Insulin Impairment and Alzheimer's Disease: Link Explained and Potential Treatment Options Reviewed

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Alzheimer's Disease (AD) is the most common form of dementia, characterized by progressive neurodegeneration that leads to memory impairment and other forms of cognitive decline. Amyloid beta protein and tau protein plaques buildup is one of the main causes of AD. As a result of this build up, several substantial structural and functional changes occur, such as vascular damage, total white matter loss, and gray matter loss. Diabetes Melitus (DM), also known as diabetes, is a metabolic disease characterized by impaired glucose regulation in the body as a result of impaired insulin delivery. The hallmark mechanism observed in DM is abnormal blood glucose levels as a result of impaired insulin supply. Despite the burden of both diseases, neither has a cure, and the treatment options are relatively limited. Recently, a link between insulin irregularities, a hallmark of diabetes, and Alzheimer's disease has become evident. Understanding the relationship between DM and AD can aid in the therapeutic development for both of the diseases. The research objective of this literature review was to describe and connect the pathophysiology of both Alzheimer's disease and diabetes and highlight the potential for glucose-specific therapy in Alzheimer's disease. Results showed that metformin is an effective treatment for AD patients because of its anti-inflammatory actions and regulation of the intestinal microbiome.

Keywords: *Diabetes Mellitus (DM), Alzheimer's Disease (AD), amyloid beta (AB) peptide, tau protein, glucose, insulin.*

Introduction

Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive neurodegeneration that leads to memory and other cognitive function impairments. According to the Alzheimer's Association, 5.8 million persons in the United States are currently diagnosed with the illness, with total expenses for AD health and social care totaling an alarming 305 million dollars[1]. However, despite its prevalence, therapy options are very limited. Alzheimer's disease is associated with many anatomical and functional abnormalities, including vascular damage and reduced gray and white matter volume.

Diabetes Mellitus (DM), generally known as diabetes, is a metabolic illness characterized by decreased insulin delivery throughout the body, which affects glucose levels. Diabetes, like Alzheimer's, affects an alarming number of people in the world. Diabetes is classified into two types: type 1 and type 2. The autoimmune death of pancreatic cells happens in type 1 diabetes (T1D), resulting in lower insulin levels and, as a result, a rise in glucose levels. While some therapies exist for each disease, neither has a cure.

Recently, a link between insulin irregularities and Alzheimer's disease has become evident. Type 2 diabetes patients are at increased risk of getting Alzheimer's disease. The goal of this review is to describe and connect the pathophysiology of both Alzheimer's disease and diabetes and highlight the potential for glucose-specific therapy in Alzheimer's disease. While much study has been conducted on each distinct disease, little is understood about the physiological consequences of glucose dysregulation in Alzheimer's. Alzheimer's disease can arise independently from glucose dysregulation, but understanding their relationship could help in treatment and therapeutic development. This review intends to add to the information filling in the gap in knowledge about how glucose dysregulation can potentially cause the diagnosis of AD, and also specify current studies that have studied this relationship.

Alzheimer's Disease and Diabetes Mellitus: Mechanisms and Effects

Alzheimer's Disease (AD): Disease Overview

Alzheimer's Risk Factors: AD is a neurodegenerative disease which leads to loss of memory and other important cognitive functions, such as language and perception. Moreover, there are two different forms of Alzheimer's. Early onset AD (EOAD), an uncommon case of AD that occurs before the

age of 65, is diagnosed. Similarly, late onset AD (LOAD) is develops after age 65, and is more common[2]. According to certain observations, EOAD may be a distinct, more severe entity than LOAD. Neuropathological examinations revealed younger AD patients had relatively larger loads of neuritic plaques and neurofibrillary tangles, as well as greater synapse loss, than older patients. Younger people also tend to have higher levels of education and cognitive reserve than older people, which could also delay diagnosis. Antidementia therapy may therefore be started at a later stage of the disease, which might decrease the success rate of therapy for EOAD[3]. Regardless of the type, genetic and environmental factors have an impact on the pathogenesis and progression of the disease.

