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Modifications and Medications to Improve Alzheimer's Disease from Type 2 Diabetes

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MODIFICATIONS AND MEDICATIONS TO IMPROVE ALZHEIMER'S DISEASE FROM TYPE 2 DIABETESAshley Robinson

ABSTRACT

Alzheimer's Disease (AD) and Type 2 Diabetes (T2D) are chronic conditions increasing in prevalence that impact the daily lives of those afflicted with them. AD and T2D are linked through the pathophysiology of insulin resistance. Thus, there are intersections that can allow the management of T2D to improve the treatment and prevention of AD. Modifiable risk factors, such as diet and physical activity level, play important roles in the health of T2D patients as well as in preventing AD. Medications traditionally used in the treatment of T2D, such as metformin, pioglitazone, and insulin, are being examined for use in the new context of treating AD. Improving patient education on chronic diseases and modifiable risk factors, as well as continuing research into applications of drugs to treat and prevent AD, can reduce much of the suffering associated with AD and other chronic illnesses, such as T2D.

KEYWORDS

Alzheimer's disease (AD) – Type 2 Diabetes (T2D) – MIND diet – DASH diet – Mediterranean diet – Okinawan diet – metformin – pioglitazone – insulin

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting around 5.5 million people in the United States (1). The progressive cognitive decline it causes creates much suffering for patients and caregivers. Due to the fact that the number of elderly individuals continues to grow in the United States, and that the incidence of AD doubles every five years starting at age sixty, the number of adults in the United States diagnosed with AD can be expected to continue to grow (1). By 2050, it has been predicted that the prevalence of AD could

increase to sixteen million instances (2). As a result of the suffering of those currently facing AD and the potential for more in the increasing numbers of those who will have it in the future, AD is a subject of research into effective treatment and prevention methods.

Prevention strategies are needed because before symptoms become noticeable to the patient or clinician, changes happen in the brain that suggest the disease is present (3). This means that there is a window for treatment that is not being accessed with current protocols. Hence, prevention is especially important. Once AD begins damaging the brain, there is a significant gap before treatment takes place. Even once treatment starts, there is not much that can be done to stall the steady progression of the disease. In treatment today, approaches to halt or delay the onset or progression of AD are needed. Currently, the largest class of medications prescribed for the treatment of AD is acetylcholinesterase inhibitors, which slow the breakdown of acetylcholine. This compensates for the destruction of cholinergic neurons in the basal nucleus of Meynert that characterizes AD.

Current research being done on AD investigates its links to Type 2 Diabetes (T2D). Unlike Type 1 Diabetes, T2D is an insulin resistance in the body, not a complete lack of insulin production from the pancreas. T2D, like AD, is another chronic illness that affects millions in the United States. Paralleling the growing elderly population and the rise in AD, an increase in T2D is correlated with the continuing increase in the obese population (4). Both T2D and AD are chronic illnesses that impact the daily lives of patients afflicted with them. Viewing AD as an insulin resistance in the brain, there are multiple aspects of T2D treatment and prevention that can be applicable in this new context, such as exercise, diet, and medication. First, I will consider the pathology connecting T2D and AD, and then explain the intersections in treatment and

prevention between the two diseases. Finally, I will provide recommendations for further research and protocols.

LINKING ALZHEIMER'S DISEASE AND TYPE 2 DIABETES

Risk

Age is well-known as the biggest risk factor for dementia. Beyond this, patients with T2D are at a higher risk for AD, as T2D is a recognized risk factor for AD. It has been shown that T2D patients, even with good blood glucose level control, have declines in executive control functions and working memory compared to those without T2D; however, these declines are not as great as in those with AD (5). These findings support the idea that T2D patients are at risk for developing AD (5).

Conversely, impaired insulin signaling in the hypothalamus increases the risk for developing diabetes in a mouse model of AD, suggesting that AD can also affect T2D (6). In another mouse model of both AD and T2D, it has been found that the diseases, over time, concurrently increase pathologies of both individual diseases (7). Metabolic dysfunction, cortical size reduction, and an amyloid- β production shift to a more toxic form were seen (7).

