

Brain Insulin Dysregulation: Consequence for Neuropsychiatric Disorders

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Abstract

Clinical and epidemiological studies have substantiated the role insulin dysfunction plays in the development and progression of neurodegenerative and neuropsychiatric disorders. This paper looks at the role of brain insulin dysregulation in the pathology of neurological disorders such as Parkinson's, Alzheimer's, and Huntington's disease, and neuropsychiatric disorders, such as dementia, depression, and schizophrenia. This paper also explores the link between insulin resistance to metabolic dysfunction, cognitive dysfunction, neuroinflammation, and the central nervous system. Some studies that claim insulin resistance is not associated to a few of these disorders are also highlighted.

Keywords: *Insulin Dysfunction; Neurological; Neurodegenerative; Neuropsychiatric; Disorders; Insulin Resistance*

Until the late 1970s insulin was known specifically for its role in glucose and amino acid metabolism and less for its role in the central nervous system ([CNS], [1]). Insulin was only considered to be a peripheral hormone, incapable of crossing the blood-brain barrier (BBB) or of influencing the CNS [2]. Considerable advancement has since been made regarding the relation between the brain and insulin, and the physiologic roles that insulin has in the CNS are now quite clear, even though brain insulin uptake happens independently of insulin [3]. The connection between CNS and insulin was reported first in the 1960s after it was noticed that injecting insulin (intracisternal) in dogs reduced the levels of glucose in cerebrospinal fluid (CSF) and blood as it directly affected the parasympathetic area of the brain stem [4]. This evidence was authenticated by Havrankova, et al. [1], who verified the relation between insulin and the central nervous system when they discovered the rats' CNS had high concentrations of insulin. Results, which validated a non-linear relationship between CSF levels of insulin and plasma, providing the initial proof for a saturable transport system for insulin from blood to brain [5]. Since then additional studies presented clear proof that insulin occurs in the brain, where it exerts lasting trophic effects on CNS after reaching elevated levels [4].

Son, Shin, and Mook-Jung [6] conveyed that insulin is a peptide hormone which includes 51 amino acids created in and released from pancreatic cells in the islet of Langerhans. As the most powerful anabolic hormone, it is essential for life because it functions both metabolically and non-metabolically [7]. Insulin controls food intake, in addition to lipid, glucose, and energy homeostasis and stimulates synthesis (along with inhibition of breakdown) of triglycerides, glycogen, and many proteins. Its rapid release is typically caused by increased levels of glucose in the blood with its most significant effect being the stimulation of growth and differentiation of cells, transcription activation or repression, and control of protein kinases and phosphatases. The adipose tissue, liver, and muscle are the most sensitive to insulin, making it the most beneficial anabolic hormone known to date [2].

Insulin maintains the body's blood glucose level by binding to the insulin receptor (IR). IR's are dispersed all through the peripheral tissues, the primary job being to carry glucose into cells, avert glucose production and raise the uptake of glucose by prompting signaling pathways in the muscle, fat, and liver [7]. The human brain contains two kinds of insulin receptors. The first, the neuronal/neuron-specific type, is plentiful in the neuron, whereas, the other, the non-neuronal/peripheral-like type, is of a lesser density in the glial cells. Insulin receptors are in abundance in the brain, and very enriched in the amygdala, olfactory bulb, cerebellum, hippocampus, cerebral cortex, and hypothalamus [7]. All of which are enmeshed in the metabolic control of insulin action, together with neuronal development and cognitive function [8].

In the hypothalamus and limbic system, insulin signaling is vital for cognitive function, despite peripheral glucose changes [6]. Insulin encourages the survival of cells by delaying apoptosis-stimulating peptides and by improving the outgrowth of neurite and formation of synapse, which helps neuronal development and differentiation. The positive effects insulin has on synaptic function, also results in the improvement of learning and memory [9]. Also, Spielman and Klegeris [10], conveyed that insulin performs distinctive neurotransmitter functions within the CNS. That is, in the CNS, insulin and insulin-like growth factor (IGF) signaling play crucial roles in controlling and maintaining cognitive function. For instance, IGFs and insulin control a broad range of neuronal functions all through life, from embryonic and fetal progression to adulthood. The binding of insulin and IGF to their own receptors, triggers the corresponding signaling pathways, resulting in phosphorylation and stimulation of intrinsic receptor tyrosine kinases [9]. Hence, signaling that is weakened through insulin, and IGF receptors have poor outcomes regarding CNS structural and functional integrity [9].

Insulin Resistance

Insulin resistance (IR) is a physiological condition wherein the sensitivity to insulin is reduced or lost. Therefore, a brain that is insulin resistant displays a profound loss of microglial proliferation, neuronal degeneration, synapse, and activation of numerous inflammatory processes [11]. Ünal, Kara, Aksak, Altunkaynak and Yıldırım [12], expressed that insulin resistance and deficiency has severe metabolic and functional difficulties on the central nervous system. Problems that can result in subcortical, brainstem damages, cerebral atrophy, and cognitive dysfunctions as insulin resistance makes neurons more susceptible to metabolic stress, thus accelerating neuronal dysfunction [13].

