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COMORBIDITY OF DIABETES AND MEMORY IMPAIRMENT: TYPE 3 DIABETES?

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ABSTRACT

Epidemiological and biological evidences hold up a link between type 2 diabetes mellitus (T2DM) and memory impairment. Persons with diabetes have an advanced prevalence of memory decline and an increased threat of developing diabetic memory impairment. Accumulating evidence entail that diabetes make a payment to the development and progression of memory impairment; however, the factors linking this association have not been determined. Insulin resistance (IR) is at the core of diabetes and probably represents the major link between diabetes and memory impairment. In the central nervous system, insulin plays vital role in learning and memory, and memory impaired patients exhibit weaken insulin signaling that is parallel to that observed in diabetes. As we face an alarming increase in T2DM in all age community, understanding the relationship between diabetes and memory impairment is crucial for the identification of potential therapeutic targets. Herein, we will discuss pathophysiological changes in diabetes as a risk factor for memory impairment as well as review the evidence that T2DM causes brain insulin resistance, oxidative stress, and memory impairment, represent early and progressive abnormalities and could account for the majority of molecular, biochemical alteration in AD. We conclude that the term “type 3 diabetes” accurately replicate the fact that memory impairment represents a form of diabetes that selectively involves the brain and has molecular and biochemical characteristics that overlies with both type 1 diabetes mellitus and T2DM.

INTRODUCTION

Diabetes mellitus (DM) is rapidly becoming one of the most common non-communicable diseases globally ¹. Diabetes mellitus (DM) is a chronic disease which defined as the high blood glucose level which may be either due to the progressive breakdown of pancreatic β -cell function and consequently a lack of insulin production (type 1: T1DM), or may be due to the expansion of insulin resistance and the subsequently loss of β -cell function (type 2: T2DM) ². Diabetes mellitus is a disease in which homeostasis of carbohydrate and protein moreover lipid metabolism is inappropriately regulated by hormone insulin which furthermore resulting in increase in fasting and postprandial blood glucose levels ³. According to the recent update by the International Diabetes Federation (IDF) more than 382 million adults aged 20–79 years had diabetes in 2013 and it is expected to increase to 592 million by 2035 worldwide ^{4, 5, 1}. Memory impairment represents a ravage disease which has currently enhanced the incidence rate of panoramic implications for uprising the health care costs. Memory impairment, a neurodegenerative disease, is the most prevalent cause for dementia in the aged population and impairs quality of life of millions of adult individuals with dementia worldwide. Memory impairment is characterized clinically by progressive memory and orientation loss and other memory deficits which including impaired judgment and decision making, apraxia and language disturbances ⁶. Memory impairment is projected to become an epidemic among the elderly in the coming decades. The Asia Pacific Regional Conference 2014 updated the estimates of memory impairment prevalence data for the region, such as the estimate that the number of people with memory impairment above the age of 60 years in India will increase from 23 million in 2015 to almost 71 million by 2050 ⁷. Novel evidence demonstrates that impaired insulin signaling may significantly contribute to the pathogenesis of Diabetes memory impairment, contributing to the idea that it is actually a neuroendocrine disease. Emerging epidemiological data indicates that DM is a significant comorbid risk factor for developing late onset memory dysfunction, signifying a underlying relationship between glucose dysfunction and also the pathogenesis of memory impairment ^{8, 9}. Kroner Z (2009) suggests that hyperglycemia is the primary element for the development of irregular memory impairment furthermore which designate the irregular memory impairment as type 3 diabetes (T3DM) ¹⁰.