Genetics is a key risk factor for Alzheimer's disease. While no single gene causes the illness to develop, there has been evidence of numerous genetic abnormalities in AD. Genes are sequences of DNA, which contain information to create specific proteins[4]. DNA is made up of nucleotide bases that are arranged in sequences which code for different proteins, but is not a protein itself[5]. In an Alzheimer's brain, mutations of certain genes can lead to abnormal protein deposits in the brain's vasculature[6]. For example, sequence changes in the amyloid precursor protein (APP) gene leads to excessive cleavage of APP, which subsequently leads to the accumulation of the amyloid beta peptide[7], one of the notable features of AD.

However, genetics cannot predict 100% of the outcomes of the disease since environmental factors and behavioral patterns may also have an impact. The six proposed environmental factors are air quality, toxic heavy metals, other metals, other trace elements, occupational-related exposures, and miscellaneous environmental factors[8]. Air pollution is one of the most problematic challenges of today's world, and leads to a wide range of diseases. For instance, particulate matter (2.5 m), such as black carbon, emitted from traffic and fossil fuel combustion can reach the brain via the olfactory nerve[9]. PM2.5 can stimulate glial and microglial activity, which leads to neuroinflammation, increased intracellular ROS generation, and ultimately neuronal death, all of which are hallmarks of AD. In addition, PM2.5 raises AD biomarkers like amyloid-beta and hyperphosphorylated-tau and alters the shape and synaptic alterations of neurons. It also increases the activity of the enzymes implicated in the amyloidogenic pathway[10].

Additionally, exposure to toxic metals, particularly lead, cadmium, and manganese, causes cognitive impairment[11]. Cadmium has been linked to an increase of amyloid beta and tau tangles11, which are the two notable features of AD, as well as an increased mortality rate in AD patients[12]. Furthermore, there have been animal studies and research on occupationally exposed persons that have demonstrated a correlation between lead exposure and AD, but there have not been many long-term studies on this association[11]. Finally, manganese has been demonstrated to worsen neurotoxicity associated with Alzheimer's disease by affecting the mitochondrial membrane, which in turn hinders ATP-dependent energy generation[13]. There have been associations between AD progression and other metals, but most of the studies were inconclusive[8].

Moreover, investigations on the association between Alzheimer's progression and climate, electric/magnetic fields, and Vitamin D resulting in substantial evidence for only the influence of low Vitamin D levels on Alzheimer's[8]. This is because vitamin D participates in the clearance of amyloid beta aggregation and has been shown to protect the brain against tau tangles caused by AB peptide[14]. In addition to the different genetic and environmental risk factors, traumatic brain injury (TBI) can contribute to the development and progression of Alzheimer's disease. The principal effects of TBI on AD are the deposition of amyloid beta protein and the hyperphosphorylation of tau. While the exact mechanism responsible for this is unknown, it has been shown that TBI can cause damage to the blood-brain barrier, which is known to cause ischemic damage and the protein aggregates[15].

Despite the various risk factors, certain behaviors can decrease the risk of Alzheimer's. According to the Center for Disease Control (CDC), a study conducted in the University of Minnesota showed that 41% of the cases they examined were due to 12 modifiable factors. Among these factors, obesity, high blood pressure, and lack of exercise contributed the most to risk of dementia[16]. Exercise helps reduce obesity, which in turn lowers blood pressure, lowering the chance of hypertension inside the brain, which is one of the complications of Alzheimer's disease[17].

