

Diabetes and Progression of Alzheimer's: Linking the Two Epidemics

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Abstract: *Recent epidemiological studies have suggested that Diabetes and Alzheimer's – the epidemic of modern world share several pathophysiological mechanisms. Insulin is not just a peripheral hormone but has a significant role in signalling pathways regulating several processes. Altered insulin levels in case of diabetes accelerate the rate of aging like symptoms and affects cognition. AD is nowadays referred to as type 3 diabetes as loss in insulin activity affects synapse plasticity by reducing neurotransmitter concentrations. Diabetic patients are at an increased risk of developing AD. This review provides a brief outline on some of the putative links such as mitochondrial dysfunction and oxidative stress and the resulting inflammation, formation of amyloid peptides and advanced glycation end products and altered insulin signalling. The molecular basis of the intersecting segments of the two diseases is still underway of research. Currently the anti-diabetic therapies have opened up a new area of pharmacotherapy for treatment of AD.*

Keywords: Diabetes, Alzheimer's, Insulin resistance, Nervous system, Anti-diabetic therapy

1. Introduction

The prevalence of Diabetes has increased paralleling over the years with the country's rapid economic development in the past several decades and has taken the place of modern epidemic resulting directly from westernization. The International Diabetes Federation anticipates that diabetes afflicted people in South East Asia will reach 82 million mark by 2025 with India contributing to its maximum [1]. The continuous rise of diabetes affected people in India have proven to be a major health problem and leading to simultaneous increase in cost of health care associated problems proving a major economic. Diabetes is basically categorized into 3 types- Diabetes Insipidus, Renal Diabetes and Diabetes Mellitus (DM). DM is further divided into type 1DM (T1DM) and type 2-DM (T2DM) on the basis of their dependency on insulin.

Diabetes is a chronic metabolic disorder characterized by increased glucose levels and associated with accelerated aging, increasing a person's susceptibility to degenerative conditions. The complications associated with the disease can be broadly classified into microvascular (heart attack, stroke, peripheral vascular diseases) and microvascular complications (neuropathy, nephropathy and retinopathy) [2] – [4]. The major problem of concern for the people suffering from the disease and also their family members is that recent studies have found that diabetes has a significant role to play in dementia- a condition wherein there is loss in cognitive function which means the loss of the ability to think, remember, or reason, as well as behavioural abilities, to such an extent that it interferes with a person's daily life and activities [5] - [7].

2. DM and Nervous System

In diabetic patients, the concentration of glucose and insulin is on a constant changing trend affecting the peripheral and central nervous systems (CNS), either directly or indirectly [8]. The blood brain barrier is an important contributor to the changes in the CNS. Diabetes causes a change in both the barrier and the transport function of the micro vessels. Obesity – a problem in diabetes increases the lipid fluidity and composition, and alters the neurotransmitter activity in the cerebral micro vessels, notably the β adrenergic neurotransmission. [9]. Persistent dyslipidemia as a result of hyperglycemia and associated problems has an important role to play in cerebral dysfunction [10]. Neurodegenerative effect in diabetes is a cumulative effect of microangiopathy, hyperlipidaemia and other risk factors leading to increased inflammation, oxidative stress, Advanced Glycation End (AGE) products, decreased neuronal repair and neurogenesis [11]. Defective insulin signaling pathways arising due to fluctuations in the body glucose level also affects the CNS. About 60–70% of diabetics also exhibit mild to severe forms of nervous system damage [12].

3. DM and Dementia

Recent studies have stated that insulin resistance, hyperinsulinemia and hyperglycaemia - the hallmarks of T2DM can lead cognitive problems. Epidemiological studies state that the risk of developing dementia is almost doubled in T2DM patients. Diabetes is not just associated with Vascular Dementia (VAD) but also other forms including Alzheimer's and Parkinson's disease. Cognitive deficits include memory impairment and at least one of the other parallel problems in verbal memory, mental flexibility, information processing speed and disturbances in executive functioning. [5], [12]-[14]. Chronic hyperglycaemic conditions impair the blood flow to the brain,