Insulin resistance is also thought to be the leading cause of metabolic syndrome, diabetes, hypertension, and cardiovascular disease [14]. Thus, there are many phenotypes of insulin resistance utilized to make a diagnosis of diabetes, like hyperglycemia, (high glucose levels in the bloodstream caused by insulin's failure to facilitate the uptake of glucose or β -cells inadequately producing insulin), and hyperinsulinemia (high levels of insulin, crucial to maintaining healthy levels of glucose in the bloodstream) (Min, Joon, and Mook-Jung, 2011). In addition, peripheral insulin resistance aids in the progress to hyperglycemia and influences additional insulin functions. Specifically, it alters decrease uptake of moving lipids and increase hydrolysis of stored triglycerides. This impaired lipid homeostasis has been recognized as one of the primary causes of insulin resistance [15]. Insulin also modifies peripheral glucose metabolism and normal brain behavior. So, insulin signaling that is defective leads to impaired neuronal functioning and amplifies neurodegeneration, which reduces insulin signaling on neurons [16]. Dysregulation of insulin signaling is hence connected to aging and metabolic and neurodegenerative disorders. The discovery of insulin resistance in many ageing-related neurodegenerative disorders was most likely due to the complications of insulin signaling pathways and the numerous places interference can influence their functions [17].

Neuroinflammation is another major mechanism contributing to neurodegeneration. Hemmati, et al. [18] articulated that toll-like receptors (TLRs), a family of type I transmembrane glycoproteins that play a significant role in the immune system, are the most critical components in the initiation and the progression of neuroinflammation and the development of various neuronal illnesses. Activating TLRs is thus one of the most vital elements in the introduction of insulin resistance in the central nervous system, as neurological diseases' pathology stems from the association of insulin resistance and insulin signaling dysregulation [18]. Evidence supporting the connection between insulin resistance and inflammation, show that inflammatory pathways are major contributors in bringing about insulin resistance. For example, TLRs role in neuroinflammation and central insulin resistance plays a major part in the induction and progression of neurological and neurodegenerative disorders [18].

Inflammation plays an important role in the development of obesity, diabetes, metabolic syndrome, and many other diseases [19]. The link between inflammation and insulin resistance in obesity has been illustrated in a study conducted by Wu, Molofsky, Liang, Ricardo-Gonzalez, Jouihan, Bando, Chawla and Locksley [20]. The researchers used IL-4 reporter mice and focused on the role of eosinophils, granulocyte myeloid cells which are related to the innate immunity and anti-inflammatory Th2 immune responses. While, eosinophil numbers in the 'lean' adipose tissue are extremely low, they have been shown to be vital for supporting the M2 ATM phenotype and therefore help in sustaining the 'healthy' M2:M1 ATM equilibrium [19]. Furthermore, IR was ameliorated in hypereosinophilic HFD-fed mice, in which eosinophil numbers were elevated via the helminth infection or transgenic IL-5 expression. Their findings support the interlinked relationship between metabolism and immunity and are consistent with the enrichment of inflammatory and immune response genes connected to corpulence in humans [20].

Diabetes Mellitus

In western countries, diabetes has reached epidemic proportions. As stated by the World Health Organization (2017), diabetes is estimated to affect 300 million persons by 2025 globally, making it a significant public health concern [2]. Akter, Lanza, Martin, Myronyuk, Rua, and Raffa [21], communicated that it is estimated that of the US population, 8% or 24 million persons has diabetes and another 57 million or more are at a greater risk of getting diabetes as they are in an intermediate state of altered metabolism. Diabetes Mellitus (DM), occurs when a person's glucose metabolism is abnormal due to insulin deficiency. DM is one of the most common metabolic disorders that develop after several years of the pancreas failing to recompense for insulin resistance. It is of multiple etiology, distinguished by chronic hyperglycemia, either resulting from: (1) a breakdown of β -cells within the pancreatic islets of Langerhans to make insulin in adequate amounts to sustain healthy blood glucose levels and or from (2) an obstruction to insulin action [22].

There are four types of diabetes mellitus: gestational diabetes, "other specific types," and the two most common forms: Type one and Type two. Gestational diabetes mellitus is not a pathophysiologic condition, but rather a functioning classification of females who, during pregnancy, develops diabetes mellitus. Women who, during gestation, develops Type one diabetes mellitus and women discovered during pregnancy to have type two diabetes mellitus are classified with Gestational Diabetes Mellitus (GDM). In most women who develop GDM, the condition begins in the third trimester of pregnancy [2]. Diabetes mellitus of several known etiologies are grouped together and classified as "Other Specific Types". This group accounts for less than 10% of all diabetes mellitus cases and includes persons with genetic deficits of beta-cell function or with defective insulin action [2].