TYPE 3 DIABETES

Insulin signaling in brain shows a vital task in the regulation of food intake, body weight, reproduction, learning and memory ¹¹ and defective insulin signaling is associated with

decreased memory skill and the progression of memory impairment¹². Memory impairment is illustrated by the improper expression and processing of amyloid precursor protein (APP) and the accumulation of insoluble neurotoxic amyloid beta (A β) into subsequent senile plaques. Recent studies show that insulin signaling regulates manifold steps of the amyloid cascade and affects the A β aggregation within the brain. Insulin augments the transcription of the anti-amyloidogenic proteins, such as the insulin-degrading enzyme (IDE) and α -secretase, and stimulates A β clearance¹³. On the other hand, GSK3 β is the chief tau kinase, GSK3 α increases A β production by stimulating γ -secretase activity¹⁴. On the other hand, A β can affect insulin signaling by reducing the affinity of insulin binding to its own receptors or by regulating the intracellular mechanisms. The soluble A β binds to insulin receptor (InsR) in hippocampal neurons to inhibit receptor autophosphorylation and following activation of PI3K/Akt¹⁵, and A β derived diffusible ligands (ADDLs) induce the abnormal expression of InsR and interrupt the insulin signaling thus prospectively contributing to the maturation of central Insulin resistance (IR)¹⁶.

Some researchers believe the connection between impaired glucose metabolisms, insulin signaling and memory is so strong that they refer to memory impairment as “type 3 diabetes”¹⁰. Briefly, T2DM—a condition stemming from broken glucose metabolism and insulin signaling—has been identified as an additional risk factor for developing memory impairment^{17,18}. Moreover, the pathological changes that occur in memory impairment in the brain physically resemble those seen in the pancreas and vasculature in T2DM^{19,20}. T2DM patients who bear ApoE4 alleles are at the greatest risk for memory impairment, with an even more severe risk reserved for those treated with exogenous insulin²¹. Furthermore suggests that both T2DM and/or related features of the metabolic syndrome bring about memory impairment, or that they are separate consequences of the same underlying cause and furthermore, that insulin is a major factor. The current review study is designed to highlight the various mechanisms and hypothesis involved in the comorbidity of diabetes and memory impairment. In contrast to the type 3 diabetes, this review also highlights the underlying pathway alterations and the role of insulin as well as its signaling associated with type 3 diabetes.

INSULIN AND MEMORY IMPAIRMENT-A CROSS TALK

It had long been supposed that glucose uptake in the brain was completely independent of insulin, as the widespread brain glucose transporters— GLUT1 and GLUT3— both are non-insulin sensitive. On the other hand, it is currently recognized that there are insulin receptors

and insulin sensitive glucose transporters (GLUT4) at the blood brain barrier (BBB) and in specific brain cells. They are mainly abundant in regions involved in memory and learning²².²³. Entry of insulin into the brain is a saturable mechanism; there comes a point when increased peripheral insulin levels no longer elevate levels in the central nervous system (CNS). Admission of glucose into the brain cells can be observed as saturate as fit. The GLUT1 transporters are saturated at the BBB by normal physiological concentrations of glucose²⁴. Therefore, increasing glucose uptake by the brain would require an upregulation of insulin receptors or else GLUT4s. Other than as the receptors have been compromise, it could be associated to a functional hypoglycemia in the brain, which would account for the declining rate of brain glucose metabolism that is one of the defining features of the memory impairment. On the other way, if physiologically normal concentration of glucose is entering the brain interstitial fluid but there's a need of insulin, this may possibly result in the augmented glycation observed in memory impaired brains. The presence of glucose with an inability to metabolize it would account for both the reduced cerebral metabolic glucose rate (CMRglu) and increased advanced glycation end product (AGE) formation.

