, thiamine, apolipoprotein E (APOE) ε4, type 3 diabetes.

Introduction

Matthews et. al (2018) states that the number of people projected to have Alzheimer's disease (AD) or dementia in the United States is expected to double by 2060. According to the Alzheimer's Association, the total cost of care for Alzheimer's disease exceeded a quarter of a trillion dollars in 2017. The number of Alzheimer's deaths increased 123 percent in 2017. By 2050, the total cost of care for AD is projected to increase to more than $1.1 trillion.

While there does not seem to be a "cure" on the horizon, evidence over the last decade indicates that blood sugar disorders play an integral role in the progression of AD. The more one becomes insulin resistant, caused by higher than normal levels of blood sugar, the greater the risk for AD. Inflammation, from either consuming too much glucose or too much fat, can lead to insulin resistance and negative genetic expression, which also leads to AD. Mitigating the development of blood sugar disorders with individualized lifestyle and dietary choices, as well as targeted medication when necessary, may reduce the progression of AD.

The purpose of this study is to assess whether blood sugar disorders can lead to AD. While there is not total agreement among researchers, the majority agree that blood sugar disorders can lead to AD. There are numerous preventive methods the data suggests to prevent this.

Methods

PubMed, Google Scholar, and ACHS library resources were used to find studies to support or dispel the thesis. 103 studies were analyzed and 15 were chosen to support or dispel the thesis. The intention was to not only include studies that showed blood sugar disorders can lead to AD, but also show ways that treating blood sugar disorders can attenuate the development

of AD. Many studies had to be discarded because they had very few subjects. Many studies were dismissed because of conflicts of interest or funding bias. Specific studies that were overtly positive without discussing their drawbacks were also removed for consideration.

Results

de la Monte and Wands (2008) could be the first to coin Alzheimer's disease (AD) "type 3 diabetes". While they cannot fully claim this phrase, there was no proof that it existed before their study was released in 2008. The authors acknowledge that insulin/insulin-like growth factor resistance is not the sole cause for the development of Alzheimer's disease, but their copious number of references make a case for it to be a major factor.

Following up on their first-of-its-kind review in 2008, de la Monte, Tong, and Wands (2018) suggest that blood sugar disorders are still a factor in the development of AD, but is more modest than they originally thought. They conclude that "it is probable that brain insulin resistance-mediated neurodegeneration can occur via two mechanisms: 1) direct injury with predominant involvement of the brain as occurs in most cases of AD; or 2) indirect injury mediated by systemic insulin resistance diseases associated with metabolic derangements leading to toxic lipid (ceramide) release from injured cells, into the bloodstream and across the blood-brain barrier".

Benedict and Grillo (2018) suggest stemming the progression of Alzheimer's disease pathogenesis by using pharmacological intranasal insulin to restore brain insulin signaling, without the side effects that usually come with pharmacological insulin. Benedict and Grillo understand the limitations of this study. The dosage, time of day, and how the intranasal insulin will work with patients on other drugs is yet unknown.

In a sweeping statement from Katsel et. al (2018), one or more antidiabetic medications, in any kind or combination of insulin only, oral agents, or insulin and oral agents, altered negative gene expression associated with AD, tamped down the brain insulin receptor signaling pathway, and ameliorated endothelial cell transcripts in diabetic AD donor postmortem brain samples. Researchers acknowledge that the majority of donors were on sulfonylureas, so they were not able to gather much data for those on metformin.

Bertram, Brixius, and Briskmann (2016) state that exercise is one of the key lifestyle measures to stem the progression of type 2 diabetes that leads into Alzheimer's disease. They state that the antioxidative properties of exercise may actually clear amyloid beta from brain tissue. The authors understand that this is just a review of current research, so they cannot claim specific discoveries themselves.

Not only does iron bind to amyloid beta, but according to Chung, Kim, and Song (2018), excess iron also contributes to insulin resistance. Alternatively, it has also been shown that iron deficiency can also contribute to memory dysfunction. Thus, the authors evaluate the importance of proper iron metabolism in the progression of neurodegeneration.

Song, Whitcomb, and Kim (2017) discovered the necessity of melatonin in attenuating type 3 diabetes. The authors link melatonin's crucial role in balancing circadian rhythm to balance glucose metabolism.