Most proteins adopt a certain three-dimensional conformation that is kept together by inter- and intra-protein covalent interactions. It is the aggregation of the proteins that causes cognitive decline, not the proteins themselves. Protein aggregates form as a result of the unfolding of the polypeptide chain, which then cannot be cleared, causing cognitive decline. The exact cause for the unfolding of the proteins is yet to be determined, but aggregations can be produced by abnormalities in the genes that code for the normally folded proteins[18]. The primary cause of the observed cognitive decline in Alzheimer's particularly is the formation of amyloid beta (AB)peptide, which causes tau protein buildup. AB peptide is a 37 to 49-amino acid peptide generated from the amyloid precursor protein (APP)[19]. AB peptide in healthy levels is essential in regulating tau levels, which are essential for MT binding, and for synaptic plasticity and memory[20]. It is only when there are excessive levels of AB peptide that signs of AD begin to show[21]. Tau is a protein found in the brain, and is responsible for regulating the assembly and maintenance of microtubules (MT's) in neurons[22], which determine cell shape and in a variety of cell movements, including some forms of cell

locomotion, the intracellular transport of organelles, and the separation of chromosomes during mitosis[23]. Additionally, certain proteins are naturally unfolded, such as tau, which increases their susceptibility to tangles[24]. AB peptide in healthy levels is essential in regulating tau levels, which are essential for MT binding, and for synaptic plasticity and memory[20]. It is only when there are excessive levels of AB peptide that signs of AD begin to show[25]. In an AD brain, mutations in the APP gene cause the overproduction of the AB peptide. This subsequently leads to tau accumulation, and is difficult to remove, because the tau removes itself from the cytoskeleton (MT's), and attaches to other tau particles, causing the formation of long chains which disrupt neuronal communication[26].

Moreover, the aggregation of AB peptide has also been noted to cause homeostasis dysregulation, which impacts calcium 2+ (Ca^{2+}) levels[27], specifically in the mitochondria. Since the calcium ion is responsible for metabolism[28], excessive Ca^{2+} production causes hypermetabolism and insufficient Ca^{2+} causes hypometabolism, both of which are seen as effects of Alzheimer's Disease. Uncontrolled levels eventually result in mitochondrial trafficking, which leads to structural failure and, as a result, cell death, which is also a characteristic of AD[29]. Moreover, the aggregates that cause uncontrolled Ca^{2+} levels extend across entire areas of the brain over time, causing Ca^{2+} levels to spike in multiple areas in the brain, advancing AD.

Physiological Effects of Alzheimer's

Alzheimer's is associated with several substantial physical and structural changes within the brain, such as vascular damage, total white matter loss, and grey matter loss. Vascular damage caused by AD includes damage done to the neurovascular unit (NVU) and blood-brain barrier (BBB). The NVU is composed of neurons, glia, and cerebral vascular cells[30], and regulates blood flow through the brain. The BBB, which is within the NVU, prevents blood from freely flowing through the brain tissue , and is responsible for regulating the entry and exit of ions, nutrients, macromolecules, and energy metabolites[31]. Post neurovascular damage, hypoxia, which is the unavailability of sufficient oxygen to maintain homeostasis[32], develops, decreasing the ab clearance from the brain. Moreover, the BBB is impaired, leading to heightened permeability of amyloid beta, worsening the amyloid beta accumulation[33]. Overall, neurovascular damage causes the accumulation of ab aggregates while also decreasing the ability to clear them.

Another major change which is observed in an Alzheimer's brain is white matter hyperintensities as a result of vascular damage. White matter hyperintensities are high areas of intensity in an MRI scan which indicates demyelination and axonal loss[34]. White matter lies beneath the gray matter and contains myelin-insulated neurons which connect the different functional regions of the brain. Gray matter, which makes up these functional regions, processes information and outputs new information through the signaling mechanism found in white matter[35,36]. The concept that white matter changes occur in Alzheimer's is a relatively new concept, and white matter is not as commonly discussed as grey matter. However, scientists have discovered that hyperintensities in the white matter vasculature occur as a result of axonal loss, which again increases accumulation of AB and tau proteins[37]. A group of researchers conducted a study in which they tested two separate groups, one with 54 people who were cognitively impaired and had AB peptide in their brain, and the other with 40 people who were relatively older and unimpaired, but had vascular risk factors, to better understand the effects of Alzheimer's on white matter. The cognitively impaired group was estimated to have white matter hyperintensities , so the association between hypertension and cognition was tested in each group. One of the controls in their experiment was cerebral amyloid burden. The results showed that people with AB peptide accumulation in their brain had higher volumes of WMH than those who were unimpaired[38]. These results suggest that axonal loss and demyelination do occur in white matter as a result of vascular damage.

