INCREASING AWARENESS OF TYPE 3 DIABETES: PRESENT AND FUTURE IMPLICATIONS

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Approval of The Dissertation

This Dissertation, by Kristen A. Rohrer has been approved by the committee members below, who recommend it be accepted by the University of Bridgeport, College of Health Sciences in partial fulfillment of requirements for the degree of Doctor of Health Sciences (D.H.Sc.)

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Abstract

Background: In the United States alone, Type 2 Diabetes is the 7th leading cause of death, with Alzheimer's Disease ahead as the 6th leading cause of mortality. While specific mechanisms have yet to be recognized by mainstream medicine, the term Type 3 Diabetes has been adopted to describe diabetes of the brain. Overarching commonalities amongst each disease include (a) oxidative stress, (b) inflammation, (c) mitochondrial dysfunction, and (d) neuroendocrine abnormalities. Collectively, these factors have been found to directly contribute to pro-death genes, impaired energy metabolism, and cerebral hypoperfusion. Yet, Type 2 Diabetes remains one of the most adjustable risk factors for the development of Alzheimer's Disease. This dissertation explores the available literature on increasing the awareness of Type 3 Diabetes in terms of present and future implications.

Methods: The review highlighted the following topics: (a) Alzheimer's disease, (b) Types 1 and 2 diabetes, (c) insulin resistance and cognitive decline, (d) Type 3 diabetes (e) ApoE(4) genetic perturbations, (f) prevention and lifestyle support for Alzheimer's disease, (g) prevention and lifestyle support for diabetes, (h) social and economic consequences of Alzheimer's disease, (I) social and economic consequences of diabetes.

Results: While AD is a complex disorder, there is a plethora of irrefutable research that supports viewing it as Type 3 Diabetes. Increasing patient education of Type 3 Diabetes and focusing on prevention strategies would decrease disease burden, increase quality of life and at the same time, save trillions of dollars in healthcare spending.

Conclusions: Since there is no pharmaceutical cure for AD, **i**ncreasing awareness of Type 3 Diabetes has the potential to provide patients with sustainable, integrative therapies, allowing them to become invested in their health choices. This will also promote individual

accountability and a sense of conscientiousness in taking back one's own health through lifestyle choices while reducing unnecessary suffering for patients, family members and society.

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Increasing Awareness of Type 3 Diabetes: Present and Future Implications

Chapter 1

Introduction

Background. Nowadays, many people are familiar with Type 1 or Type 2 Diabetes Mellitus, however, there is another form of diabetes that has just recently been identified, known as Type 3 Diabetes. This lesser-known type manifests as insulin resistance within the brain and has major potential to impact neurocognition and contribute to the etiology of Alzheimer's Disease [AD]. Type 3 Diabetes is more commonly denoted as diabetes of the brain, putting people at an augmented risk of developing AD within their lifetime. Alzheimer's Disease has already been identified as the sixth leading cause of death in the United States, and the fifth leading cause of mortality in people 65 and older (Kandimalla, Thirumala & Reddy, 2017). Unfortunately, diabetes is following right behind AD as the 7th leading cause of mortality and has been projected to affect almost 400 million people by the year 2030 (Centers for Disease Control & Prevention [CDC], 2017). At the same time, type 2 diabetes has remained one of the most adjustable risk factors for the development of Alzheimer's Disease (Pugazhenthi, Qin & Reddy, 2017).

Both diseases have been recognized to have multifactorial interactions involving both the environment and to a lesser degree, genetics. Yet, insulin insensitivity has been linked to memory deficits, cognitive decline, and many of the characteristic symptoms that have been displayed in Alzheimer's Disease (Kandimalla, Thirumala & Reddy, 2017). Evidence has also concluded that while most cases of AD are "sporadic and do not exhibit clear familial or genetic clustering" there are multiple overlapping neurodegenerative mechanisms in both diabetes and AD, leading to the discovery of type 3 diabetes (Pugazhenthi, Qin & Reddy, 2017). Specific

overarching mechanisms that have been identified include, (a) oxidative stress, (b) inflammation, (c) mitochondrial dysfunction, and (d) neuroendocrine abnormalities (Steen et al., 2005). Collectively, these factors have been found to directly contribute to "pro-death genes and signaling pathways, impaired energy metabolism, and cerebral hypoperfusion" (Steen et al., 2005).

How Are Populations Affected?

Economic & Social Consequences. In the world today, 44 million people have been diagnosed with AD, with an estimated global healthcare burden of $605 billion (Song, Bischoff, Song, Uyemura & Yamaguchi, 2017). At the same time, diabetes diagnoses have increased worldwide from "108 million in 1980 to 422 million in 2014" and have costed Americans $300 billion in 2012 alone (Song, Bischoff, Song, Uyemura & Yamaguchi, 2017). Unfortunately, AD has been projected to affect 106 million people by 2050 (Hyman, 2016). These numbers have been particularly crippling in the face of AD because we have yet to develop "efficient disease-modifying therapies" or low-cost diagnostic measures, (Chen & Zhong, 2013). There is no question that AD is a "pressing issue in today's society" that has the potential to affect every family (Chen & Zhong, 2013). If lifespan continues to increase due to pharmacological and scientific advancements in medical technology, current projections have estimated that close to 100% of people worldwide have the potential of developing cognitive decline in the form of Alzheimer's Disease at some point in their existence (Chen & Zhong, 2013). This information not only identifies the gravity of our current chronic disease crisis regarding Type 3 Diabetes, but it also pinpoints the indispensable and immediate need for preventative measures.

Newly emerging research has highlighted the importance of diagnosing prediabetes, or impaired glucose tolerance with a hemoglobin A1C level on the threshold of elevation, to

prevent progression to Type 2 Diabetes (Hyman, 2016). This research also indicates that prediabetics have an augmented risk of developing pre-dementia or mild cognitive impairment [MCI] (Hyman, 2016). Diabetics have characteristically exhibited a four-fold increased risk for developing AD (Hyman, 2016). At the same time, prediabetics are a rapidly rising subgroup in the development of pre-dementia symptoms including sporadic forgetfulness, memory loss, and deficiencies in performing everyday tasks (Hyman, 2016). Unfortunately, today, it is very commonplace for families to utilize outside care for once thriving members of society, contributing to both the economic burden of disease, but also psychological stress from all sides. The most debilitating aspects have traditionally involved loved ones who fail to recognize family members or the need to sell all possessions to pay for care. Afflicted individuals perceived as "slipping away" have a significantly reduced quality of life while families are forced to drain household resources. Other major consequences include gradual loss of autonomy coupled with no home, very few personal possessions and a healthcare system that has yet to provide any effective clinical treatment. The emotional anguish and stress on family members forced to make these difficult decisions while watching a loved one suffer has the potential to contribute to even more detrimental health outcomes in the process.

Immediate Need for Improvement. AD has been identified as the most common form of dementia, affecting nearly 15 million Americans by the year 2050 (Song, Bischoff, Song, Uyemura & Yamaguchi, 2017). At the same time, Type 2 Diabetes has been projected to reach epidemic numbers within the next decade (CDC, 2017). The identification of preventative strategies has the capacity to alleviate a significant amount of death, unnecessary suffering and financial burden for all of humankind (Song, Bischoff, Song, Uyemura & Yamaguchi, 2017). According to Song et al. (2017), unhealthy lifestyle choices that (a) perpetuate the inflammatory

cascade (b) induce insulin resistance, and (c) provoke oxidative stress have been identified as "the most significant risk factors for AD" (p. 42). It has also been established that while genetic predispositions in ApoE(4) allele variations may play a role in the etiology of AD, this traditionally has accounted for "5-7% of all cases worldwide" leaving the other 93 to 95% attributable to the interplay between multifactorial environmental complexities as epigenetic mediators (Wang & Ding, 2008).

On the same note, it has been well ascertained in the literature that Type 2 Diabetes is largely preventable (CDC, 2017). While the specific mechanisms between AD and all forms of diabetes remain convoluted and unclear, increasing the awareness of AD as a third form of diabetes has the potential to provide a plethora of proactive and therapeutic strategies to current patients. These include prevention through weight control, healthy lifestyle choices that can reduce AGE formation and anti-inflammatory nutritional support to thwart the oxidative cascade both systemically and within the brain (Wang & Ding, 2008). This realization also identifies the need for patient education in prediabetic phases as a proactive approach against chronic disease etiology (Wang & Ding, 2008). According to Hyman (2016), in order to properly target such a multifaceted disease, all contributing factors must be addressed when developing patient protocol and these include (a) addressing hormonal imbalances, (b) reducing inflammation through diet and lifestyle, and, (c) preventing disease progression through proper neuronal support.

AD has been associated with conspicuous diminutions in both insulin and IGF-1 mRNA expression and "downregulation of the corresponding receptors" within the brain (Steen et al., 2005). This suggests that a different or more multifaceted disease process within the CNS may provoke these outcomes, hence the term "Type 3 Diabetes" (Steen et al., 2005). Increasing evidence has also identified oxidative stress, mainly due to excessive formation of free radicals,

as a main contributor to the "pathogenesis of neuron degeneration" (Markesbery & Carney, 1999). Type 3 Diabetes has been recognized in conjunction with a diagnosis of AD because of the communal mechanisms among Type 1, Type 2 Diabetes Mellitus and AD, particularly due to the breakdown in the "action of glucose absorption in the neurons for energy production" (Kandimalla, Thirumala & Reddy, 2017). These interconnected physiological mechanisms include inflammation as a hallmark feature, mainly neuroinflammation in relation to AD and systemic inflammation characteristic of diabetes (Silzer & Phillips, 2018). Interestingly enough, increased oxidative stress measured through lipid peroxidation products has been identified as a potential measurement tool in identifying patient risk factor for AD development (Silzer & Phillips, 2018). This, along with mitochondrial distress, coupled with the natural effects of aging have all been hypothesized to precipitate hyperphosphorylation of tau protein and neurofibrillary tangles also deemed as classic signs of AD in postmortem research (Silzer & Phillips, 2018). Therefore, treating AD as a disease of diabetes-like complexities that manifests in the brain may have the potential to reveal powerful therapies in combating this debilitating and progressive condition (Silzer & Phillips, 2018).

Since Type 2 Diabetes is preventable and reversible, this information has the potential to open the door for proactive and preemptive approaches that target the overlapping mechanisms described in this dissertation (Kandimalla, Thirumala & Reddy, 2017). Therefore, improvements in targeting the causative inflammatory mechanisms of AD will be crucial in thwarting the progression of the disease. One such improvement can begin in the medical community with recognizing that cognitive decline and progressive brain damage can begin with prediabetes and chronic insulin resistance (Hyman, 2016). Along with increasing awareness for the term, Type 3 Diabetes, recognizing that the brain and the body are "one elegant and symbiotic unit" can help

reveal the detrimental and shared impacts that poor lifestyle choices can have on both the body and the brain (Hyman, 2016). It is also crucial to increase both patient and clinician education as proactive tools in developing sustainable and effective therapeutic interventions before neurological damage has time to progress (Malik et al., 2012).

Key Terms

The following definitions are illustrated to ensure uniformity and understanding of these terms throughout the dissertation.

Advanced glycation end products (AGEs): Also known as glycotoxins, which are a distinct group of highly oxidant compounds with pathogenic significance in chronic diseases, specifically diabetes (Uribarri et al., 2010).

Alzheimer's disease (AD): A degenerative brain disease named after Dr. Alois Alzheimer characteristic of irreversible, progressive memory loss. Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain, resulting in premature neuronal death (National Institutes of Health [NIH], 2016).

Diabesity: A term used to suggest a causal pathophysiological link between obesity and type 2 diabetes (Amen, 2015).

Insulin resistance: A condition characterized by the inability of the body to respond to and use the insulin it produces. It is associated with hypertension and obesity (CDC, 2014).

Neurofibrillary tangles (NFTs): These insoluble, jumbled masses are made up of abnormal proteins and twisted fibers that are typically seen in postmortem AD diagnoses (Bright Focus Foundation, 2017).

Persistent Organic Pollutants (POPs): Long-lasting chemical toxins that are transported by wind and water that adversely affect human health and the environment (Kovner, 2009).

Receptor for advanced glycation end products (RAGEs): A prime member of the immunoglobulin family of molecules that has multiple ligands and has been identified to play a crucial role in chronic disease pathology including diabetes, cancer, heart disease and AD (Pugazhenthi & Reddy, 2017).

Tau: Microtubule-associated proteins fostering the formation of characteristic neurofibrillary tangles and neuritis in Alzheimer's disease (Steen et al., 2005).

Type 1 Diabetes Mellitus: Also known as Juvenile diabetes or rapid onset. A condition characterized by high blood glucose levels caused by lack of insulin production due to autoimmune targeting of the insulin-producing beta cells in the pancreas (CDC, 2014).

Type 2 Diabetes Mellitus: A condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently (CDC, 2014).

Type 3 Diabetes Mellitus: An emerging term describing Alzheimer's disease as a form of diabetes that selectively implicates the brain and has molecular and biochemical features that overlap with both type 1 and type 2 diabetes mellitus (de la Monte & Wands, 2008).

Research Rationale

We currently live in an era classified as a healthcare crisis where wait times to see a primary care provider are at an all-time high. There are major shortages in the healthcare workforce, and current practitioners are overworked and overstressed. In fact, the typical time spent with a doctor lasts roughly 9 minutes, leaving very little time for patient insight, disease-

specific education or even the answering of any pertinent questions (See Appendix A), (Gold, 2014).

The detrimental effects of quantity over quality regarding patient care has created a mechanical-like reactive response to disease management through deferment-strategies that have typically hinged on disease recurrence or the development of severe disease (Hu, 2016). Prevention and implementation of subsequent approaches have become subordinate, inferior concepts partly due to the overwhelming numbers of patients requiring care. However, this area has greatly contributed to the relevance and potential of increasing awareness of Type 3 Diabetes as research has been built on the premise of providing patients with the tools to take back their own health (Hu, 2016).

Presently, there is no greater need than to provide some sustainable, proactive approaches to a problem projected to afflict most people within their lifetime, especially since aging has been identified as the number one risk factor for AD (Leszek et al., 2017). By the year 2030, 12% of the population will be considered elderly (Leszek et al., 2017). At the same time, Type 2 Diabetes has become a worldwide emergency that continues to decimate both the healthcare system in general and the economy of every nation (Leszek et al., 2017). Due to the lack of effective strategies in AD management, research has focused on specific molecular foundations that contribute to AD pathology, which has revealed the potential of AD as a brain-specific, third type of diabetes (De Felice et al., 2014). Increasing awareness of Type 3 Diabetes has the possibility of providing effective therapeutic strategies to millions of people suffering from AD or any range of cognitive decline. This is hugely relevant because modern medicine has few treatments for AD, none without major side effects, and we have yet to identify any long-term treatments successful in preventing disease progression.

As chronic diseases like diabetes and AD continue to rise to epidemic proportions, preventative measures remain vital players in the fight against the current reactive healthcare cycle. According to Castelnuovo et al. (2014), nutrition persists as a fundamentally influential factor when it comes to disease etiology, prevalence, incidence and prognosis. Raising awareness of Type 3 Diabetes as a disease with largely modifiable risk factors can empower an individual with the knowledge and the tools to forecast his or her own individual health based on proactive information, screenings, and lifestyle education (Hu, 2016). This empowered patient will then make lasting and sustainable changes to achieve health instead of becoming a casualty of a system that leads to predisposed healthcare destinies like AD with no effective protocol (Bashshur et al., 2014).

Purpose of the Research

AD diagnoses are expected to upsurge exponentially within the next few years and will continue stalling an already overly taxed healthcare system. With this in mind, increasing the awareness of a biochemical link between AD and type 2 diabetes can have serious health implications for current and future generations. Moreover, emerging evidence links prevention as a key factor in reducing disease prevalence by fostering patient education, empowerment and improving access for underserved populations (Bashshur et al., 2014). This just may be what the doctor ordered in reducing disease pervasiveness, adopting preventative strategies and increasing awareness of Type 3 Diabetes, which is the main purpose of this research.

Examining this evidence is an objective of this paper, along with identifying the potential of multitargeted Type 3 Diabetes therapies as the foundation for effective disease management. Pharmaceutical interventions will be explored that convalesce insulin sensitivity, thanks to their success in the treatment, reversal and prevention of Type 2 Diabetes (De Felice et al., 2014).

This literature review will also include the possibilities of non-pharmaceutical approaches like diet, exercise, and anti-inflammatory lifestyle choices. Based on the current evidence identifying Type 2 Diabetes as largely preventable and reversible, a major goal of this research is to discover the implications this information has going forward for Type 3 Diabetics.

Other research questions that will be explored in this dissertation include:

1. What are the current and future implications of increasing the awareness of the term Type 3 Diabetes?
2. What are some recommendations for proactive therapeutic approaches to Type 3 Diabetes?
3. What are the overlapping neurodegenerative mechanisms that explain the term Type 3 Diabetes?
4. Why should Type 3 Diabetes be more widely accepted?
5. How are ApoE(4) genetic carriers specifically affected regarding faulty insulin signaling?
6. Should ApoE(4) screening be incorporated for Type 2 Diabetics and possibly prediabetics?
7. If Type 2 Diabetes is preventable and reversible, what promise does this have for Type 3 Diabetes and the stages of cognitive decline?
8. What does the research reveal about AD patients without Type 2 Diabetes?
9. How can future research take advantage of the term Type 3 Diabetes in developing effective strategies for the progressing stages of AD?

This research intends to demonstrate the powerful effects of recognizing AD as Type 3 Diabetes and to present the current evidence-based literature. The hope is for the medical community to accept this term so that going forward, effective therapies can be adopted for every

stage of the disease. While providing the current evidence in the field of Type 3 Diabetes, this dissertation will also deliver recommendations and possible solutions to the problem in order to identify the importance of viewing the disease as a manifestation of multifaceted mechanisms. This information will allow the birth of treatment options that have the potential to be developed. At the same time, it will also provide a deeper understanding of disease pathology so that proactive approaches can reduce pain, suffering and overall disease burden. Most importantly, a final purpose is to provide evidence to current patients who have been waiting anxiously for effective clinical interventions, and to deliver hope for relief with the potential for improvements in quality of life.

Chapter 2

Review of Literature

Alzheimer's Disease and Insulin Resistance

This literature review addresses Alzheimer's Disease, the well-established links between neurodegenerative disease and Type 2 Diabetes, and the potential for increasing awareness of Type 3 Diabetes. Due to the overlapping yet distinct pathological features among diabetes, insulin resistance and cognitive decline, multitargeted drug therapies along with lifestyle interventions are also explored (Kandimalla, Thirumala & Reddy, 2017, p. 1078). Extensive amounts of current literature have recognized the increased risk factor for the development of Alzheimer's Disease in people with Type 2 Diabetes and correlations have suggested roughly half or more of all diabetics will develop some form of cognitive decline (Heerema, 2018). Both diseases have been recognized to have multifactorial interactions involving both the environment and to a lesser degree, genetics. Yet, insulin insensitivity has been linked to memory deficits, cognitive decline, and many of the characteristic symptoms that have been displayed in Alzheimer's Disease (Kandimalla, Thirumala & Reddy, 2017). Evidence has also concluded that while most cases of AD are "sporadic and do not exhibit clear familial or genetic clustering" there are multiple overlapping neurodegenerative mechanisms in both diabetes and AD, leading to the discovery of type 3 diabetes (Pugazhenthi, Qin & Reddy, 2017). While associations are complex and severity is dependent upon (a) the extent of inflammation (b) insulin resistance, and (c) other subjective environmental factors, there have been patients that develop Alzheimer's disease without prior diabetic diagnoses (de la Monte & Wands, 2008, p. 1105). This may be because thousands of people have gone undiagnosed with diabetes for

many years, or in some people, the effects of insulin resistance may remain relatively sequestered to the neural tissues of the brain (de la Monte & Wands, 2008, p. 1105).