Type one diabetes mellitus occurs when there is a partial or total loss of beta cells, which results in uncontrolled levels of blood glucose (hyperinsulinemia hyperglycemia) and weakened insulin secretion [23]. This is distinguished by the destruction of beta cell brought about by an autoimmune process, usually resulting in complete insulin deficiency. Type one diabetes is typically portrayed by the existence of islet cells, anti-glutamic acid decarboxylase or insulin antibodies which recognize the autoimmune processes that cause the ruin of beta cell [2]. The most typical form of diabetes is Type two Mellitus, which accounts for 90-95% of all diagnosed diabetes cases worldwide [21,24].

Type 2 diabetes mellitus (T2DM) is a disorder in which high blood glucose level develop from increased production of hepatic glucose, decreased the production of insulin by pancreatic β -cells and reduced insulin release in response to hyperglycemia stimuli or insulin resistance [2]. Thus, inadequate glucose control leads to health complications including effects on the CNS, possibly due to defective leptin signaling [21]. For instance, initially, when insulin is released it can return blood glucose concentrations back to its normal state specifically hyperinsulinemic euglycemia. However, when the beta cells are no longer capable of maintaining normal blood glucose because they reached their maximum insulin-producing capacity, the state of hyperinsulinemia hyperglycaemia or type 2 diabetes occurs [23]. Unfortunately, to date, more than 100 neurodegenerative syndromes have been defined and, of these, about 20 are linked to DM, suggesting that approximately 20% of neurodegenerative diseases are related to DM [22].

Dementia

Dementia is an increasingly common disorder that traverses worldwide along with the T2DM epidemic. In fact, mounting epidemiologic evidence has implied that individuals with diabetes mellitus are at a greater risk for the development of dementia. The connection between dementia and insulin resistance is validated by research regarding ailments related to insulin dysfunction [25]. Insulin resistance is the underlying cause of diabetes mellitus and several chronic diseases and, as such, a likely key risk factor for dementia. Dementia is a complicated condition that contributes to a rising number of wide-reaching diseases with the most recent estimates proposing that there are 44 million affected persons globally and another 7.7 million new cases every year [26]. Also, pre-diabetic stages of insulin resistance and primary risk factors for IR and T2DM related to changes in the brain leads to a higher chance of dementia developing [27]. Arvanitakis, *et al.* [28] conveyed that diabetes mellitus is a risk factor for neurological illnesses including dementia. Moreover, clinical reviews have linked insulin resistance and T2DM to dementia and cognitive impairment. For example, a meta-analysis of epidemiological studies revealed that the risk of dementia was 73% greater in individuals with type 2 diabetes mellitus than in people without diabetes; indicating that between 1 and 10 and 1 and 15 dementia cases globally might be because of T2DM [27].

Dementia is a syndrome that affects thinking, memory, behavior, and the ability to perform normal activities. It usually manifests in old age, in most people, with the most common cause being Alzheimer disease. Davis, Zilkens, Starkstein, Davis and Bruce [29], designed a longitudinal observational study to evaluate the incidence, age of onset, survival and relative hazard of dementia consisting of 1291 participants with type 2 diabetes assessed with a corresponding group of 5159 persons without diabetes. They found that throughout 13.8 ± 5.8 years of follow-up, incident dementia happened in 13.9% and 12.4% of the groups of contributors with and without diabetes,

respectively ($p = 0.15$). With type 2 diabetes, the occurrence of dementia was greater (incidence rate ratio [IRR] 1.28, 95% CI 1.08, 1.51), as was the contending risk of death (IRR 1.50, 95% CI 1.38, 1.64). The ages when dementia was first documented and when death with dementia come about were both earlier with diabetes, by 1.7 (95% CI 0.6, 2.9) and 2.3 (95% CI 1.1, 3.6) years, respectively (both $p \leq 0.004$). Type 2 diabetes was linked with an adjusted sub-distribution HR of 1.18 (95% CI 1.00, 1.39), and a cause specific HR of 1.51 (95% CI 1.27, 1.78) for all-cause dementia. Consequently, type 2 diabetes was linked to an increased occurrence and risk of all-cause dementia and an increased risk of premature death [29].

Ott, Stolk, Hofman, van Harskamp, Grobbee and Breteler [30], also analyzed the connection involving dementia and diabetes utilizing a large population-based analysis of 6330 subjects, aged 55 to 99 years old, and discovered that diabetes existed in 724 (11.4%) of the subjects. Also, diabetes was found to be present in 59 (22.3%) of the 265 dementia patients. Moreover, many logistic regression studies, changing for sex and age differences, showed an active connection between dementia and diabetes (odds ratio: 1.3, 95% confidence interval: 1.0 - 1.9). Specifically, strong links were also discovered between dementia and diabetes treated with insulin (odds ratio: 3.2, 95% confidence interval: 1.4 - 7.5), with vascular dementia being the strongest link [30]. These findings propose that diabetes is associated with dementia and that several diabetic problems and comorbidities (e.g. stroke, hypertension, and depression) have been attributed to risk factors for dementia [30].