neurotransmitter function and nutrient delivery to the brain. It also leads to cardiovascular events, transient ischemic attacks, and strokes. This has a major effect on the hippocampus and the temporal lobes which has a role to play in the declarative memory. The brain requires energy for its various activities and glucose acts as the primary substrate. Since the neuronal cells are unable to synthesize and store glucose, the brain receives its share from the systemic circulation and subsequent transport through the Blood Brain Barrier (BBB). Elevated levels of insulin and blood glucose create a pro-oxidative environment. The glucose reacts with oxygen generating Reactive Oxygen Species (ROS). Oxidative stress is known to cause neuronal death. It has been observed that blood glucose concentration of 8–10 mmol/l is optimal for improved memory. [12] - [19]. Obesity – a major problem arising from hyperlipidaemia also contributes to the cognitive decline. Apart from increasing the inflammation, oxidative stress and brain atrophy, the adipose tissue secretes a protein known as adipocytokine or adipokine which crosses the blood brain barrier and plays a role in learning and memory. When diabetes sets in, the cells synthesizing the protein become resistant to the insulin signal and hence decreased production affecting cognition [5]. Furthermore hyperglycaemia is accompanied by increased AGE production thereby accumulating amyloid and triggering tau formation [5], [18] – [20]. Alzheimer's is the most common cause of dementia characterized by the presence of neurofibrillary tangles and β amyloid plaques in the brain. VAD is the second most common form of dementia resulting from cerebrovascular disease or cardiovascular pathology [20]-[22].

4. Type 3 Diabetes

Dementia is a big problem affecting the quality of life. The number of people with Alzheimer's is predicted to triple in the next few decades. AD accounts for 60-80% of the cases related to dementia. Studies have shown that insulin resistance arising due to various factors is a major factor which robs the memory of a person [12], [24]. Diabetes and AD share several common pathophysiologies and hence AD has now also been referred to as type 3 diabetes or Brain diabetes. Increased sugar consumption sets your brain on fire. This is because it leads to onset of diabetes which causes inflammation leading to further insulin imbalance and obesity. This enhances the release of inflammatory cytokines such as TNF- α and IL-6 which produces systemic inflammation thereby damaging the brain and worsening the condition. The neuropathology of AD is characterized by the presence of senile plaques, neurofibrillary tangles and loss of basal cholinergic neurons [24] - [27]. Several factors arising in diabetes have been linked to accelerate cognitive impairment and onset of AD. The linking factors include hyperglycaemia resulting in increased formation of advanced glycation end products (AGEs), mitochondrial dysfunction and oxidative stress, inflammation, diacylglycerol activation of protein kinase C and, increased glucose shunting in the hexosamine pathway [25], [28]–[30], defective insulin signalling and decrease in the insulin degrading enzymes [28], [31]-[32].

5. Connections between DM and AD

5.1 Obesity and Metabolic Syndrome

Metabolic syndrome refers to a cluster of inter related metabolic risk factors such as diabetes, obesity, hypertension, insulin resistance and dyslipidaemia. Obesity and metabolic syndrome are important contributing factors to T2DM and also have been involved in cognitive decline. Studies have postulated that the occurrence of AD increases by 36% for every 1% increase in BMI (Body Mass Index) [12], [22]. Defective leptin signalling has a common pathway leading to obesity and also increases the risk of AD. Leptin- a kind of adipocytokine secreted by the adipocytes is a best known hormone marker for obesity. Higher circulating levels of leptin decreases the risk of developing dementia whereas low levels have been linked to neurodegenerative diseases such as AD. Studies carried out display that diabetic patients show a decrease in leptin production. This may be due to altered distribution of fat in the adipose tissue involved in leptin secretion. Patients with high HbA1c levels (around 8.5%) have also reported low leptin levels [34], [35]. Leptin receptors are expressed in the hippocampus – area dealing with learning and memory. Leptin is known to affect the production of A β plaques by inhibiting the first enzyme known as β -secretase in the formation of A β peptide from Amyloid- β precursor protein (A β PP). Leptin also increases the levels of IDE by activating the Akt pathway, thereby augmenting to clearance of the A β plaques. Leptin also increases synaptogenesis which aids in better cognition. Expression of Mn- superoxide dismutase and anti apoptotic protein Bcl- XL is up regulated by leptin, thereby preventing oxidative stress and neuronal cell death [34]-[38].