Alzheimer's disease can be diagnosed with greater than 85% accuracy via postmortem identification of neurofibrillary tangles, amyloid precursor proteins and plaque deposits in specific regions (de la Monte & Wands, 2008). This has led to the discovery of diabetes-like malfunctions in the brains of AD patients that may embody a "brain-specific form of diabetes mellitus" or Type 3 Diabetes (de la Monte & Wands, 2008). Mounting postmortem evidence has seemed to classify AD as a selective form of diabetes involving the brain with the potential for "molecular and biochemical features" that intersect with Type 1 and Type 2 Diabetes (de la Monte & Wands, 2008). These features have been shown to diminish normal neuronal pathways over decades and "contribute to cognitive decline" while compromising quality of life (Pugazhenthi & Reddy, 2017). It has been established that weakened dynamics within metabolism have positive associations with "AD-related pathology in humans" (De Felice et al., 2014). The metabolic parameters most implicated have included hyperglycemia, hyperinsulinemia and more specifically, faulty pathways within insulin signaling that has the potential to leave the brain starved for energy (De Felice et al., 2014). The exact connections between this interplay have yet to be elucidated but have been hypothesized to lie within the hippocampus, which serves as the memory center of the brain (De Felice et al., 2014). From what we know about healthy cognitive functioning, the hippocampus can generate roughly 700 new hippocampal stem cells daily (Amen, 2015). This is important to consider regarding AD and Type 3 diabetes because through environmental considerations, we have the power to either grow or shrink neuronal tissues that directly influence memory and cognition (Amen, 2015). Neurogenesis is no longer a hypothetical notion but a proven phenomenon under the proper

conditions, which means that it is possible for people to regrow brain cells even in AD-related pathology (Amen, 2015). At the same time, certain conditions foster the continuation of premature cell death and further cognitive decline.

Why Type 3 Diabetes Should Be Widely Accepted

Diabetes Distinctions. Type 1 Diabetes is associated with a complex pathology in which autoimmune reactions target pancreatic beta-cells, severely diminishing or halting insulin production altogether (Boles, Kandimalla & Reddy, 2017). This results in insulin resistance and the need for lifelong support in the form of exogenous insulin (Boles, Kandimalla & Reddy, 2017). Patients diagnosed with Type 1 Diabetes have characteristically shown increased glutamic acid decarboxylase [GAD] activity, which functions as an "autoantigen" in the brain and pancreas (Boles, Kandimalla & Reddy, 2017). Heightened GAD action has also been known to perpetuate the autoimmune response through inflammatory responses within the brain (Boles, Kandimalla & Reddy, 2017). Individuals who have been diagnosed with Type 2 Diabetes have "blood sugar levels that are higher than normal" along with insulin resistance and deficiency and an augmented risk factor for the development of other chronic diseases, most notably, AD (Boles, Kandimalla & Reddy, 2017). Persistently high glucose levels have been shown to take a major toll on every organ system by reducing normal signaling and starving healthy cells from receiving the appropriate fuel for survival (Boles, Kandimalla & Reddy, 2017). Type 2 Diabetes has been identified as a major 21st century problem with detrimental implications for the heart and vascular system, the kidneys, the liver, and most recently, the brain.

Type 3 Diabetes is a form that distinctly affects neurocognition within the brain. Like Type 2, it has been linked to "metabolic derangements of carbohydrates, lipids, proteins" coupled with cognitive decline in the presence of excessive oxidative stress from insulin

resistance and faulty mitochondrial signaling within the brain (Mittal & Katare, 2016). Type 3 Diabetes has also been identified in the phosphorylation of tau proteins through increased glycogen synthase kinase signaling leading to mitochondrial malfunction and significant decreases in energy production (Mittal & Katare, 2016). Consequences include premature neuronal death and the cognitive degeneration exhibited in AD (Mittal & Katare, 2016).

Diagnosis of Type 3 Diabetes. Both Type 1 and Type 2 Diabetes can be definitively diagnosed by measuring fasting glucose and glycated hemoglobin to detect hyperglycemia (Amen, 2015). However, multiple indicators coupled with clinical observations must be utilized to ultimately diagnose Type 3 Diabetes, mainly because it is related to insulin resistance within the brain. Metabolic markers that can point to a potential Type 3 Diabetes diagnosis include utilizing many of the same markers that confirm a Type 2 Diabetes diagnosis, like fasting glucose and glycated hemoglobin to examine blood sugar levels (Hyman, 2016). Symptoms and clinical observations that can be used in identifying Type 3 Diabetes include prolonged memory loss or decline (beyond mere forgetfulness), an assessment of independent function, memory assessment in planning, judgement, and key thinking skills (Amen, 2015). Brain imaging and/or neuropsychological testing can also shed light on structural deficits within the brain itself that can be characteristic of Type 3 Diabetes (Amen, 2015). Serum C-peptide as a measure of insulin production may be one of the best indicators for insulin resistance, yet it is often overlooked by mainstream medicine (Zanardini et al., 2018). According to Zanardini et al. (2018), high levels of C-peptide along with high fasting insulin levels are associated with an increased risk of neurodegenerative disease.

The downstream and detrimental effects of untreated diabetes on the vascular system have been well documented in the literature. Yet, many times, researchers leave the vascular

system of the brain out of the equation when examining systemic outcomes (Amen, 2015). At the same time, the vessels of the brain may be even more fragile and reactive to hyperglycemia and insulin resistance than the vessels within the extremities (Amen, 2015). Because of this, brain imaging tests like MRIs or CT scans can provide a picture of the vasculature of the brain (Amen, 2015). Cerebrospinal fluid samples can also reveal inflammatory peptides circulating within the central nervous system that precipitate AD (Amen, 2015). People with symptoms of Type 2 Diabetes who have symptoms of poor memory, declining cognition, and unexplainable brain fog can be educated on the connections between brain health and optimal blood sugar levels in managing their diabetes and at the same time, slow the progression of AD (Amen, 2015).

According to a study from the University of Pennsylvania Perelman School of Medicine, insulin resistance may be the single most important contributor to cognitive decline "above and beyond other known causes of AD" (2012). This information makes diagnosing Type 3 Diabetes much more feasible particularly in people who have already been diagnosed with Type 2 Diabetes. At the same time, this study found evidence of insulin resistance in non-diabetics "hence the absence of hyperglycemia outside the brain" (Arnold & Talbot, 2012). This may illustrate a brain-specific phenomenon in glucose uptake for cellular "growth, survival, remodeling and functioning" (Arnold & Talbot, 2012). Evidence identifying the need for normalization or re-sensitization of brain cells to insulin may hold the key to "slow down, prevent or perhaps even improve cognitive decline" (Arnold & Talbot, 2012). This information combined with the utilization of other inflammatory biomarkers like C-reactive protein, can shed light on the extent of the inflammatory cascade in relation to the neurological microenvironment (Amen, 2015). This is all vital information in the diagnosis of Type 3 Diabetes in people who

may not have systemic blood sugar problems, which may explain the need for genetic screening to identify potential ApoE(4) carriers who demonstrate severe malfunctions in insulin signaling (Arnold & Talbot, 2012). Genetic predisposition is expanded upon further in the literature review, along with Type 3 Diabetes in non-diabetics.

Pharmaceutical connections. Alzheimer's Disease and diabetes have also been linked from the perspective of research in the pharmaceutical industry. Recent discoveries have revealed that diabetes medications from the thiazolidinedione class "have intrinsic neuroprotective and anti-inflammatory effects" along with the capacity to reduce brain-related insulin resistance (De Matos, De Macedo & Rauter, 2017). While metformin has been traditionally associated with cognitive decline and stress-induced oxidative damage in Type 2 Diabetics, current research in mice has challenged these prior findings (See Appendix B) (De Matos, De Macedo & Rauter, 2017). De Matos, De Macedo and Rauter (2017) have found that metformin has the potential to "exert neuroprotective effects, being able to prevent scopolamine-induced cognitive impairment" and brain damage in rats. Though the need for larger clinical trials in humans is required before drawing fixed conclusions, intranasal insulin has shown promise in vivo (De Matos, De Macedo & Rauter, 2017). Specific research shows perception improvements in ApoE(4) carriers "with mild cognitive impairment or early AD stage" (De Matos, De Macedo & Rauter, 2017). Galantamine, which has been approved by the FDA for AD treatment, has also been indicated as a "potential antidiabetic agent" since it has shown potential to improve "insulin signaling pathways, lipid metabolism, and beta cell function" with multitarget potential (See Table 1, Appendix C), (de Matos, de Macedo & Rauter, 2017).

At the same time, metformin drugs come with a slew of nutritional depletions and side effects like abdominal pain, anxiety, painful urination and general discomfort (de Matos, de

Macedo & Rauter, 2017). Berberine, a natural alterative to metformin, has natural glucose-lowering properties and research has even identified it as a possible anti-diabetic agent (Cai, Wang & Yang, 2016). According to Cai, Wang and Yang, berberine exhibits beta-amyloid clearing by lowering the "activity of beta-site amyloid precursor protein cleaving enzymes" (2016). Berberine can easily pass through the blood brain barrier, target and clear beta-amyloid plaques and exhibit neuroprotective effects (Cai, Wang & Yang, 2016). This prevents neurodegeneration, particularly in the hippocampus, which is extremely susceptible to cellular impairment (Cai, Wang & Yang, 2016).

While Alzheimer's Disease was originally discovered in 1906 by Dr. Aloysius Alzheimer, very few pharmaceutical advancements have been made in prevention or disease treatment protocol (Stein, Schettler, Rohrer & Valenti, n.d.). At the same time, we have expanded our knowledge of brain neurochemistry particularly within the last decade. We now know that brain scans of people with chronically high levels of blood glucose show detrimental effects within various structures of the brain, predominantly the hippocampus, or the memory center of the brain (Kerti et al., 2013). Deficits in both short-term and long-term recall have been established as hallmark symptoms of cognitive decline, as identified by Dr. Alzheimer in his initial protocol for suspected patients (Stein, Schettler, Rohrer & Valenti, n.d.). This phenomenon has even been identified in people without a formal Type 2 Diabetes diagnosis and has suggested that the hippocampus is particularly susceptible to instabilities in glucose regulation (Kerti et al., 2013).

Overlapping Neurodegenerative Mechanisms

Oxidative Stress and AGEs. Alzheimer's Disease represents the largest field where oxidative stress has been extensively examined (See Appendix D), (de Matos, de Macedo &

Rauter, 2017). According to Markesbery and Carney (1999), the accumulation of free radical damage within the brain has been implicated for some time in premature neuronal death and plays a major role in AD pathogenesis (p. 133). Postmortem examinations have collectively revealed "increases in lipid peroxidation, a decline in polyunsaturated fatty acids (PUFA)" along with augmented oxidation of proteins (Markesbery & Carney, 1999). All of the individual mechanisms collectively lead to a discernable deterioration of enzymatic functioning (Markesbery & Carney, 1999). This is showcased through various functional biomarkers measuring DNA oxidation, most specifically, hyperoxidation of 8-hydroxy-2'-deoxyguanosine (Markesbery & Carney, 1999). The study utilized organic acids testing (OAT) for this marker, which has the ability to provide information about biochemical imbalances within the body by measuring urinary metabolic byproducts (Markesbery & Carney, 1999).

Steen, et al. (2005), has suggested that oxidative damage reduces the ability of the brain to properly utilize glucose, mainly through weakened signaling in insulin and insulin-like growth factor types I and II within the central nervous system [CNS] (p. 64). Since neuronal death perpetuates the loss of the ability of the CNS to produce appropriate growth factors, insulin expression is greatly reduced, potentially favoring the development of tau mRNA and amyloid precursor proteins as compensatory mechanisms (Steen et al., 2005). This oxidative cascade has elicited characteristics similar to diabetes (Steen et al., 2005) However, in many patients who never had diabetes, the phenomenon remained sequestered to the brain, distinct from both Type 1 and Type 2 Diabetes (Steen et al., 2005).

Hyperglycemia and dyslipidemia have been identified as hallmark features of diabetes and in many cases, precede AD (Silzer & Phillips, 2018, p. 17). At the same time, accumulation of advanced glycation end products [AGEs] has been detected in diabetic animals and in humans

through postmortem analyses (Pugazhenthi & Reddy, 2017, p. 1039). AGEs have been established as glycotoxins or oxidized compounds created excessively through the Maillard reaction (Uribarri et al., 2010). They are also produced as a result of normal metabolic processes and their accumulation has been associated with pathologic inflammatory effects in diabetes (Uribarri et al., 2010). In a state of chronic inflammation where most antioxidant stores have been exhausted, AGEs accumulate and perpetuate the inflammatory cycle by inducing the formation of fibrillary tangles and amyloid plaque found in AD (Pugazhenthi & Reddy, 2017).

According to a systematic review by Pugazhenthi and Reddy (2017), AGE formation provokes an upsurge in the inflammatory receptor known as RAGE (receptor for advanced glycation end products). RAGE has been identified as a "putative receptor for excessive tau phosphorylation" which decreases the brain's capacity to clear Aβ proteins (p. 1039). According to Silzer and Phillips (2018), oxidative stress "via measurement of specific lipid peroxidation products" has been detected in patients with notable cognitive decline prior to recognition of the "classic indicators of AD" (p. 17). These metabolic end products have emerged as important biomarkers for early detection, even in dementia patients without diagnosed diabetes (Silzer & Phillips, 2018). AGEs have also been shown to enhance vascular cell adhesion in "endothelial cells and subsequent inflammation" while aggravating arteriosclerotic conditions (Shinohara & Sato, 2017). Of particular interest is this exact phenomenon in "acceleration of vascular injury" within the brain in hypertensive patients since hypertension is another diagnosis of which half of all diabetics experience (Shinohara & Sato, 2017).

While prior research has undoubtedly uncovered the toxic nature of high levels of AGEs in both the serum and cerebrospinal fluid, very little research has investigated specific links between AGEs and AD (Leszek et al., 2017). With this being said, AGEs have been detected

within neurofibrillary tangles, which have been concomitant in the pathogenesis of AD (Leszek et al., 2017). At the same time, it has been well founded that Type 2 Diabetics have extremely high levels of AGEs in systemic circulation based on serum markers, leading to further correlation between AD, AGEs and Type 2 Diabetes (Leszek et al., 2017). This has provided additional evidence in connecting the dots between each phenomenon, which may hold the promise for exposing the complexities in each etiology while revealing concurrent manifestations.

Mitochondrial Dysfunction. The mitochondria have been established as the powerhouse of the cell, responsible for metabolism, cellular signaling, and apoptosis when damage occurs (Chornenkyy, Wang, Wei & Nelson, 2018). For these reasons and as a central player in energy metabolism, mitochondrial dysfunction plays a crucial role in the pathogenesis of AD and diabetes (Chornenkyy et al., 2018). According to Baloyannis (2006), "mitochondrial mass, size and copy number" have been shown to be decreased in the brains of AD patients." However, the most fascinating evidence has revealed a reciprocal relationship between mitochondrial diversity and β-amyloid peptide deposits (See Appendix E), (Lee et al., 2018). This suggests a detrimental effect, mainly increased "mitochondrial membrane permeability" in the presence of β-amyloid deposits (Baloyannis, 2006). Also indicated is the potential for a "self-propagating cycle with increasing β-amyloid peptide production" and deteriorating mitochondrial functionality (Baloyannis, 2006).

In well-balanced neural cells, impaired mitochondria are distinctly recognized and degraded "via an autophagy pathway" known as *mitophagy* (Chornenkyy et al., 2018). This process is triggered by standard signaling within and among cells as an innate quality control mechanism (Chornenkyy et al., 2018). In the early stages of AD, mitophagy has been shown to

be upregulated which decreases clearance of autophagic substrates (Chornenkyy et al., 2018). Mitochondrial homeostasis is also disrupted, favoring the production of tau and β-amyloid deposition via compensatory pathways (Chornenkyy et al., 2018). Mitochondrial dysfunction has been identified as a hallmark feature in both diabetes and Alzheimer's etiology (Silzer & Phillips, 2018). Instead of viewing these diseases as 'copathologies' this research shows the need to view mitochondrial abnormalities as a root cause. With this being said, mitochondrial support may provide a therapeutic strategy for both AD and Type 2 Diabetes (Silzer & Phillips, 2018).

Inflammation. Proinflammatory cytokines (through markers such as C-reactive protein and IL-6**)** have been identified in "CSF and β-amyloid plaques" of postmortem AD patients (Chornenkyy et al., 2018). These markers are also amplified in diabetes diagnoses and have generally been associated with cognitive impairments (Chornenkyy et al., 2018). Proinflammatory particles have even been linked to "inducing a prothrombotic state" by triggering "vascular events leading to brain infarction," hence their direct and detrimental influence on cognition (Marioni, Strachan, Reynolds, Lowe, Mitchell, & Fowkes, et al., 2010). Neuroinflammation has been identified as "a main contributor to the AD pathogenesis" and according to de Matos, de Macedo and Pilar Rauter (2017), underlying inflammation has been isolated as a culprit in amyloid plaque formation, extreme oxidative cycles, endothelial malfunction, enzymatic signaling along with possible genetic connections. Certain individuals may be more genetically susceptible to higher inflammatory markers, like interleukin-6 (IL-6) due to single nucleotide polymorphisms (Feng et al., 2014). Based on research from Feng et al. (2014), serum levels of IL-6 "were found to be significantly higher with genotypes containing the G allele in healthy subjects." This has suggested that there is a genetically predetermined

dissimilarity in the degree of IL-6 measurements in individuals and highlights the importance of genetic markers as potential inflammatory indicators (Feng et al., 2014).

Pharmaceutical implementations including metformin have been criticized and linked to the possible perpetuation of cognitive decline (de Matos, de Macedo & Pilar Rauter, 2017). This highlights the need for more research in disease prevention and anti-inflammatory strategies (de Matos, de Macedo & Pilar Rauter, 2017). Ferreira, Clarke, Bomfim and De Felice (2014) have identified the term "inflamm-aging" in the etiology of both AD and diabetes. This underscores the immediate requirement for preventive strategies targeted at alleviating inflammatory mediators and thwarting the inflammatory cascade from a metabolic perspective. Increasing awareness of Type 3 Diabetes from a clinical perspective can support the proactive notion of preventative medicine through early screening and patient education. Diagnostic measures for confirming Type 3 Diabetes are discussed on page 22 of the literature review.

Diabesity. In our modern society, roughly 40% of Americans are considered obese (CDC, 2017). This statistic combined with the current diabetes epidemic has birthed the term *diabesity*, particularly considering recent findings of the reciprocal relationship between weight gain and brain size in humans (Amen, 2012). According to the research, waist-to-hip ratio is inversely correlated with hippocampal size, which stands as the memory processing center of the brain (Amen, 2012). At the same time, overweight people in the study had 4% less brain volume than healthy controls with a biological brain age eight years older than the patient's chronological age (Amen, 2015). When brain scans of obese subjects were compared to healthy controls, they revealed 8% less brain volume with biological brain ages that averaged nearly 16 years older than the subjects' chronological ages (Amen, 2015). The connections lie within the prefrontal cortex which has shown decreased function along with hippocampal atrophy as weight

increases (Amen, 2015). Of interest is the notion that fat on the body stores toxins and increases inflammatory cytokines. Diabesity combined with genetic predisposition has the power to damage the entire vasculature, including blood vessels within the brain (Amen, 2015). This leads to ongoing brain damage in the form of premature cell death and the exact inflammatory cascade showcased in AD (Amen, 2015).