Additionally, as a result of AD, grey matter volumes decrease, impairing cognitive function. In patients who have severe AD, significant loss of gray matter occurred in the hippocampus, temporal pole, temporal cortex, precuneus, parietal lobe, and cerebellum. While gray matter volumes are known to decline in moderate cognitive impairment (MCI) and AD patients, the pattern of progression from MCI to AD is not well understood. To identify the differences in gray matter structure, including cortical thickness, patterns of gyrification (process of forming patterns of sulci and gyri[39], and sulcus depth, 80 patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were split into healthy controls, early MCI, late MCI, and AD. Differences between the scans were used to analyze patterns of grey matter deterioration across the four groups. Additionally, the patterns of recurring genetic mutations[40] were also studied. Results demonstrated that patients with MCI and AD had significantly reduced cortical thickness. Sulcus depth was also greatly affected by the progression of AD. Lastly, analysis showed that patterns of cortical thickness and sulcus depth are present in AD progression. Using this information, researchers concluded that there is a link between Alzheimer's disease and gray matter degradation. Furthermore, it was shown that the clinical phenotypes of Alzheimer's disease appear long before the illness is recognized due to amyloid beta toxicity[41]. Overall, the effects of Alzheimer's disease are vascular damage, complete white matter loss, and grey matter loss. AD also shares processes with diabetes, a metabolic condition that causes glucose dysregulation, which leads to the advancement of AD.

Diabetes Mellitus (DM): Disease Overview

Diabetes Risk Factors

Diabetes Melitus (DM), simply known as diabetes, is a metabolic disorder that is characterized by hyperglycemia (abnormal glucose levels) and is caused by impaired insulin levels. Insulin is a 51-amino acid hormone secreted by pancreatic beta cells that regulate glucose levels, cell development, and metabolism[42]. The two types of diabetes are type 1 (T1D) and type 2 (T2D). In T1D, autoimmune destruction of pancreatic beta cells occurs, which reduces insulin production and therefore causes higher levels of glucose in the body. This usually occurs in children and adolescents and the three main symptoms are abnormal hunger, thirst, and dilute volumes of urine[43]. In T2D, by contrast, the body rejects the insulin that is produced, which also increases glucose levels in the body. However, according to the Center for Disease Control and Prevention, the exact causes for insulin resistance are not yet fully known[44]. Some of the major risk factors for T2D are genetic influence and gut microbiome composition[45]. Current medications for diabetes include insulin therapy, and metformin (mostly for Type 2 diabetes, but can be used for type 1).

There is no single risk factor for T2D, and genes only increase or decrease likelihood of developing the disease. Developing T2D is based on both environmental and hereditary factors. Genome wide association studies involve scanning markers across sets of DNA or genomes of a wide population in order to find genetic variations within a disease which are correlated with a disease phenotype and therefore often identify functional, causal genes[46]. At least 120 genetic variations have been identified which increase the risk of developing diabetes[47]. Additionally, candidate genes for T2D were discovered[48]. The overall trends in the study are DNA methylation and genetic variation within T2D and the discovery of genetic traits linked to obesity, metabolic memory, pancreatic islet function, and inflammation[49]. Overall, it can be said that genes do play a significant role in the contraction of diabetes.

Moreover, Researchers proposed that the communication between insulin signaling and the mitochondria might be involved in the pathology of T2D. In order to identify the molecular level processes involved, the researchers examined from various databases, specifically protein–protein interactions, gene co-expression, signaling, and metabolic pathway interactions. It was found that 286 genes are directly related to insulin signaling and mitochondrial genes[48].