Pathology

One theory that links AD and T2D is insulin resistance. T2D is known to be a peripheral insulin resistance, while AD has been proposed to be an insulin resistance of the brain (8). In the periphery, insulin is responsible for the uptake of glucose from the blood stream into cells to be used for energy. In the brain, insulin and insulin-like growth factor-1 (IGF-1) affect the central nervous system and regulate learning, memory, energy use, and neuronal health (9). Insulin is produced in the periphery by the pancreas and is transported across the blood-brain barrier (8). Insulin receptors are found throughout the periphery, but in the brain are most prevalent in areas

such as the cerebral cortex, hippocampus, and amygdala (9). Insulin has been linked to improved cognition based on its effects in the hippocampus (8). The hippocampus is one of the areas that feature the most neuronal death in AD. Insulin resistance has been found in the hippocampus of AD patients who do not have T2D (10).

The two hallmark characteristics of AD, plaques and tangles, have been linked to insulin signaling in the brain. Tangles are made up of abnormally folded and phosphorylated tau protein. Insulin and IGF-1 have been found to regulate tau phosphorylation (8). Plaques are made of amyloid- β protein. Defective insulin signaling increases the rate of amyloid- β protein production and aggregation, leading to the characteristic plaques of AD (11). Additionally, amyloid- β proteins disrupt insulin signaling, leading to an upregulating cycle of protein production and plaque formation (10). Disrupted insulin signaling has also been linked to neuronal death through excitotoxicity, neuroinflammation, and the disruption of energy production in neurons (8).

Plausibility

Despite the research linking AD and T2D through insulin resistance, arguments have been made against this relationship. It is debated whether insulin resistance is a cause or effect of AD (12). This becomes more difficult to determine, as researchers report that there is a lack of studies that examine whether diabetes more commonly occurs before or after the diagnosis of AD (12). Additionally, links to Type 1 Diabetes, not just T2D, are being explored (13). Links to both Type 1 Diabetes and T2D have led researchers to propose that AD is "Type 3 Diabetes," as it may not correlate so clearly with T2D (13). Although current literature provides complications to the link between AD and T2D, the evidence that has been found suggests that T2D may serve as an important key to treating and preventing AD.

INTERSECTIONS IN TREATMENT

As a result of their similar pathology, there are multiple intersections in treatment that can be applied from T2D to AD. Once diagnosed with T2D, it is important for patients to control their condition, as rapid progression and more severe diabetes increases dementia risk (14).

Controlling T2D has a two-fold effect on AD: not only do treatments for T2D directly affect a patient's risk for AD due to their shared pathology, but controlling T2D also lowers the risk for AD because T2D is a risk factor for AD. Conversely, treatments aimed at reducing the incidence of AD have the potential to be useful in T2D treatments.

Exercise

Weight loss is one of the first steps taken to control T2D as a result of its links with obesity. It has been shown that physical activity may play a role in preventing AD. Various types and durations of exercise, from walking and running to weight training, have been shown to be linked with improvements in biomarkers related to AD including TNF- α , ROS, and ceramides (15). Increases in these biomarkers as seen with T2D have effects on AD and other forms of dementia, including insulin resistance of the brain and other subsequent effects. Exercise has been found to have protective effects on cognition and neural function, including neurogenesis (15).

Exercise is often something that is lacking in a typical T2D patient, as well as in the elderly. The American College of Sports Medicine recommends that individuals over the age of sixty-five and those over the age of fifty with a chronic disease, such as T2D, perform regular physical exercise of various types ranging from balance to aerobic exercises (16). These recommendations would include Type 2 Diabetics and others at risk for AD and other forms of dementia. Mini-Mental State Examination scores have been found to be negatively correlated

with increased pulse rate, an indirect measure of physical fitness, in elderly subjects (17). This suggests that regular physical activity would have a benefit on cognition and Mini-Mental State Examination scores, as it would decrease pulse rate. This idea is reinforced by the finding that older individuals who engaged in 150 or more minutes per week of at least moderate physical activity were forty percent less likely to develop AD (18).

Diet

Dietary changes are some of the most important factors in the treatment of T2D, as diet is a modifiable risk factor for diabetes and other chronic conditions. It is essential for Type 2 Diabetics to control their carbohydrate intake in order to maintain their blood glucose levels. Specifically, it is important to consume carbohydrates low on the glycemic index to prevent spikes in blood glucose levels. A high fat and high cholesterol diet can be detrimental to any person's health, but is especially detrimental to those with T2D who need to regulate their weight and blood sugar. In an animal model, it has been shown that a diet high in cholesterol and fat leads to cognitive impairment and biomarkers of AD, such as higher levels of tau protein (19).