Another research involving nine community-based longitudinal studies [31-38], analyzed the association of diabetes to the risk of developing dementia. The results, although mixed regarding the connection of diabetes to specific causes of dementia, revealed that when diabetes is present the danger of incident dementia becomes greater by two-to-threefold. For instance, of six studies that looked at the link between diabetes and vascular dementia, five reported an increase and one reported a null finding [24]. To date, there are over 100 different types of dementia and research show that the risk of developing dementia may be doubled for persons with type 2 diabetes mellitus compared to individuals who do not have diabetes [39].

Alzheimer's Disease

One of the most widespread neurodegenerative diseases is Alzheimer's disease (AD). The number of persons diagnosed with this disease is estimated to be approximately 30 million, a rapidly growing number, presumed to increase fourfold in the next 40 years [3,4]. Alzheimer's affects memory as well as other cognitive domains, which leads to the decline of a person's independence in daily life. AD places a considerable burden on the family members of persons diagnosed with AD and is also responsible for a significant economic cost to society [40]. Clinically, this disease has a deceitful beginning, usually starting with mild deterioration in the patient's memory that progresses to the total decline in cognitive and adaptive functioning [2]. Neuropathologically, it is characterized by intracellular neurofibrillary tangles (NFT), the presence of extracellular senile plaques (SP), and a decline in the basal forebrain cholinergic neurons that supply the cortex and hippocampus with nerves.

Damage is extensive in Alzheimer's disease as many neurons stop working, lose connections with other neurons, and die [2].

Deng, Li, Liu, Iqbal, Grundke-Iqbal and Gon [41], communicated that recent studies proposed that insulin dysfunction takes part in the pathogenesis of AD. There are also studies, which reveal that in the brains of persons with Alzheimer's disease, the glucose metabolism is impaired, which precedes pathology and clinical symptoms of the disease. However, exactly how the impaired insulin signaling contributes to AD is not known [41]. The correct amount of pathological deficiencies in AD are unidentifiable, but major theories imply an accumulation of neurofibrillary, tangle or soluble b-amyloid oligomers or insoluble plaques [21]. Karelina and Weil [42] conveyed that a significant amount of evidence has arisen linking clinical symptoms and the pathophysiology of AD to insulin resistance. For instance, early clinical reviews found poor glucose regulation and peripheral hyperinsulinemia in patients with AD, which resulted in extensive studies verifying that type 2 diabetes considerably increases the possibility of AD developing. Also, postmortem analysis of AD patients' brain tissue showed a progressive decrease of IGF receptor mRNA and brain insulin receptor, both of which revealed up to an 85% decrease in late stages of AD [42].

Holscher [43] expressed little is known about the processes that initiate the beginning of Alzheimer's disease; however, risk factors have been identified that might shed light on the progressions that may activate or facilitate the development of AD. For instance, it was observed that insulin receptors are less sensitive in the brains of persons with AD and that insulin, which is neuroprotective, acts as a growth factor in the brain. Hence, insulin dysfunction may facilitate the development of AD [43]. De Felice, Lourenco, and Ferreira [44] expressed that inflammation, altered metabolism, and insulin resistance are key pathological characteristics of AD. Also, defective insulin signaling, altered levels and, or signaling pathway, and reduced responsiveness to insulin is visible in the brains of persons with AD [44].

Epidemiologic and clinical studies have also verified that both hyperglycemia and hyperinsulinemia is associated with the development of AD-related pathology in humans. Talbot, *et al.* [45], stated that many studies specified that peripheral insulin resistance could bring about the beginning of AD by decreasing the uptake of brain insulin and elevating brain levels of A β , τ phosphorylation, dyslipidemia, proinflammatory cytokines, oxidative stress, apoptosis, and advanced glycation end products. The disruption of insulin signaling is also proposed to be associated with the pathological signs of AD so much that it has been theorized that Alzheimer's disease may be 'type 3 diabetes' [21].

Traditionally diabetes and Alzheimer's disease were believed to be self-governing disorders. However, recent epidemiological findings and other scientific investigation have indicated a potential link as well as some shared pathophysiological mechanisms [21]. Ghasemi, *et al.* [4], expressed that a number of epidemiological studies concentrated on the link between diabetes mellitus and AD. One such study, a population-based cross-sectional study of 980 older adults, discovered that distinguishing traits of insulin resistance syndrome were associated with the risk of Alzheimer's disease, and APOE-4 phenotype did not influence this association.

Furthermore, Peila, Rodriguez, and Launer [36] communicated that the connection between diabetes and AD is incredibly high among carriers of APOE ϵ 4 allele, as APOE ϵ 4 radically modifies the possibility of Alzheimer's in persons with diabetes. That is, the combined effects of diabetes and APOE ϵ 4 was synergistic, resulting in individuals with both diabetes and APOE ϵ 4 being five times more at risk of developing AD compared to people without the two risk factors [36]. Similarly, Ghasemi, *et al.* [4], expressed that the results of a community-based cohort study, that examined the link between borderline diabetes mellitus and the likelihood of developing AD revealed that during nine years of follow-up, 307 of the 1,173 participants with borderline diabetes mellitus developed Alzheimer's disease.