5.2 Acetylcholine- the cholinergic hypothesis

The cholinergic hypothesis suggests a link between hyperglycaemia, insulin resistance and inadequate production of Acetylcholine (ACh). ACh is synthesized by Choline Acetyltransferase (ChAT). Research carried out at the Brown Medical School demonstrates that some level of ChAT is expressed in insulin and Insulin like Growth Factor-1 (IGF-1) receptor positive cortical neurons. The expression of ChAT increases with increase in insulin and IGF-1 stimulation. The co-localization of ChAT in insulin or IGF-1 receptor is found to reduce in AD. Thus insulin resistance and supra optimal levels of insulin contribute to decrease in the level of acetylcholine. [12], [39], [40]. Acetylcholine also has a major role to play in the function of insulin secreting pancreatic β cells. It stimulates insulin secretion by increasing the cytoplasmic free Ca²⁺ concentration via inositol phosphate production. It also enhances the exocytosis of Ca²⁺ in the β cells via protein kinase C [41]. These evidences thus predict that AD represents a type of neuro - endocrine disorder that resembles a form of DM- Type 3.

5.3 Glucose metabolism

Alzheimer's is coupled with abnormalities in glucose metabolism. Brain has the highest rate of glucose consumption. The energy generated by oxidation of glucose

maintains the ionic balance associated with synaptic transmissions [42, 43]. Significant reductions in cerebral glucose metabolism have been observed in DM and also the energy generated in the form of ATP showed a drastic decline. The cause of this decrease is related to diversion of the oxidation substrate from glucose to others such as amino acids thus minimizing the energy [19], [42], [43]. Recent studies have proposed that tau in human brain is also modified by O-Glc N-Acylation in addition to phosphorylation and that the former negatively regulates the latter [44]. Studies carried out by Planel et. al. showed that tau hyperphosphorylation was due to hypothermia which is due to altered glucose metabolism. The study also demonstrated that low temperature rapidly inhibited brain phosphatases [45], [46]. Protein phosphatase 2A (PP2A) is a major serine threonine phosphatase in the mammalian brain. Tau proteins present in the axon under normal healthy condition promote polymerization of the tubulin and stabilization of the microtubule. It is involved in dephosphorylation of the paired helical filaments thereby preventing the formation of neurofibrillary tangles and helps restore the activity of the tau protein in microtubule formation. Thus hypothermia mediated inhibition of PP2A induces AD like neuropathology [46, 47].

5.4 Apolipoprotein

Diabetes is characterized not only by hyperglycaemia and hyperinsulinemia but also dyslipidaemia. APOE is a major gene to be associated with lipid metabolism and brain physiology [12], [20]. Human apoE is a polymorphic gene with 3 isoforms namely - apoE2, apoE3 and apoE4. These isoforms differ by a single gene substitution involving cysteine – arginine replacement at positions 112 and 158. This gene product plays a key role in cholesterol transport in brain and therefore is essential in synapse plasticity [48]. It is also known to cope up with oxidative stress and reduces inflammation. Inheritance of the E4 allelic variant along with diabetes increases the risk of dementia with cognitive impairment. The E4 allele has a far reduced ability to clear off the neuronal damage and moreover stabilizes the β - amyloid plaques and accumulates a more stable insoluble amyloid. The AGE binding ability of the E4 variant is comparatively greater. Recent studies have illustrated that the IDE (endopeptidase degrading cerebral A β) concentration in the hippocampus [49], [50].