Neuroendocrine Abnormalities. Nearly a century ago, Sir Harold Himsworth observed the declining relationship between "insulin resistance and central nervous system function" (Cholerton, Baker & Craft, 2011). Insulin has since been dubbed the "master regulator of corporeal ageing in all known species" and has also been linked to systemic expression of ageing, specifically in the brain (Cholerton, Baker & Craft, 2011). It is also well known that insulin works as a transport mechanism of the amino acids tryptophan and tyrosine in crossing the blood brain barrier (Cholerton, Baker & Craft, 2011). These building blocks directly regulate the neurotransmitters serotonin and dopamine, which work together to regulate excitatory impulses within the brain. Cognitive decline has been associated with diminished insulin efficiency either from deficient cellular response or "reduced insulin transport across the blood-brain barrier (Cholerton, Baker & Craft, 2011). Normally, insulin has the ability to cross the blood brain barrier through transcytosis in order to reach different regions throughout the brain (Ferrannini et al., 1999). However, chronically high insulin production propagates excitatory impulses "to the sympathetic nuclei" while binding receptors that stimulate the systemic stress response through cortisol and prolactin release (Ferrannini et al., 1999).

Based on original research from Steen et al. (2005), postmortem brain tissue in patients with diagnosed AD has demonstrated significant reductions in "insulin and IGF-1 receptor expression levels in AD frontal cortex, hippocampus and hypothalamus" (p. 75). A majority of

the samples examined showed no significant observational changes to the cerebellum (Steen et al., 2005). These changes have been investigated beyond the downstream manifestation of neuronal death, demonstrating the connection between impaired signaling and neurodegeneration (Steen et al., 2005). This research has pointed to abnormalities at the receptor-level regarding insulin expression, "which may have future therapeutic implications" (Steen et al., 2005).

It has also been well established that insulin or IGF-1 has the ability to upregulate or downregulate tau phosphorylation (Steen et al., 2005). This is a precipitating factor in the accumulation of neurofibrillary tangles in the pathogenesis of AD (Steen et al., 2005). While high peripheral insulin levels in relation to AD development have been established as a common risk factor for neurodegeneration, not every AD patient has been or will be diagnosed with diabetes (Steen et al., 2005). However, "a clear relationship has been established between impaired insulin signaling and premature neuronal death, which reveals a selective disparity localized to the brain, which may indicate type 3 diabetes" (Steen et al., 2005). Retrospective research has proposed that senile plaque formation is analogous among patients with both AD and diabetes as well as in patients with AD absent of diabetes (Shinoharo & Sato, 2017).

Peripheral glucose metabolism has been a particular field of interest, specifically regarding impairments in CNS control of glucose levels in patients with AD (Ngandu et al., 2015). A large, randomized, controlled trial identifying lifestyle and dietary interventions in patients with dementia demonstrated "improvements in cognitive function" in at-risk populations (Ngandu et al., 2015). These results directly reveal "bidirectional interactions" between AD and diabetes (Ngandu et al., 2015). According to the Baltimore Longitudinal Study of Aging autopsy cohort investigation, glucose metabolism "is affected early in AD" and findings have revealed "neural insulin resistance" (An, Varma, Varma, Casanova, Dammer, Pletnikova et al., 2018).

The acuteness of AD pathology may hinge on GLUT3 levels. For instance, the lower the levels, the more severe the AD symptoms (An et al., 2018). Duran-Aniotz and Hetz (2016) found that "overexpression of GLUT-1" improves glucose metabolism and reduces AD-associated cognitive alterations. This indicates the possible therapeutic effect of restoring normal glucose metabolism within the brains of AD patients. While these findings were exhibited in drosophila species, more mammalian studies are needed to demonstrate connections. At the same time, it is well established that the pathology of AD occurs decades before clinical onset. Conclusions of this study identify the need to define specific mechanisms behind failure of glucose transporters within the brain and not just compensatory mechanisms like plaque formation or tau phosphorylation (Duran-Aniotz & Hetz, 2016).

The notable downstream effects of chronic insulin resistance are of particular importance for current and prospective research. Research continues to shed light on "the weakening of insulin transition by the blood brain barrier" and possibly, the facilitation and modulation of tau-protein formation due to activation of insulin resistant reductions in phosphorylating kinase activity (Leszek et al., 2017). The literature shows that insulin resistance itself leads to (a) mitochondrial abnormalities, (b) oxidative stress, (c) "reductions in synaptic plasticity in the hippocampus" (Leszek et al., 2017). Research also shows that these effects are greatly exacerbated with the natural aging process coupled by a sedentary lifestyle and lack of proper nutrition (Leszek et al., 2017). However, the positive aspect of this literature reveals that the problem can also be the solution in the form of anti-inflammatory lifestyle choices (See Appendix F), (de Matos, de Macedo & Pilar Rauter, 2017). This information, combined with anti-diabetic therapy targeted to normalize insulin signaling within the central nervous system,

has the potential to reroute insulin resistant pathways and possibly foil AD pathogenesis (Leszek et al., 2017).

ApoE(4) Genetic Carriers and Insulin Signaling

Genetic Connections. Both the vascular alterations exhibited in patients with Type 2 Diabetes along with the inflammatory cascade characteristic of obesity have the potential to increase risk of dementia by nearly four-fold (Zhao et al., 2017). At the same time, research in genetics has highlighted the role the ApoE(4) gene may play in defective insulin signaling (Zhao et al., 2017). According to Zhao et al. (2017), people who carry the ApoE(4) gene have accelerated impairments with insulin signaling, which has been linked to decreased neuronal functioning (See Appendix G). Research has shown that in ApoE(4) carriers, insulin receptor signaling becomes trapped inside the neuron, specifically within the endosome, due to the production of the ApoE(4) protein (Zhao et al., 2017). This deflects signaling by blocking receptors located on the surface of the neuron, stalling insulin utilization further (Zhao et al., 2017). As the process continues, the ApoE(4) protein continues to "clump," advancing the detrimental cycle, resulting in cellular starvation and ultimately, apoptosis (Zhao et al., 2017). Research has shown that roughly 20% of the population has this genetically-rooted error in "insulin trafficking," placing this population at an augmented risk for AD (Zhao et al., 2017). When coupled with Type 2 Diabetes and the natural aging process, genetic carriers may be subjected to the perfect storm of detrimental factors for brain health (Zhao et al., 2017).

Current research has also linked amyloid-beta plaque production to potential genetic predisposition. Yet, considering the findings from Zhao et al. (2017), "it is still unclear whether amyloid beta and ApoE(4) play synergistic or competing roles in disrupting insulin signaling." At the same time, ApoE(4) has been found to have a much higher binding affinity to insulin

receptors, even in cases where amyloid-beta fails to be present (p. 124). The presence of ApoE(4) alone has not been established as an independent risk factor for Type 2 Diabetes or for AD (Zhao et al., 2017). However, the culmination of molecular mechanisms underlying genetic signaling, combined with the insulin resistance already present in Type 2 Diabetes have the capability to produce brain-specific insulin signaling abnormalities (Zhao et al., 2017). According to Johnson et al. (2017), mice carriers of the ApoE(4) gene have shown a "global metabolic shift toward increased lipid oxidation" as a compensatory mechanism to make up for "cerebral glucose hypometabolism." It has yet to be established, however, as to the origin of this occurrence. The question of whether these metabolic shifts transpire primarily during oxidative phosphorylation, through glycolysis or "at the level of the blood brain barrier" still remain (Johnson et al., 2017). Going forward, this may be further evidence that the mechanisms within the brain as a result of loss of insulin signaling have distinct regulatory pathways within the central nervous system (Johnson et al., 2017). Increasing awareness of Type 3 Diabetes in the clinical realm may provide the exact culminating designation that can harness both improvement and treatment strategies of this multifaceted disease (Zhao et al., 2017).

Genomic research has further identified the role that both epigenetics and metabolomics continue to play in discerning amongst risk factors for AD between carriers versus noncarriers of the ApoE(4) gene (Johnson et al., 2017). Imaging reports have revealed signs of "brain hypometabolism in the same regions affected by AD" in carriers of the ApoE(4) gene in their early twenties (Johnson et al., 2017). This further supports an augmented risk in allele carriers compared to noncarriers (Johnson et al., 2017). Additionally, the presence of genetic alterations like ApoE(4) and amyloid beta plaques underscore the notion that increased carbohydrate intake has a significantly higher inflammatory effect in genetically predisposed individuals (Johnson et

al., 2017). Epigenetic signaling has been established as having a crucial role in both the "functional impairments" and succeeding revitalization of healthy pathways, highlighting the importance of individualized dietary interventions as a "novel therapeutic target for AD and related dementias" (Johnson et al., 2017). Research has also connected the ApoE(4) gene with other conditions like (a) vascular dementia, (b) mild cognitive impairment, (c) elevated LDL cholesterol, and (d) cardiovascular disease due to its role in macronutrient transportation (Stein, Schettler, Rohrer & Valenti, n.d.). These correlations have further illustrated the inflammatory cycle that perpetuates in chronic disease and may hold major promise for utilizing proactive genetic screening for prevention (See Appendix H), (Stein, Schettler, Rohrer & Valenti, n.d.).

Metabolomics. Future research is also vital in emerging fields like genetics, epigenetics and metabolomics, which studies small molecules or metabolites of physiological pathways. The dynamic interplay of environmental factors and metabolism is vital for further understanding of signaling routes, suppression or promotion of repair mechanisms in carriers versus non carriers of implicated genes and biochemical individuality (Johnson et al., 2017). Gene therapy "to deliver glucose transporters into the hippocampus and other areas affected in AD could emerge as attractive strategy" to stop cognitive damage and even reverse these alterations for AD patients (Duran-Aniotz & Hetz, 2016). These types of individualized therapies have shown promise in vitro in restoring energy imbalances within the brain. They may pave the way for mitochondrial support by "improving the buffering capacity of the cell against abnormal protein aggregation" which is critical for carriers of the ApoE(4) gene (Duran-Aniotz & Hetz, 2016). It has been made abundantly clear that the "neuropathological cascade of AD" manifests its subtleties decades before clinical inception (Duran-Aniotz & Hetz, 2016). Delineating the mechanism that facilitates the breakdown of energy transport may enhance patient protocol while

providing preventative strategies for such an incapacitating disease (Duran-Aniotz & Hetz, 2016).

Epigenetics. We have only recently begun to understand the gene-environment interchange. As a rule, the disease or health of every organ system has the potential to be influenced by various circumstances and environmental components (Stein, Schettler, Rohrer & Valenti, n.d.). Traditionally, these circumstances have been apportioned into either genetic variances or environmental factors. Yet, often, there is an intermingling amongst phenomenon, which has launched the field of epigenetics (Stein, Schettler, Rohrer & Valenti, n.d.). In cases of ApoE(4) genetic carriers, observational research has identified Westernized lifestyle factors as a potential indicator in assessing individual disease risk for AD and diabetes (Stein, Schettler, Rohrer & Valenti, n.d.). One such observational study has determined that (a) physical inactivity, (b) drinking alcohol, (c) smoking, and (d) consuming a Westernized diet as potent modifiers in determining dementia risk "particularly among genetically susceptible individuals" (Stein, Schettler, Rohrer & Valenti, n.d.). Other evidence has been supportive in identifying the Westernized diet as a "key driver of ApoE(4)-associated risks" particularly when having been exposed to high levels of environmental chemicals (Stein, Schettler, Rohrer & Valenti, n.d.). The most common offenders include lead, aluminum, air pollution and persistent organic pollutants or POPs (Stein, Schettler, Rohrer & Valenti, n.d.). The current evidence has accentuated the role that chronic inflammation plays in the etiology of both AD and Type 2 Diabetes (Mushtaq et al., 2014). Consequently, the manipulation of various "inflammatory pathways and the development of new treatments for both of these diseases" may effectively treat type 2 diabetes while delaying the onset of AD (Mushtaq et al., 2014). Research has undoubtedly established the importance of adjusting environmental aspects in preventing "risks

associated with ApoE(4) and potentially a major portion of the Alzheimer's/dementia burden" (Stein, Schettler, Rohrer & Valenti, n.d.). However, future endeavors must expand on this by shedding light on individual vulnerability and dietary and environmental exposures in determining disease risk (See Appendix I), (Stein, Schettler, Rohrer & Valenti, n.d.)

Implications of Increasing Awareness of Type 3 Diabetes

Early Detection. Chronic disease statistics both globally and domestically have revealed staggering increases in diagnoses (CDC, 2017). Projections for medical costs "associated with treatment and hospital stays" due to complications are also skyrocketing (Boles, Kandimalla & Reddy, 2017). This has identified the indispensable need for early detectable markers for prediabetics and the necessity for future AD research in teasing out the complexities among diabetes and cognitive decline (Boles, Kandimalla & Reddy, 2017). Modifiable factors that may reduce diabetes have the probability of preventing AD, which starts with patient education regarding physical activity, diet, avoiding unnecessary inflammatory substances and having proactive clinical support regarding disease monitoring (Song, Bischoff, Song, Uvemura & Yamaguchi, 2017). In the insightful words of Dr. Daniel Amen (2015), "we cannot change what we do not measure." Systemic biomarkers of inflammation can provide much needed insight into an individual's biochemical makeup and potentially thwart disease if caught early (Amen, 2015).

Significance of Information Presented. The brain-specific alterations exhibited in post-mortem AD research cannot be ignored, particularly regarding the "deterioration of the brain's ability to use and metabolize glucose" (Heerema, 2018). It also well noted in the literature that if a person is diagnosed with diabetes, their risk of developing AD doubles (Heerema, 2018). Add obesity, genetic factors, and inflammatory conditions like high blood pressure and the risk is

further heightened (Heerema, 2018). According to de la Monte and Wands (2008), "epidemiologic studies provide convincing evidence for a significant association between T2DM and AD" (p. 1103). However, the degree of association is based on individual factors that directly influence underlying inflammation including (a) exposure to AGEs; (b) blood pressure; (c) patient age, and (d) BMI (de la Monte & Wands, 2008). Significant associations between poor lifestyle choices, Type 2 Diabetes and AD have been established epidemiologically (Ferreira, Bomfim & De Felice, 2014). However, the greatest associations have been made clinically as "mounting recent evidence indicates undeniable shared mechanisms of pathogenesis between metabolic disorders and AD" (Ferreira, Bomfim & De Felice, 2014). Based on research from Steen et al. who first coined the term Type 3 Diabetes, "the neurodegeneration that occurs in sporadic AD is consistently associated with a number of histopathological, molecular and biochemical abnormalities" (2005, p. 63). Further evidence has revealed that impaired insulin signaling plays a major role in AD pathogenesis, based on epidemiological findings (Steen et al., 2005). Based on a systematic review conducted by Leszek et al., (2017), cumulative evidence has evoked a strong correlation between AD and DM, birthing the term Type 3 Diabetes (p. 1333).

Research has also identified a strong association between brain-specific insulin resistance and cognitive decline, highlighting the need for new or current therapies to target insulin signaling (Steen et al., 2005). This information is vital in pursuing "multi-modal" and effective treatments that "target distinct impairments at different levels within the insulin signaling cascades" in the brain (de la Monte et al., 2012). This has the potential to relieve a significant burden of disease both nationally and worldwide as healthcare costs are projected to reach $4 trillion by 2020 (Kandimalla, Thirumala & Reddy, 2017).

Effective Pharmaceuticals for AD

Anti-Diabetic Agents. Clinical trials exploring AD medications have notoriously fallen short, mainly because they have traditionally focused on the elimination of plaque deposits or tau phosphorylation (Chen & Zhong, 2013). While these deposits within the brain are a hallmark feature of AD, medications targeting their clearance have shown minimal, if any cognitive improvements (Chen & Zhong, 2013). Instead of treating the proverbial 'smoke,' proactive Type 3 Diabetes support has the possibility of providing therapeutic strategies to treat the 'fire,' also known as multifaceted inflammatory precursors from a chronic perspective. This may also open the door to integrative treatments that merge modern medical science with metabolic mitochondrial support in targeting the disease at the core of its inflammatory cascade (See Appendix I), (Stein, Schettler, Rohrer & Valenti, n.d.).

Since much of the previous AD-specific clinical trials have yielded less than hopeful results regarding potential pharmaceutical therapies, future research should continue to examine insulin-based therapies as multitargeted drugs (De Felice et al., 2014). This can provide restorative potential for both age-related insulin signaling deficits while targeting ApoE(4) carriers before detrimental damage ensues (De Felice et al., 2014). Intranasal insulin may provide opportunities for current AD patients and possibly reestablish healthy insulin function since this has been found to be the "preferred route for central nervous system delivery" (De Felice et al., 2014). A main benefit of this delivery route is that "circulating levels of insulin or glucose" are not normally impacted (De Felice et al., 2014). Regardless of the AD therapy, the true prospects lie in identifying the complex molecular links between AD and diabetes (De Felice et al., 2014). This can allow further understanding and interpretation of "the mechanisms

underlying neuronal dysfunction in AD" while birthing much needed interventions for control and possibly, harnessing this connection for prevention (De Felice et al., 2014).

Therapeutic Approaches to Type 3 Diabetes

Nutraceuticals. One field of research that has dramatically improved the quality of life in both Type 2 Diabetics and AD patients has focused on natural compounds known as nutraceuticals relatively annulled of harmful pharmaceutical side effects (De Matos, De Macedo & Rauter, 2017). Prior nutraceutical research has identified curcumin as a brain permeable compound with the ability to target abnormal protein aggregates (De Matos, De Macedo & Rauter, 2017). Curcumin may also thwart "proapoptotic signaling pathways in primary hippocampal neuron cultures" (De Matos, De Macedo & Rauter, 2017). Forthcoming research in improving bioavailability of curcumin may have the potential to lift the veil on promising natural substances for AD patients. Techniques to boost absorption include combining it with piperine, or creating supplements containing water-soluble analogues (De Matos, De Macedo & Rauter, 2017). Previous research has also shown the benefit of metformin in mice when coupled with curcumin and piperine supplementation, particularly regarding enhanced insulin sensitivity, signaling, and better systemic glucose tolerance (De Matos, De Macedo & Rauter, 2017). It is abundantly clear that both the "nutraceutical and pharmaceutical development of structures should be highly encouraged" to improve pharmacokinetic profiles and efficacy with "higher selectivity toward desired molecular targets" (De Matos, De Macedo & Rauter, 2017).

Antioxidant Activity. There have been too few human epidemiological studies examining high intake of fruits and vegetables specifically regarding AD, which suggests the vital need for future endeavors pertaining to cognitive decline (Stein, Schettler, Rohrer & Valenti, n.d.). However, the anti-inflammatory benefits of fruits and vegetables have been

widely publicized for decades, particularly regarding antioxidant action in reducing inflammatory damage (Stein, Schettler, Rohrer & Valenti, n.d.). Rodent research has linked various vegetables and fruits as protective "against cognitive and brain neuropathology from dietary oxidative stress" due to innumerable bioactive constituents like carotenoids, antioxidant vitamins, polyphenols and flavonoids (Stein, Schettler, Rohrer & Valenti, n.d.). It has also been established that diets void of antioxidants in fruits and vegetables, like the Westernized diet coupled with sedentary habits, have the potential to be independent risk factors for disease etiology and cognitive decline (Stein, Schettler, Rohrer & Valenti, n.d.).

The need for prospective antioxidant research has been great, mainly because "studies on the effects of vitamin C and E supplements have generally been negative" (Stein, Schettler, Rohrer & Valenti, n.d.). This suggests that future research should incorporate food-based support to examine the symbiotic relationship between these constituents physiologically (Stein, Schettler, Rohrer & Valenti, n.d.). Major problems have arisen in vitamin E research because of the complexities of the tocopherol family. Vitamin E-based supplements have customarily been comprised of one or two of "at least eight naturally occurring forms of tocopherol" that may or may not be physiologically bioactive when isolated (Stein, Schettler, Rohrer & Valenti, n.d.). Another issue is that most of our current research on vitamin E focuses on tocopherols, instead of tocotrienols, which may provide better and more consistent results. According to Muller, Theile and Bohm, tocotrienols may exhibit increased oxygen radical absorbance capacity with an enhanced "reducing ability and radical chain breaking activity" (2010). At the same time, various antioxidant activities are greatly contingent upon circumstances and assays techniques, like lipophilic methods in non-polar antioxidants versus hydrophilic means (Muller, Theile & Bohm, 2010). This illustrates the need for more tocotrienol research reflective of appropriate

methods based on the constituents of the medium being measured (Muller, Thiele & Bohm, 2010).