According to Talbot, *et al.* [45] Alzheimer's disease and type 2 diabetes share numerous age-related pathophysiological features such as disturbances in non-neural tissues glucose metabolism, inflammatory stress and peripheral oxidative, neural atrophy and, or degeneration, insulin resistance, amyloid aggregation, and cognitive decline. Of these shared features, insulin resistance is perceived as the most likely etiological factor in AD, due to its reduced cellular responsiveness to insulin. To validate, Talbot, *et al.* [45], used *ex vivo* stimulation experiments on postmortem brain tissue with near-physiological doses of insulin or IGF-1, to present, perchance, the first direct substantiation that the brain in AD is insulin and IGF-1 resistant. The brain areas the researchers studied in AD displayed insulin resistance that was associated with dysfunctional insulin receptor substrate 1 (IRS-1) as well as insulin-like growth factor 1 (IGF-1) resistance that was associated with dysfunctional insulin receptor substrate 2 (IRS-2). Their study highlighted that serine phosphorylation of IRS1 is a common pathophysiologic mechanism of Alzheimer's disease and diabetes. The levels of IRS1 serine phosphorylation and their stimulated kinases presented a positive correlation with levels of oligomeric b-amyloid (Ab) plaques and an inverse connection with memory and cognition [45]. Since cerebral insulin resistance is a characteristic of AD, it is easy to argue that for this reason, persons with T2DM are at a greater risk of developing AD. Despite this reasoning, however, post-mortem research of brain tissue imply that T2DM is linked to a reduction, rather than an increase of neurofibrillary tangles and amyloid plaques [27].

The connection between AD and DM is controversial, as many studies have verified that diabetic patients are at a greater danger of developing AD. However, these discoveries have not been fully endorsed in neuropathological studies [46]. For this reason, some studies contradict this point. For example, in a study that evaluated the neuropathological features of post-mortem brains from 701 elderly persons, Alafuzoff, Aho, Helisalimi, Mannermaa and Soyninen [47] reported that in patients with diabetes, hyperglycemia is not a risk factor for lesions related to Alzheimer's. As a matter of fact, this analysis asserted that it is only in the last stages of AD and when APOE-4 is present, that diabetes may multiply the tau protein hyperphosphorylation. After investigating the APOE genotype of diabetic dementia patients, and before this, Neilsen, *et al.* [48] had stated that AD and DM are independent of each other. The authors [48] held that coincidence of DM and AD as indicated in other analyses is only attributable to the high occurrence of these diseases, which increases the likelihood of their coexistence. Then again, it has been expressed that the primary lesions bring on by diabetes and responsible for diabetic dementia monitored in other studies are not AD pathology, but cerebral infarction and vasculopathy [24,47].

Huntington's Disease

Huntington's disease (HD), an autosomal neurodegenerative disease is characterized by a severe movement disorder, cognitive deficiency, psychiatric problems and premature death [49]. It is also distinguishable by irregular huntingtin polyglutamine aggregates that lead to an advancement of neuronal dysfunction and loss, particularly in the cortex and striatum. Initial information from quite a few investigational and clinical analyses reveal that HD is linked to insulin disruptions and diabetes. For instance, it has been stated that hyperglycemic chorea-ballism or acute exacerbation of Huntington's chorea occur in patients with diabetes and can be improved by administering insulin. HD is hence, a neurodegenerative disease wherein neuroinflammatory processes play a significant part in the growth and

progress of illness [4]. Ghasemi, *et al.* also affirmed that evidence confirms that insulin dysfunction accompanies the pathology of HD via abnormal glucose tolerance testing and damaged insulin secretion due to reduced beta-cell mass and their insulin content, reduced β -cell duplication and deteriorated exocytosis from mutant huntingtin. When insulin secretion capacity is impaired in HD patients, it can result in the inability to offset insulin resistance [4].

Block, Dorsey, Beck, Brenna, and Shoulson [50], expressed that a pathogenic element in Huntington disease might be insulin resistance. That is, a link between HD and diminished insulin secretion is implied by the R6/2 transgenic mouse model categorized by 150 CAG repeats. For instance, at the age of 9 weeks these mice developed glucose and glycosuria intolerance, and by 14 weeks more than 70% had developed diabetes. Also, intranuclear inclusions, a histopathologic trademark of HD was discovered in the pancreatic cells and brain tissue in this same murine model of HD [50]. These statistics are in accordance with the discovery that in neurons, functional similarities with insulin-secreting pancreatic cells are shared and that these likenesses have been hypothesized to be because of islet cell growth from a familial insulin-secreting neuron [50]. In another study, Crocker, Costain, and Robertson [51] used microarray analysis to identify shared pathways that may be a factor in the pathology of HD. A 15 K high-density mouse EST array not used before for HD was questioned in this study, resulting in the identification of 170 differently expressed ESTs in symptomatic R6/2 mice. This study revealed that of the 80 genes with known function, nine genes was identified previously as being modified in HD, the remaining 71 genes, however, was linked with HD for the first time. The information acquired from this review gave an understanding of how genes contribute to adaptive and pathological processes associated with Huntington disease.