A notable feature of memory impairment is the intriguing combination of hyperinsulinism (too much) in the periphery and hypoinsulinism (not enough) in the CNS. Patients with advanced memory impairment show higher plasma but lower CSF insulin concentrations than healthy controls²³. Clearly, then, the lower concentration of insulin in the brain is not a result of reduced circulating levels in the blood. Someway—partly throughout the effects of A β , but more likely due to long lasting overconsumption of refined carbohydrates the brain becomes insulin resistant. Insulin plays a specific task in cognitive function. However, as is true of nearly all biological mechanisms, framework must be taken into account: acute administration of insulin improves performance on tests of memory and cognition, but chronically high insulin levels have the opposite effect²⁵⁻²⁷. This is akin to the pathology of T2DM, in which normal, acute doses of insulin help regulate glucose uptake, but chronically high levels lead to hyperglycemia, insulin resistance, and the attendant inflammation moreover vascular damage. Chronically high insulin levels in the periphery, it gives the impression, lower insulin sensitivity at the BBB and therefore glucose utilization in the brain. In the lack of an optional fuel source, brain cells are malnourished. Metabolic energy is inside the body, but the brain cells are unable to harness energy from it. The analogous to T2DM are remarkable, assembled the term “type 3 diabetes” incidentally. For non-ApoE4 carriers, diabetes alone is a significant risk factor for memory impairment¹⁸. The combination of

diabetes and carrying an ApoE4 allele increases the risk even further—five-fold over non-diabetic patients, non-E4 carriers^{17, 21}. Better glycemic control has been correlated to better cognitive performance in type 2 diabetic patients.

EPIDEMIOLOGY OF DIABETES MEMORY IMPAIRMENT

Memory impairment is projected to become an epidemic among the elderly in the coming decades. The Asia Pacific Regional Conference 2014 updated the estimates of memory impairment prevalence data for the region, such as the estimate that the number of people with memory impairment above the age of 60 years in India will increase from 23 million in 2015 to almost 71 million by 2050⁷. Individuals with DM have been shown to have a risk of memory refuse that is 1.2–1.5 times as great as that of individuals without DM²⁸. In developed countries, 10% of the population, 65 years or older, have memory impairment. The prevalence doubles every five years after the age of 60 and reaches nearly 50 percent after the age of 85 years. The prevalence of DM memory impairment has been rising in many regions of the world.

RISK FACTORS ASSOCIATED WITH DIABETES MEMORY IMPAIRMENT

There are various risk factors for the memory impairment development has been suggested such as^{29, 30}.

Advanced age: The single greatest risk factor for developing memory impairment is age. Most cases of AD are seen in older peoples, ages from 65 years or over. Patient ages in between of 65 and 74 years, about 5 percent of people have memory impairment. For those peoples who are over 85 years, the risk increases to 50 percent³¹.

On other hand, risk factors for memory impairment are; Poor glycemic management, Long time of diabetes and Dyslipidemia³².

CLINICAL STAGES AND SYMPTOMS OF MEMORY IMPAIRMENT

As described before, Memory impairment is characterized by memory refuse. Memory impaired patient's reveal insufficiency in memory and spatial orientation, poor judgment, inability to planning of skills, alteration in mood and personality. The patient also manifests a changed perception of the world all around, pauperization of verbal communication and complexity in keep a correct gait. The motor functions are gradually impaired and simple actions like the swallowing become very difficult to execute. According to the symptoms showed, Memory impairment can be categorized in three main stages of the disease, each with its own symptoms and varying severity³¹:

Early-Stage Memory impairment: This mild stage, which typically lasts 2 to 4 years, is frequently when the disease is first time diagnosed. General symptoms at this stage comprise difficulty in retaining new information, difficulty with problem solving or decision making, personality changes and misplacing belongings. The patient may have difficulty to find the way in familiar surroundings.

Moderate Memory impairment: This stage lasts for 2-10 years and is longest stage of the disease. Patients often experience increased difficulty with memory and may need help for activities of daily living. Symptoms frequently reported during this stage include greater memory loss and increasingly poor judgment and confusion.

Severe Memory impairment: In this final stage of the disease the cognitive capability continues to refuse and physical ability is severely shocked. This stage can last 1-3 years. Due to the family's decreasing ability to care for the patient, this stage often results in admission to nursing home or other long term care facility residency. General symptoms come out in this stage include ³¹: loss of ability to communicate, reliance on others for personal concern, like eating, bathing, dressing and toileting moreover inability to function physically.