In addition to genetic factors, the study of gut microbes highlights that these microbes play a critical role in human health and diseases, including T2D. There are many kinds of bacteria that can live in the human gut. Because of this, scientists have termed the gut genomes, or the qualitative or quantitative structure of the bacterial enterotype, as the gut metagenome[50]. Changes in in bacterial enterotype composition are correlated with the stimulation or inhibition of metabolic pathways. In a study on mice, the alteration of the intestinal microflora makeup, which are a type of microbiota, improved fasting glycemia, glucose tolerance, and insulin sensitivity in comparison to the untreated control group[51]. Moreover, in a study conducted on 60 Northern Chinese patients, researchers compared the fecal microbiota of T2D patients and healthy controls, in order to identify the gut microbes in T2D patients. Characterization via sequencing allowed the researchers to see that there was a decreased amount of gut microbial diversity[52]. The results of the first study demonstrate that microbiota are essential for glucose and insulin tolerance, and the second study demonstrates that in T2D, the diversity of microbiota is decreased. It can be inferred that T2D causes a decrease in microbial diversity, which leads to glucose and insulin dysregulation, a key mechanism in diabetes.

Long term effects of diabetes on the brain include nervous damage in the brain (similar to how it causes nervous damage in one's eyes, feet, and hands), and hyperglycemia (high glucose levels), which causes problems with memory and thought processes. Similarly, hypoglycemia (low glucose levels), cuts oxygen supply to the brain, and unlike hyperglycemia, the effects of hypoglycemia are more immediate[53]. AD may occur as a result of impaired glucose regulation in the brain, which is also caused by the progression of T2D. Some pathological mechanisms are shared by both AD and T2D. One of the most prevalent links between AD and T2D is the amyloid deposition[54] which causes metabolic abnormalities, and therefore advances the phenotypes of the diseases.

Significance of Amyloid Beta in Diabetes

While the amyloid beta protein is one of the hallmarks of the pathogenesis and progression of AD, it has also been identified as a progression factor for T2D. Amyloid formation by the neuropancreatic hormone (Islet amyloid polypeptide or IAPP) leads to islet transplant failure. In a healthy body, IAPP maintains energy homeostasis by regulating numerous metabolic factors such as blood glucose levels. However in a diabetic body, IAPP is prone to non-enzymatic, post translational changes, which increases its tendency to aggregate[55]. The hormone itself contains 37 amino acids and is synthesized and secreted from beta cells in pancreatic cells along with insulin. It has been found that Ca^{2+} signaling triggers the IAPP gene expression[56]. Aggregated IAPP increases the risk of AD as it leads to excessive synthesis, and therefore aggregation of AB peptide. This aggregation, as discussed earlier, leads to cognitive impairment associated with AD, such as loss of memory and spatial awareness.

Moreover, T2D may not only increase risk of AD, but also potentially vice versa. As we discussed earlier, Ca^{2+} signal-

ing is an important factor for metabolism. However, AD may additionally increase the risk for T2D because amyloid accumulation in the brain causes excess Ca^{2+} signaling, which then causes excess IAPP expression. Additionally, Ca^{2+} damages the mitochondrial structure, which causes a disruption in the communication between the insulin signaling system and mitochondria, causing impaired glucose metabolism. This ultimately leads to the progression of T2D. This leads into the role of blood glucose regulation in the brain, and the consequences of insulin resistance on the regulation.

Role of Insulin Regulation in the Brain

While much is known about the separate pathologies of T2D and AD, it is unknown if the two are linked in any way. However, there is increasing evidence of the link[57]. Moreover, unlike in peripheral tissues, insulin in the brain does not modulate glucose uptake but rather promotes many functions that are disrupted during Alzheimer's Disease progression, such as cerebral blood flow, AB clearance, tau phosphorylation, and memory formation[58]. Hence, it can be said that insulin resistance plays a role in the progression of AD. It has also been concluded that insulin resistance in the brain, with or without T2D present, is a risk factor for AD[59].