5.5 Insulin resistant brain state: Defective insulin signalling

Insulin – a two chain peptidal hormone has been known to be involved in the glucose metabolism since ancient times. Insulin is not just a peripheral hormone but also plays significant role in the CNS. Studies have found out that the concentration of insulin in brain is 10 times higher than that in the plasma. Most of the insulin present in the brain is derived from the pancreatic β cells and transported to the brain via the blood brain barrier [12], [51]-[53]. De novo synthesis of insulin by the pyramidal neurons has also been proposed as a source of insulin in the CNS [25], [53]. Within the brain the insulin binds to insulin receptor widely distributed in the CNS, thereby activating the downstream

secondary messengers and signal transduction pathways. Insulin has a key importance in maintaining the synaptic plasticity by enhancing the gamma- amino butyric acid (GABA) receptor mediated transmission of signals (by increasing the associated Ca²⁺ channels). It also modulates the excitatory and the inhibitory activity of the receptors such as glutamate and the GABA thereby activating the shc/ Mitogen Activated Protein (MAP) kinase and the Phosphatidylinositol 3 Kinase/ Protein Kinase C (PI3K/PKC) pathways which is involved in the consolidation and recollection of new memories [54] - [58]. Recent evidences suggest that dementia is not just related to the formation of amyloid plaques but loss of synapse is a major problem. AD brains exhibit a varied form of defective insulin signalling and decreased response to insulin – a state known as insulin resistant brain state [59]-[63]. Under normal condition, IR activation recruits and phosphorylates IR- substrates (IRS). The phosphorylation takes place at either tyrosine or serine residues. Phosphorylation at the former stimulates the major pathway involved in the metabolic and cognitive functions whereas inhibitory effects are seen in the latter case. Hence a balance is required to be maintained between serine and tyrosine phosphorylation. In T2D, the stress kinase c- Jun NH₂ terminal kinase gets activated and phosphorylates the IRS at the serine residues thereby inactivating the insulin signalling pathway and leading to peripheral insulin resistance. The formation of A β plaques in AD triggers the removal of IRs from the hippocampus neuronal zone and thereby reduced PTK activity and insulin resistant brain state [64]. The insulin signalling pathway also interferes with the leptin signalling pathway as mentioned earlier. When the cholesterol intake increases, the β amyloid oxidises it to 7 β hydroxy cholesterol – a type of oxysterol which is highly toxic and potent inhibitor of PKC signal transduction pathway which is essential for all phases of learning including memory, consolidation and reconsolidation. Oxidised cholesterol acts as second messenger and inhibits insulin dependent signalling pathways thus affecting synaptogenesis and thereby cognition impairment [55], [65], [66].

5.6 Amyloid and tau

Many of the age related degenerative disorders such as AD, Parkinson's, Huntington's and T2DM are characterised by the formation and accumulation of amyloid plaques. The amyloid fibrils arise as a consequence of protein misfolding which may occur due to mitochondrial dysfunction or due to the formation of ROS. Since many of the degenerative disorders share a common structural and a common pathway of fibril synthesis, researchers predicted that there might be some common factor by which these fibrils pose toxic. Many of the amyloid arises from cytosolic proteins while many arise from extracellular or secretory proteins. Plasma membrane is the only structural element exposed to both the types. It has been postulated that these fibrils increase the membrane permeability and alter the Ca²⁺ ion concentration. Destabilization of the Ca²⁺ ion concentration renders the neurons more vulnerable to metabolic insults. This is because the A β plaques enhance Ca²⁺ uptake by stimulating the excitatory amino acids and calcium ionophore [33], [67], [68]. A concomitant increase in the intracellular calcium

levels directly affects a number of pathways including generation of ROS, alters insulin signalling and induces mitochondrial stress. Since many of the protein folding stages require ATP, a decrease in the ATP production as a result of mitochondrial dysfunction may trigger the upstream pathways [33]. The A β plaques also interact with the insulin signalling pathways and activate a key enzyme in the formation of the neurofibrillary tangles. The enzyme glycogen synthase kinase -3 (GSK-3) catalyses the formation of glycogen is found to increase in case of T2DM and AD as a result of dysregulation of the PI3K pathway [12], [33], [69].