There are many diets that have been investigated in order to improve health. The Mediterranean diet has long been known as a healthy diet that is related to decreased incidences of cardiovascular disease and diabetes, and the MedDietScore has been used to determine that increased adherence to this diet leads to a reduced risk of coronary heart disease (20, 21). Additionally, it is thought to have protective effects with regards to cognition (21, 22). It has not only been linked to a reduced risk of AD, but has been found to slow cognitive decline (21). This diet is culturally based on the consumption of fruits, vegetables, fish, legumes, and olive oils (21). Another diet linked to cognitive protection and other health benefits is the DASH diet, or Dietary Approaches to Stop Hypertension. The DASH diet focuses on eating more fruits,

vegetables, and low fat dairy items in order to reduce hypertension. The DASH diet was also found to be related to higher executive function-memory-learning scores, which was enhanced by weight loss (23). Both diets, with their focus on vegetable consumption and limited intake of lean meats, will provide benefits not only for cardiovascular disease and cognition, but also for T2D, which would benefit from the reliance on low glycemic index foods and low fat intake. Increased adherence to the Mediterranean diet or the DASH diet has been shown to decrease both the risk and incidence of AD (22).

Based on the benefits seen from the Mediterranean and DASH diets, the MIND diet, or the Mediterranean-DASH Intervention for Neurodegenerative Delay, was developed. The MIND diet emphasizes plant-based nutrition and limits consumption of animal and high fat foods. Specific foods, such as berries and leafy, green vegetables, which are thought to improve brain health, are emphasized (22). The MIND diet has been shown to reduce the risk of AD in participants who followed the dietary protocol to at least a moderate degree (22). A correlation between the MIND diet and global cognitive measures has been found, meaning this diet is linked to slowing cognitive decline (24). The rate of cognitive decline reduction was shown to be the equivalent of being seven and a half years younger for participants who adhered most strongly to the MIND diet (24).

Beyond the Mediterranean, DASH, and MIND diets, other diets that can decrease the risk for chronic and age-related diseases. One of these is another culturally based diet, the Okinawan diet. The diet is based on the consumption of low glycemic index carbohydrates like vegetables and soybean-based foods. Additionally, it is based on a consumption of seafood and small amounts of other lean meats (25). The Okinawan diet is similar to the Mediterranean and DASH diets, as it reduces the risk of cardiovascular disease (25). Additionally, based on the fact that it

emphasizes foods low on the glycemic index, like sweet potatoes, it also is a good choice for diabetics (25). Based on its similarities to other diets that have been shown to prevent and slow cognitive declines related to neurodegenerative diseases, it is likely that the Okinawan diet would show similar benefits.

Overall, a Western diet high in meat, fatty dairy products, and sugary sweets is related to an increase in AD incidence, as meat consumption has been found to be a large contributor to one's risk of AD (26). Meat consumption is also related to other chronic conditions, such as T2D. In countries moving from previous diets to the Western diet, such as Japan, rates of AD rose six percent over a twenty-three year period (27). Based on the benefits seen previous studies, transitioning from the Western diet to healthier diets such as the Mediterranean, DASH, MIND, or Okinawan diets has the potential, I believe, to decrease chronic conditions including both T2D and AD.

Medication

Many Type 2 Diabetics turn to medication to control their blood glucose levels when dietary choices and physical exercise are not sufficient. One of the most popular of these is metformin. Metformin activates AMP-activated protein kinase (AMPK), decreases glucose production by liver cells, and increases glucose uptake in skeletal muscle cells (28). Overall, this lowers blood glucose levels. In mice, metformin has been shown to protect against amyloid- β protein plaques in the hippocampus and high fat diets (29). Amyloid- β plaques are one of the distinguishing features of AD, and the hippocampus is one of the major sites of neuronal loss in AD and is involved in learning and memory.