Polyphenols. A separate class of antioxidants known as polyphenols, found in colorful fruits and vegetables, has been "suspected to be responsible for some of the health benefits in animal and in vitro studies" (Stein, Schettler, Rohrer & Valenti, n.d.). Blueberries have been named as one such category of polyphenols known as acanthocyanins and are implicated in preventing and possibly reversing "age-related deficits in neuronal signaling and cognition in rats" (Stein, Schettler, Rohrer & Valenti, n.d.). Polyphenols have also been identified as mediators of free radical formation, regulators of nitric oxide, and inhibitors of cancer cell propagation (Stein, Schettler, Rohrer & Valenti, n.d.). Catechins in green tea, dark chocolate and unprocessed cocoa have been recognized as a separate class of polyphenols with substantial neuroprotective effects in animals (Stein, Schettler, Rohrer & Valenti, n.d.). Yet, limited research has looked "specifically at the possible influence of polyphenols in cognitive decline" (Stein, Schettler, Rohrer & Valenti, n.d.).

While current research has identified roughly 6,000 different polyphenols from various families of flavonoids, it has been estimated that we have only scratched the surface with the potential therapeutic implications that they provide in vivo (Stein, Schettler, Rohrer & Valenti, n.d.). This is mainly because studies have traditionally focused on single nutrients instead of overarching patterns involving synergistic mechanisms available in polyphenol food sources (Stein, Schettler, Rohrer & Valenti, n.d.). Moving forward, "a focus on dietary patterns can capture complex interactions among many components that are difficult or impossible to see when looking at one or two nutrients individually" (Stein, Schettler, Rohrer & Valenti, n.d.).

This has significant potential to advance our understanding of proactive approaches toward preventing AD and inhibiting progression (Stein, Schettler, Rohrer & Valenti, n.d.).

Omega-3 Fatty Acids. The essential role of omega-3 fatty acids in brain development and maintenance has been well recognized, particularly in the past ten years, yet only recently "have their effects on brain aging been explored" (Stein, Schettler, Rohrer & Valenti, n.d.). The long-chain omega-3 fatty acid docosahexaenoic acid, commonly referred to as DHA, had originally showed promise in the early 1980s in improving memory-related learning in aged rodents (Stein, Schettler, Rohrer & Valenti, n.d.). However, major epidemiological evidence has been published since then that supports dietary omega-3s and/or fish consumption as substantially beneficial in reducing the risk of Alzheimer's disease/cognitive decline (Stein, Schettler, Rohrer & Valenti, n.d.). Research has also shown that lower than recommended intake has been associated with increased decline in verbal fluency among men and women ages 50 to 60 (Stein, Schettler, Rohrer & Valenti, n.d.). One rather large study that examined 2,200 people found that the subjects with hypertension and dyslipidemia "showed the greatest benefit" with omega-3 fatty acid supplementation when compared with control groups (Stein, Schettler, Rohrer & Valenti, n.d.).

At the same time, research that has examined omega-6 fatty acids in conjunction with omega-3 supplementation have found that the inflammatory risks related to high n-6 intake was not able to be offset with n-3 consumption (Stein, Schettler, Rohrer & Valenti, n.d.). Omega-6 rich oils have been identified as the major source of fatty acids in Westernized eating styles. High intake has been found to "more than double the risk of dementia" possibly because excessive n-6s have been shown to inhibit cognitive benefits in spite of ample supplementation (Stein, Schettler, Rohrer & Valenti, n.d.). At the same time, it has been estimated that roughly

98% of the American population consumes suboptimal amounts of omega-3 fatty acids (Amen, 2015). This has identified a major dietary intervention for people at risk for AD or suffering from mild cognitive decline as increasing omega-3 intake alone has been unsuccessful at restoring cognitive function. Incorporating high quality fish oils or omega-3 rich fish sources while eating fewer processed foods to reduce omega-6 exposure could provide an easy fix to halt cognitive decline (Amen, 2015). Diets rich in omega-3 fatty acids and naturally low in omega-6 fatty acids may hold the key for nutritional therapy for AD patients (Stein, Schettler, Rohrer & Valenti, n.d.).

Preventing and Reversing Type 3 Diabetes

The Ketogenic Diet. Omega-3 fatty acids represent anti-inflammatory sources that have a positive effect on the body systemically when omega-6 intake is reciprocally reduced (as described above). At the same time, increasing omega-3 fat intake and decreasing processed carbohydrate intake when following the ketogenic diet has also shown promise in mitigating glucose impairments by providing ketones as complementary energy (Broom, Shaw & Rucklidge, 2019). The ketogenic diet may even diminish and clear beta amyloid plaques within the brain, while convalescing damaged mitochondria and reducing universal inflammation (Broom, Shaw & Rucklidge, 2019). New research has shown that glycated ApoE(4) protein and faulty insulin signaling leads not only to impaired energy transport for brain tissues, but also impaired lipid transportation, mainly cholesterol (Broom, Shaw & Rucklidge, 2019). By inducing a chronic ketogenic state through carbohydrate restriction, the body utilizes ketones as a primary source of fuel within the body and more importantly, the brain (Broom, Shaw & Rucklidge, 2019). Ketone production can override shortfalls with insulin production and faulty

carbohydrate transport, which has implicated this style of eating as an effective treatment for AD (Broom, Shaw & Rucklidge, 2019).

Lifestyle Support. There is no pharmaceutical intervention that has ever existed that has been more potent in improving overall vasculature throughout the body, than exercise (Amen, 2015). When blood flow is improved, the heart works more efficiently, allowing blood cells to naturally widen to increase healthy blood flow (Amen, 2015). We previously discussed mitochondrial dysfunction as a hallmark feature of type 3 diabetes and cognitive decline (See Appendix J). Amazingly, exercise produces more mitochondria due to increased energy needs. Yet the most dynamic connections exist within the brain, between the cerebellum and the prefrontal cortex, which both show activation within the frontal lobes (Amen, 2015). At the same time, the size of the hippocampus in people who exercise regularly is notably larger than non-exercisers, displaying the neurogenic affect of physical activity (Amen, 2015). It has been hypothesized that the way to amp up brain derived neurotrophic factor, allowing neurogenesis or the growth of new brain cells, is through moderate, habitual exercise (Amen, 2015). At the same time, exercise is one of the most effective interventions for restoring insulin sensitivity while lowering peripheral insulin concentrations (Wood & Setter, 2010). In a world with little to no interventions for AD, exercise remains the only proven neuroprotective therapy because of several mechanisms (Wood & Setter, 2010). But most importantly, exercise triggers the production of brain-derived neurotrophic factor which facilitates the growth of new brain cells, known as neurogenesis (Wood & Setter, 2010). This also has extensive implications for AD patients and type 2 diabetics thanks to increases in quality of life, neurochemical messaging within the brain, restorative power over insulin resistance, and the ability to clear beta-amyloid plaques in certain individuals (Wood & Setter, 2010).

Brain-Gut Connections. It is becoming increasingly difficult to discuss any inflammatory disease without mentioning that our 60 trillion human cells house ten times more bacterial cells than human cells, meaning our cells are constantly mediated by bacteria (Amen, 2015). With this emerging knowledge, we have only just begun to uncover the connections between the gut microbiome and systemic health. These microenvironments within our gut includes resident bacterial populations that contain characteristic genetic material while producing a plethora of metabolic byproducts (Bonfil et al., 2016). The capacity theses microbes play as regulators of systemic inflammation to every single body system has yet to be realized (Bonfil et al., 2016). Knowing that human cells belong not to us but to bacterial colonies that can influence mood, hormonal balance, vitamin and mineral absorption, production and most importantly, systemic inflammation, can help us harness gut health as a foundation to brain health (Bonfil et al., 2016). Underlying inflammation has been identified as a hallmark feature of both AD and type 2 diabetes, which has brought up the potential of interventions that "balance the gut microbiome and reduce inflammation" naturally (Bonfil et al., 2016).

Genetic modification of seeds and crops in the United States is a major hot topic issue because these foods are sprayed with glyphosate as a pesticide (Amen, 2015). However, the chemical compounds in glyphosate disrupt the gut microbiome, potentially triggering inflammation and even leaky gut as the cell lining recedes (Amen, 2015). This chronic gut-mediated inflammation continues to perpetuate as pesticide laden foods are consumed, disrupting the gut microflora and fostering a vicious cycle (Amen, 2015). Research shows that people who consume a Westernized diet have dramatic increases in excretion of glyphosate metabolites, which significantly alters the natural synergistic nature of the gut microbiome (Amen, 2015).

The biggest offenders in the standard American diet include corn, soy, sugar, and vegetable oils with pro-inflammatory fatty acid profiles (Amen, 2015).

While we have only scratched the surface of the gut brain connection, animal research has identified that positive changes within the microbiome of mice "positively impacted neuronal pathways in their brains, slowing cognitive decline and the progression of Alzheimer's disease" (Bonfil et al., 2016). Prior studies have looked specifically at *Bifidobacterium* strains in transgenic mouse models with early stages of AD, which was found to induce anti-inflammatory activity by "negatively modulating mRNA levels of pro-inflammatory cytokines" (Bonfil et al., 2016). The benefits that have been illustrated further in mouse models have included reduced levels of cytokines leading to decreases in β-amyloid plaque accumulation while reversing cognitive decline in AD (Bonfil et al., 2016). In vitro studies have revealed the capacity of certain probiotic strains like *Lactobacillus* and *Bifidobacterium* to help produce fundamental neurotransmitters including gamma-aminobutyric acid (GABA), and acetylcholine for further mediation of neurological function (Bonfil et al., 2016). At the same time, these bacteria generate aromatic amino acids like tryptophan and tyrosine, which are vital in neurotransmitter synthesis (Bonfil et al., 2016). These are the first amino acids to be destroyed by glyphosate, mentioned in the beginning of this section (Bonfil et al., 2016). Although animal research has been unable to directly correlate these findings to humans, this evidence holds significant potential for future research in microbiota-related interventions as another modifiable strategy in the treatment and prevention of AD (Bonfil et al., 2016).

AD Patients Without Type 2 Diabetes

The Obesity Paradox. Diabetes research has revealed that nearly 80% of all individuals diagnosed with type 2 are obese (Chadt et al., 2018). However, not every obese individual

develops type 2 diabetes related to hyperglycemia, which reveals the need for more research into these unknown complexities (Chadt et al., 2018). According to Chadt et al. (2018), "the molecular mechanisms underlying these complications are still poorly understood" but there are a number of hypotheses worth mentioning here. The "inflammation hypothesis" in regard to obesity ascertains that "a state of chronic inflammation produced by infiltrating macrophages in adipose tissue exert pathological changes" (See Appendix K), (Chadt et al., 2018). The most notable changes occur in "insulin-sensitive tissues and β-cells" as described previously in this section (Chadt et al., 2018). A second hypothesis in explaining type 3 diabetes in non-diabetics includes the "lipid overflow hypothesis" which indicates that "obesity may result in increased ectopic lipid stores due to limited capacity of adipose tissue to properly store fat" (See Appendix L), (Chadt et al., 2018). These lipid components "and their metabolites may exert cytotoxic effects on peripheral cells" resulting in insulin resistance, and apoptosis (Chadt et al., 2018). While more research is needed to support obesity-specific genetic alterations in leptin and cholesteryl ester transfer protein (CETP), some studies have shown increased AD risk factors in carriers of the 1405V polymorphism within the CETP gene (Murphy et al., (2012). Faulty leptin signaling, which is a satiety-inducing hormone, has also been implicated in the pathogenesis of obesity and AD (Marwarha & Ghribi, 2012). According to Marwarha and Ghribi (2012), leptin receptors are mainly located throughout the hippocampus, and as low expression fosters increased beta-amyloid production along with tau phosphorylation. Polymorphisms in leptin signaling may provide further answers within this arena for current and prospective patients (Marwarha & Ghribi, 2012).

We know that future genetics research will shed more light on the variations in insulin signaling within the brain of ApoE(4) carriers, and perhaps it will further our grasp on why some

obese individuals never develop insulin resistance (Chadt et al., 2018). Nevertheless, this directly correlates with the notion that type 3 diabetes can occur in people without type 2 diabetes or systemic hyperglycemia since its consequences remain sequestered within the brain tissues (Hyman, 2016). Also, of interest are the symptoms of cognitive decline, brain fog, forgetfulness and inattention in people without type 2 diabetes with high C-reactive protein, which may serve as a direct indicator of neuroinflammation (Amen, 2015).

Chapter 3

Methods and Procedures

Methods

The main search method strategy used internet-based search engines, libraries, and databases to examine publications, to research Alzheimer's disease, insulin resistance, ApoE(4) research, and the potential for utilizing the term "Type 3 diabetes" for AD patients. Another search strategy examined assessing the effect of AD treatment through diabetic interventions, nutraceuticals, and diabetes-related screenings, published between 2005 and 2019.

Procedures

Search procedure. A careful review of the literature related to Alzheimer's disease and insulin resistance was conducted. The review highlighted the following topics: (a) Alzheimer's disease, (b) Types 1 and 2 diabetes, (c) insulin resistance and cognitive decline, (d) Type 3 diabetes (e) ApoE(4) genetic perturbations, (f) prevention and lifestyle support for Alzheimer's disease, (g) prevention and lifestyle support for diabetes, (h) social and economic consequences of Alzheimer's disease, (i) social and economic consequences of diabetes.

Libraries used. There were two libraries used for the sources search for this paper. The Wahlstrom Library at the University of Bridgeport and the Wiley Online Library were both employed for research purposes.

Search engines and databases used. The following databases were used to search for the sources for this project. The databases used were PubMed, EBSCOhost, Google Scholar, and Citations and Abstracts for Literature from the National Center for Biotechnology Information Division Databases.

Search terms. Several search terms were used to identify sources for this project. The search terms included (a) Alzheimer's disease, (b) cognitive decline and dementia, (c) Type 1, 2 and 3 diabetes, (d) insulin resistance, (e) risk factors in neurodegeneration, (f) prevention strategies for diabetes, (g) prevention strategies for Alzheimer's disease, and (h) anti-inflammatory nutraceuticals.

Boolean strings. Boolean strings were considered for the literature search. Three Boolean strings were used: Alzheimer's disease AND insulin resistance AND type 3 diabetes.

Age of the sources. The significant literature has been reviewed. Sources from the last twenty-one years have been considered for inclusion in the review of literature, mainly for comparative purposes. Pertinent historical or seminal articles have also been considered, specifically to shed light on the discovery of Alzheimer's disease.

Inclusion criteria. There were four inclusion criteria. Inclusion criteria included (a) literature published since 2008, except historical sources; (b) English-language text; (c) peer-reviewed articles; and (d) Web sites relating to Alzheimer's disease, insulin resistance, types 1, 2 and 3 diabetes mellitus. The authenticity of the information utilized from the internet was critically appraised based on (a) authorship; (b) publishing body; (c) date of webpage publication; (d) objective reasoning; (e) point of view or bias; and (f) accuracy and verifiability of the information presented based on references.

Exclusion criteria. There were four exclusion criteria. The exclusion criteria included (a) literature published before 2008, except historical sources; (b) text not published in English; (c) articles not peer reviewed; and (d) Web sites not relating to Alzheimer's disease, insulin resistance, types 1 and 2 diabetes mellitus.

Chapter 4

Results

This literature review has provided substantial evidence that while AD is a complex disorder, there is a plethora of irrefutable research that supports viewing it as type 3 diabetes. Some of these commonalities, to name a few, include (a) oxidative stress, (b) hyperglycemia, (c) insulin resistance, and (d) endothelial dysfunction (de Matos, de Macedo & Rauter, 2017). There is also substantial evidence that type 2 diabetes is fundamentally attributable to lifestyle factors and can be reversed and prevented (Wang & Ding, 2008). This information has the power to breathe new life into current AD research efforts with fresh optimism for prospective studies that can focus on AD as type 3 diabetes. At the same time, we have expanded our knowledge of brain neurochemistry particularly within the last decade and we now know that brain scans of people with chronically high levels of blood glucose have shown detrimental effects on brain structure (Kerti, et al., 2013). These changes predominantly occur within the hippocampus or the memory center of the brain (Kerti et al., 2013). This phenomenon has even been identified in people without a formal type 2 diabetes diagnosis and has suggested that the hippocampus is particularly susceptible to instabilities in glucose regulation (Kerti et al., 2013). Deficits in both short-term and long-term recall have been hallmark symptoms of cognitive decline, as identified by Dr. Alzheimer in his initial protocol for suspected patients (Stein, Schettler, Rohrer & Valenti, n.d.). This is further evidence that the asymptomatic nature of type 2 diabetes can wreak silent but deadly havoc on neurocognition.

Regarding type 3 diabetes, the evidence directly identifies chronic levels of high glucose as a main inflammatory marker, which takes a major toll on every organ system by reducing normal signaling and starving healthy cells from receiving the appropriate fuel for survival

(Boles, Kandimalla & Reddy, 2017). Like type 2, type 3 diabetes, has been linked to "metabolic derangements of carbohydrates, lipids, proteins" coupled with cognitive decline in the presence of excessive oxidative stress from insulin resistance and faulty mitochondrial signaling within the brain (Mittal & Katare, 2016). According to Pocernich and Butterfield, "the ratio of oxidized to reduced glutathione is utilized as a measure of intensity of oxidative stress" (2012). The higher the ratio favors oxidation, the more extensive the protein oxidation and free radical formation (Pocernich & Butterfield, 2012). Glutathione acts as one of the most potent antioxidants in the body and increasing levels has long been considered a therapeutic strategy in AD treatment as well as prevention (Pocernich & Butterfield, 2012).

Extensive amounts of current literature have recognized the increased risk factor for the development of Alzheimer's disease in people with type 2 diabetes (Heerema, 2018). Correlations have suggested roughly half or more of all type 2 diabetics will develop some form of cognitive decline (Heerema, 2018). Evidence examining the characteristic neurofibrillary tangles seen in AD has also linked faulty glucose signaling to neuronal death and cognitive degeneration (Mittal & Kattare, 2016). Specifically, type 3 diabetes has been identified in the phosphorylation of tau proteins through increased glycogen synthase kinase signaling, resulting in mitochondrial malfunction and significant decreases in energy production, (Mittal & Katare, 2016).

It has been made abundantly clear that increasing patient education of type 3 diabetes and focusing on prevention strategies would decrease disease burden, increase quality of life and at the same time, save trillions of dollars in healthcare spending (Boles, Kandimalla & Reddy, 2017). While clinical medicine has been slow to acknowledge the fact that type 2 diabetes is a manifestation of adjustable factors, it has been even slower to connect these same dots regarding

AD (Boles, Kandimalla & Reddy, 2017). Only recently has research correlated the metabolic disturbances in AD and diabetes, birthing the term type 3 diabetes, which may explain the stalls in recognition and the shortcomings of clinical trials thus far.

The evidence has emphasized an unequivocal need to view AD as type 3 diabetes so that proactive screening efforts can become commonplace, particularly for ApoE(4) carriers. There is no doubt that in patients who have the ApoE(4) gene, insulin receptor signaling becomes trapped inside the neuron, specifically within the endosome, due to the production of the ApoE(4) protein (Zhao et al., 2017). This deflects signaling by blocking receptors located on the surface of the neuron, stalling insulin utilization further (Zhao et al., 2017). As the process continues, the ApoE(4) protein continues to "clump," further perpetuating the cycle and resulting in cellular starvation and ultimately, apoptosis (Zhao et al., 2017). If roughly 20% of the population has this genetically-rooted error in "insulin trafficking," it is abundantly clear that genetic screening can identify this risk factor. Since ApoE(4) carriers have a substantially augmented risk for AD, particularly when coupled with type 2 diabetes and the natural aging process, genetic screenings can identify candidates so that sustainable interventions can take place (Zhao et al., 2017).