Parkinson's Disease

The second most common degenerative disease is Parkinson's Disease (PD), affecting 0.6% of the population between ages 65 - 69 and 2.6% of those ages 85 - 89 [52]. Age is the most reliable predictor of PD; however, the sickness is not limited to older adults, as five to ten percent of person's experience PD symptoms before age 40. Progression of PD in midlife is described as "young-onset Parkinson's disease." The illness impacts all racial groups, but more Caucasians are diagnosed compared to African Americans and Asians. Furthermore, males are diagnosed with PD more frequently than females [53]. Santiago and Potashkin [54] stated that in the substantia nigra pars compacta (SNpc) area of the brain of a person with Parkinson's disease, it shows a loss of dopaminergic neurons and the existence of intracytoplasmic Lewy bodies containing aggregated filamentous α -synuclein. The leading medical indicators of persons with PD are bradykinesia, a shakiness in their posture, resting tremor, and muscle stiffness. Furthermore, dopamine deficiency in the striatum cause nearly all the symptoms, because of the deterioration in the SNpc [54]. Clinically, Parkinson's disease is unrelated to diabetes. However, both disorders are believed to have underlying pathological mechanisms in common. For instance, chronic inflammation is thought to significantly influence the development of both PD and diabetes [18]. PD and diabetes also have genetic vulnerabilities in common that put individuals at risk for both diseases. For example, in protein kinase B, also known as Akt, a single nucleotide polymorphism, which converts the kinase Akt that controls metabolism and cell survival, raises a person's risk for PD and diabetes. Furthermore, DJ-1, the protein which is converted by the PD-related park7 gene is decreased in diabetic patients' pancreatic islets [54].

According to Ghasemi, *et al.* [4], the effect that insulin disruptions have on midbrain dopaminergic transmission confirms the relation of insulin dysfunction to PD development. For that reason, evidence from various postmortem studies [4], reveals that neuroinflammatory processes marked by activation of microglial, astrogliosis and lymphocytic infiltration are recognized as playing a part in the pathology of neuronal loss in PD [4]. Ghasemi, *et al.* also expressed that seeing the role neuroinflammation plays in insulin resistance, and how insulin signaling elements intercede in the inflammatory processes, it can be assumed that neuroinflammation may well provide a connection between PD and insulin dysfunction. Consequently, medium to a high density of insulin receptors in substantia nigra dopaminergic neurons and ventral tegmentum emphatically proves that insulin function can affect midbrain neurons. There is also proof that insulin receptors immunoreactivity and mRNA from the substantia nigra pars compacta neurons are reduced in the brains of persons with PD, resulting in dysfunction of insulin, which might precede the loss of dopaminergic neurons [4].

Ghasemi, *et al.* [4] further revealed that many epidemiological studies show that DM and PD are connected. For example, Sandyk [55], discovered that virtually more than 50% of PD patients have irregular glucose tolerance. To add, Arvanitakis, Wilson, Bienias, and Bennett [56], examined the connection between T2DM and PD in older adults. Arvanitakis, *et al.* found that DM is linked with more separation of parkinsonian symptoms as well as vascular issues such as congestive heart failure and body mass index which both play a role in this connection. Another large population-based case-control study [57], using Danish population registers randomly select 1931 persons with a first-time diagnosis of Parkinson's disease during 2001 - 2006. Schernhammer, *et al.* found that having diabetes was linked with a 36% increased chance in the development of Parkinson disease and that diabetes was related to a 35% increased possibility of Parkinson disease [57].

Recently, De Pablo-Fernandez, Goldacre, Pakpoor, Noyce and Warner [58], investigated the connection between type 2 diabetes mellitus (T2DM) and subsequent PD with a retrospective group study of 2,017,115 persons in the T2DM cohort and 6,173,208 in the reference cohort. Using Cox regression model's consequent PD risk was assessed, and they found that there were notably higher rates of PD following T2DM (hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.29 - 1.35; $p < 0.001$). The comparative increase was greater in those with complex T2DM (HR 1.49, 95% CI 1.42 - 1.56) and when relating to younger persons (HR 3.81, 95% CI 2.84 - 5.11 in age group 25 - 44 years). The authors reported an increased rate of subsequent PD following T2DM and concluded that their results may indicate shared genetic predisposition and/or disrupted shared pathogenic pathways [58]. It must be noted, however, that although clinical information proposes decreased glucose tolerance and many persons with PD is described as insulin dysregulation, only some of the latest reviews have thoroughly described dysregulation's distinctive pattern. Also, a sound logic is yet to be made about the part insulin dysregulation play outside of hyperglycemia [17].