As mentioned earlier, Insulin is a peptide hormone produced by the beta cells of the pancreas, and is responsible for maintanance of blood glucose levels. It does this by facilitating how much glucose cells uptake, regulating carbohydrate, lipid and protein metabolism, and promoting cell division and growth. It is a dipeptide, containing 51 amino acides, and is synthesized by the beta cells as its precursor, proinsulin. After this, secretory vesicles transfer proinsulin from the rough endoplasmic reticulum to the golgi apparatus. Enzymes acting outside the golgi convert proinsulin to insulin. Insulin secretion is induced by the detection of increased glucose levels by an enzyme called glucokinase[60].

Insulin resistance is the altered response of insulin receptors to a given concentration of insulin. Insulin plays a significant part in the brain as this peptide and its receptor genes are abundant in neurons and glia, including neurodegeneration-targeted structures. Recent research reveals that insulin resistance triggers AB42, a type of AB peptide that only contains 42 amino acids, and has been found to be particularly toxic to the human brain. Insulin resistance has also been linked to abnormalities in tau in AD. Many preclinical studies have linked not only T2DM but also type 1 diabetes to increased tau phosphorylation, and higher levels of tau have been found in type 2 diabetic patients' cerebrospinal fluid (CSF) compared with healthy patients[61].

Structurally, insulin resistance impacts the structure of arteries in the brain as well as the physiology of blood vessels resulting in impaired blood flow. The arterial blood supply is divided into two major routes in the brain, one of which branches into the anterior cerebral artery, and the other one comes from the basilar artery, which is formed by the merge of left and right vertebral arteries. While both arteries supply blood to different parts of the brain, they do not operate independently . Intracerebral arterioles and capillaries form a component of the neurovascular unit, which is constantly communicating simultaneously between neurons, glial cells, and the vasculature in order to connect neural impulses to vascular responses[62]. In an Alzheimer's brain, neurovascular dysfunction occurs, and as stated earlier, according to the two-hit vascular hypothesis, this causes the accumulation of the amyloid beta protein. This leads to hyper-phosphorylation of the tau protein, which eventually leads to the progression of AD.

Considering that insulin has a different role in the brain and insulin resistance in the brain has different effects during Alzheimer's, the disease has been named Type 3 diabetes (T3D). T3D is characterized by the link between T1D and T2D and Alzheimer's, and occurs when neurons are unable to respond to insulin supply to the brain, which progresses the disease[63]. It is not necessarily differentiated from Alzheimer's, but it can be said that T3D describes the molecular processes that cause the phenotypes of Alzheimer's Disease. Although T3D is not an officially recognized condition, there has been a lot of debate around the topic. This is likely because while there are connections between the progression of T2D and AD, as discussed earlier, insulin functioning works entirely differently in the brain compared to other organs in the body. T3D is not an independent condition on its own, but is thought to overlap with T2D. It is important to note that T3D is not an established medical term, but a thereotical concept discussed by many researchers.

Methods of Glucose Regulation in the Brain

In order to improve outcomes of glucose regulation in AD, the treatments used for T2D and AD must be taken into consideration. Currently for diabetes, the most common form of treatment is metformin and it is usually prescribed by doctors along with lifestyle modifications. Metformin successfully decreases blood glucose levels by reducing glucose synthesis in the liver, lowering intestine absorption, and increasing insulin sensitivity[64]. Apart from its well known effect on glucose levels, it also has the potential to regulate gut microbiota, which is dysregulated by T2D.