The literature has also established the fact that neuronal death perpetuates the loss of the ability of the CNS to produce appropriate growth factors, greatly reducing insulin expression, while favoring the development of tau mRNA and amyloid precursor proteins as compensatory mechanisms (Steen et al., 2005). The oxidative cascade in both AD and type 2 diabetes has been extremely well studied. However, in many patients who never had diabetes, the phenomenon remained sequestered to the brain, distinct from both type 1 and type 2 diabetes (Steen et al., 2005). This further underscores the need for an increased awareness of type 3 diabetes, since

cognitive degeneration can develop in people without an official diagnosis of type 2 diabetes (Steen et al., 2005). Moreover, the literature has been well established in utilizing diminished baseline glucose metabolism as a sensitive biomarker in examining and measuring AD-related cognitive decline" (Godoy et al., 2014) At the same time, the FDA has already recognized the need for developing multitargeted pharmaceutical support for current and future AD patients. These two factors alone carry major weight in the emerging field of type 3 diabetes so that strategies can "slow down or attenuate metabolic deficits" observed in AD (Godoy et al., 2014).

The literature has also directly identified defective glucose metabolism and neural insulin resistance as early indicators of AD (An, Varma, Varma, Casanova, Dammer, Pletnikova et al., 2018). The acuteness of AD pathology may hinge on GLUT3 levels; the lower the levels, the more severe the AD symptoms (An et al., 2018). Ample evidence has also found that "overexpression of GLUT-1" improves glucose metabolism and reduces AD-associated cognitive alterations (An et al., 2018). This evidence also indicates the possible therapeutic effect of restoring normal glucose metabolism within the brains of AD patients. It is well established that the pathology of AD occurs decades before clinical onset, so this evidence identifies the need to define specific mechanisms behind failure of glucose transporters within the brain and not just compensatory mechanisms like plaque formation or tau phosphorylation (Duran-Aniotz & Hetz, 2016).

There has also been undeniable evidence documenting the downstream effects of chronic insulin resistance, particularly "the weakening of insulin transition by the blood brain barrier" (Leszek et al., 2017). Other possible effects include facilitating the modulation of tau-protein formation due to activation of insulin resistant reductions in phosphorylating kinase activity (Leszek et al., 2017). Insulin resistance itself has led to (a) mitochondrial abnormalities, (b)

oxidative stress, (c) “reductions in synaptic plasticity in the hippocampus” and has shown to be exacerbated with the natural aging process coupled by a sedentary lifestyle and lack of proper nutrition (Leszek et al., 2017). Moreover, study after study has revealed that the problem can also be the solution in the form of anti-inflammatory lifestyle choices combined with anti-diabetic therapy targeted to normalize insulin signaling within the central nervous system (Leszek et al., 2017). These preventative strategies can reroute insulin resistant pathways and possibly foil AD (Leszek et al., 2017).

Major epidemiological evidence has also identified the role that dietary choices can play in both disease etiology and prevention, particularly concerning nutraceuticals. Research concerning omega-3 fatty acids is no doubt the nutraceutical field where the most extensive brain-related research has been documented. Study after study points to dietary omega-3 fatty acid consumption as a substantial mediator in the reduction of AD/cognitive decline (Stein, Schettler, Rohrer & Valenti, n.d.). The literature also highlights repercussions in populations who consumer lower than recommended intake, which has been associated with increased decline in verbal fluency among men and women ages 50 to 60 (Stein, Schettler, Rohrer & Valenti, n.d.). It has also been recognized that subjects with the greatest amount of inflammation in the form of hypertension and dyslipidemia “showed the greatest benefit” with omega-3 fatty acid supplementation (Stein, Schettler, Rohrer & Valenti, n.d.). At the same time, irrefutable evidence has found that the inflammatory risks related to high n-6 intake was not able to be offset with n-3 consumption (Stein, Schettler, Rohrer & Valenti, n.d.). Omega-6 rich oils have been identified as the major source of fatty acids in Westernized eating styles, and high intake has been found to “more than double the risk of dementia” possibly because excessive n-6s have been shown to inhibit cognitive benefits in spite of ample supplementation (Stein, Schettler,

Rohrer & Valenti, n.d.). This has identified a major dietary intervention for people at risk for AD or suffering from mild cognitive decline as increasing omega-3 intake alone has been unsuccessful at restoring cognitive function. Diets rich in omega-3 fatty acids and naturally low in omega-6 fatty acids may hold the key for nutritional therapy for AD patients (Stein, Schettler, Rohrer & Valenti, n.d.). Abundant research also has shown that it is much easier to protect a healthy brain than to try to repair damage once it is widespread. This highlights the importance of preventative measures as providing extremely beneficial implications for current and future patients (Colino, 2017).

Today's statistics involving AD and diabetes as chronic disease epidemics have shed light on the desperate need for improvements in both disease prevention and management. The literature has shown that viewing AD as type 3 diabetes as well as increasing awareness of the term have potential to provide sustainable and integrative therapies, allowing patients to become invested in their health choices. This may also help to promote individual accountability and a sense of conscientiousness in taking back one's own health through lifestyle choices (Hu, 2016). It remains safe to say that we still have much to learn about the exact correlations and downstream effects exhibited in AD, type 2 diabetes and the underlying etiology of type 3 diabetes. At the same time, current literature has established the onset of AD as a manifestation of largely modifiable metabolic changes that specifically affect the brain.

Since AD was first identified over 100 years ago, most of the methods that have been identified as potential treatments have been disappointing in clinical trials, leaving today's patient with a very limited standard of care. This is largely due to the lack of correlation of common metabolic disturbances, particularly with cerebral glucose metabolism, that have only been established within the last decade. Since the discovery of neurofibrillary formations within

the brain, clinical trials have habitually focused on the elimination of plaque deposits or tau phosphorylation. These methods have targeted the proverbial 'smoke,' instead of examining therapeutic strategies to treat the 'fire' also known as multifaceted and chronic inflammatory precursors. The evidence shows that increasing awareness of the progression of type 3 diabetes may also open the door to integrative therapies that merge modern medical science with metabolic support in targeting the disease at the core of its inflammatory cascade. It goes without saying that redirecting future research efforts to expand the view of AD as a multifaced type 3 diabetes will help "break the bottleneck of currently stalled AD research" (Chen & Zhong, 2013). The term type 3 diabetes already exists because of the overwhelming evidence that links all of the aforementioned diabetes-like factors in the etiology of cognitive decline. While we have yet to even comprehend the full benefit of approaching AD proactively, this research highlights the abundant need for increased awareness of type 3 diabetes and resolves the basic notion of this dissertation.

Chapter 5

Discussion, Conclusions, Implications, and Recommendations

Discussion

A main concentration of this dissertation involves the ability to shed light on both the complexity and gravity of Alzheimer's disease as a multifactorial condition culminating from (a) oxidative stress, (b) hyperglycemia, (c) insulin resistance, and (d) endothelial dysfunction (de Matos, de Macedo & Rauter, 2017). All these factors, which have been established as hallmarks of type 2 diabetes, have been recognized as contributors of cognitive decline by "blocking or reducing blood flow to the brain" (de Matos, de Macedo & Rauter, 2017). Interestingly enough, the production of both beta amyloid proteins and tau proteins characteristic in post mortem diagnoses of AD both have pathologies "triggered by hyperglycemia" based on both in vivo and in vitro research (de Matos, de Macedo & Rauter, 2017). Unfortunately, the cumulative effect of diabetes coupled with the harmful consequences of the systemic inflammatory cascade has resulted in the etiology of preventable chronic diseases that were once almost nonexistent (de Matos, de Macedo & Rauter, 2017). These are many of the reasons we are now in the middle of a healthcare crisis (de Matos, de Macedo & Rauter, 2017). However, this current changing healthcare paradigm has led to the publication of more research in the area of type 3 diabetes even though future research is still imperative in establishing fundamental connections once a for all. This has placed us at an advantage, thanks to modern technology, brain scans, and years of post-mortem findings that have led to the notion of adopting the term 'type 3 diabetes' which was relatively overlooked even a decade ago.

Since AD has been examined for more than a century, there has been much documentation and observational evidence pertaining to long-term progression of the disease.

This has helped fuel prospective studies on various parts of the brain and how they have been affected (Kerti et al., 2013). Correlations from this evidence have further promoted the connections between insulin resistance, hyperglycemia and oxidative stress in AD patients (Kerti et al., 2013). This has been identified as a major strength because we now have significant data and therapeutic lifestyle support for lowing blood sugar levels through lifestyle management and lower carbohydrate intake to improve glucose control and even prevent cognitive decline (Kerti et al., 2013). "Diet-induced changes in markers of glucose metabolism directly correlate with increases in memory function," which has identified daily dietary choices as one of the most powerful mediators of health and disease, particularly concerning neurochemistry (Kerti et al., 2013). This evidence has further identified pathways for potential research in people without type 2 diabetes with augmented glucose control. It has created a possible basis for further examination of the effect of lifestyle modifications in both AD progression and prevention (Kerti et al., 2013).

An additional strength in the form of a tentative solution has included our comprehensive understanding of "chronically elevated glucose on brain function and structure" based on evidence from insulin transport and signaling within brain tissues examined from type 2 diabetics compared with non-diabetics (Kerti et al., 2013). Physical activity has long since been established as another important lifestyle modification that has the direct ability to lower glucose levels in everyone, particularly in type 2 diabetics (Kerti et al., 2013). This is yet another tentative solution in preventing disease advancement (Kerti et al., 2013). Of particular interest is recent research in epigenetics identifying healthy lifestyle choices as main factors that reduce the risk for cognitive decline in older adult carriers of the ApoE(4) gene. This directly implicates 20% of the population who are projected to be at an augmented risk for AD simply based on

genetic predisposition (Lourida et al., 2019). While more research in this field continues to shed light on specific mechanisms, this further illustrates the power that daily lifestyle choices can have in genetic signaling regardless of genetic inclination (Lourida et al., 2019).

Regular exercise has also been linked to optimal mitochondrial functionality within the cell, better glucose utilization, and exponential increase in the number of mitochondria present (Silzer & Phillips, 2018). It has also been shown that systemic mitochondrial dysfunction "originating from obesity or T2DM or from altered cellular homeostasis" has the potential to create a deleterious cascade which ensues in premature cell death along with subsequent mitochondrial decay (Silzer & Phillips, 2018). This knowledge has presented a potential therapeutic strategy in targeting mitochondrial health through exercise, lifestyle, supplemental support, and blood sugar modulation in order to prevent initial mitochondrial deterioration (Silzer & Phillips, 2018). We have yet to even realize the future implications of targeting mitochondrial health. At the very least, the literature has pointed to the importance of utilizing complementary mitochondrial therapy in any progressive inflammatory condition, specifically AD and type 2 diabetes (Silzer & Phillips, 2018).

At this time, there has been little evidentiary support in the form of a pharmaceutical cure for AD, however, much research has uncovered numerous threats to cognitive health as well as protective influences that have the ability to modulate overall risk (Woodward, 2007). Thanks to these advances in the field, research has established the natural aging process, genetic factors, family history, and inflammatory conditions such as diabetes as the top four most-established risk factors for the development of AD (Woodward, 2007). While not all risk factors have the ability to be modified, blood sugar and diabetes have responded extremely well to dietary interventions and physical activity (Woodward, 2007). Well-controlled diabetes along with

frequent monitoring of blood sugar have the potential to thwart neuronal damage from chronic oxidative stress and possibly prevent excessive formation of AGEs (Stein, Schettler, Rohrer & Valenti, n.d.). According to Stein et al. (n.d.), "not unexpectedly, the dietary factors that reduce risks of diabetes and cardiovascular disease likewise appear to reduce risk for cognitive decline" (p. 124). This has highlighted nutritional support and education as therapeutic and proactive strategies in the prevention of AD, providing further evidence of the notion that AD truly has the potential to be considered type 3 diabetes (Stein et al., n.d.).

Research has shed a great deal of light on type 2 diabetes just within the past two decades and with the increasing availability of "a wide range of drugs for managing diabetes and its complications, the life expectancy of persons with diabetes is steadily increasing" (Pugazhenthi et al., 2017). At the same time, this has continued to create opportunities in future research to solidify the associations between AD and type 2 diabetes, particularly because now, more than ever, people have the ability to live longer with a diabetes diagnosis (Pugazhenthi et al., 2017). While this has been identified as a positive aspect from a research perspective, the type 2 diabetes projections in the United States over the next decade have the potential to further perpetuate the chronic disease epidemic and have been viewed as anything but positive (Pugazhenthi et al., 2017). Modern research has established type 2 diabetes as largely a disease of lifestyle and modifiable factors not only play a major role in prevention, but also in reversing the disease (Silzer & Phillips, 2018). Using this information when examining AD and having the ability to view this debilitating disorder as type 3 diabetes has given new hope to the possibility of both treatment and prevention where very little hope has been preestablished (Silzer & Phillips, 2018).

Of all the revealing research in the field of AD, type 2 diabetes, and the interplay of chronic inflammation coupled with metabolic disturbances and genetic alterations, more questions have arisen than answers. While much of the evidence has pointed to type 2 diabetes as a risk factor for developing dementia, other research has supported the opposite notion, that "AD patients are the higher risk factor for type 2 diabetes" spawning the proverbial question of 'which came first, the chicken or the egg' (Leszek et al., 2017). Many AD and type 2 diabetes studies have traditionally included small sample sizes, not particularly representative of the general population without the ability to have randomization, which has led to the increased potential for confounding factors (Kerti et al., 2013).

The randomized, controlled trials that have been identified as the gold standard for research protocol have been designed to examine a specific and measurable intervention at a designated concentration over a predetermined course of time in a controlled environment. This, however, has resulted in the lack of useable data regarding human physiology and real-world environmental scenarios where the general population has been exposed to a plethora of environmental toxins simply upon waking in the morning. In relation to nutritional biochemistry and physiological interactions to specific factors, RCTs in the pharmaceutical world of AD have been extremely disappointing, yielding only a handful of drugs that temporarily thwart progression with multiple debilitating side effects (Kerti et al., 2013). To further complicate research up to this point, most lifestyle and dietary studies have been observational and based on self-reported measures like 24-hour recalls, food frequency questionnaires and survey information related to daily habits (Larson et al., 2006). Many times, these subjective parameters of assessment have the ability to be manipulated to produce favorable outcomes in a given patient population, particularly when research is left unblinded (Larson et al., 2006). This has

continued to present as one of the most difficult problems facing research in nutrition and lifestyle today.

Antioxidant research and nutraceutical interventions have produced extremely diverse results due to the isolation of constituents that have been meant to work in conjunction with one another physiologically (Stein, Schettler, Rohrer & Valenti, n.d.). This may explain why high levels of antioxidant supplementation have been detrimental in some patients since the naturally occurring combination of flavonoids has traditionally allowed the regenerative relationship of vitamins to thrive in vivo (Stein, Schettler, Rohrer & Valenti, n.d.). This is especially true when considering the ability of vitamin C to regenerate vitamin E and vice versa (Stein, Schettler, Rohrer & Valenti, n.d.). While discussions in nutritional biochemistry have not been included in the scope and purpose of this literature review, it is important to identify the potential for single antioxidants to become oxidized in vivo unless regenerated by other antioxidants. This may explain the conflicting results in this field of research.

Another difficulty has been reaching an unreachable population in diagnosing AD, which has presented a major barrier in research efforts since a definitive diagnosis has typically involved invasive techniques like measuring inflammatory markers in CSF (Chornenkyy et al., 2018). To further muddy the waters in the pharmaceutical realm, there has been a desperate demand for more "specific inhibitors targeting inflammatory pathways in order to gain maximum benefit in prevention or treatment of T2DM and AD at the same time (Mushtaq et al., 2015). Pharmaceutical interventions for controlling blood glucose levels and type 2 diabetes have been identified as potential mediators of AD (Mushtaq et al., 2015). However, only thiazolidinedione derivatives have been proven to "have the best potential" for improving systemic glucose tolerance (Mushtaq et al., 2015). Unfortunately, these medications have had a track record of

extremely severe side effects including further cognitive degeneration (Mushtaq et al., 2015). It has gone without saying that much more research needs to be performed regarding pharmaceutical interventions for AD particularly since we have yet to fully establish the etiology of the disease in general (Mushtaq et al., 2015). This may also potentially explain why "no safe and effective anti-AD drug to prevent, halt or reverse the progression of AD" has ever existed (Mushtaq et al., 2015).

Regrettably, one of the biggest problems hindering progress has involved stagnation in diabetes prevention particularly in recognizing prediabetes since it has been known to go asymptomatic for years and even decades (Ferreira, Clarke, Bomfim & De Felice, 2014). Implementations must also be chronically assessed for success in order to accurately identify the unique needs of an individual (Ferreira, Clarke, Bomfim & De Felice, 2014). This has conventionally involved lots of manpower, money and government delegation of services, which may be difficult to achieve in rural areas with poor access to care (Ferreira, Clarke, Bomfim & De Felice, 2014). We have just begun connecting many dots between overarching mechanisms linking AD and type 2 diabetes, prompting the need to publish future human-based research in order to tease out various patterns and conflicting data. For instance, amyloid beta plaque and tau protein formation have been commonly observed in postmortem brain analyses (Leszek et al., 2017). However, in some AD diagnoses, their presence has been nonexistent and rather sporadic (Leszek et al., 2017). These controversial findings have further muddied the waters in linking these two diseases conclusively. This has also identified the need for "further studies on (a) molecular mechanisms, (b) medicinal chemistry, (c) pathological evidences and (d) epidemiological research" involving the entire spectrum of cognitive decline, from early indications to late stages of the disease (Leszek et al., 2017). Having the ability to grasp the

"molecular basis of neuronal dysfunction and memory loss" in AD has turned out to be a key challenge in the public health arena today. This will continue to be a problem since diagnosis projections have been predicted to upsurge exorbitantly within the next ten years, with treatment options severely deficient (De Felice et al., 2014).

The fact that the brain has been identified as an "insulin sensitive organ" is still a relatively new concept (Felice et al., 2014). Within the last two decades, modern science has just outlined the extent insulin plays as a main facilitator for "synaptic plasticity, learning, and memory" (De Felice et al., 2014). AD has remained a perplexing disorder "in search of mechanisms that fully explain memory loss and lead the way to development of effective therapies" that have remained unable to thwart progression of the disease (De Felice et al., 2014). It has also remained virtually impossible to develop controlled human studies that fully mimic the ambiguities of varying environments in order to account for "any influence that negatively impacts cognition" (Chornenkyy et al., 2018). This further highlights the controversies behind environmental factors and risk of developing AD (Chornenkyy et al., 2018). Evidence about AD pathophysiology in animal research has been abundant, however, another major weakness in the literature has involved the lack of evidence "upstream of NFT formation and beta-amyloid deposition" (Chornenkyy et al., 2018). These upstream components of insulin signaling within the brain have yet to be fully identified in AD pathogenesis (Kandimalla et al., 2017). There have also been more questions raised regarding long-term insulin action and potential related to "long-term depression across synaptic contacts" in order to fully outline "how stimulators of insulin signaling act to promote neuroprotection in AD brains" (Kandimalla et al., 2017).

Other uncertainties have arisen in genetic-based research, particularly regarding the ApoE(4) connection to blocked insulin signaling with the brain (Kandimalla et al., 2017). This

has included queries as to whether other genes have played a role and whether or not animal studies have the ability to parallel to humans (Kandimalla et al., 2017). The lack of genetic research regarding ApoE(4) in humans has presented major problems with drawing any real conclusions and formally identifying carriers with potentially augmented risk factors (Kandimalla et al., 2017). While research in genetics has continued to show promise in the field of AD, discoveries have been slow-coming, expensive, and extremely time consuming. This information has been of little solace to current patients who have been given a limited protocol and timeline.