5.7 Insulin degrading enzyme: link between insulin and amyloid degradation

IDE also known as insulysin is a highly conserved Zn²⁺ endopeptidase contributing towards regulating peripheral insulin levels and the amyloid plaques in case of Alzheimer's. The expression of IDE is under the control of insulin signalling in the peripheral tissues. During onset of diabetic conditions, the body offers a lower response to insulin – a state known as insulin resistance. This results in lower IDE concentration and slow turnover rate. As IDE contributes significantly to decomposition of amylin in the pancreatic β cells and A β plaques in the CNS, reduced levels of IDE leads to progression of both diabetes and AD [70]-[72]. Castaño et al. proposed that under conditions wherein hydrolysis is unfavourable, the IDE traps the peptide monomers inside its cavity thereby preventing the formation of amyloid polymers. These complexes are then routed to the lysosomes and the proteosomes wherein they are degraded and flushed out of the cell via exosomal pathway. Therefore IDE dysfunction leads to increased amylin concentration damaging the pancreatic cells and leading to the state of insulin resistance. Also altered cerebral IDE interferes with insulin signalling and accumulation of the A β plaques [72].

5.8 Advanced glycation end (AGE) products

Hyperglycaemia and resulting oxidative stress are the main factors leading to the formation of AGE in the cerebral region thereby leading to brain damage. AGE comprise of a heterogeneous group of molecules indentified as the end products of Maillard reaction in 1912 [12], [39]. These are formed when reducing sugars react with the amino group of proteins leading to an irreversible, cross linked and unstable compound. The accumulation of these products in the cells is a normal phenomenon, but in case of DM it is highly exacerbated. AGE accumulates within the cell due to presence of phosphates and reactive sugars and auto oxidation of glucose. Extracellular accumulation is mainly due to the oxidation of the glycated proteins [12], [73]. AGE is known to interfere with the signal transduction pathways leading to increased production of free radicals. This creates oxidative stress and cell damage and increase in membrane rigidity [74]. Oxidative stress again enhances AGE formation creating a viscous cycle. Mice with diabetic condition expressed a higher number of receptor for AGE in the neuronal and glial cell further complicating the disease. AGE causes increased glycation of proteins and hence has been accepted an active participant in the formation of A β plaques

and neurofibrillary tangles [73], [74].

5.9 Neurodegeneration, Mitochondrial Dysfunction, and Oxidative Stress

Mitochondria play a major role in energy metabolism and hence known as the power house of the cell. Within here maximum numbers of free radicals are produced in the form of reactive oxygen species, super oxide, hydrogen peroxide, and hydroxyl radical. Brain tissue consumes high amount of oxygen, therefore brain tissue is highly sensitive to oxidative stress since it has low activity of scavenging the free radical. Improper functioning of mitochondria affects the central nervous systems. Phosphorylated tau protein play a role in scavenging the free radical which helps protect the early pathogenesis in Alzheimer's patients. Loss of function by triggering receptor expressed in myeloid cells 2 (TREM) enhances the oxidative stress in central nervous system. [45], [75]. Blood containing protein ceruloplasmin and ferritin also binds the free metal ion and scavenging the metal ions induces free radical. Recent studies predict the mechanism of endoplasmic reticulum stress induced neuronal cell death, which is related to the AD. Generation of oxidative stress affects the blood brain barrier and tight junction protein expression. P.F. Schuck et al. showed that trans- glutaconic acid is toxic to brain cells in vitro causing alterations in cell ion balance and probably neurotransmission, as well as oxidative stress in rat cerebral cortex. Mitochondrial K-ATP channel also control the microglial activity ceases AD progression. [12], [45], [76].

5.10 Inflammation

Inflammation is a key feature of diabetes and AD and plays a major role in the pathogenesis of both disorders. Inflammation is also part of body's defense mechanism against different types of injury, wound and cell rupture and microorganism infected cell damage. Similar types of inflammatory processes occur in the brain and in peripheral tissues. Presence of different inflammatory markers in the AD brain elevates levels of cytokines/chemokines and gliosis. In type 2 diabetes, increase blood concentration of inflammatory mediators such as tumor necrosis factor - α (TNF- α), interleukin-6 (IL-6) and IL-1 β are also involved in AD [12], [77]. It increases the neuronal insulin resistance as well as damaging the muscle, liver, pancreatic β cells, because of infiltration/activation of macrophage in adipose tissue and causing peripheral insulin resistance. Inflammation also underlies by hypothalamic dysfunction in obesity. The hypothalamus is also called as master gland which secretes maximum number of hormone. Type 2 diabetic followed obesity activates different type of cytokine mediated pathway and affect the proper functioning of hypothalamus. Aging is most common important risk factor for AD. Its increases the proinflammatory cytokines and markers such as IL-1 β , IL-6, C-reactive protein, which changes biochemical pathway leading to neuronal dysfunction. Recent studies say that T2D affect the blood brain barrier permeability. Postmortem analyses of diabetic AD brains containing IL-6 levels are high as compared to non diabetic AD brains. Adipose tissue and adipose resident macrophage also participate in a cross talk between the periphery and CNS, adipose tissue react