Schizophrenia

Schizophrenia has also been linked with decreased glucose tolerance and insulin resistance, which play an essential part in its psychopathology [4]. For, instance, a family history of type 2 diabetes has been found in 18 - 19 percent of people with schizophrenia [59]. According to Mukherjee, Decina, Bocola, Saraceni and Scapicchio [60] investigations performed in the United States and Japan show that DM is more common among patients with schizophrenia than among the general population. The occurrence of known diabetes was studied in 95 patients ages 45 to 74 years with schizophrenia in an Italian continuing care facility. The outcome revealed that the overall frequency of diabetes was 15.8% (95% confidence interval, 12.1% to 19.5%). An increased from 0% in those 50 years and under, through 12.9% in the 50 to 59 age group, and to 18.9% in the 60 to 69 age group, and then declined to 16.7% in those aged 70 to 74 years [60].

In a meta-analysis published in JAMA Psychiatry, Oliver D Howes and colleagues [61], conducted a systematic review of several past studies to investigate whether persons showed a change in blood sugar regulation at the time of their first schizophrenic incident, before starting antipsychotic therapy. This meta-analysis, which was based on 16 studies and encompassed 731 patients and 614 controls confirmed that individuals with first-episode schizophrenia already showed evidence of difficulties in sugar regulation. That is, blood sugar levels, insulin levels, and insulin resistance were all significantly raised in patients likened to controls. Also, the findings, irrespective of the mechanism, proposed that individuals with schizophrenia are at higher risk for developing diabetes [61].

Zhao., *et al.* [62] conveyed that insulin resistance mediated signal transduction is reduced in the dorsolateral prefrontal cortex of postmortem patients with schizophrenia. Also, in patients with schizophrenia, moving levels of insulin and its peptides are increased, suggesting that this rise in insulin levels relates to insulin resistance in schizophrenia patients [63,64]. Measurement of insulin sensitivity in schizophrenia patients has shown that these patients are obviously insulin resistant and also more vulnerable to type two diabetes mellitus [62,65-67]. Ghasemi., *et al.* [4] also communicated that hyperinsulinemia might well play a role in persons developing schizophrenia.

Neurodegeneration and the advancing of central nervous system inflammatory processes have also been assumed to be involved in schizophrenia's pathology. Glutamatergic neurotransmission and disturbed dopaminergic in the brain are without question, related to the pathophysiology of schizophrenia. However, the precise underlying mechanisms are unclear [4]. In addition to hyperinsulinemia, damaged glucoregulatory and insulin resistance, schizophrenia is also connected with irregularities in the metabolic outline of lipids as well as energy metabolism [68,69]. Altar., *et al.* [70] suggested that insulin signaling deficiency may be the cause of schizophrenia, and showed that IGF-treatment of neuroblastoma cells along with insulin augments, the expression of the genes involved in mitochondrial functions, hydrogen ion transport, energy, and glucose metabolism. As well as synaptic function, are all reduced in schizophrenia. Diabetes is hence, a significant medical comorbidity in schizophrenia that demands serious attention and understanding [70].

Depression

Ghasemi., *et al.* [4] articulated that there are many pieces of evidence linking diabetes mellitus with depression. However, exactly how they are connected remains rather contradictory. On the one hand, depression is well-thought-out to be an outcome of diabetes mellitus. Whereas, on the contrary, it is thought to be the factor that increases the chance of type 2 diabetes mellitus occurring [71]. For instance, in a cross-sectional study of 1732 healthy Australian adults between the ages of 26 - 36 years, the connection between depression and insulin resistance was examined. A self-administered written questionnaire was used to collect sociodemographic information, including age, sex, marital status, highest level of education, and occupation; and an electronic version of the Composite International Diagnostic Interview ([CIDI], World Health Organization [WHO]) was used to assess depression. The results revealed that insulin resistance was sig-

nificantly associated with depressive disorders [72]. Whereas, a meta-analysis carried out by Knol, *et al.* [71] to evaluate the risk factor of depression to the development of T2DM, found that for depressed persons the risk of developing T2DM is increased by 37% compared to non-depressive persons. Biessels and Reagan [27] also affirmed that type 2 diabetes mellitus increases the possibility of depressive illness as individuals with T2DM exhibit a lack of glycaemic control, which increases the occurrence of depressive disorder.