In contemporary societies, AD has remained so common that many cultures have viewed it as a normal age-related consequence destined to afflict anyone and everyone randomly (Larson et al., 2006). Unfortunately, much of the available research in AD has also echoed these sentiments by excluding patients with senile dementia that has traditionally been explained as an age-related occurrence and not truly a disease (Godoy et al., 2014). Little research has been done to truly elucidate the biological basis behind preventative strategies (Larson et al., 2006). These include blood sugar modulation, healthy eating habits, exercise and increased oxygen delivery in improved quality of life for the aging populace (Larson et al., 2006). While newly emerging fields like epigenetics have turned the 'genetics = destiny' mentality completely on its head, there have been major weaknesses and even disconnects in patient education regarding disease risk and prevention (Larson et al., 2006). It has not helped that the current healthcare paradigm has continued to forego evidence of environmental exposures on genetic inclinations and signaling (Larson et al., 2006). Unfortunately, the current healthcare paradigm focuses on reactive medicine where people live their lives the way they choose without thinking about repercussions down the road. Once a problem arises, like cognitive decline, the first thought is

medication to ameliorate the problem (Amen, 2015). However, there is no magic pill especially when it comes to AD (Amen, 2015). Failure to educate patients on modifiable lifestyle factors has led to many missed opportunities to sustainable solutions that not only have the potential to prevent disease, but also have the capacity to reduce disease burden in general (Larson et al., 2006).

In our modern society, it has been customary for companies to introduce hundreds of new chemicals and toxins onto the consumer market on a weekly basis (Fell, 2018). This has produced countless new barriers in human research regarding type 3 diabetes due to the subjective nature of environmental factors along with age and exposures (Fell, 2018). For instance, certain pesticides like DDT have been banned since 1972 when identified as potential neurotoxins and carcinogens (Fell, 2018). However, before being restricted, DDT had widespread use globally and has remained legal in several countries (Fell, 2018). This has significant pertinence to AD patients, particularly from the baby-boomer generation and beyond because DDT was legal and present throughout their adolescent and youth years (Stein, Schettler, Rohrer & Valenti, n.d.). Epidemiological research that has examined PCBs in older adults has identified major cognitive deficits, yet they have been criticized for being mostly case-control studies that have lacked longitudinal, prospective research (Stein, Schettler, Rohrer & Valenti, n.d.). While many studies have continue to draw conclusions among chemical exposure and AD, methodologic problems, confounding factors, difficulty distinguishing exposed participants from non-exposed participants, misclassifications from low exposures, and “lack of long-term exposure biomarkers” have all continued to create weaknesses in current literature (Stein, Schettler, Rohrer & Valenti, n.d.).

Conclusion

The outcomes of this research reveal the dire need to examine AD as a possible type 3 diabetes in order for effective AD therapies to emerge (Godoy et al., 2014). While future evidence has the potential to further our understanding of AD etiology, pathology and reveal undeniable evidence to adopt the term 'type 3 diabetes,' the connections that have been uncovered up to this point are undeniable. As the population of the world continues to grow as well as age, proactive efforts must be made in order to prevent detrimental downstream effects of chronic inflammation with lifestyle and education (Godoy et al., 2014). Arming patients with this information while also examining the potential benefit of multitargeted medications can provide support and possibly improve quality of life (Godoy et al., 2014). There have been numerous associations made between "neurodegenerative diseases, such as increased oxidative stress, decreased autophagy and formation of misfolded proteins, impaired neuronal metabolism and mitochondrial dysfunction" (Godoy et al., 2014). Of particular interest for prospective research are both the chronic effects of insulin resistance and faulty signaling based on ApoE(4) genetic discoveries (Godoy et al., 2014).

In conclusion, this research has highlighted the need to increase awareness of type 3 diabetes. The gravity of Alzheimer's disease and type 2 diabetes as growing epidemics that have been attributable to both chronic and acute diseases and millions of preventable deaths each year is backed with irrefutable statistical evidence from the field. Alzheimer's Disease has already been identified as the sixth leading cause of death in the United States, and the fifth leading cause of mortality in people 65 and older (Kandimalla, Thirumala & Reddy, 2017). Unfortunately, diabetes is following right behind AD as the 7th leading cause of mortality and has been projected to affect almost 400 million people by the year 2030 (Centers for Disease

Control & Prevention [CDC], 2017). At the same time, type 2 diabetes has remained one of the most adjustable risk factors for the development of Alzheimer's Disease (Pugazhenthi, Qin & Reddy, 2017). It has been well ascertained in the literature that Type 2 Diabetes is largely preventable (CDC, 2017). While the specific mechanisms between AD and all forms of diabetes remain convoluted and unclear, increasing the awareness of AD as a third form of diabetes has the potential to provide a plethora of proactive and therapeutic strategies to current patients. These include prevention through weight control, healthy lifestyle choices that can reduce AGE formation and anti-inflammatory nutritional support to thwart the oxidative cascade both systemically and within the brain (Wang & Ding, 2008).

This research has focused on selected literature related to Alzheimer's Disease, overlapping mechanisms related to diabetes and the potential for increasing awareness of the term 'type 3 diabetes' in relation to AD. Another purpose of this literature review has been to investigate the available evidence regarding commonalities between type 2 diabetes and AD and to examine the brain-specific effects of chronic hyperglycemia considering a type 3 diabetes term. There has been growing literature published that has linked insulin resistance, which has traditionally been implicated in type 2 diabetes, "to the pathogenesis of AD" and has emerged as a major risk factor for cognitive decline due to neurologically-specific mechanisms that have been identified to impair normal blood flow and result in vascular lesions (Chornenkyy et al., 2019). One final purpose of this research has been to provide potential recommendations for modulation of AD with multitarget pharmaceuticals, combination therapies, adjuvant nutrition and lifestyle support, and nutraceuticals. The only way the implications of type 3 diabetes can be fully realized is if the healthcare system acknowledges, supports, and plans a proper transition regarding application along with constructing a system that better supports proactive services

while placing critical needs at the forefront (Hu, 2016). Future goals have also been integrated below, which have included specific research topics along with the overarching requirement for a profound grasp of how "metabolic perturbations contribute to AD-type pathology" to develop innovative treatment strategies and foster prevention of type 3 diabetes (Chornenkyy et al., 2019).

Implications

The research findings have several significant implications. First, increasing the knowledge and awareness of the term type 3 diabetes has the potential to pave the way for disease treatment, prevention and possibly even deliver a cure (de la Monte & Wands, 2008). Original AD literature that has revealed "impairments in cerebral glucose utilization and energy metabolism represent very early abnormalities that precede or accompany the initial stages of cognitive impairment" which has played a significant role in the etiology of AD (de la Monte & Wands, 2008). These initial connections from AD research very early in the field have spawned even more studies to examine AD as a "form of diabetes mellitus that selectively afflicts the brain" (de la Monte & Wands, 2008). Viewing AD as type 3 diabetes would provide real solutions that have been far and few to existing patients (de la Monte & Wands, 2008). Currently, there have been no particular treatments with established efficacy in counteracting cognitive decline and/or AD, so the implications of identifying AD as a disorder with an etiology rooted in faulty insulin signaling and irregular energy pathways could be critical in disease management (Wood & Setter, 2010). At the same time, patients could be provided with strategies that target glycemic control (Wood & Setter, 2010). Contrary to AD, there have been a plethora of pharmacological therapies designed to target and manage diabetes (Wood & Setter, 2010). One such drug class known as peroxisome proliferator-activated receptor-gamma

agonists or PPAR-gamma agonists have been heavily studied regarding glucose and lipid metabolism (Wood & Setter, 2010). This drug class has shown promise as potential modulators of inflammation, which has been established as a well-recognized risk factor for AD (Wood & Setter, 2010). While these medications have yet to be approved by the FDA as effective AD treatment, they may have the ability to prevent cognitive decline in patients with diabetes (Wood & Setter, 2010). They may also provide a proactive intervention for current diabetic patients who already have an increased risk for cognitive decline (Wood & Setter, 2010).

Additionally, one of the most successful yet disregarded methods of naturally reducing insulin resistance has been exercise, which has been proven to "improve insulin sensitivity and lower peripheral insulin levels" (Wood & Setter, 2010). New evidence shows that aerobic activities may provide the most health benefits (Pederson, 2018). Simple exercises like vigorously walking 75 minutes per week showing the greatest benefit when compared to high intensity interval training, yoga, and combination activities (Pederson, 2018). The positive health implications of daily exercise for people with AD have not been discussed enough, as physical activity "independent of weight, is associated with a lower risk of AD, making it the only proven neuroprotective therapy" (Wood & Setter, 2010). Exercise has been established as a hallmark of any healthy lifestyle, with remarkable beneficial effects for the entire body. Yet, the most specific positive effects have been exhibited within the brain. Exercise has the potential to "promote the clearance of beta-amyloid proteins and increase brain -derived neurotrophic factor vital to cognition and neuronal survival" in patients with AD (Wood & Setter, 2010). Exercise has a significant aptitude to increase quality of life and decrease disease burden in general and should be included in any patient protocol, particularly because it has proven advantageous effects within the brain and at the cellular level.

Furthermore, it has been established that the disease burden caused by both diabetes and AD has resulted in epidemic numbers, with diabetic diagnoses projected to reach 366 million people by the year 2030 (Leszek et al., 2017). To put this into perspective, these numbers make up almost 5% of the total world population (Leszek et al., 2017). AD has remained the number one most frequent form of dementia and has affected "more than 36 million people worldwide" (Leszek et al., 2017). At the same time, most people are completely unaware of the modifiable risk factors that have demonstrated significant reductions in "key triggers of oxidative and inflammatory damage" leading to "synaptic dysfunction and neuronal death" (Leszek et al., 2017). New "multitarget therapies" may have the potential to confront both conditions when administered along with adjuvant lifestyle support in preventing the progression of each disease (Leszek et al., 2017). This integrative support has the potential to diminish or possibly inhibit aggregate neurodegeneration that has been documented in "the earliest stages of T2D" (Leszek et al., 2017). The most powerful screening tools in clinical medicine include HbA1C, fasting glucose and C-peptide levels as mentioned in chapter 2. Screening patients for prediabetes has the potential to reach even more people before the inflammatory cascade has time to induce irreversible damage to the brain (Leszek et al., 2017). This is especially true considering the cognitive deterioration that has been documented in prediabetic patients where "fasting glucose levels are abnormally high but below the threshold for diabetes" (Leszek et al., 2017). Uncovering inflammatory markers well in advance of downstream cumulative effects has the potential to provide desirable therapeutic lifestyle support for an emergent public health crisis (Leszek et al., 2017).

Studies that have examined a single therapeutic intervention unaccompanied, (i.e. one pharmaceutical medication), have failed to recompense the accumulative impairments in both

disease pathologies (Leszek et al., 2017). This has the potential to explain the disappointing results in AD research to date (Leszek et al., 2017). AD has been identified as extremely multifaceted, requiring treatment options that target multiple inflammatory cascades that utilize "more than one bioactive compound" (Leszek et al., 2017). Key areas for current and future research include the expansion of advanced therapies "able to tackle multiple targets at once" (Leszek et al., 2017). Increasing awareness of Type 3 Diabetes by integrating lifestyle and nutritional support into patient protocol provides multitargeted support without pharmaceutical side effects (Leszek et al., 2017).

Finally, it has been ascertained that not everyone who has been diagnosed with type 2 diabetes will go on to also be diagnosed with AD (Colino, 2017). At the same time, not everyone with AD has type 2 diabetes (Colino, 2017). However, statistically speaking, diabetics have double the risk of developing AD within their lifetime and people with "poorly controlled blood sugar and central obesity" have even greater risk of cognitive decline (Colino, 2017). While these facts are well established in the literature, many patients have not been provided with this information or educated on the neurotoxic dangers of chronic inflammation (Colino, 2017). These shortcomings in patient education can have a profound effect both on short-term and long-term cognition (Colino, 2017).

According to Colino (2017), "it is easier to protect a healthy brain than to try to repair damage once it is extensive" which highlights the importance of preventative measures. Healthy day-to-day choices can have extremely beneficial implications for current and future patients (Colino, 2017). Polyphenols and other natural compounds have also been recommended as dietary support due to their inherent plant-based potential to provide multi-target support at a biological level (Leszek et al., 2017). These benefits include "antioxidant, anti-inflammatory

and antihyperglycemic activities" (Leszek et al., 2017). Polyphenols have even shown promise in the interference of enzymes that have been implicated in the etiology of both AD and type 2 diabetes including PDE and GSK-3β (Leszek et al., 2017). While the bioavailability of many polyphenols has been identified as a barrier in current research, these compounds "still come across as promising multitarget starting points for structural optimization, namely through the introduction of water-soluble sugar moieties" (Leszek et al., 2017). Research shows that hydrophilic factors have been implicated as natural plant-sources that may enhance bioactivity in vivo (Leszek et al., 2017). The positive repercussions from simply educating patients on easy lifestyle changes to convalesce blood sugar and reduce insulin resistance cannot be overly emphasized, especially because the average life expectancy post-AD diagnosis is less than nine years (Chornenkyy et al., 2018).

Recommendations

It has been well established that at least half of the underlying risk of developing AD has been associated with modifiable factors including dietary choices that lower the need for insulin production, and participating in moderate physical activity to reducing inflammatory pathways (Colino, 2017). Research has also outlined the dramatically increased risk factor of ApoE(4) carriers in developing AD due to genetic abnormalities that deflect insulin signaling within the brain in roughly 20% of the population (Johnson, 2017). Furthermore, as these risk factors accumulate, the danger of developing AD increases exponentially. While we have been unable to change our genetic makeup, we have the ability to make modifiable alterations within our environment to control epigenetic expression and potentially make up for predetermined risk factors.

In utilizing the term of type 3 diabetes to identify distinct pathogenic mechanisms related to neurodegeneration in AD, clinical medicine would be able to combat the disease accordingly (Steen et al., 2005). Type 3 diabetes is a complex disorder characterized by (a) cell loss, (b) neurofibrillary tangles, (c) abnormal protein deposits within the brain, (d) augmented early cell death through abnormal signaling pathways, and (e) chronic oxidative stress, resembling, yet distinct from, type 2 diabetes mellitus (Steen et al., 2005). Viewing and terming AD as type 3 diabetes would also help induce a paradigm shift in our current reactive cycle (Steen et al., 2005). Cognitive deficits typically progress to full blown dementia before patients are able to recognize precursors that may provide lifesaving tools as therapeutic interventions in restoring brain function as well as possibly thwarting progression.

Based on this review of the literature, current medical science should address AD as type 3 diabetes and recognize the following goals and objectives:

Clinician Education

1. Type 3 diabetes must be a priority on America's national healthcare agenda.
2. Medical science must establish routine screening and pre-screening assessments with standardized tools to uncover genetic factors, environmental risks and comorbid diagnoses (type 2 diabetes) that increase the risk of cognitive decline, particularly in susceptible populations.
3. High risk populations including the elderly, prediabetics, patients presenting with pro-inflammatory profiles, recurrent infections, early onset cognitive decline, type 2 diabetes, and/or ApoE4 carriers must be identified and educated about anti-inflammatory therapies.

Early Patient Identification

4. Emphasis must be placed on prediabetes education and therapeutic lifestyle changes that can restore blood sugar levels (the ketogenic diet discussed in chapter 2).
5. The utilization of cerebrospinal fluid to measure AGEs should be employed as an inflammatory marker for early AD diagnosis.
6. Roughly 194 million people with diabetes are undiagnosed and "unaware of the long-term damage" that ensues, underscoring the need for multitargeted therapies to reduce the "cumulative neuropathological events that begin to take place in the earliest stages of diabetes" (De Matos, De Macedo & Rauter, 2017).

Pharmaceuticals

7. The potential for antidiabetic agents must be examined as innovative beneficial approaches in treating AD and should be considered in patient protocol.
8. Specific prospective research must include the effects of intranasal insulin-based strategies in restoring healthy brain functioning particularly in ApoE(4) carriers.

Patient Education on Lifestyle Changes

9. The need for nutraceutical support like curcumin and piperine must be further examined as part of adjuvant anti-inflammatory therapy, particularly for metformin patients.
10. Efforts must be made to educate people on anti-inflammatory lifestyle choices so they can make informed decisions about their own health and prevent chronic disease and cognitive decline.
11. Mitochondrial support as a therapeutic intervention for both AD and diabetes must be considered in patient protocol, particularly in halting the vicious cycle of inflammation commonly exhibited in chronic diseases.

Biomarkers

12. Effective biomarkers must be established in identifying exposures to neurotoxic pesticides and chemicals for the general public in order to identify sources and reduce the cumulative effects of daily low-dose exposure.
13. Current research must continue to make strides in creating genetic screening tools for use on the front lines of medicine to identify ApoE(4) carriers in order to educate them on prevention strategies.

These strategies have been recommended for current and prospective research as part of an action plan to support a more efficient and feasible therapeutic protocol for AD patients. Therefore, continuing research in these areas and implementing this proposed action plan has the potential to improve quality of life in AD patients while further illustrating the need to increase awareness of type 3 diabetes. This would allow corresponding anti-inflammatory strategies to be assessed on a patient-by-patient scenario, sooner rather than later. Going forward, a type 3 diabetes diagnosis may provide the missing link for personalized therapy for AD patients in order to target multiple "pathogenic cascades in different disease stages with more efficient diagnostic procedures and treatment techniques with greater effectiveness and fewer side effects (Chen & Zhong, 2013). It is always said in the nutrition field that the best way to treat a disease is to prevent it in the first place. Increasing awareness of type 3 diabetes will no doubt shed light on prevention as the first line of defense while saving Americans millions of dollars in healthcare costs and needless pain and suffering (Levine & Goldschlag, 2015).