Bae and Song (2017) suggest that glucagon-like peptide 1 (GLP-1) attenuates neuroinflammation and improves neurogenesis and insulin sensitivity in AD and should be manipulated for improvement of cognitive dysfunction in diabetes-induced dementia. They explain that along with amelioration of inflammatory responses in the brain caused by amyloid

beta-induced oxidative stress, GLP-1 could invigorate microglia to protect neurons. GLP-1 could also champion neurogenesis in the AD brain. Thus, GLP-1 could eschew damaged neurons and engender new neurons in the AD brain.

Chen and Zhong (2013) conclude that Alzheimer's disease is exacerbated by cerebral glucose metabolism. They suggest dysfunction related to glucose metabolism, such as altered thiamine metabolism, may serve as as a way to test for dysfunction. At this time, there are no specific pharmacologic therapies that can fight against all dysfunctional pathways, and they suggest developing cocktail therapies.

Verdile et. al (2015) elucidate the connection between chronic inflammation and oxidative stress and type 2 diabetes and Alzheimer's disease. They explain that there is an increase in AD diagnoses in those with type 2 diabetes. They suggest that this is directly due to impaired insulin signaling that increases inflammation, oxidative stress, and mitochondrial dysfunction.

Zheng et. al (2018) performed a study comparing those with prediabetes and diabetes versus those without prediabetes and diabetes and the risk of cognitive decline. The significance of this study was its length, which was over eight years. In addition, it was the first to track three cognitive assessments over the length of the study. The authors acknowledge that while the observed associations were statistically significant, the effect sizes were small.

Zhao et. al (2017) made a discovery in mice exposing a stronger association between diabetes and AD-associated amyloid pathology among carriers of the apolipoprotein E (APOE) ε4 gene allele, the strongest genetic risk factor for late-onset AD. They found that impaired glycolysis from a high fat diet was the culprit in the negative APOE expression.

Kandimalla, Thirumala, and Reddy (2017) performed a critical appraisal of all potential blood sugar imbalance mechanisms that could lead to AD. They feel there are still numerous questions that remain unanswered. Specifically, they believe scientists have yet to elucidate how brain insulin and insulin-like growth factor signaling contributes to the pathogenesis of AD. They suggest focusing on latter, as well as studying the effect of APOE4 gene mutations on insulin signaling, using CRISPR-gene editing. Until there is a consensus, the authors feel type 3 diabetes is still a term in flux.

Discussion

It seems the bulk of research supports the idea that blood sugar disorders lead to AD. The methods of how this occurs and what paradigms should be used to ameliorate AD by balancing blood sugar is still being fleshed out. Three aforementioned studies, showing benefits from exercise, maintaining melatonin levels, and optimizing circadian rhythm, are inexpensive preventive methods in which blood sugar disorders could be mitigated to prevent AD. In situations where diet and lifestyle are not enough, several other studies exhibit the benefits of diabetes medications.

There are certain research methods that focus on blood sugar disorders and AD that need more time to gestate. For example, gene expression, or even knowing what and how many genes could be associated with AD, are still in the discovery phase. CRISPR, a groundbreaking but still unproven method of fixing genetic abnormalities, may be beneficial in the future, but is still in its infancy. While researchers suspect insulin, insulin-like growth factor, oxidative stress, inflammation, all play some role in the progression from blood sugar disorder to AD, there is no definitive conclusion. Other limitations linking blood sugar disorders to AD include studies'

length. The longest study comparing the risk of cognitive decline in prediabetics versus diabetics was only eight years long. Studies of longer duration to gather sufficient results are needed.

Conclusion

The evidence points to an inextricable link between blood sugar disorders and AD. While the exact cause(s) for why blood sugar disorders lead to AD has yet to be agreed upon, the data is definitive about prevention being one major paradigm that should be promoted immediately. Gathering stakeholders in government and commerce to come up with better paradigms to prevent blood sugar disorders is imperative. When an action plan is agreed upon, public health experts en masse need to encourage preventive methods to ameliorate blood sugar disorders, focus on managing those with blood sugar disorders, and explain to the public how blood sugar disorders can lead to AD.

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