Webb, Davies, Ashra, Bodicoat, Brady, Webb, Moultron, Ismail, and Khunti K (2017), investigated whether depressive symptoms were associated with an increase in indicators for T2DM, cardio vascular disease and inflammation within a healthy population. The authors research was a secondary analysis of baseline data gathered during the screening stage of the ADDITION-Leicester study (NCT00318032), an Anglo-Danish-Dutch randomized control trial evaluating the cost effectiveness of populace screening and rigorous multi-factorial medication for Type 2 diabetes. Baseline data and samples were gathered from $n = 6749$ contributors (healthy participants with no diagnosis of T2DM) between 2004 and 2008. Between 2008 and 2009, $n = 987$ arbitrary samples were analyzed for the following biomarkers: leptin, CRP, TNF- α , IL-6, adiponectin, insulin, PGF, resistin and apolipoprotein A1 and B. Examination of the mixed gender cohort revealed that depressive symptoms were positively linked to higher leptin and CRP levels (along with a higher probability of smoking and lower physical activity levels) (Webb, *et al.* 2017). Stratification of the statistics for gender seemed to validate that men and women show a dissimilar metabolic profile with depression. Depression in women correlated with a higher waist circumference and greater levels of adiposity/T2DM related markers specifically HOMA IR, leptin and TNF- α when compared with women without depression. On the other hand, depression in men correlated with lower body fat and 49% higher CRP levels when contrasted to men without depression. Though, interaction analysis showed that the metabolic disturbances connected to depressive symptoms did not significantly change with gender (Webb, *et al.* 2017).

Cognitive Decline

Ghasemi, *et al.* [4] conveyed that from the discovery of insulin there was a possible connection between cognitive decline and insulin disturbances. A link proposed, due to, the exposure of hypoglycemia. Hemmati, *et al.* [18], confirmed that insulin has neuromodulatory effects on the primary neurotransmitters, and consequently cognition and memory modulation is another area in the brain affected by insulin dysfunction. Evidence obtained from animal models also helped researchers understand the role insulin signaling plays in cognition. Also, clinical and experimental studies of the brains of AD subjects have shown that insulin resistance connects metabolic dysfunction to the cognitive deficiencies linked with AD [42]. The brain has been found to have critical neuromodulatory functions, including roles in learning and memory. As a result, abnormal insulin signaling ends in synaptic failure and memory decline [44]. Cognitive impairments are thus linked with insulin signaling abnormalities [45]. In fact, the first likely process underlying insulin's role in memory function is its controlling influence on energy substrates uptake [4]. According to Ghasemi, *et al.* the association between Non-insulin-dependent diabetes mellitus (NIDDM) and a decline in cognitive functioning has been examined in several studies. For example, in a large-scale cohort study (Elias, *et al.* 1997), 187 NIDDM and 1624 persons without diabetes cognitive functions inclusive of verbal fluency, attention, visual organization, learning, and memory were assessed. The results, poor cognitive performance is associated with history and length of NIDDM [4]. Hence, in CNS, insulin resistance is an automatic mediator for cognitive impairment [27].

According to Xia, Wang, Spaeth, Rao, Wang, Yang, Huang and Haixia [73] type 2 diabetes (T2DM) is associated with poor cognition, including memory and visuospatial ability. Insulin resistance (IR), the token indicator of T2DM, has related to brain functional connectivity changes in T2DM patients' brain as pathogenesis may possibly be facilitated by insulin resistance (IR). As a result, the authors evaluated homotopic resting-state functional connectivity (RSFC) using the Voxel-mirrored homotopic connectivity (VMHC) approach to determine the existence of abnormal interhemispheric functional connectivity in T2DM patients while examining whether interhemispheric functional connectivity related to cognitive performance. A total of 62 participants, including 32 diabetic patients and 30 healthy subjects, contributed [73]. Participants had been previously diagnosed with diabetes for 3 to 20 years and were on a range of oral hypoglycemic agents without any insulin-sensitizing medications. Their results revealed that participants with T2DM are subjected to changed interhemispheric connectivity in numerous brain regions, especially in the middle temporal gyrus (MTG). Additionally, changed interhemispheric connectivity was negatively connected to IR in patients with T2DM. Determining, that altered interhemispheric connectivity may play a part in the cognitive dysfunction shown by T2DM patients [73-76].

Conclusion

Analyzing the findings of both epidemiological and clinical studies reveal that there is concrete evidence supporting the hypothesis that insulin resistance plays a significant role in the pathophysiology of several neurodegenerative and neuropsychiatric disorders [23]. While the role and processes that influence insulin action in the central nervous system still raise many questions, the significance of

insulin dysregulation in the development and progression of certain neurodegenerative and neuropsychiatric disorders is emphasized in an array of studies. Also, the evidence reviewed herein verifies that a decrease in brain insulin function is also connected to cognitive decline. For that reason, insulin may represent a promising treatment based on neuroprotective, metabolic, and neuromodulatory effects [4]. Ghasemi, et al. declared that the only method used to raise insulin levels in the brain successfully was intranasal administration. Biessels and Reagan [27] affirmed that intranasal insulin administration is a therapeutic strategy used to alleviate cognitive dysfunction. Resultant of intranasal administration being directly transported to the central nervous system which avoids systemic effects of the hormone. A combination of intervention studies confirms the theory that enhancing hippocampal insulin receptor signaling activity can potentially reverse neuroplasticity deficits induced by insulin resistance [27]. The fact that insulin is used to treat patients with cognitive dysfunction confirms the importance of insulin to brain functioning. Notwithstanding the successes of intranasal insulin administration, it should be noted, however, that intranasal insulin affects regions of the brain, for example, the hypothalamus, which may well result in adverse effects such as dysregulation [4].

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