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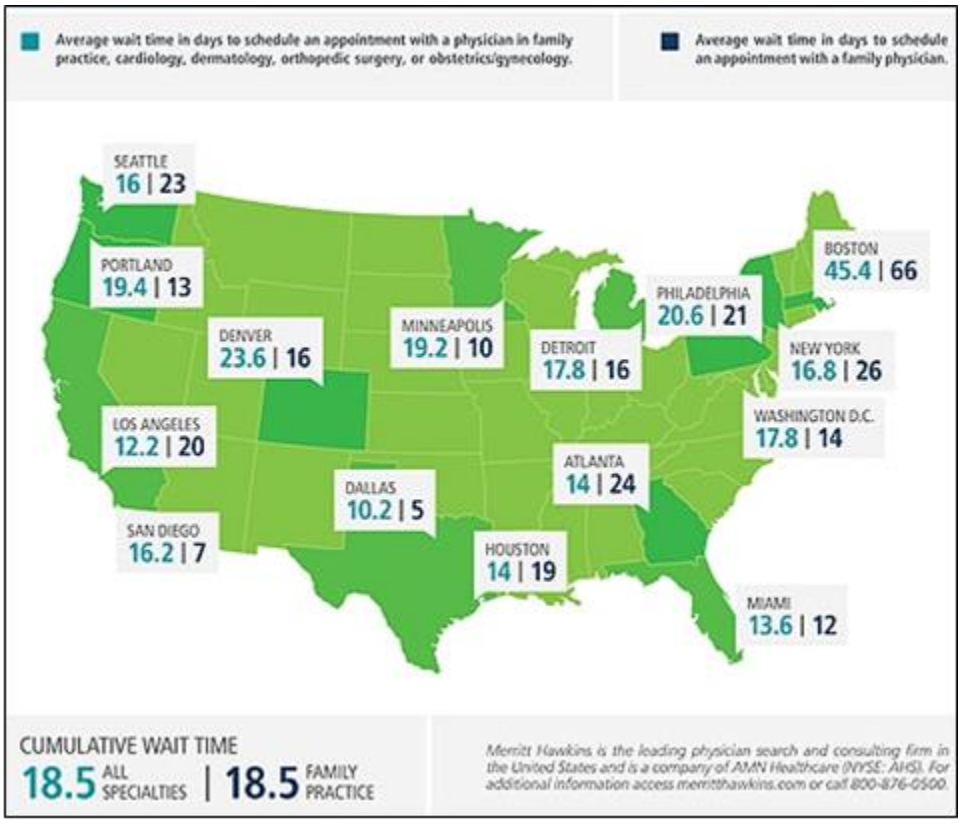
Appendix A

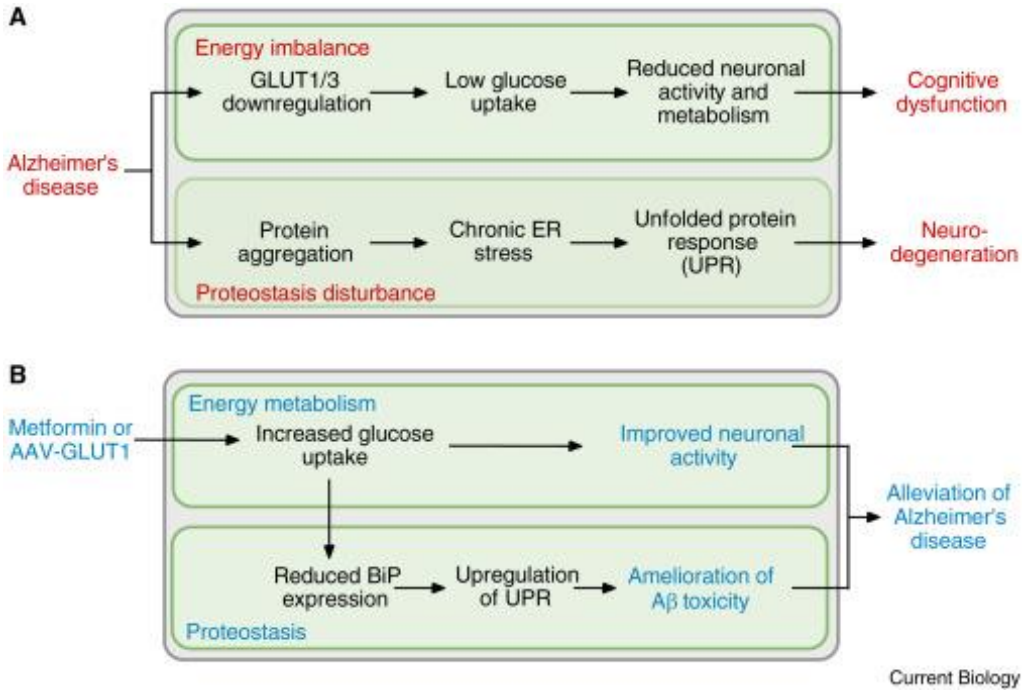
Figure 1: U.S. Average Wait Time in Days



Note: Adapted from Gold, J. (2014). In cities, the average doctor wait-time is 18.5 days. The Washington Post. Retrieved from https://www.washingtonpost.com/news/wonk/wp/2014/01/29/in-cities-the-average-doctor-wait-time-is-18-5-days/?noredirect=on&utm_term=.4b073043d6a5

Appendix B

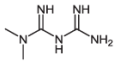
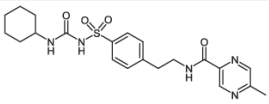
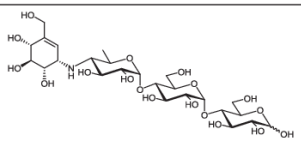
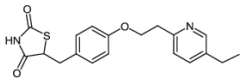
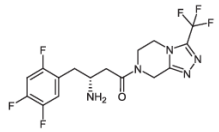
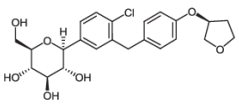
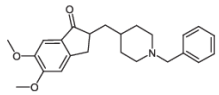
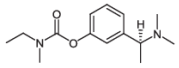
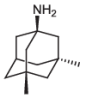
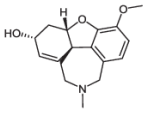
Figure 2: Energy Imbalances in AD & Metformin Mechanism of Action



Note. Adapted from Duran-Aniotz, C. & Hetz, C. (2016). Glucose metabolism: a sweet relief of Alzheimer's disease. *Current Biology*, *26,* R794-R815. doi: 10.1016/j.cub.2016.07.060

Appendix C

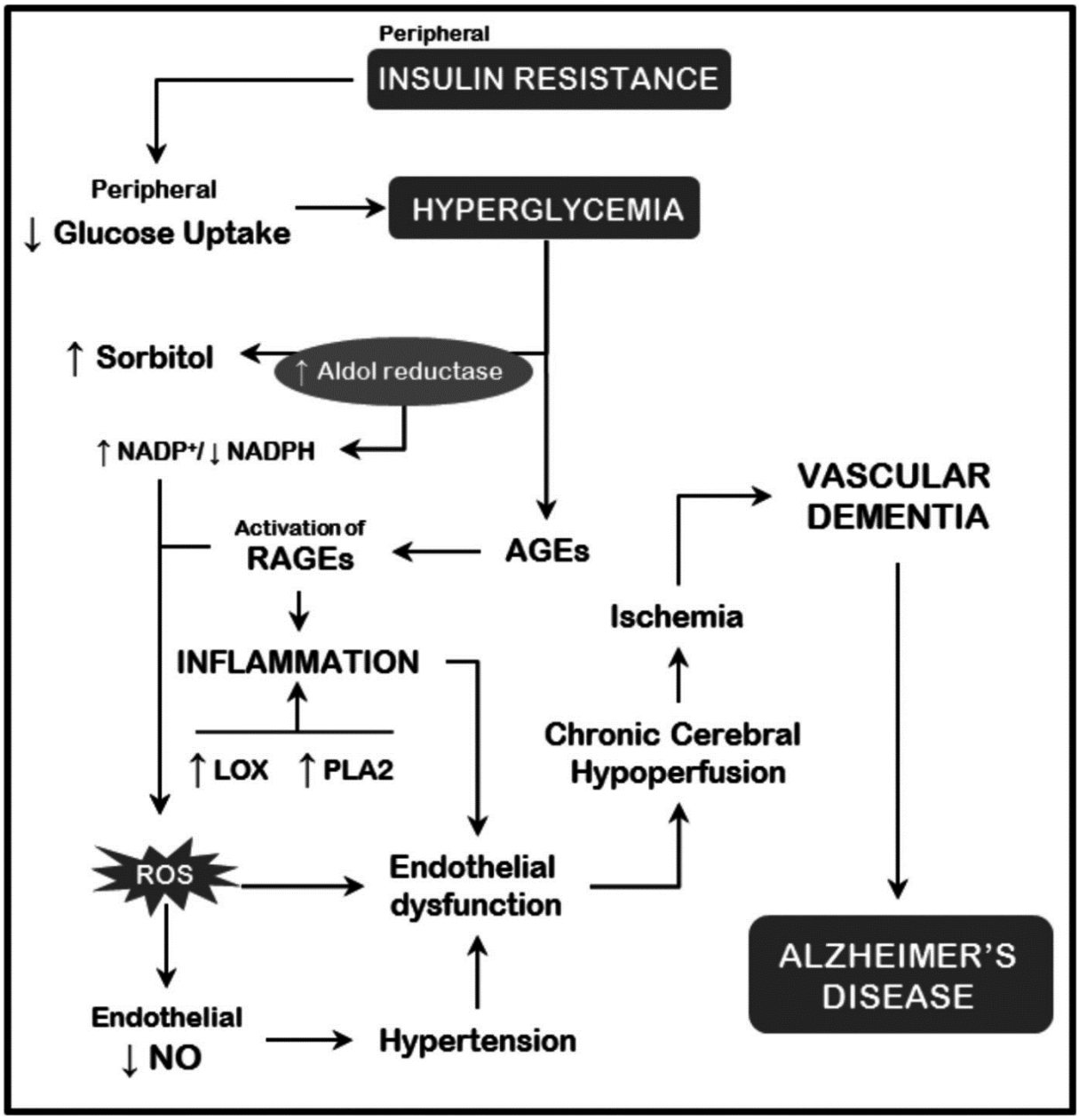
Table 1: Type 2 Diabetes and AD Drug Class, Structure and Effect

Drug	Class	Structure	Effect	References
TYPE 2 DIABETES				
Metformin (1)	biguanide		Suppressed gluconeogenesis, increased peripheral insulin sensitivity, increased peripheral glucose uptake	259 - 261
Glipizide (2)	sulfonylurea		Increased glucose-stimulated insulin secretion, increased peripheral insulin sensitivity, suppressed gluconeogenesis	262, 263
Acarbose (3)	α-glucosidase inhibitor		Decreased intestinal glucose absorption, increased peripheral insulin sensitivity	264, 265
Pioglitazone (4)	thiazolidine-dione		Enhanced insulin signalling, increased peripheral glucose uptake, improved lipid metabolism, suppressed gluconeogenesis	266, 267
Sitagliptin (5)	DPP-4 inhibitor		Increased glucose-stimulated insulin secretion, suppressed gluconeogenesis	268, 269
Empagliflozin (6)	SGLT-2 inhibitor		Reduced renal glucose reabsorption	270
ALZHEIMER'S DISEASE				
Donepezil (7)	Selective AChE inhibitor		Enhanced acetylcholine brain levels	271
Rivastigmine (8)	AChE and BChE inhibitor		Enhanced acetylcholine brain levels	272, 273
Memantine (9)	NMDA receptor antagonist		Reduced NMDA receptor-mediated excitotoxicity by inhibiting prolonged Ca^{2+} neuronal influx	274
Galantamine (10)	Alkaloid		Enhanced acetylcholine brain levels, potentiation of nicotinic acetylcholine activity, attenuation of Aβ deposit formation and neuroinflammation	275, 276

Note. Adapted from de Matos, A., de Macedo, M.P. & Rauter, A.P. (2017). Bridging type 2 diabetes and Alzheimer's disease. *Medicinal Research Reviews, 38*, 1, 261-324. doi: 10.1002/med.21440

Appendix D

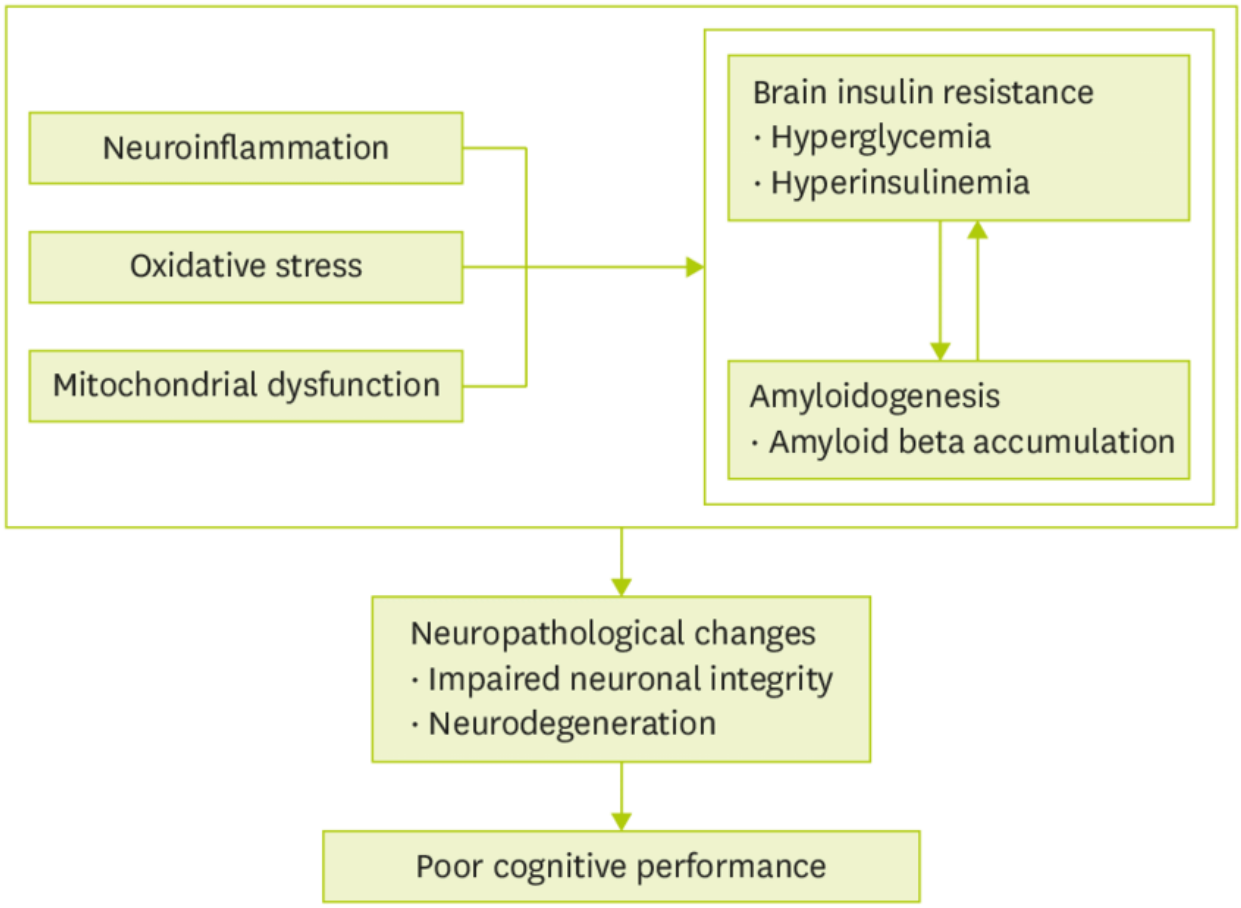
Figure 3: Insulin Resistance through Oxidative Stress



Note. Adapted from de Matos, A., de Macedo, M.P. & Rauter, A.P. (2017). Bridging type 2 diabetes and Alzheimer's disease. *Medicinal Research Reviews, 38*, 1, 261-324. doi: 10.1002/med.21440

Appendix E

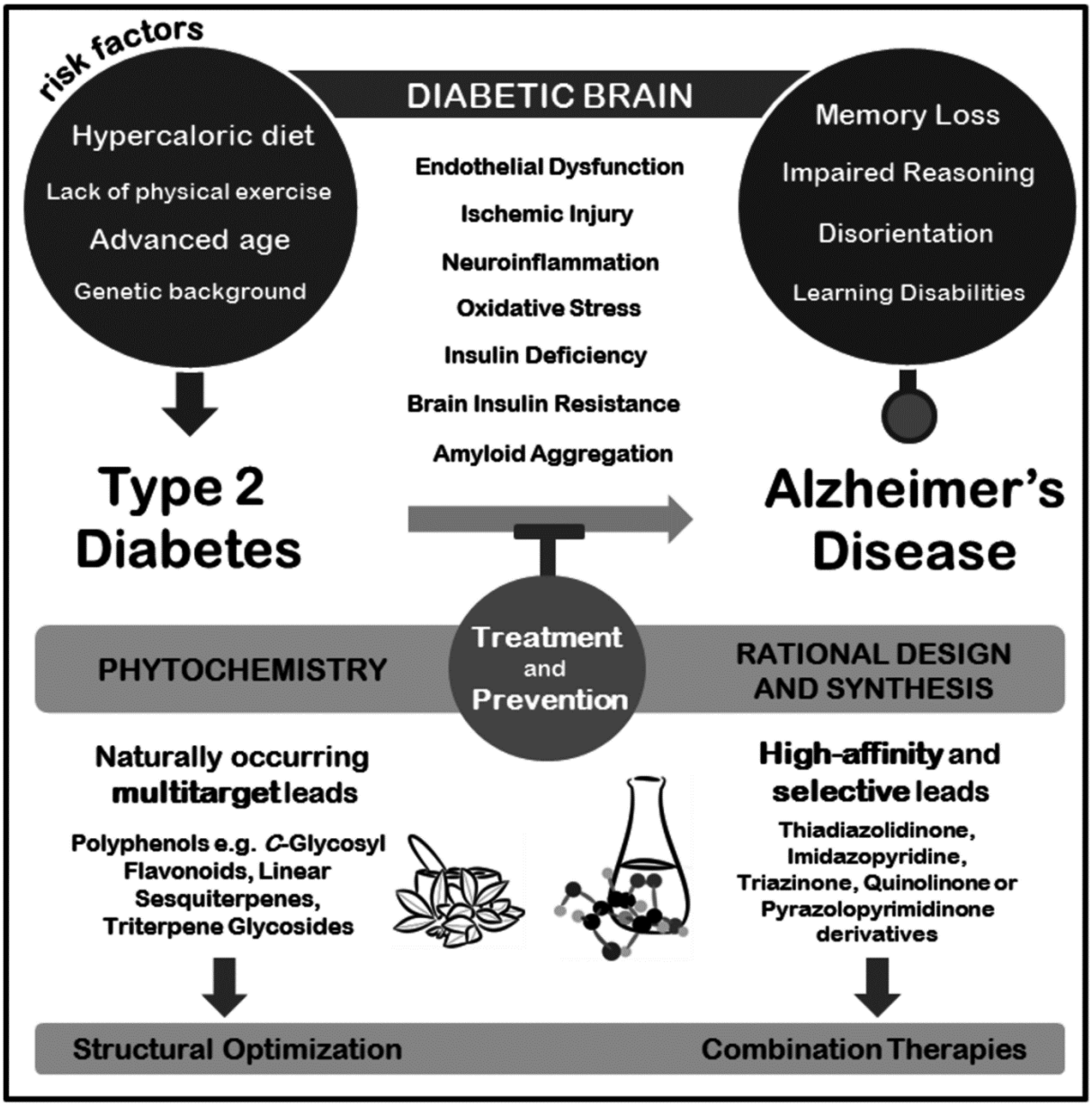
Figure 4: Hyperglycemic-induced Cognitive Dysfunction



Note. Adapted from Lee, H.J., Seo, H.I., Cha, H.Y, Yang, Y.J., Kwon, S.H & Yang, S.J. (2018). Diabetes and Alzheimer's disease: mechanisms and nutritional aspects. *Clinical Nutrition Research, 7,* 4. 229-240. doi: 10.7762/cnr.2018.7.4.229