DEGENERATIVE CASCADES IN MEMORY IMPAIRMENT

Recent studies and debate are expanding our understanding beyond the definitions and details of memory impairment pathology to explore how the sequence and timing of events within the life cycle influence the development of symptoms and illness progression. Central to the degeneration process is the development of plaques and tangles, although many other abnormalities are also occurring during the progression of memory impairment.

Amyloid cascade hypothesis: As per the well accepted hypothesis of the amyloid cascade projected by Hardy et al 1992, the tangles formation is a end result of neurotoxic effect of A β . The disturbed balance between the formation and degradation of A β is the cardinal point that justifies the aggregation of A β in the brain and the following toxic effects with synaptic dysfunctions and neuronal cell loss which show the way to memory and behavioral abnormalities typical of memory impairment ³³. As per the amyloid cascade, in the premature stages of memory impairment, the disproportion between formation and clearance of A β cause A β to deposit in plaques and synaptic dysfunction ³⁴. Afterwards, activation of microglia and astrocytes increases the levels of complement factors, cytokines, nitric oxide (NO) and other mediators of inflammation and oxidative stress that lead to ulterior synaptic damage with deficits in neurotransmitters properly firing and onset of first memory impaired

symptoms. As impair of synapses development, a changed neuronal ionic homeostasis and oxidative injury is shown. At this time, altered activity of kinases and phosphatases lead to tau pathology as tangles appear ³⁵.

Tau protein and neurofibrillary tangles: Neurofibrillary tangles (NFTs) have been identified as a chief pathological characteristic of memory impairment. These tangles are bunch of paired helical filaments (PHF) enclosed hyper-phosphorylated tau proteins that are originate within cell bodies or dendrites of neurons. Tau is major microtubule associated proteins that play a large key role in the outgrowth of neuronal processes and the development of neuronal polarization. Tau endorses microtubule assembly, become stable microtubules, and influences the dynamic of microtubules in neurons ^{36, 37}. Tau is plentifully present in the CNS and is primarily expressed in neuronal axons and also in glia and astrocytes ³⁸. Normal tau stabilizes microtubules in the cytoskeleton of neurons. In contrast, pathological tau becomes hyper-phosphorylated, which destabilizes microtubules by decreased binding to microtubules, resulting in the accumulation of hyper-phosphorylated tau. Tau hyper-phosphorylation and NFT pathology are associated with severe late onset memory impairment. Phosphorylation of tau and NFT formation has been widely reported in the literature of memory impairment ^{39, 40}. Recent study has revealed several important factors in hyperphosphorylation of tau.

Cholinergic hypothesis: Acetylcholine is an important neurotransmitter in brain regions involving memory. As expected, failure of cholinergic activity correlates with memory impairment. In memory impairment, cholinergic hypothesis is the most well-known of neurotransmitter changes, principally because of the reduced activity of choline acetyltransferase (an enzyme involved in acetylcholine synthesis). By late stage of memory impairment, the numeral of cholinergic neurons is noticeably reduced, predominantly in the basal forebrain (i.e., more than 75% loss of cholinergic neurons) ⁴¹. Acetylcholine binds to two types of postsynaptic receptor: nicotinic and muscarinic. The pre-synaptic nicotinic receptors persuade the release of neurotransmitters important for memory and mood (i.e. acetylcholine, glutamate, serotonin and norepinephrine). It is known that blocking nicotinic receptors impairs memory (seen in humans and animals), while nicotinic agonist may perk up memory (based on studies in rodents and non human primates) ⁴². Loss of nicotinic receptor subtypes in the hippocampus and cortex has been examined in memory impairment ⁴³. Muscarinic receptors are not engaged in the development of memory impairment, but blocking these receptors (as seen with anticholinergic agents) can cause confusion. The

cholinesterase inhibitors, act by blocking the acetylcholinesterase enzyme, which are accountable for acetylcholine degradation, thereby increasing acetylcholine levels in the synapse. It is deliberation that by maintaining or increasing acetylcholine levels in the synaptic cleft, memory failure and memory function throughout cholinergic neurons could be restored or maintained, even during neuronal degradation ⁴⁴.