Research is being done to investigate AMPK as a target for the treatment of neurodegenerative diseases. Activation of AMPK by an agonist, such as 5-aminoimidazole-4-

carboxamide riboside (AICAR), has been shown to improve both motor function and memory in mice (30). AMPK is activated by exercise as well as AICAR; however, in the case of the elderly who are most at risk for AD, getting the protective effect of physical activity on AD and benefits to cognition from physical exercise may not be possible due to their physical frailty. In addition, activation of AMPK by metformin may provide benefits to neurological function in a manner similar to AICAR, helping to prevent AD and improve motor function in a population at an increased risk for AD.

Another medication used to control blood sugar levels is pioglitazone. This medication is a peroxisome proliferator activated receptor γ (PPAR γ) agonist. Activation of PPAR γ has been shown to prevent the deposit of amyloid- β proteins and plaques by decreasing the activation of beta secretase (31). Beta secretase is one of the enzymes involved in converting amyloid precursor protein into amyloid- β protein. Long-term use of pioglitazone has been shown to lower the risk of dementia by forty-seven percent below that of patients without diabetes (32). If they did not receive pioglitazone, diabetic patients exhibited a twenty-three percent increased risk for developing dementia (32).

Some T2D patients use insulin to control their blood sugar. Although more commonly associated with Type 1 Diabetes, insulin can be used in patients for whom lifestyle choices and oral medications are not sufficient to control their blood glucose levels. Benefits to AD patients have been shown with intranasal insulin (33). Although it has only been studied in a mouse model of AD, intranasal insulin reduces anxiety and improves cognitive deficits (33). Additionally, intranasal insulin has beneficial effects on the biomarkers of AD. Specifically, intranasal insulin reduces amyloid- β plaque levels and deposits in the brain by modifying amyloid precursor protein in a non-amyloidogenic way through the use of alpha secretase. (33).

Amyloid- β plaques, along with tau tangles, are one of the major hallmarks of AD. Additionally, intranasal insulin enhances neurogenesis in the hippocampus (33).

RECOMMENDATIONS

This is not an exhaustive list of all of the connections between AD and T2D; more research is necessary to fully examine the links between these two diseases. Specifically, more research is needed with human subjects. Investigations currently being done on T2D medications being used for AD and long-term models of T2D and AD are being done in mice. The current use of animal models to investigate neurodegenerative diseases like AD is useful due to the ability to use animals to perform trials and manipulations that would be unethical in humans. Additionally, animal models provide results much faster than human trials, as the lifespan of animals is shorter and disease conditions can be induced in animals. Despite these benefits, more research is needed in human subjects since results in animal models are not always applicable to humans.

Beyond research, it is necessary to provide patient education on the subjects of diet and exercise in regards to the prevention of AD and T2D. Prevention and early intervention are the best ways to reduce the suffering caused by neurodegenerative diseases like AD. Lifestyle choices such as those related to nutrition and physical activity decrease the risk of T2D, which in turn lowers the risk of AD. HbA1C level, an indicator of blood glucose control over time, can be lowered through a patient's choices in regards to self-management of their disease. In addition to nutrition and exercise, this includes taking medication as prescribed (34). Outside of T2D, lifestyle choices can reduce the risk of AD outright due to the related pathology of AD and T2D. As such, the intersections between AD and T2D lead to the potential of broader applications of these links to a larger population beyond that of Type 2 Diabetics. For example, although it is

well established that T2D is a risk factor for AD, it has been shown that increased blood glucose levels are a risk factor for dementia, even in those without T2D (35).

CONCLUSION

AD is the most common form of dementia and only continues to become more widespread. T2D is another chronic illness that continues to increase in prevalence. Due to their similar insulin resistance pathology, AD and T2D affect each other over time and are risk factors for each other. As a result of their similarities, managements and preventative measures for T2D can fill in the current gaps in the treatment and prevention of AD. Modifiable risk factors are the easiest ways for patients at risk for AD to lessen the chance of developing the neurodegenerative disease. Increasing levels of physical activity and transitioning from a Western diet to healthier diets will allow them to reduce their risk. At the same time, these measures help to control blood glucose levels to control or prevent the onset of T2D. Beyond modifiable risk factors in the hands of the patient, medications used to treat T2D can be used to treat AD. Overall, increased patient education and continued research can greatly reduce and prevent the suffering caused by both T2D and AD.

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