Appendix F

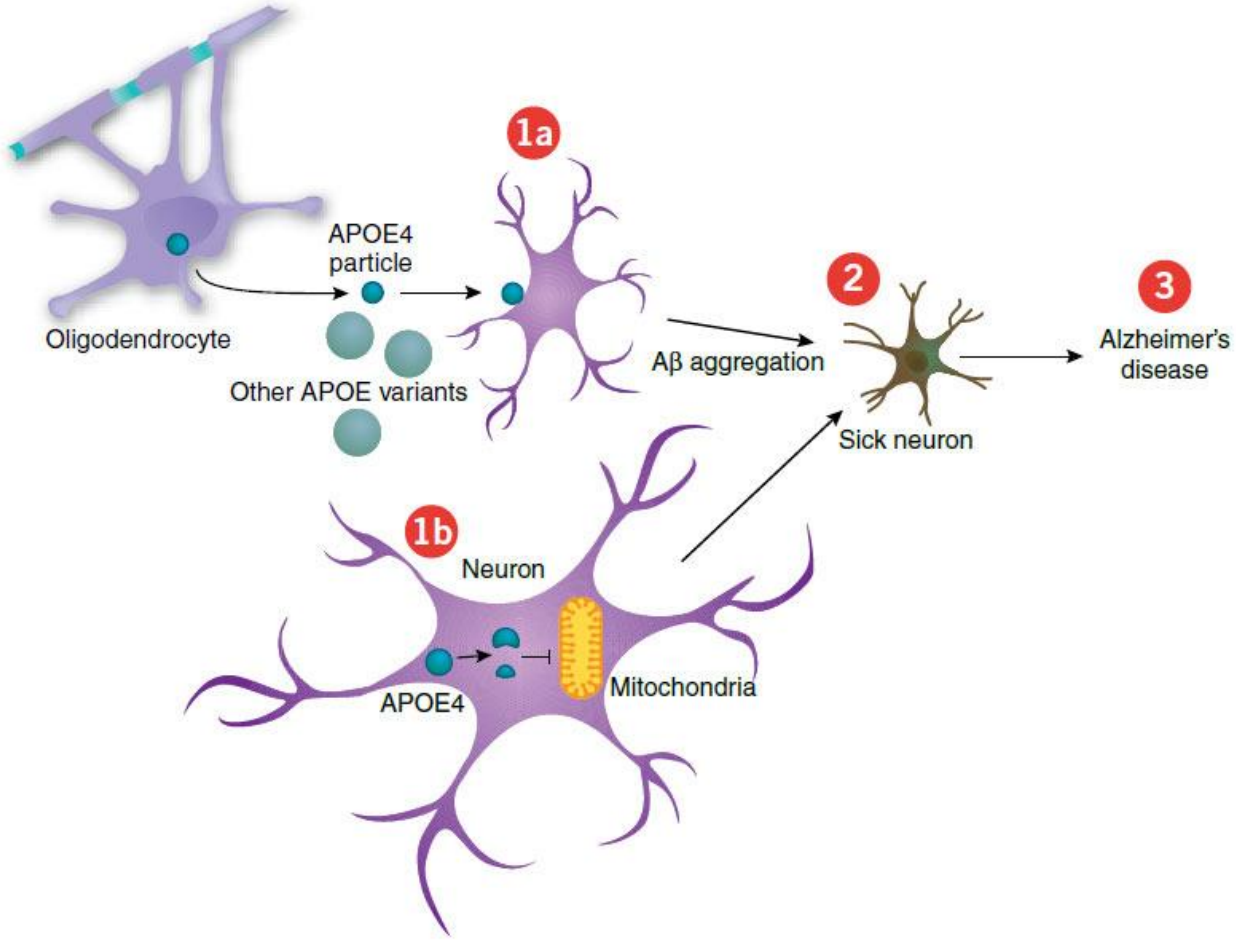
Figure 5: Summary of Treatment, Prevention of T2D and AD



Note. Adapted from de Matos, A., de Macedo, M.P. & Rauter, A.P. (2017). Bridging type 2 diabetes and Alzheimer's disease. *Medicinal Research Reviews, 38*, 1, 261-324. doi: 10.1002/med.21440

Appendix G

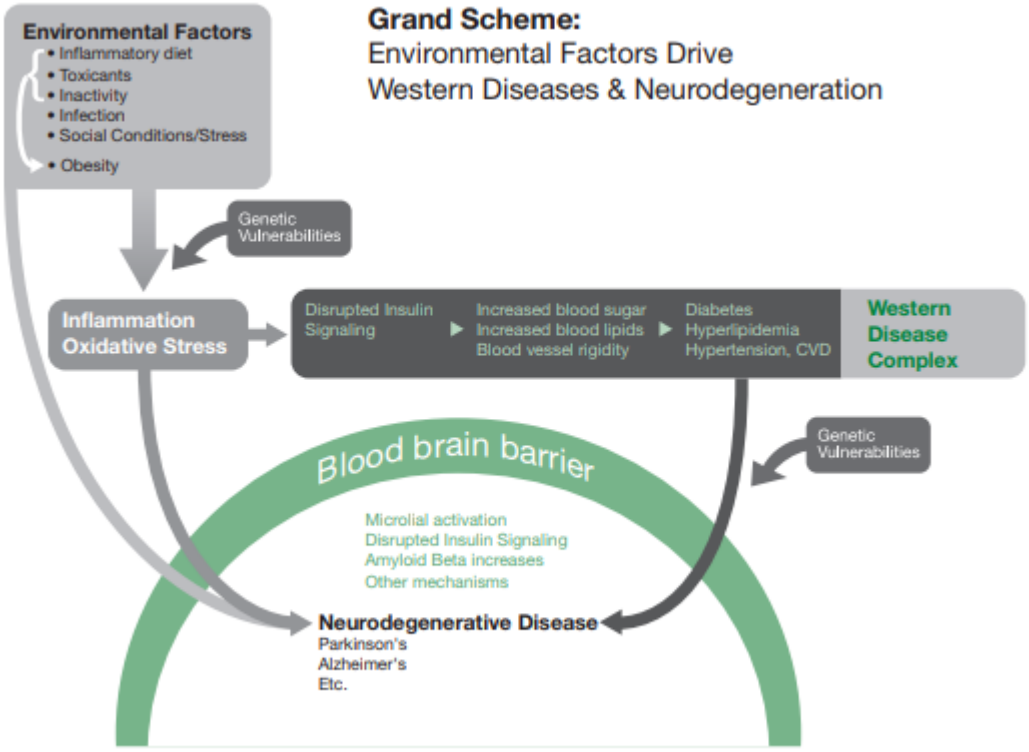
Figure 6: ApoE Mechanism of Action in Impaired Insulin Signaling



Note. Adapted from Zhao, N., Liu, C.C., Ingelgom, A.J., Painter, M.M., Sullivan, P.M., Bu, G. et al. (2017). Apolipoprotein E4 impairs neuronal insulin signaling by trapping insulin receptor in the endosomes. *Neuron, 96,* 1. 115-129. doi: 10.1016/j.neuron.2017.09.003

Appendix H

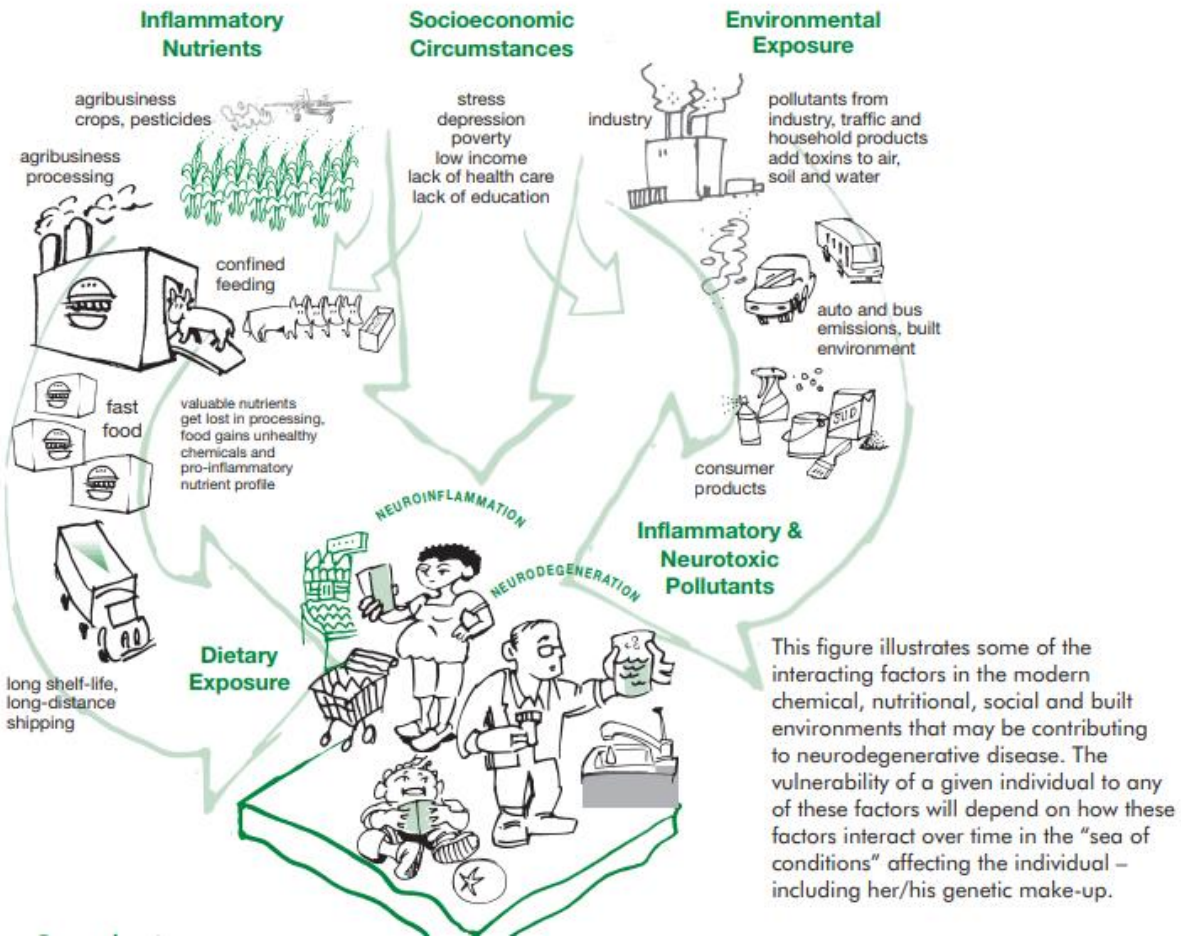
Figure 7: Complex Interplay of Environment, Western Disease & AD



Note: Adapted from Stein, J., Schettler, T., Rohrer, B. & Valenti, M. (n.d.). Environmental factors in the Development of dementia focus on Alzheimer's disease and cognitive decline. Greater Boston Physicians for Social Responsibility and Science and Environmental Health Network. Retrieved from http://action.psr.org/site/DocServer/chap7_0926.pdf?docID=5924

Appendix I

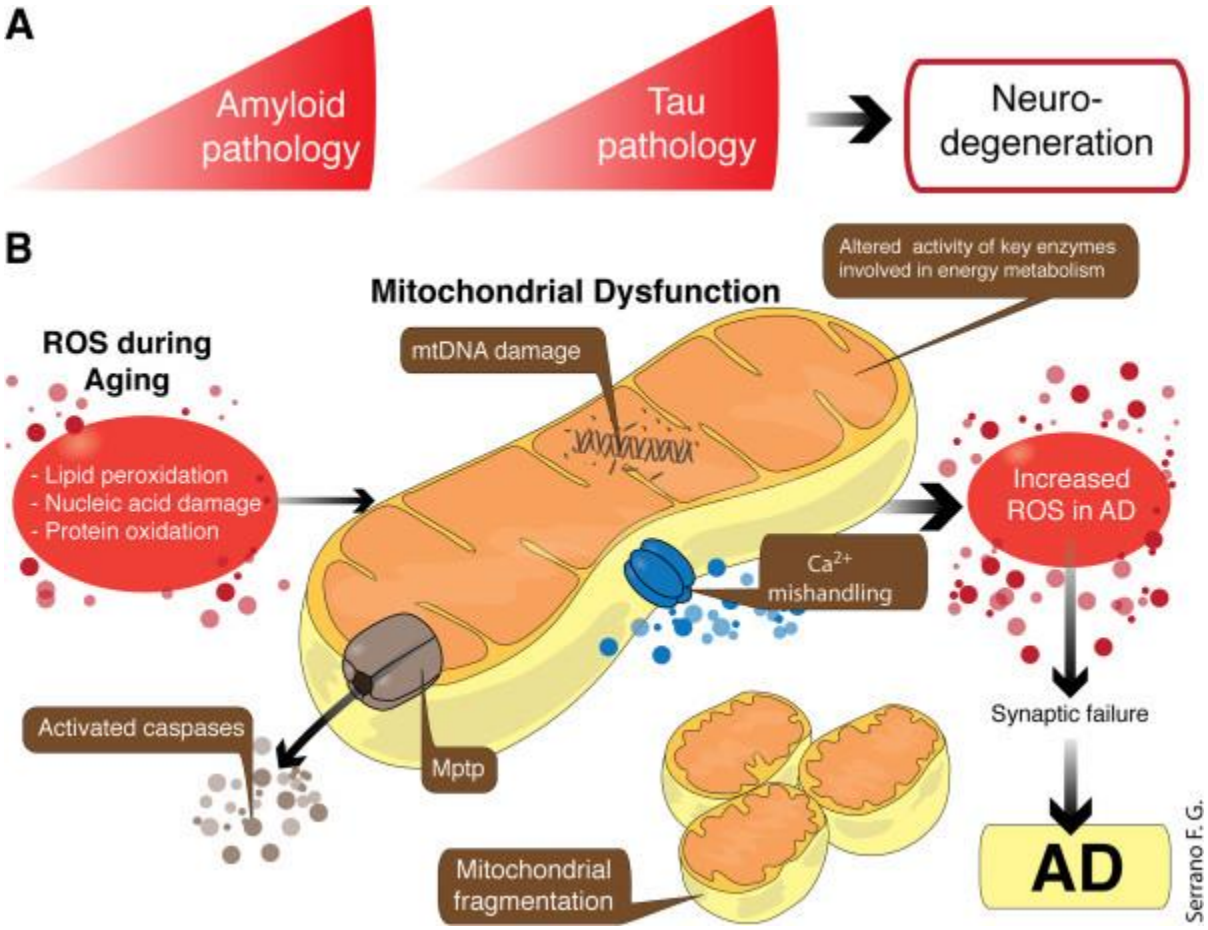
Figure 8: Inflammation, Environmental Exposure & Neurotoxic Pollutants



Note: Adapted from Stein, J., Schettler, T., Rohrer, B. & Valenti, M. (n.d.). Environmental factors in the Development of dementia focus on Alzheimer's disease and cognitive decline. Greater Boston Physicians for Social Responsibility and Science and Environmental Health Network. Retrieved from http://action.psr.org/site/DocServer/chap7_0926.pdf?docID=5924

Appendix J

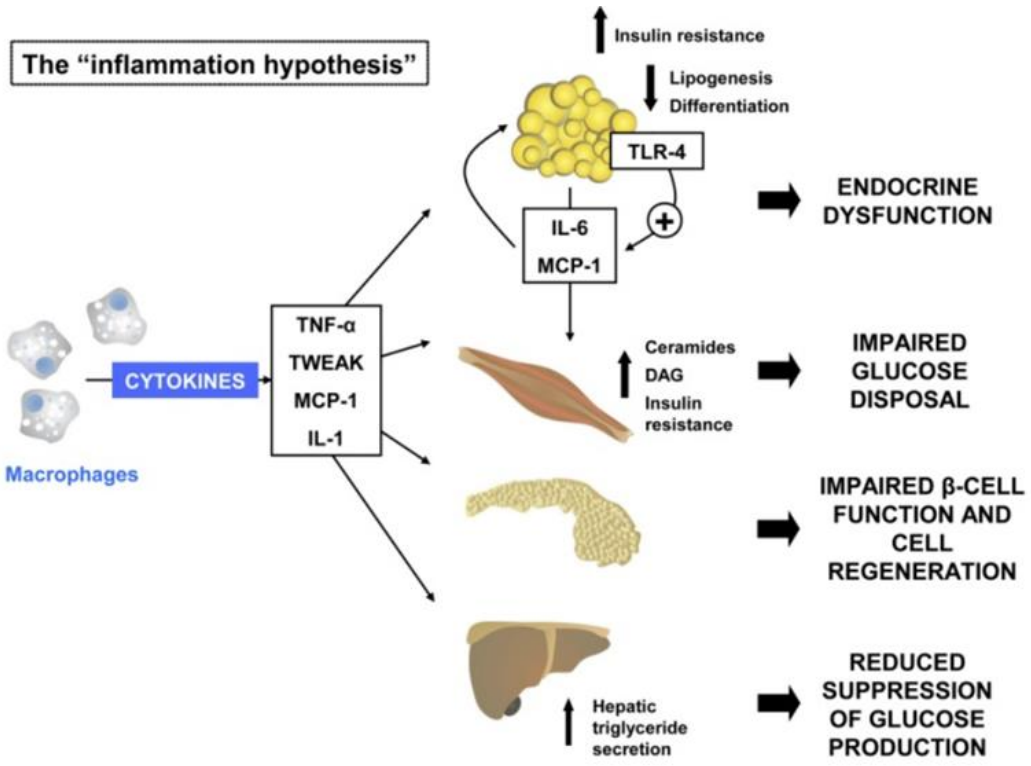
Figure 9: Mitochondrial Dysfunction in AD



Note: Adapted from Godoy, A., Leal, J.A, Zolezzi, J.M., & Braidy, N. (2014). Signaling pathway cross talk in Alzheimer's disease. Cell Communication and Signaling, 12, 23. 10.1186/1478-811X-12-23.

Appendix K

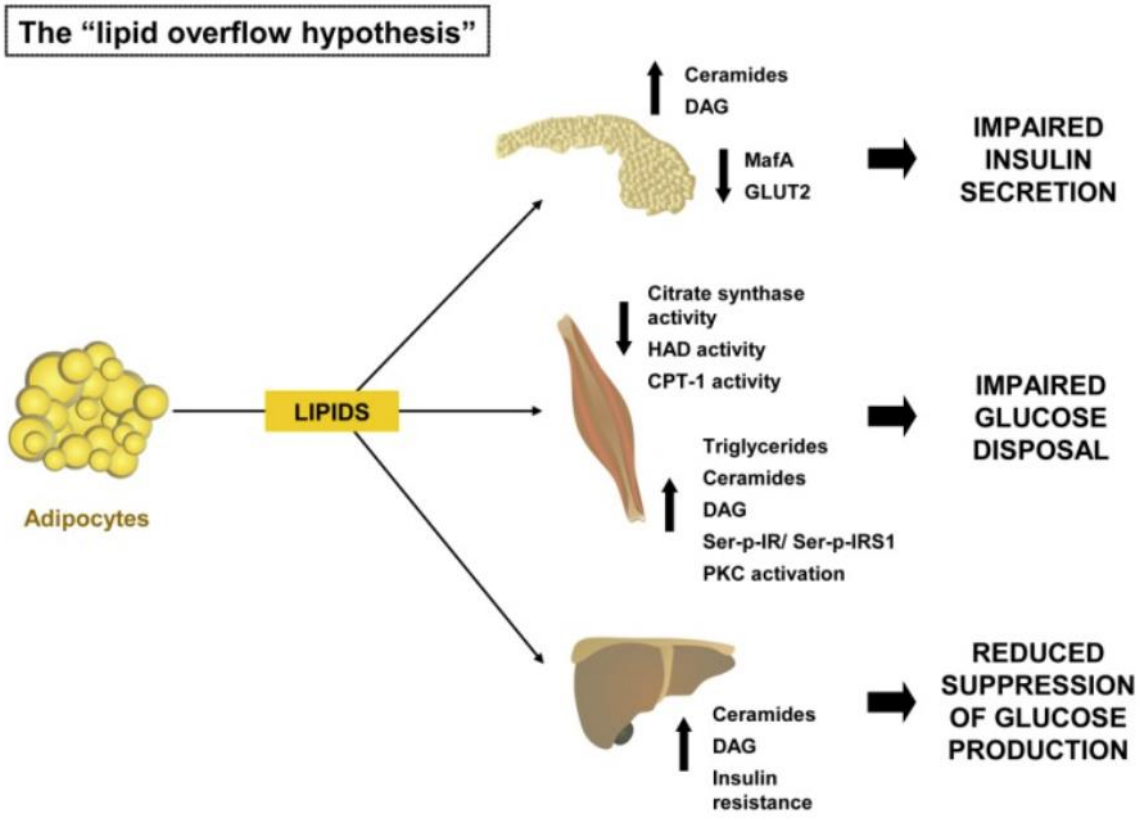
Figure 10: The "Inflammation Hypothesis" of obesity-induced chronic inflammation and peripheral insulin resistance.



Note: Adapted from Chadt, A., Scherneck, S., Joost, H.G. & Al-Hasani, H. (2018). Molecular links between obesity and diabetes: "diabesity." Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK279051/

Appendix L

Figure 11: The "Lipid Overflow Hypothesis" of obesity-induced ectopic lipid stores that cause peripheral insulin resistance and impaired β-cell function.



Note: Adapted from Chadt, A., Scherneck, S., Joost, H.G. & Al-Hasani, H. (2018). Molecular links between obesity and diabetes: "diabesity." Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK279051/