with proinflammatory cytokines, adipokines, and chemokines which leads to increase the level of TNF- α , IL-1 β , IL-6 production and cross the blood brain barrier. Neuronal cell containing spingolipids, namely ceramide causes inflammation and it is associated with T2D. Ceramide changes the lipid raft environment and generating the antibody and disrupting the neuronal insulin signaling [22], [64].

6. Anti Diabetes Therapies as Anti – Alzheimer’s Therapy

As DM and AD are molecularly associated disease, controlling on the hyperglycaemic conditions may help in to decrease the progression rate of the AD. Also clinical trials have also been conducted to test the currently approved anti diabetic for the treatment of AD. Some of the drugs tested against AD have been summarized below:

Dipeptidyl peptidase IV inhibitors: DPP-4 such as Sitagliptin or vildagliptin has been shown to prevent mitochondrial dysfunction in the hippocampus area and helps in improving memory. It is also associated with decreased oxidative stress, reduced nitrosative stress and inflammation in the brain and restoring the insulin signalling. This acts as a cumulative effect in reducing the A β deposits [78].

Metformin: It is the most widely used biguanide for the treatment of diabetes. It reduces hyperglycaemic conditions by suppressing hepatic gluconeogenesis and controls blood insulin levels. It also increases the sensitivity of the liver and the muscle cells to insulin via AMP mediated pathway. Besides its anti- hyperglycaemic role it has also been proved to be neuroprotective by decreasing the insulin receptor phosphorylation and increasing neuronal survival [12], [78].

Intranasal insulin: Administration of insulin through intranasal route rapidly delivers insulin to the brain via olfactory and trigeminal perivascular channels and improves insulin signalling. Clinical trials conducted showed improved cognition on insulin delivery as it protects against insulin resistance induced by amyloid peptides [12], [78].

Thiazolidinediones: These are a class of compounds having insulin secretagogue property, decreases hepatic gluconeogenesis, improve glycaemic control, promote cholesterol homeostasis, neuronal Ca²⁺ homeostasis in hippocampus and reduce cerebral inflammation through inhibition of IL-6 and tumour necrosis factor. Thiazolidinediones such as rosiglitazone and pioglitazone work by stimulating peroxisome proliferator activated receptor gamma (PPARs). Clinical trials have proved this drug to be anti-amyloidogenic and anti-inflammatory reducing oxidative stress and improving cognition [12], [78].

Certain other drugs such as Sulphonylureas and Glucagon like peptide-1 receptor agonists improves cognition by interacting with ATP-sensitive potassium (K_{ATP}) channels in the pancreas stimulating insulin secretion and activating cAMP in the brain thereby inducing neurogenesis in the brain respectively. Combination therapies of insulin and oral

anti- diabetics showed a drastic decline in the cognition impairment [78].

7. Conclusion

Diabetes and AD initially known to be independent disorders have recently found several common linking factors at molecular level. The two disease have now become epidemic sharing several pathophysiological mechanisms. Increased hyperglycaemic condition and insulin resistant brain state are the major contributing factors to both DM and AD. AD is referred to as Type 3 diabetes since insulin resistant state and fluctuating levels of plasma insulin are create conducive conditions for AD progression as insulin play a key role in neuronal signalling. Improper metabolism as in case of Diabetes exacerbates several complications such as oxidative stress, mitochondrial dysfunction, AGE production and inflammation initiating a viscous cycle of disorders. As AD and diabetes share several common mechanisms, clinical trials are taken in to slow down the progression of AD using anti- diabetic therapies. This opens up a new era in the field of AD treatment.

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