Glutamatergic and excitotoxic hypothesis: Glutamate, the chief excitatory neurotransmitter, is nearly ubiquitous in the CNS and involved in essentially all CNS functions. It is estimated to be involved in roughly 66% of all brain synapses ⁴⁵. Glutamatergic neurotransmission is concerned in learning, memory and the determining of nerve cell architecture (plasticity). Importantly, most glutamatergic neurons are considered as projection neurons that provide information from one brain area to another. As projection neurons, they influence memory through connections to cholinergic neurons in the basal forebrain and cerebral cortex. A significant finding is that memory impaired brains have smaller amount NMDA receptor (1 of 3 types of glutamate receptors, including AMPA and kainate) than normal ⁴⁶. There also appears to be excessive or unregulated the signaling of glutamate, which are ultimately leads to neurotoxicity. This is not caused by excess glutamate formation or release, but this is caused by post synaptic receptor defects that result in sustained low-level activation. Based on animal studies, dysregulation at the glutamate NMDA receptor is thought to perpetuate a vicious cycle of neuronal damage. Continuous activation of the glutamate NMDA receptors lead to chronic calcium influx that interferes with normal signal transduction and increases production of APP. Increase concentration of APP are associated with higher rates of plaque development and hyperphosphorylation of tau protein (thus NFT formation) followed by neuronal toxicity ^{47, 48}. The second kind of receptor defect occurs during glutamate reuptake. During normal transmission, glutamate is cleared from the synapse by reuptake into the nerve terminal and surrounding glial cells ⁴⁹.

UNIFYING MECHANISMS OF DIABETES AND MEMORY IMPAIRMENT

It has been established that DM is associated with memory dysfunction. Extensive research has implicated on various pathways of glucose metabolism in the development of type 3 diabetes. There are various mechanisms and pathways and their role has been reported in the pathogenesis of diabetic memory impairment are as following discussed (figure: 1).