In Alzheimer's, the most common treatment option is cholinesterase inhibitors. These drugs prevent the breakdown of acetylcholine, a chemical in the brain believed to be important for memory and thinking. However, as AD progresses, the brain produces less acetylcholine, so the drugs eventually become ineffective. The three cholinesterase inhibitors

are galantamine, rivastigmine, and donepezil[65]. All three drugs inhibit the enzyme AChE, which is the main enzyme that breaks down acetylcholine. Rivastigmine, on the other hand, targets both AChE and BuChE, another cholinesterase enzyme, in a different way than donepezil and galantamine. Although BuChE accounts for only 10% of total ChE activity in the temporal cortex of a healthy human brain, new findings using responsive histochemical techniques show that the enzyme is capable of hydrolyzing ACh and plays a larger role in normal cholinergic transmission than previously thought. Because AChE activity drops by up to 45% and BuChE activity increases by 40% to 90% as the illness advances, the relevance of BuChE in cholinergic neurotransmission is predicted to grow in AD. Rivastigmine results reveal that cognitive gains correspond independently with the suppression of AChE and BuChE in the cerebrospinal fluid[66]. Overall, the inhibitors used to treat Alzheimer's are only effective to an extent, and do not target metabolic issues present in AD.

Recent studies have found that metformin can be used in the treatment of Alzheimer's Disease. Firstly, metformin was shown to inhibit neural cell death, which is an immediate cause of Alzheimer's phenotypes[67]. Furthermore, metformin has been proven to prevent or delay the development of dementia in persons with diabetes. Researchers investigated the impact of metformin in senior adult US veterans with T2DM and neurodegeneration in 2019. According to the findings of this investigation, metformin medication for 2-4 years provides a significant risk reduction in the onset of neurodegeneration in patients with T2D when compared to individuals who do not get metformin therapy. Furthermore, research conducted at the University of Pennsylvania from 2013 to 2015 examined the effect of metformin on biomarkers of Alzheimer's disease in 20 non-diabetic persons with mild cognitive impairment or dementia attributable to the condition. To validate the diagnosis of Alzheimer's disease, MRI, FDG-PET, and amyloid biomarkers were utilized. In a crossover trial, each participant received metformin at a daily dose of 2000 mg for eight weeks, then a control drug for eight weeks, or vice versa. Cognitive performance across several learning and memory domains, as well as executive processing, focus, expressiveness, and motor speed were evaluated based on the experiment[68]. Overall, metformin was shown to be effective with preventing cognitive decline. While this is an important step forward in the study of glucose control in Alzheimer's disease, much more research is needed to clarify potential treatments for glucose dysregulation in Alzheimer's disease.

There are other antibiotics and therapies that have been used for the treatment of AD. An example is glucose specific treatment, such as Insulin Therapy. AD patients given insulin therapy have been shown to have improved memory and cognition. However, the positive affects of this method does not last through the progression of AD when AB peptide levels increase, causing an increase in insulin resistance[69]. Moreover, there are adverse side effects of this treatment, such as hypoglycemia, weight gain, and waking up with higher blood sugar levels after taking insulin before sleeping. Furthmore, some precautions that should be taken when giving a patient insulin doses are to adjust the dosage for patients with renal impairement and/or liver failure, carefully monitoring insulin and glucose levels in patients with a history of hypoglycemia, and not giving insulin therapy with other drugs[70].

Conclusion

Given that diabetes and Alzheimer's are two of the most common diseases in the world, there has been substantial study into the pathology of both diseases. However, the relationship between glucose management and improved Alzheimer's outcomes has just recently been uncovered. The primary goal of this work was to examine the relationship between the two diseases in order to establish a potential for prospective therapies that target and prevent glucose dysregulation in AD. The key findings were that there are various connections between diabetes and Alzheimer's. Moreover, the connection between insulin dysregulation and the development of AD was also highlighted. We hope that this brings awareness about Alzheimer's disease and diabetes to those who it may be useful, especially if they or loved ones are seeking treatment. For researchers and/or medical professionals, our hope is that there will be in depth research about how glucose specific therapies can be implemented in AD treatment, and that those therapies are considered when prescribing treatment for AD. Moreover, the practical information that can be drawn from this review is that there is indeed a possibility of a relationship between glucose dysregulation and AD, and on a molecular level, the relationship between AB peptide and insulin signalling is a potential starting point for understanding how to create glucose specific therapy for AD.

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