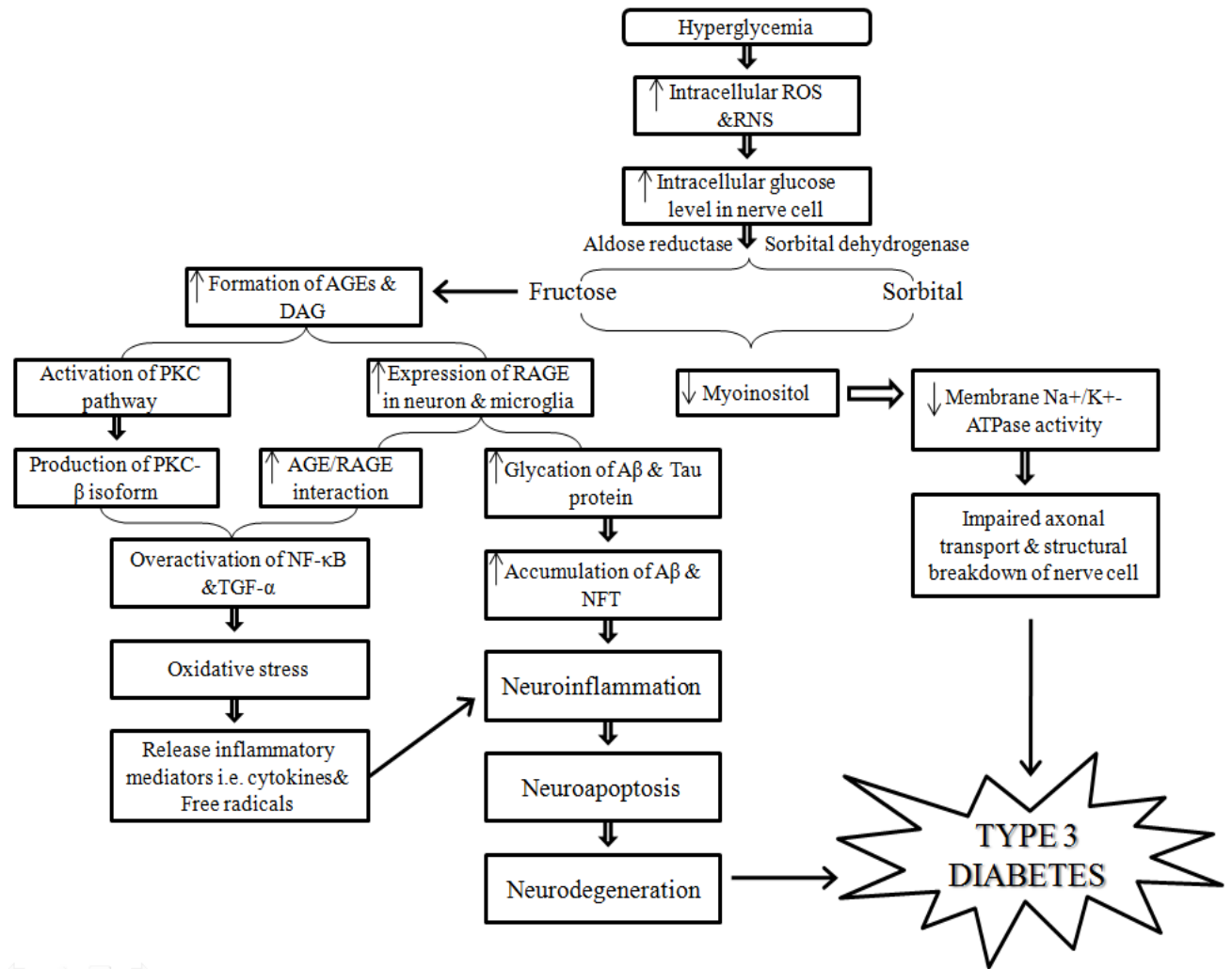


Figure: Mechanism involved in Diabetic memory impairment

Polyol pathway in diabetic memory impairment: Hyperglycemia causes extreme increased in the levels of intracellular glucose in nerve cells, which furthermore leading saturation of normal glycolytic pathway. Excess glucose shunted to polyol pathway and then converted to sorbitol and fructose due to the enzyme aldose reductase and sorbitol dehydrogenase³. Accumulation of sorbitol and fructose leads to reduced myoinositol, which decreases membrane activity of Na⁺/K⁺ ATPase and impairment of axonal transport and structural breakdown of nerve cells. Fructose formation promotes AGE formation and increase formation of diacylglycerol (DAG), which activate PKC pathway and cause oxidative stress moreover neurodegeneration⁵⁰.

Protein kinase C activity in diabetic memory impairment: The protein kinase C (PKC) pathway is an additional mechanism by which hyperglycaemia causes injury in the obstacle prone nerve cell. High glucose levels stimulate the diacylglycerol (DAG) concentration,

which in turn activates the PKC pathway. Furthermore increased the production of the PKC- β -isoform in particular has been implicated in over expression of the NF- κ B and TGF- β moreover the development of microvascular diabetic complications such as diabetic memory impairment⁵¹.

AGEs in diabetes induced memory impairment: AGEs are well thought-out biomarkers of oxidative stress and accumulating during aging and diseases, markers of carbonyl stress, which grow due to an enhanced level of sugars and reactive dicarbonyl compounds for example glucose, fructose, deoxyglucose, glyoxal, and methylglyoxal furthermore triosephosphates⁵². AGEs are personalized heterogeneous and extracellular moreover intracellular biomolecules⁵³. AGEs product are produced because of non-enzymatic reaction of glucose which is in excess with proteins, nucleotides, and lipids that may have role in altered neuronal homeostasis and repair mechanisms⁵⁴. These products interfere with metabolism of nerve cell and axonal transport and thus play a key role in disturbing neuronal integrity and repair mechanisms⁵⁵. AGEs bind with their receptor, known as receptor for advanced glycation end products (RAGE) and put forth their actions moderately by influencing intracellular functions. RAGE has been recognized as a receptor concerned in A β -induced neuronal dysfunction. Augmented levels of AGEs and RAGE are found in diabetic human cell.

A widespread pathological aspect between DM and memory impairment has been the presence of AGEs-modified proteins in both diseases^{56, 57}. These modified proteins are ligands for their receptor RAGE, as is A β peptide⁵⁸. AGE's positive neurons and astroglia amplify in memory impairment with the development of disease, which might contribute to numerous forms of neuronal dysfunction in memory impairment by course, such as inflammatory activation of microglia, in turn direct cytotoxicity via formation of free radicals, most probably mediated through activation of their receptor such as "RAGE"⁵⁹. As binding of ligands such as AGEs and A β , RAGE switch on intracellular signaling pathways by way of mitogen-activated protein kinases (MAPK), phosphatidylinositol-3 kinase (PI3K) moreover Erk1 and Erk2. Those pathways culminate in the activation of the transcription factor nuclear factor kappa B (NF- κ B) and subsequent transcription of a variety of factors, including endothelin-1, tissue factor, interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)- α ⁶⁰. NF- κ B regulates several of activities including inflammation and apoptosis in nerve cell⁶¹. Activation of NF- κ B and induction of cytokines can also contribute to neuronal plasticity and the cellular response to cellular dysfunction when chronically activated

resulting neurodegeneration⁶². Especially, NF- κ B induces the expression of RAGE, leading to a positive loop, which amplifies the cellular response to external stress. The overexpression of RAGE in microglia aggravates significant increases in A β levels in the hippocampus and cortex⁶³, suggesting a probable role of RAGEs in the progression of cerebral dysfunction⁶⁴. Therefore, RAGE can be considered a key mediator of AGE-induced oxidative stress by its capability to amplify a hassle signal, which contributes for the development of neurodegenerative processes in unbalanced memory impairment.

Oxidative stress in diabetic memory impairment: Oxidative stress in diabetes takes place due to numerous pathways including enzymatic, non enzymatic as well as mitochondrial pathways⁶⁵. Oxidative stress is defined usually as unnecessary production and/or insufficient removal of reactive oxygen species (ROS)⁶⁶. The increased formation of free radicals in diabetes may be harmful via several pathways. Unpredicted pathophysiology of diabetes memory impairment involves role of oxidative stress and nitrate oxide mechanism and their interaction. Oxidative spoil plays an important role in the pathogenesis of DM induced memory impairment and other neurodegenerative diseases⁶⁷. In diabetic status, AGE's are established to be one of chief source for increased oxidative stress. Oxidative stress is capable to induce A β accumulation and that the onset of A β deposition is associated with an increase in the level of ROS and reactive nitrogen species (RNS). There are a lot of inflammatory mediators release from neutrophils and macrophages after neurodegeneration that impairs tissue in normal condition and allow accumulation of free oxygen radicals that accelerate tissue destination. Oxidative stresses are critically involved in the development and progression of diabetes memory impairment and related condition⁶⁸.

CONCLUSION

Altogether, the outcomes from these studies provide strong confirmation in support of the hypothesis that memory impairment represents a form of diabetes mellitus that selectively afflicts the brain. It is one of the most alarming illnesses especially to elderly people. Markedly, lot of further essential research studies is looked-for the molecular, cellular and systemic level moreover behavioral levels. At the same time, it is essential to recognize that T2DM and T3DM are not solely the end results of insulin resistance and/or insufficiency, because these metabolic syndromes are explicitly accompanied by significant activation of various processes such as oxidative stress, inflammatory mediators, DNA breakage and mitochondrial dysfunction, which contribute to the deterioration surge by exacerbating insulin resistance. Referring to AD as T3DM is acceptable, because the abnormalities on

basic molecular and biochemical level are overlap with T1DM and T2DM rather than mimic the effects of either one. The objective of this review is to highlights the functioning of key mechanisms and hypothesis concerned in the progression of the comorbidity of diabetes and memory impairment.

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